The Ramanbhai Foundation 7th International Symposium
Current Trends in Pharmaceutical Sciences

"Advances in New Drug Discovery & Development"

Feb 2-4, 2015
Ahmedabad, India

Scientific Abstracts

www.rbfsymposium.net

Advancing Drug Discovery & Development

Zydus dedicated to life

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 alleviate

human sufferings.

Contents

Message from the Chief Patron

Dear Delegates,

It's a pleasure to welcome you all to the Ramanbhai Foundation 7th International Symposium.

This year's RBF symposium will focus on Advances in New Drug Discovery and Development through state-of-the-art lectures, cutting-edge poster presentations, panel discussions and informal scientific networking.

At Zydus, innovation truly forms the core of our being. Our journey of discovery just got more luminous as we launched our own patented NCE – Lipaglyn, the world's first drug to be approved for the treatment of diabetic dyslipidemia in 2013 and recently launched Exemptia, the world's first biosimilar Adalimumab, the largest selling therapy worldwide for inflammatory arthritis. This has truly been the result of a long and exciting journey of learning and enrichment.

Our overarching aim through the RBF Symposium has been to create a platform for knowledge-sharing where researchers, scientists, academicians and the industry can converge, discuss and share new trends in Drug Discovery and Development. We believe that there are abundant opportunities for innovation waiting to be explored in every sphere of healthcare and pharmaceuticals and there are ideas that can make a significant improvement or a difference.

Your support and involvement has played an important role in making this happen. Over the next three days, our panel of distinguished speakers will be sharing their knowledge and experience. We are confident that you will find the Ramanbhai Foundation 7th International Symposium, an enriching experience.

With warm regards,

Pankaj R. Patel
Chief Patron

About Ramanbhai Foundation

A first-generation entrepreneur, Mr. Ramanbhai Patel was one of the stalwarts of the Indian Pharmaceutical Industry. At a time when the newly independent nation was heavily dependent on imports of drugs and pharmaceuticals, he had set out to prove that an indigenous company could provide innovative, research-based quality medicines.

Born at Kathor in South Gujarat on the 19th of August 1925, he began his career as an academician at the L.M. College of Pharmacy, a premier institute in Ahmedabad. This short stint in academics formed a lasting imprint on his mind and the resolve to contribute to the cause of research and education grew stronger over the years.

In 1952, Mr. Ramanbhai Patel turned a pharma entrepreneur. Armed with a sound business acumen, he laid a strong foundation for Cadila and contributed to the growth of the Indian Pharmaceutical Industry. Zydus Cadila today enjoys the coveted distinction of being one of the leading pharma groups in the country and a global healthcare provider.

Mr. Ramanbhai Patel had published several outstanding research papers and had taken a keen interest in research activities of the group. Today, Zydus Cadila is amongst the top investors in research. Mr. Ramanbhai Patel's contributions in the field of pharmaceutical education were equally noteworthy. Gujarat which earlier had only one pharmacy college now has several reputed pharmacy colleges. More importantly, Ramanbhai was instrumental in taking pharmaceutical education to the rural heartland of Gujarat, making professional courses more accessible to students in smaller townships.

In recognition of his services, Mr. Ramanbhai Patel had been bestowed with several prestigious awards: President of India's Import Substitution Award in 1973. Prof. M.L. Shroff Memorial National Award in 1987, The Glory of India Award in 1991 at Washington, Grahak Suraksha Award in 1992, Acharya Prafulla Chandra Ray Memorial Gold Medal in 1993 and the Eminent Pharmacist Award in 1994.

In a fitting tribute to his outstanding contributions to the growth of the pharma industry in India, he was conferred the Gujarat Businessman of Year Award in the year 2000. He was also honoured by Express Pharma Pulse with the 'Lifetime Contribution Award' for his contributions to the Indian pharma industry.

On the occasion of Gujarat's Pharma Centenary Celebrations in January 2008, Mr. Ramanbhai B. Patel was posthumously awarded a special plaque in recognition for his efforts in laying a firm foundation for Gujarat's pharmaceutical industry in the Post Independence era.

With a firm belief that new avenues would surely emerge, if one has the will to discover it, he dedicated his life to the quest for knowledge, as an academician, entrepreneur and a researcher.

The Zydus Research Centre, a state-of-the-art facility which was set up during his lifetime, spearheads the research initiatives of the Zydus group and supports the quest for innovations and excellence in the field of research.

The Ramanbhai Foundation today continues to spearhead programmes in the field of pharmaceutical research, education and healthcare – areas close to the Late Founder Chairman's heart.

The Ramanbhai Foundation is committed to a number of special initiatives in the field of education. The Zydus School for Excellence which was a dream nurtured by Mr. Ramanbhai B. Patel has been set up to provide a rich academic environment where children can seek creative expressions for their endeavours.

The Ramanbhai Patel - AMA Centre for Excellence in Education has also been set up to raise the bars of excellence in the field of education through progressive learning programmes for academicians, knowledge sharing forums and by studying successful models of education and creating a platform for sharing these experiences.

The Ramanbhai Foundation alongwith the Indian Pharmaceutical Association has set up the IPA-Shri Ramanbhai B. Patel Foundation (IRF) to recognise and honour lifetime achievements of senior pharmacists who have contributed to the growth of the profession of pharmacy in India. The IRF also awards merit scholarships to deserving students in the field of Pharmaceutical Sciences.

The Ramanbhai Patel International Symposium held every two years is devoted to the discussion on the current trends and developments in Pharmaceutical Sciences. Through the symposia, the Foundation aims to bridge the research endeavors taking place across the world and create a platform for knowledge sharing, tracing the development of new molecules from the laboratory to the market.

About Zydus

Zydus Cadila is an innovative global pharmaceutical company that discovers, develops, manufactures and markets a broad range of healthcare products. With a core competence in the field of healthcare, Zydus Cadila provides total healthcare solutions ranging from formulations, active pharmaceutical ingredients and animal healthcare products to wellness products. Headquartered in the city of Ahmedabad in India, the group has global operations in four continents spread across USA, Europe, Japan, Brazil, South Africa and 25 other emerging markets. The group aims to be a leading global healthcare provider with a robust product pipeline and aspires to post revenues of Rs. 10000 crore by 2015 and be a research-based pharmaceutical company by 2020.

In its mission to create healthier communities globally, Zydus Cadila delivers wide ranging healthcare solutions and value to its customers. With over 15,000 employees worldwide, a world-class research and development centre dedicated to discovery research and eight state-of-the-art manufacturing plants, the group is dedicated to improving people's lives.

Zydus' Innovation programme is spearheaded by 1200 researchers across 19 sites, working on differentiated medicines for the future. From NCEs to vaccines, biosimilars and niche technologies, the group is exploring different ideas and concepts to bring in a relentless flow of innovation. In 2013, the group was the first to identify and develop Lipaglyn™ (Saroglitazar) and launch India's first NCE in the market. Recently, the group launched Exemptia, the world's first biosimilar for Adalimumab, the largest selling therapy worldwide for inflammatory arthritis.

- **NCE research**
  - Cardio-Metabolic diseases
  - Inflammation & pain
  - Oncology
- **Biologics**
  - Biosimilar Therapeutic proteins
  - Biosimilar Monoclonal antibodies
  - Biobetters and Novel biologics
- **Vaccines**
  - Infectious diseases

About Zydus Research Centre

The Zydus Research Centre is the dedicated research arm of the Zydus Group. With its team of over 400 research professionals, ZRC spearheads the group's quest of creating healthier and happier communities globally. Spread over an area of over 4,75,000 sq ft, ZRC is working on cutting edge technologies in 14 different scientific disciplines to discover novel therapeutic agents. The center has capabilities to conduct drug discovery & development from concept to IND enabling preclinical and clinical studies.

About Vaccine Technology Centre

Vaccine Technology Centre (VTC) is the Vaccine division of the Zydus Group. VTC has two state-of-the-art R & D Centers, one located in Catania, Italy; and the other in Ahmedabad, in the western part of India.

Zydus Vaccine division has indigenously developed, manufactured and launched India's first vaccine against H1N1 (Vaxiflu-S). The Vaccine Division's Rabies Vaccine Manufacturing facility has received WHO pre-qualification, and is one of the largest Rabies manufacturing facility in India.

The current programs under development include vaccine candidates designed to address infectious diseases like next-generation Influenza, Measles-Mumps-Rubella-Varicella, Typhoid, DPT-HiB, Hepatitis-B, Hepatitis-A, Hepatitis-E, Japanese Encephalitis, HPV and combination vaccines. Research is also focused on developing a Malaria vaccine.

About Zydus Biologics

Zydus Biologics is the biologics divisions of the Zydus group. The Zydus Biologics division has capabilities to discover and develop therapeutic proteins and monoclonal antibodies.

The division has a cGMP facility for manufacturing therapeutic protein based drugs and has developed and launched several therapeutic protein based drugs. The division also has an 11,000 litre cGMP facility for manufacturing monoclonal antibodies.

Speakers at previous symposia

The RBF 6th International Symposium February 4-6, 2013	**"Advances in New Drug Discovery Technologies & Translational Research"**
The RBF 5th International Symposium February 1-4, 2011	**"Advances in Translational Research and Medicines"**
The RBF 4th International Symposium February 3-5, 2009	**"Advances in Cardiometabolic Research - Basic Science and Clinical Aspects".**
The RBF 3rd International Symposium February 1-4, 2007	**"Current Trends in Pharmaceutical Sciences: Advances in Diabetes Therapy - Basic Science and Clinical Aspects"**
The RBF 2nd International Symposium January 23-25, 2005	**"Current Trends in Pharmaceutical Sciences: Role of Genomics and Proteomics"**
The RBF 1st International Symposium January 23-24, 2003	**"Current Trend in Pharmaceutical Sciences: Drug Discovery - Journey from Mouse to Man"**

Program Schedule

February 2, 2015

09.00 hrs — Welcome address

Mr. Pankaj R. Patel

Chief Patron
The Ramanbhai Foundation
7th International Symposium

09.15 hrs — Lighting of the lamp

09.20 hrs — Introduction to the keynote speaker

Dr. Sharvil P. Patel

Deputy Managing Director
Zydus Cadila

09.30 hrs — Keynote address:

Nuclear reprogramming and cell replacement prospects.

Sir John Gurdon, DPhil DSc FRS

2012 Nobel Prize in Medicine
Distinguished Group Leader in the Wellcome Trust / CRUK Gurdon Institute, Cambridge, UK

10.50 hrs — Vote of Thanks

Dr. Ganesh Nayak

COO & Executive Director
Zydus Cadila

11.00 hrs — **Exhibition & Poster Session Inauguration**

11.45 hrs

Introductory Remarks

Richard DiMarchi, Ph.D.

Standiford H. Cox Distinguished Professor of Chemistry
Linda & Jack Gill Chair in Biomolecular Sciences
Indiana University

Session I:

Chairpersons:

- T. K. Chakraborty, Ph.D., Professor, Department of Organic Chemistry, Indian Institute of Science, Bangalore
- Dhavalkumar D. Patel, M.D., Ph.D., Head, Novartis Institute for Biomedical Research, Basel, Switzerland

12.00 hrs

Design of drugs to treat influenza A virus infections and tissue fibrosis.

Bill DeGrado, Ph.D.

Professor, The DeGrado Laboratory
Department of Pharmaceutical Chemistry
University of California, San Francisco, USA

12.45 hrs

Adapting Proteostasis to Ameliorate Disease Pharmacologically

Jeff Kelly, Ph.D.

Lita Annenberg Hazen Professor of Chemistry
Chairman, Department of Molecular and Experimental Medicine
The Kelly Group, The Scripps Research Insitute
La Jolla, California, USA

13.30 hrs **Lunch**

14.30 hrs

Cell-penetrating Mini-proteins

Gregory L. Verdine, Ph.D.

Erving Professor of Chemistry
Harvard Department of Stem Cell and Regenerative Biology
Harvard University, Cambridge, USA

15.00 hrs

New drug discovery from natural products at CSIR-IIIM Jammu

Ram Vishwakarma, Ph.D.

Director
IIIM Jammu and CSIR-Central Drug Research Institute / Council of Scientific & Industrial Research, Lucknow, UP, India

15.30 hrs

Design, Development and Clinical Evaluation of Ligand-Targeted Therapies and Imaging Agents

Phil Low, Ph.D.

Ralph C. Corley Distinguished Professor of Chemistry and Director of the Purdue Center for Drug Discovery Biochemistry, USA

16.00 hrs **Tea Break**

16.30 hrs

Butelase 1 for C-terninal-specific Ligation and Macrocyclization of Peptides and Proteins

James P. Tam, Ph.D.

Professor, Division of Structural Biology & Biochemistry
School of Biological Sciences, Nanyang Technological University, Singapore

17.00 hrs

Chemical Biotechnology Applied to Metabolic Diseases

Richard DiMarchi, Ph.D.

Standiford H. Cox Distinguished Professor of Chemistry
Linda & Jack Gill Chair in Biomolecular Sciences
Indiana University, USA

17.45 hrs **Panel Discussion**

Session II:

Chairpersons:

- Dr. D. Ramaiah, F.A.Sc; Director, CSIR-North East Institute of Science and Technology (CSIR-NEIST), Jorhat
- Professor Alok Dhawan; Director, Institute of Life Sciences (ILS), Ahmedabad

09.00 hrs

Novel approaches to the prevention and treatment of type 2 diabetes

Matthias H. Tschöp, M.D., Ph.D.

Alexander-von-Humboldt Professor, Research Director, Helmholtz Diabetes Center
Director, Institute for Diabetes and Obesity, Helmholtz Zentrum München
Chair, Division of Metabolic Diseases, Department of Medicine, Technische Universität München

09.45 hrs

A small antidiabetic molecule prevents lipid induced insulin resistance through PPARγ dependent and independent pathways

Samir Bhattacharya, Ph.D., FNA, FASc, FNASc

(Former Director Indian Institute of Chemical Biology, Kolkata)
Emeritus Professor, NASI Senior Scientist,
School of Life Science, Visva-Bharati , Santiniketan
CSIR-North-East Institute of Science and Technology, Jorhat, INDIA

10.15 hrs

Vitamin D deficiency and insulin resistance

Satinath Mukhopadhyay, M.D., D.M

Professor, Department of Endocrinology and Metabolism, Institute of Postgraduate Medical Education & Research, Kolkata, India.

10:45 hrs — **Tea Break & Poster Session**

Session III:

Chairpersons:

- Dr. D T Mourya, Director, National Institute of Virology, Pune
- Dr. Reinhard Glueck, CSO, Zydus Vaccines

11.30 hrs

Targeting The IL-17 Pathway In Autoimmune Diseases

Dhavalkumar D. Patel, M.D., Ph.D.

Head, Novartis Institute for Biomedical Research, Basel, Switzerland

12.15 hrs

Challenges and Opportunities in Development of Innovative Vaccines for the 21st Century

Rahul Singhvi, ScD

COO, Global Vaccine Business Unit,
Takeda Pharmaceuticals, Inc. USA

13.00 hrs — **Lunch**

Session IV:

Chairpersons:

- Charles F. Burant, M.D., Ph.D.; Dr. Robert C. and Veronica Atkins Professor of Metabolism, The Burant Lab, University of Michigan Medical School, USA
- Bill DeGrado, Ph.D.; Professor, The DeGrado Laboratory, Department of Pharmaceutical Chemistry, University of California, San Francisco

14.00 hrs

In search of novel therapeutic approaches to improve insulin sensitivity

Philip Larsen, MD, Ph.D.

Global Head of Diabetes Research and Translational Science, Sanofi Aventis, France

14.30 hrs

Cardiovascular risk milieu in nonalcoholic fatty liver disease

Naga Chalasani, MD,FACG

Professor of Medicine, Professor of Cellular & Integrative Physiology Division of Gastroenterology and Hepatology, Indiana University School of Medicine, Indianapolis, USA

15.00 hrs

Saroglitazar: a potential new drug for non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH)

Mukul Jain, Ph.D.

Senior VP, Pharmacology & Toxicology
Zydus Research Center, Ahmedabad, India

15.30 hrs

NASH/NAFLD biomarkers: Are we stuck with biopsies?

Marcus Hompesch, M. D.

President, CEO and Founder
Profil Institute for Clinical Research, Inc, USA

16.00 hrs **Tea Break**

16.30 hrs

Diabetes: The Greatest Epidemic in the 21st Century?

Paul Zimmet, AO MD PhD FRACP FRCP FTSE

Director Emeritus, Victor Smorgon Diabetes Centre, Baker IDI Heart and Diabetes Institute
Adjunct Professor, Monash University, Honorary President, International Diabetes Federation,
Chair, Programme Committee, World Diabetes Congress 2013, Melbourne, Australia

17.00 hrs

Controlling the Tsunami: In our "Stars" or in our "Hands"

Shaukat M. Sadikot, M.D.

President-Elect, International Diabetes Federation 2013-2015,
President of DiabetesIndia ,Consultant Endocrinology, Jaslok Hospital and Research Center,
Mumbai, India

17.30 hrs

Achieving Better Research and Clinical Outcomes in Health Age

Viren Mehta, Ph.D.

Chairman, Gather Health Limited
Founder, Mehta Partners, LLC., USA

18.00 hrs **Panel Discussion**

Session V:

Chairpersons:

- Naga Chalasani, MD,FACG; Professor of Medicine, Professor of Cellular & Integrative Physiology, Division of Gastroenterology and Hepatology, Indiana University School of Medicine, Indianapolis, USA
- Paul Zimmet, AO MD PhD FRACP FRCP FTSE; Director Emeritus, Victor Smorgon Diabetes Centre, Baker IDI Heart and Diabetes Institute, Australia

09.00 hrs

Discovering and Developing Drugs in India: A Scientific and Regulatory Perspective

Y.K.Gupta, MBBS, MD, FAMS, FNASc, FIPS, FIAN

Professor and Head, Pharmacology, AIIMS, India

09.30 hrs

Reprogramming of PPARγ super-enhancers during browning of human adipocytes

Susanne Mandrup, Ph.D.

Professor, Department of Biochemistry and Molecular Biology
University of Southern Denmark

10.15 hrs

Parenchymal-stromal Cell Interaction in Metabolic Diseases

Yoshihiro Ogawa, M.D., Ph.D.

Professor and Chairman
Department of Molecular Endocrinology and Metabolism, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Japan

11.15 hrs — **Tea Break**

11.30 hrs

Innate Mechanisms of Metabolic Homeostasis

Ajay Chawla, M.D., Ph.D.

Professor, Cardiovascular Research Institute, University of California, San Francisco, USA

12.15 hrs

Multifaceted function of the transcription regulator PPAR

Walter Wahli, Ph.D.

Professor, Center for Integrative Genomics, University of Lausanne, Switzerland, Professor of Metabolic Disease, Lee Kong Chian School of Medicine, Imperial College London & Nanyang Technological University, Singapore General Hospital, Singapore

13.00 hrs — **Lunch**

Session VI:

Chairpersons:

- Philip Larsen, MD, Ph.D.; Global Head of Diabetes Research and Translational Science, Sanofi Aventis
- Richard DiMarchi, Ph.D.; Standiford H. Cox Distinguished Professor of Chemistry, Linda & Jack Gill Chair in Biomolecular Sciences, Indiana University, USA

14.00 hr		**Non-HDL cholesterol in the management of CVD** **Anil Bhansali, MD, DM** Head, Department of Endocrinology, PGIMER, Chandigarh, India
14.45 hrs		**Clinicians perspective into current and future therapies of type-2 diabetes mellitus** **Shashank R. Joshi, MBBS, MD, DM, FACP, FRCP, FACE** Consulting Endocrinologist, Lilavati Hospital in Mumbai, India
15.30 hrs	**Tea Break**	
16.00 hrs		**Clinical and Regulatory Challenges in New Drug Development Case Studies of Saroglitazar, ZYDPLA1 and ZYAN1** **Rajendra Jani, Ph.D.** Sr. VP, Clinical R & D, Zydus Cadila, Mumbai, India
16.45 hrs		**Metabolism modulation by diet and drugs, insights into mechanisms of action by metabolomics profiling** **Charles F. Burant, M.D., Ph.D.** Dr. Robert C. and Veronica Atkins Professor of Metabolism, The Burant Lab University of Michigan Medical School, USA
17.30 hrs	**Best poster awards**	
18.00 hrs	**Vote of Thanks**	

Speaker Profiles & Abstracts

Inaugural Address

Sir John Gurdon, DPhil DSc FRS

2012 Nobel Prize in Medicine

Distinguished Group Leader in the Wellcome Trust / CRUK Gurdon Institute, Cambridge, UK

Dr John Gurdon did his undergraduate work in Zoology in the University of Oxford and later a one-year postdoctoral position at CalTech in USA. He returned to Oxford and became a university lecturer in Embryology. In 1971 he moved to the MRC Molecular Biology Laboratory in Cambridge, continuing his work on Amphibian developmental biology. In 1983 he moved to the University of Cambridge as John Humphrey Plummer Professor of Cell Biology. He co-founded a research Institute of Developmental and Cancer biology with Professor Laskey as co-chairman and was Chairman of this Institute until 2002. During his career, Dr Gurdon concentrated on nuclear transplantation in the frog Xenopus. He has also carried out a range of experiments with this material, discovering the value of messenger RNA microinjection, mechanisms of response to morphogen gradients, and, most recently, mechanisms of nuclear reprogramming by Xenopus oocytes and eggs. Dr Gurdon served as Master of Magdalene College Cambridge from 1995-2002, and has received various recognitions, including, most recently, the Lasker Award for Basic Medical Science, and the Nobel Prize for Physiology or Medicine in 2012.

Topic

Nuclear reprogramming and cell replacement prospects.

The different cell types that compose our bodies are remarkably stable. Hardly ever do we find skin cells in the brain or liver cells in the heart. In those very special cases where some regeneration can take place in vertebrates, there is little if any evidence for a switch in cell-type. Nevertheless, nuclear transfer, cell fusion, and induced pluripotency can result in pluripotent embryo cells being derived from specialized adult cells. This talk will summarize the original nuclear transfer experiments and explain how they have led to induced pluripotency by transcription factor overexpression. The combination of nuclear transfer, embryonic stem cells, and induced pluripotency give encouraging prospects for the eventual use of cell replacement therapy. The prospects and limitations of this field will be discussed.

Chairpersons: Session I

Tushar Kanti Chakraborty, Ph.D., FNA, FASc, FNASc

Professor, Department of Organic Chemistry, Indian Institute of Science, Bangalore

Prof. Tushar Kanti Chakraborty is currently Professor, Department of Organic Chemistry at Indian Institute of Science, Bangalore. Previously, he was the Director CSIR-CDRI, Lucknow from 2008-2013. He had a long illustrious career at CSIR-IICT Hyderabad from 1987-2008, where he excelled in various capacities from scientist to Chief Scientist. He is a Ph.D. in 1984 from IIT, Kanpur (Prof. S. Chandrasekaran); and did his Postdoctoral Fellowship during 1984-87 at University of Pennsylvania, Philadelphia, USA (Prof. K. C. Nicolaou). His areas of Research Interests include Organic synthesis; peptides and peptidomimetics; designing new amide-linked molecular entities based on sugar amino acids and related compounds and studying their structures and properties. His work has brought him multiple recognitions and awards, including the prestigious JC Bose Fellowship in 2008. He has guided over 26 PhD students and published over 162 papers in international journals with >3000 citations.

Dhavalkumar D. Patel, M.D., Ph.D.

Head, Novartis Institute for Biomedical Research, Basel, Switzerland

He obtained a BS in Zoology at Duke University in 1982. Through the Medical Scientist Training Program, he earned a Ph.D. from the Department of Microbiology and Immunology as well as a M.D. from the Duke University School of Medicine in 1989. Dhaval joined the Medicine faculty at Duke where he was Assistant Professor (1994), Associate Professor (1999) and Chief of Allergy and Immunology (2001). In 2003, Dhaval joined the faculty at the University of North Carolina (UNC) as Professor of Medicine, Professor of Microbiology and Immunology, Chief of the Division of Rheumatology, Allergy and Immunology and Director of the Thurston Arthritis Research Center. He was recognized in 2006 for his contributions by being named the Joseph P Archie, Jr. Eminent Professor of Medicine. Since 2006, Dhaval has joined the Novartis Institutes for BioMedical Research in Basel and has held the positions of: Head, Fully Integrated Program in Rheumatoid Arthritis; Head, Autoimmunity and Transplantation Research Basel; Global Head, Autoimmunity, Transplantation and Inflammation Disease Area; Head, NIBR Basel; and Head, NIBR Europe. He is a member of the NIBR Executive Committee.

Bill DeGrado, Ph.D.

Professor, The DeGrado Laboratory, Department of Pharmaceutical Chemistry,
University of California, San Francisco, USA

William (Bill) DeGrado's work focuses on the design of peptides, proteins, and small molecule drugs. He received his Ph.D. in organic chemistry from the University of Chicago (1981). Bill was a member of DuPont Central Research and DuPont Merck Pharmaceutical Company from 1981 to 1996. In 1996, Bill moved to the Department of Biochemistry and Biophysics at the University of Pennsylvania, where he was a professor in the department of Biochemistry & Biophysics and an adjunct member of the Chemistry Department. In 2011 he moved to the Department of Pharmaceutical Chemistry at the University of California San Francisco, where he is currently a professor and member of the Cardiovascular Research Institute. He is a member of the National Academy of Science and the American Academy of Arts and Sciences. He also was the scientific founder of PolyMedix, which was recently purchased by Cellceutix. Some of Bill's research interests include: de novo design of proteins and peptide design; peptide mimetics; structure, stability, and function of membrane proteins, including integrins and viral ion channels; design of biomimetic polymers; bioinorganic chemistry; and computational approaches to small molecule and protein design.

Topic

Design of drugs to treat influenza A virus infections and tissue fibrosis.

M2 is the target of the anti-influenza drugs amantadine and rimantadine. Although this class of compounds was used to treat influenza A virus infections for several decades, currently circulating strains of the virus are largely resistant to these drugs. Structural and molecular dynamics investigations of the channel have shown the mechanism by which protons are stabilized as they transit through the pore, leading to a new understanding of drug-inhibition as well as the development of new classes of drugs that address the problem of drug-resistance.

The second topic addresses the need for effective therapies specifically targeting fibrosis, which is a major cause of organ failure. Transforming growth factor β is a central mediator of fibrotic processes, and its activation thorough αv integrins has been increasingly important in therapeutic development. We have developed a potent and highly specific small molecule inhibitor of the αvβ1 integrin and show that this inhibitor completely inhibits TGFβ activation by primary fibroblasts from several organs. We also show that the inhibitor is therapeutically effective in vivo in mouse models of lung, liver and kidney fibrosis. This study suggests that αvβ1 inhibitors may be useful therapeutics for treating fibrotic diseases of multiple organs.

Jeff Kelly, Ph.D.

Lita Annenberg Hazen Professor of Chemistry, Chairman, Department of Molecular and Experimental Medicine
The Kelly Group, The Scripps Research Insitute, La Jolla, California, USA

Dr. Kelly is currently the Lita Annenberg Hazen Professor of Chemistry, Chairman, Department of Molecular and Experimental Medicine at The Kelly Group, The Scripps Research Insitute, La Jolla, California. Jeff was a professor of chemistry at Texas A&M University before coming to Scripps Research, and before that a researcher at The Rockefeller University. The central focus of his research is to understand the principles of protein folding and to comprehend the basis for misfolding diseases. His laboratory studies the etiology of neurodegenerative diseases linked to protein aggregation, including Alzheimer's disease, Parkinson's Disease, and the familial gelsolin and transthyretin-based amyloidoses–publishing over 295 peer-reviewed papers in this area to date (h-index = 75). Kelly has won numerous awards, to name a few: the Biopolymers Murray Goodman Memorial Prize, 2012; The American Chemical Society, Ralph F. Hirschmann Award in Peptide Chemistry, 2012; The Protein Society Emil T. Kaiser Award, 2011; The American Peptide Society Rao Makineni Lectureship (Award), 2011.

Kelly has cofounded three biotechnology companies, FoldRx Pharmaceuticals (with Susan Lindquist), now owned by Pfizer, Proteostasis Therapeutics, Inc. (with Andrew Dillin and Richard Morimoto) (a private corporation) and Misfolding Diagnostics (with Xin Jiang and Justin Chapman; a private corporation). The Kelly laboratory discovered the first regulatory agency-approved drug (Tafamidis or Vyndaqel) that slows the progression of a human amyloid disease.

Topic

Adapting Proteostasis to Ameliorate Disease Pharmacologically

Gregory L. Verdine, Ph.D.

Erving Professor of Chemistry, Harvard Department of Stem Cell and Regenerative Biology, Harvard University, Cambridge, USA.

Gregory L. Verdine is Erving Professor of Chemistry at Harvard University, in the Departments of Chemistry & Chemical Biology and Stem Cell & Regenerative Biology. His research interests lie in the emerging area of chemical biology – particularly in the biologic processes underlying control of gene expression and preservation of genomic integrity. He has made major contributions to the understanding of DNA damage recognition and repair by base-excision DNA repair enzymes. He has also pioneered new and powerful approaches for the discovery of unconventional bioactive ligands for targets that have proven difficult to target with conventional drugs. Verdine holds a PhD in Chemistry from Columbia University and completed an NIH Postdoctoral Fellowship at M.I.T. and Harvard Medical School with Chris Walsh.

Topic

Cell-penetrating Mini-proteins

One of the most vexing problems in life science is that of "undruggability," the difficulty of targeting certain biological macromolecules in vivo using existing drug or ligand discovery technologies. It has been estimated that as many as 80-90% of all potential targets, including many that have been extensively validated in humans and in animal models, are undruggable. The Verdine laboratory is developing powerful new chemistry-based platform technologies to address these undruggable targets. Specifically, the lab is developing cell-penetrating mini-proteins, molecules that, like protein therapeutics, possess the ability to target large flat surfaces, but that, like small molecules, are fully synthetic and hence can be modified at will. Progress on the development of one class of cell-penetrating mini-proteins – hydrocarbon-stapled alpha-helical peptides – will be reviewed in this talk.

Ram Vishwakarma, Ph.D.

IIIM Jammu and CSIR-Central Drug Research Institute / Council of Scientific & Industrial Research, Lucknow, UP, India

Ram Vishwakarma is director of CSIR - Indian Institute of Integrative Medicine, Jammu

He was also Vice-President and Head (Medicinal Chemistry) Piramal Life Sciences (Nicholas Piramal Research Centre), Mumbai (2005-2009): Responsible for new drug discovery projects in the areas of inflammation, cancer, diabetes and drug-res istant infections

Dr Ram Vishwakarma received his Post-doctoral studies from the Cambridge University, England (with Sir Alan Batter sby FRS on biosynthesis of Vitamin B_{12} and related corrins and porphyrins) (1991-1993) Also received Ph.D. (Medicinal Chemistry) from Central Drug Research Institute Lucknow and M.Sc. (Organic Chemistry) from Bundelkhand University, India (1978-1980)

Having 28 years of research experience (both in scientific institution and pharma company) in drug discovery, medicinal chemistry, natural-products chemistry, organic-synthesis, chemical-biology and glycobiology, Chemical biology of Glycosylphosphatidylinositol (GPI) anchors in parasitic protozoa Molecular target based drug discovery for cancer, diabetes, inflammation and infections.

Research and leadership exper ience in both academic as well as industrial setting. Specific interest in the questions related to the chemistry of small molecules in biology

Topic

New drug discovery from natural products at CSIR-IIIM Jammu.

Small molecule natural products have remained the most consistent source of diverse structures exhibiting remarkable pharmacological properties, and have provided a large number of “first-in-class” drugs for untreatable diseases. For example, currently used 60% of anti-cancer and 75% of anti-infective drugs owe their origin in natural product scaffolds. A number of life-saving drugs used in other therapeutic areas are also natural products derived or inspired (e.g. opiates and statins). Besides being remarkably rich source of drugs, many privileged natural products (e.g. cytochalasins, monensin, brefeldin, rapamycin, FK-506, forskolin etc) have enabled fundamental advances in cell biology, immunology and synthetic chemistry. Among the primary sources for the natural products include medicinal plants, fungi, bacteria and marine species. However, much of the Indian biodiversity (terrestrial plants, bacteria, fungi and marine species) remain unexplored and offer greater opportunities for biotechnological interventions (directed biosynthesis and pathway engineering) and new drug discovery. We at CSIR-IIIM have integrated the natural-products chemistry with our strong medicinal chemistry and biotechnology programs in the disease areas of cancer, inflammation and multi-drug resistant infections, and have initiated efforts towards questions related to chemical ecology and stem cell biology. This presentation will discuss results of some of our new drug discovery projects based on natural product scaffolds.

Phil Low, Ph.D.

Ralph C. Corley Distinguished Professor of Chemistry and Director of the Purdue Center for Drug Discovery - Biochemistry, USA

Dr. Philip S. Low is the Director of the Purdue Center for Drug Discovery and the Ralph C. Corley Distinguished Professor of Chemistry. Dr. Low has spent over 39 years exploring novel methods of targeted drug development, and on characterizing the structure and function of the human erythrocyte membrane. During this period, he has published over 350 scientific articles in refereed journals and has over 45 US patents/patents pending. Seven drugs stemming from his research are currently undergoing human clinical trials and three companies (Endocyte Inc., OnTarget Laboratories Inc., and HuLow Inc.) have been founded to commercialize these discoveries. Dr. Low has served on several National Institutes of Health Study Sections and has received an NIH MERIT Award. Dr. Low has also received both of Purdue's awards for outstanding research as well as the University's highest career achievement recognition (Morrill Award). Dr. Low received his B.S. in Chemistry from Brigham Young University in 1971and his Ph.D. in Biochemistry from the University of California, San Diego in 1975.

Topic

Design, Development and Clinical Evaluation of Ligand-Targeted Therapies and Imaging Agents

We are developing methods to target drugs specifically to pathologic cells, thereby avoiding collateral toxicity to healthy cells. In the case of cancer, we have exploited up-regulation of the folate receptor on cancers of the ovary, lung, kidney, endometrium and breast to target imaging and therapeutic agents to these cancers. Clinical trials of six folate-linked drugs demonstrate that the aforementioned strategy holds promise for increasing drug potency while reducing unwanted toxicity.

We have also developed a targeting ligand that selectively delivers attached drugs to PSMA on prostate cancer cells. Imaging and therapeutic studies suggest that this targeting ligand can not only improve diagnosis of the disease, but also enhance treatment of prostate cancer. Recent pre-clinical and clinical data on this targeting ligand confirm this anticipation.

Additional cancer-specific ligands that target malignancies of the pancreas, stomach, brain, liver, colon, skin and esophagus are also under investigation. Moreover, use of these ligands to "light up" cancer tissues with tumor-targeted fluorescent dyes during surgeries are being developed and videos of recent surgeries of ovarian and lung cancer patients will be presented.

Finally, targeted imaging and therapeutic agents for the diagnosis and treatment of autoimmune, inflammatory and infectious diseases will also be briefly described. Included in this part of the talk will be a brief description of novel targeted therapies for rheumatoid arthritis, heart disease, Crohn's disease, psoriasis, influenza virus infections and malaria.

James P. Tam, Ph.D.

Professor, Division of Structural Biology & Biochemistry, School of Biological Sciences, Nanyang Technological University, Singapore

James P. Tam is the Director of the Herbalomics and Drug Discovery Laboratory. He served as the Founding Dean of the School of Biological Sciences, the Founding Director of Biological Research Center and the Founding director of the double-degree program in Biomedical Science and Chinese Medicine at Nanyang Technological University, Singapore.

He received his Ph.D. in Medicinal Chemistry from the University of Wisconsin, Madison, USA and held appointments as Associate Professor at The Rockefeller University, USA (1982-1991), Professor at Vanderbilt University, USA (1991-2004) and The Scripps Research Institute, USA (2004-2008). His research work focuses on the discovery, design and development of therapeutics, particularly orally active biologics, immunologics, anti-infectives, anti-proliferatives and synthetic vaccines.

Professor Tam has published more than 330 papers in these areas of research. He received the Vincent du Vigneaud Award in 1986, the Rao Makineni Award by American Peptide Society in 2003, the Ralph F. Hirschmann Award by the American Chemical Society (ACS) in 2005, and the Merrifield Award by American Peptide Society in 2013 for his outstanding contributions to peptide and protein sciences. The Merrifield and Hirschmann Awards, administered by the APS and ACS respectively, recognize the highest achievements in the chemistry, biochemistry and biophysics of peptides at an international level. In addition to his scientific research, he has also been active in the peptide community. Besides serving on many editorial boards, he organizes international peptide and protein symposia and was co-founder of the past ten International Chinese Peptide Symposia. He received the Cathay Award from the Chinese Peptide Society, China in 1996. He was also honored as Honorary Professor by Peking University and Peking Union Medical College.

Topic

Butelase 1 for C-terninal-specific Ligation and Macrocyclization of Peptides and Proteins.

Proteases are ubiquitous whiereas ligaes, peptide-forming enzymes that catalyze the revere reaction are rare. Here we present the discovery and application of butelase 1, a C-terminal Asn/Asp (Asx)-specific ligase for ligation and macrocyclization of peptides and proteins. Butelase 1, isolated from Clitoria ternatea of the legume family, requires an Asx as the recognition residue in a sorting signal such as a tripeptide motif Asx-HisVal at the C-terminus of a peptide or protein substrate with HisVal dipeptide as a leaving group. Butelase 1 accepts most amino acids as a nucleophile to form an Asx-Xaa bond. Among the known ligases including Sortase A, TraF, PATG and PCY1, butelase 1 is the fastest ligase with Kcat values as high as 17s-1 and catalytic efficiencies 542,000 M-1s-1. These favorable properties: broad specificity, fast kinetics and traceless ligation product, bode well for butelase 1 in ligation, macrocyclization and labeling of petides, proteins and live cells.

Macrocyclization often enhances metabolic stability and has been used as a strategy to stabilize peptides and proteins. In addition, the covalent closure of the amide backbone induces a constrained structure that may improve biological activity. In this presentation, we show butelase 1 efficiently cyclizes various peptides and proteins ranging in size from 10 to 300 residues, including non-cysteine-containing peptides and a green fluorescent protein (GFP). In addition, we will present examples in designing and engineering macrocyclic peptides in the under-appreciated druggable natural product space of the “bigger, better and orally-active, small molecule-like peptides”.

Richard DiMarchi, Ph.D.

Standiford H. Cox Distinguished Professor of Chemistry, Linda & Jack Gill Chair in Biomolecular Sciences, Indiana University, USA

Dr. DiMarchi's contributions in peptide & protein sciences consists of three decades of work in academia, the pharmaceutical industry and biotechnology companies. He is the Cox Distinguished Professor of Biochemistry and Gill Chair in Biomolecular Sciences at Indiana University. He is a co-founder of Ambrx, Inc., Marcadia Biotech, Assembly and Calibrium Biotech. He has served as a scientific advisor to multiple pharmaceutical companies and three venture funds; 5AM, TMP, and Twilight. He is Chairman of the Peptide Therapeutics Foundation and external board member at Assembly Biosciences and Ontarget Therapeutics. Dr. DiMarchi is a retired Group Vice President at Eli Lilly & Company where for more than two decades he provided leadership in biotechnology, endocrine research and product development. He is readily recognized for discovery and development of rDNAderived Humalog® (LisPro-human insulin). As scientist and executive, Dr. DiMarchi also significantly contributed to the commercial development of Humulin®, Humatrope®, rGlucagon®, Evista®, and Forteo®. His current research is focused on developing macromolecules with enhanced therapeutic properties through biochemical and chemical optimization, an approach he has termed chemical-biotechnology. Dr. DiMarchi is the recipient of numerous awards including the 2005 AAPS Career Research Achievement Award in Biotechnology, the 2006 ACS Barnes Award for Leadership in Chemical Research Management, the 2006 ACS Esselen Award for Chemistry in the Service of Public Interest, the 2007 Carothers Award for Excellence in Polymer Sciences, the 2009 Watanabe Award for Life Sciences Research, the 2011 Merrifield Award for Career Contributions in Peptide Sciences, the 2012 Phillip Nelson Innovation Award, the 2014 Erwin Schrödinger-Preis, and a 2014 inductee to the National Inventors Hall of Fame.

Topic

Chemical Biotechnology Applied to Metabolic Diseases

The epidemic of obesity and its associated comorbidities represents a medicinal challenge that recruits broad molecular diversity. We have pioneered the application of endogenous hormones and physiological mechanisms optimized for pharmacological purposes as a means to address the broad heterogeneity constituted by the multiple diseases associated with the metabolic syndrome. From the earliest demonstration with lispro-insulin to the most recent discovery of incretin-based poly-pharmacophores we have pursued the discovery of therapeutics directed at the successful management of insulin-dependent diabetes, obesity and related diseases. We have coined the term "chemical biotechnology" to reflect the integration of classical small and large molecule-based chemistries. The integrated pharmacology of these peptides, proteins and nuclear hormones has provided a library of medicinal agents to be interrogated in cardio-metabolic diseases.

Chairpersons: Session II

D. Ramaiah, Ph. D, F.A.Sc

Director, CSIR-North East Institute of Science and Technology (CSIR-NEIST), Jorhat, India

Dr. D. Ramaiah received his Ph. D. degree in Chemistry from Indian Institute of Technology, Kanpur in 1988.

He was a scientist and held various positions at the CSIR-National Institute for Interdisciplinary Science and Technology, Trivandrum for 25 years from 1988 to 2013. He has recently (since October 2013) taken over the charge as the Director of the CSIR-North institute of Science and Technology, Jorhat, AssaM. D.r. Ramaiah was a visiting scientist at the University of Wurzburg and University of Mainz, Germany and Georgia Institute of Technology, Atlanta, USA.

He was a recipient of the Humboldt Fellowship, CRSI Bronze and MRSI medals and elected Fellow of the Andhra Pradesh Akademy of Sciences and Indian Academy of Sciences and currently is an Associate Editor of Photochemistry and Photobiology. His group current research interests include photochemistry, sensitizers for photodynamic therapy, DNA cleaving agents and molecular probes.

Alok Dhawan, Ph. D.

Director, Institute of Life Sciences (ILS), Ahmedabad.

Professor Dhavan is currently Director, Institute of Life Sciences, Ahmedabad University, Gujarat lien from CSIR-Indian Institute of Toxicology Research, Lucknow where he is Principal Scientist and Area Coordinator, Nanomaterial Toxicology Group. He obtained his Ph.D. Biochemistry from University of Lucknow, India in 1991. Professor Dhawan started the area of nanomaterial toxicology in the country and has recently published a guidance document on the safe use of nanomaterials. Professor Dhawan has won several honours and awards including the INSA Young Scientist Medal in 1994, CSIR Young Scientist Award in 1999 the Shakuntala Amir Chand Prize of ICMR in 2002 and the Vigyan Ratna by the Council of Science and Technology, UP in 2011. He was awarded two Indo-UK projects under the prestigious UK-IERI programme. He also has two European Union Projects under the FP7 and New INDIGO programmes. He has been elected Fellow of several bodies as: The National Academy of Sciences, India; Fellow, The Academy of Toxicological Sciences, USA; Fellow, The Academy of Environmental Biology; Fellow, Academy of science for Animal Welfare, etc. He has to his credit over 100 publications in peer reviewed international journals. Five reviews/book chapters and four patents.

Matthias H. Tschöp, M.D., Ph.D.

Alexander-von-Humboldt Professor, Research Director, Helmholtz Diabetes Center, Director, Institute for Diabetes and Obesity, Helmholtz Zentrum München, Chair, Division of Metabolic Diseases, Department of Medicine, Technische Universität München

Matthias Tschöp is the Research Director of the Helmholtz Diabetes Center, the Director of the Institute for Diabetes and Obesity at Helmholtz Zentrum München, and serves as the Chair of Metabolic Diseases at Technische Universität München. He is the first physician to receive the prestigious Alexander-von-Humboldt Professorship. Prof. Tschöp discovered the orexigenic, adipogenic, and metabolic effects of the "hunger hormone" ghrelin as well as its secretory control by nutrients. He also discovered how specific CNS circuits directly "remote control" lipid metabolism of fat tissue and liver to modulate circulating cholesterol, fatty acids and triglycerides. Together with the chemist Richard DiMarchi, Tschöp discovered and functionally characterized a series of novel gut hormone-based single molecule combinatorial therapeutics, which are currently in clinical development for the treatment of diabetes and obesity. Most recently, DiMarchi and Tschöp engineered and validated peptides capable of delivering small molecules to distinct cell populations. Prof. Tschöp has been awarded numerous awards including the 2010 NIH/NIDDK Scholar Award, the 2011 Outstanding Scientific Achievement Award of the American Diabetes Association, the prestigious Paul Martini Prize for clinical pharmacology in 2014 and the Erwin Schrödinger Prize, the highest German Award for interdisciplinary biomedical research (2014). He was elected into the German National Academy of Sciences (Leopoldina) in 2013.

Topic

Novel approaches to the prevention and treatment of type 2 diabetes

All metabolic processes, from single cell substrate oxidation to complex behaviors, are under the control of specific CNS circuits, aiming to maintain homeostasis. Afferent signals include gut hormones, adipokines and nutrient components, while efferent information primarily originates from the hypothalamic nuclei and involves components of the autonomic nervous system as well as the classic endocrine axes. We recently observed that diet-induced metabolic diseases, such as obesity and type 2 diabetes, are associated with (and preceded by) pathological processes in these hypothalamic control centers. Such pathophysiology concerns the hypothalamic cell matrix beyond key neuronal populations and includes astrocytosis, microgliosis, hypervascularisation as well as increased presence of pro-inflammatory cytokines. Specific targeting of such "hypothalamic inflammation" using novel gut-peptide based delivery of glucocorticoids to key metabolic disease regions improved both local pathophysiology and systemic metabolic health. Such a novel unimolecular dual agonism and steroid delivery approach may not only offer superior therapeutic option for at least some patient subpopulations, but also suggests a pathogenetic relevance for this novel hypothalamic syndrome.

Samir Bhattacharya, Ph.D., FNA, FASc, FNASc

(Former Director Indian Institute of Chemical Biology, Kolkata) Emeritus Professor, NASI Senior Scientist, School of Life Science, Visva-Bharati , Santiniketan. CSIR-North-East Institute of Science and Technology, Jorhat

Prof Samir Bhattacharya is an Emeritus Professor in the School of Life Science, Centre of advanced study in Zoology, Visva-Bharati University (a Central University). He is also the mission director, NEEP Project at the North Eastern Institute of Science and Technology, Jorhat Assam. He has served as the director of CSIR Institute IICB, Kolkata between 1999-2004. He has been elected as fellow of the prestigious bodies like Indian National Science Academy (FNA), National Academy of Sciences, India (FNASc.) and Indian Academy of the Sciences (FASc) in India. He has obtained Senior Fulbright Award from Federal Government, USA, twice, in 1975 and 1983. He has served as president of Asia and Oceania Society for Comparative Endocrinology (AOSCE) from 2000 to 2004. He obtained, prestigious Barclay Memorial Gold Medal Award for the year 2001 for his conspicuously important contribution to Science including Medicine from The Asiatic Society. He has published more than 134 articles in peer reviewed journals including Nature and PLoS ONE. He is also reviewer and in the board of journals like Biochem. J., PLoS ONE, Biochemical Pharmacology, Molecular Biology Report, Cancer Letter, J. Biosciences, Current Sciences. He has also more than 25 patents to his name.

Topic

A small antidiabetic molecule prevents lipid induced insulin resistance through PPARγ dependent and independent pathways

Prevalence of obesity induced diabetes has been dramatically increased over the past decades to an estimated number of 400 million people over the world. Oversupply of lipid that causes excessive deposition of intracellular fat in insulin target tissues is the most important factor for this insidious disease. Except TZDs there is practically no drug which addresses lipid induced defects responsible for Type 2 diabetes (T2D). TZDs are PPARγ ligands, they activate PPARγ and being a transcription factor it expresses genes related to insulin sensitization. We lost this remarkably advantageous drug because of its adverse side effects and toxicities. We prepared a peroxy Vanadate molecule with 3, 5 dimethylpyrazole (dmp) henceforth referred as dmp, it is toxicity free, soluble in water and stable at room temperature. Its primary effect is on lipid induced insulin resistance of adipose tissue and skeletal muscle cells. dmp dramatically changes the inflammation of adipose tissue which include increase in the number of pre and mature adipocytes, decline of atrophied adipocytes, increased uptake of free fatty acids and elevation of glucose uptake by adipose tissue and skeletal muscle from HFD and db/db mice. These results indicate dmp's role as insulin sensitizer which they perform through PPARγ upregulation which remains suppressed in inflamed adipose tissue of HFD mice. PPARγ does not act directly for such improvement, but through the increase of adiponectin, CD36 and AP2 gene expressions. Besides PPARγ dependent effects, dmp also markedly reduced Fetuin A expression which is one of the important players in adipocytes inflammation. In addition, dmp protects mitochondrial damage due to excess lipid and stimulated Ampk activation in skeletal muscle cells. Taken together, dmp has an overall effect in preventing lipid induced insulin resistance in two major insulin target tissues.

Satinath Mukhopadhyay, M.D., D.M.

Professor, Department of Endocrinology and Metabolism, Institute of Postgraduate Medical Education & Research, Kolkata, India.

Prof. Dr. Satinath Mukhopadhyay is a Professor at the Institute of Post Graduate Medical Education and Research (IPGME&R) in Kolkata. He has been associated with this institution since the mid-nineties, when he studied and trained for the postdoctoral DM superspeciality degree and specialised in Endocrinology.

Prior to his current designation as Professor (which he took on in September 2009), Dr. Mukhopadhyay has held the titles of Lecturer, Assistant Professor and Associate Professor at IPGME&R, for various periods since July 1999.

Dr. Mukhopadhyay has been involved in many research studies, surveys and clinical trials over the years, and some of these projects are still in progress. Many of the studies culminated in research papers that Dr. Mukhopadhyay authored or collaborated in writing, and these and other articles of his have been published in prominent peer-reviewed, indexed journals.

Dr. Satinath Mukhopadhyay is a member of various esteemed associations related to his field of specialisation, and he actively participates in their annual conferences and other events. He has often made presentations and delivered guest lectures at these events, on topics in Endocrinology and Diabetes.

Topic

Vitamin D deficiency and insulin resistance

Chairpersons: Session III

D. T. Mourya, Ph. D.

Director, National Institute of Virology, Pune

Dr. Mouriya is scientist G and Director at the National Institute of Virology, Pune, India. His field specialization is in Microbiology and Immunology and he did his masters (1976) and Ph.D from University of Indore in 1979. He also did an Advanced Course in Medical Entomology from National Institute of Communicable diseases, Delhi (1981). He was the first recipient of Dr. T. Ramachandra Rao, ICMR award (1990) for meritorious work in the field of Medical Entomology. His major achievements include working on the vector potential of mosquitoes to arboviruses of public health importance in India. His research work on pathogens and parasites of mosquitoes, vector-pathogen relationship and its application in the studies on certain mosquito-borne diseases has received great appreciation from the scientific community. He has made significant contribution in vector biology aspects of vectors of Dengue, Chikungunya and Japanese encephalitis viruses and has established biochemical techniques for detection of insecticide resistance in mosquito vectors in this country. He has more than 100 publication as an outcome of his years of research, in peer reviewed international journals.

Reinhard Glueck, Ph. D.

Chief Scientific Officer, Vaccines Technology Centre, Zydus Cadila, Ahmedabad, India

Dr. Reinhard Glueck is the Chief Scientific Officer at Zydus Cadila Healthcare, Ahmedabad. He is chairing the Zydus research center, Etna Biotech, Catania, Italy, too. Previously he hold the same position at former Berna Biotech, today Crucell. He is an expert in innovative vaccine development. He has first in history developed the so called Immunostimulatoary reconstituted influenza virosome or virosome technology which is today applied in millions of influenza and hepatitis A vaccines worldwide. He also introduced new adjuvants such as non-toxic HLT for influenza vaccines which has obtained marketing authorization in Switzerland in 2001. In his role of CSO at Zydus Cadila Healthcare Ltd. he has entered into collaboration with world class institutions (IDRI, Thelormedix, Statens Serum Inst. Denmark, ICGEB, New Delhi and others) to evaluate new and better adjuvants. Reinhard Glueck was until recently the President of Swiss Biotech Association and has been awarded with the Honorary Membership of this organization. He is member of many scientific boards, worldwide. In his career he published more than 100 peer reviewed papers and holds more than 10 patents.

Dhavalkumar D. Patel, M.D., Ph.D.

Head, Novartis Institute for Biomedical Research, Basel, Switzerland

Dr. Dhavalkumar Patel is Head of NIBR Europe and Global Head, Autoimmunity, Transplantation and Inflammation (ATI) Disease Area at the Novartis Institutes for BioMedical Research.

Born in India, Dhaval immigrated to the United States at age 7, and obtained a BS in Zoology at Duke University in 1982. Through the Medical Scientist Training Program, he earned a Ph.D. from the Department of Microbiology and Immunology as well as a M.D. from the Duke University School of Medicine in 1989. He performed residency training in Internal Medicine and fellowship training in Rheumatology as well as Allergy and Immunology at Duke University Medical Center. Dhaval joined the Medicine faculty at Duke where he was Assistant Professor (1994), Associate Professor (1999) and Chief of Allergy and Immunology (2001). In 2003, Dhaval joined the faculty at the University of North Carolina (UNC) as Professor of Medicine, Professor of Microbiology and Immunology, Chief of the Division of Rheumatology, Allergy and Immunology and Director of the Thurston Arthritis Research Center. He was recognized in 2006 for his contributions by being named the Joseph P Archie, Jr. Eminent Professor of Medicine. Since 2006, Dhaval has joined the Novartis Institutes for BioMedical Research in Basel, and has held the positions of: Head, Fully Integrated Program in Rheumatoid Arthritis; Head, Autoimmunity and Transplantation Research Basel; Global Head, Autoimmunity, Transplantation and Inflammation Disease Area; Head, NIBR Basel; and Head, NIBR Europe. He is a member of the NIBR Executive Committee.

Topic

Targeting The IL-17 Pathway In Autoimmune Diseases

Th17 cells, and their hallmark effector cytokine IL-17A, are now recognized as an important driver of multiple autoimmune diseases, including psoriasis and the seronegative spondyloarthropathies: ankylosing spondylitis and psoriatic arthritis. Several molecules that selectively target components of the Th17 pathway are being tested for efficacy in immune-mediated diseases, including those that target IL-17A, and the IL17 receptor. I will discuss the rationale and results of clinical trials using these molecules, focusing on secukinumab (AIN457), a recombinant, highly selective, fully human monoclonal anti–IL-17A antibody of the IgG1/kappa isotype. The results indicate that IL-17A is a primary effector molecule that plays an important pathogenic role in many autoimmune diseases, and its blockade is safe and effective in the treatment of psoriasis, psoriatic arthritis and ankylosing spondylitis.

Rahul Singhvi, ScD

COO, Global Vaccine Business Unit, Takeda Pharmaceuticals, Inc. USA

Dr. Rahul Singhvi is a business leader in the vaccine and pharmaceutical industry. He is Managing Partner and co-Founder of MLV Healthcare Partners (MLVHCP), a New York based merchant bank. Prior to cofounding MLVHCP, Dr. Singhvi served as the President & CEO of Novavax, Inc, a NASDAQ listed, development stage biotechnology company. During his tenure at Novavax, he transformed Novavax from a distressed specialty pharmaceutical company into a premier vaccine development company. Under his leadership, Novavax's valuation rose from $35M to almost $300M and enjoyed a robust pipeline of important clinical and preclinical stage vaccine candidates, including those against influenza, respiratory syncytial virus (RSV), and other infectious diseases. At Novavax, Dr. Singhvi developed a non-dilutive financing strategy through partnerships with governments and international companies. These partnerships included a major contract with the United States government agency HHS-BARDA worth over $179MM that was critical for Novavax to finance its pandemic and seasonal flu vaccines through late stage clinical development. Other key partnerships included those with GE Healthcare (manufacturing), LG Life Sciences (Korea), Cadila Pharmaceuticals Limited (India) and Avimex (Mexico). In addition, Dr. Singhvi raised over $100 million for Novavax through multiple equity financings. Prior to joining Novavax in 2005, Dr. Singhvi served in a number of positions at Merck & Co., where he helped develop several vaccines, including Zostavax®, the only vaccine on the market to prevent shingles.

Dr. Singhvi was named one of the most influential Marylanders in the healthcare field by The Daily Record in 2010. During the same year, Novavax was named one of the ten most innovative companies in the biotechnology industry by Fast Companymagazine. Dr. Singhvi has served as a member of the Clinton Global Initiative andcurrently serves on the Board of Directors of Immunocellular Therapeutics (OTCBB: IMUC), a US public company working on cancer vaccines.

Dr. Singhvi graduated as the top ranked chemical engineer from IIT, Kanpur, India and obtained both his M.S. and Sc.D degrees in chemical engineering from MIT. He also received an MBA degree from the Wharton School of the University of Pennsylvania where he graduated as a Palmer Scholar.

Topic

Challenges and Opportunities in Development of Innovative Vaccines for the 21st Century

Recent outbreaks of H1N1 influenza, Dengue, Chikungunya, SARS, MERS and Ebola are constant reminders of the threat of emerging infectious diseases to human life and the world economy. Vaccines can serve as an important defense against these threats, butdevelopment of innovative vaccines is complex, time consuming and expensive. This has led to consolidation of innovative vaccine players within the global pharmaceutical industry. In parallel, increasing demand for basic childhood vaccines, driven by supranational organizations such as UNICEF, PAHO and GAVI, has spurred growth of the vaccine industry within emerging economies. These trends are leading to partnerships between innovative multinational companies and developing country vaccine manufacturers, with the promise of greater output of innovative vaccines at affordable prices. These opportunities and associated challenges will be discussed in this presentation.

Chairpersons: Session IV

Charles F. Burant, M.D., Ph.D.

Dr. Robert C. and Veronica Atkins Professor of Metabolism, The Burant Lab, University of Michigan Medical School, USA

Charles F. Burant, MD, PhD is the Dr. Robert C. and Veronica Atkins Professor of Metabolism. Dr. Burant received his bachelor's degree from the University of Wisconsin and his graduate and medical degrees from the Medical University of South Carolina in Charleston. He completed his residency training at the University of California, San Francisco along with a fellowship in Endocrinology at the University of Chicago. He joined the faculty at the University of Michigan Medical Center in 1999. Dr. Burant's clinical interests are in the area of metabolic syndromes and management of Type II Diabetes. His research laboratory investigates the mechanisms of insulin resistance and utilizes animal models of diabetes to identify pathways important in understanding diabetes progression. Additionally, his lab also studies adult pancreatic progenitor cells and how they might be used to generate new insulin secreting β-cells.

Bill DeGrado, Ph.D.

Professor, The DeGrado Laboratory, Department of Pharmaceutical Chemistry, University of California, San Francisco, USA

William (Bill) DeGrado's work focuses on the design of peptides, proteins, and small molecule drugs. He received his Ph.D. in organic chemistry from the University of Chicago (1981). Bill was a member of DuPont Central Research and DuPont Merck Pharmaceutical Company from 1981 to 1996. In 1996, Bill moved to the Department of Biochemistry and Biophysics at the University of Pennsylvania, where he was a professor in the department of Biochemistry & Biophysics and an adjunct member of the Chemistry Department. In 2011 he moved the Department of Pharmaceutical Chemistry at the University of California San Francisco, where he is currently a professor and member of the Cardiovascular Research Institute. He is a member of the National Academy of Science and the American Academy of Arts and Sciences. He also was the scientific founder of PolyMedix, which was recently purchased by Cellceutix. Some of Bill's research interests include: de novo design of proteins and peptide design; peptide mimetics; structure, stability, and function of membrane proteins, including integrins and viral ion channels; design of biomimetic polymers; bioinorganic chemistry; and computational approaches to small molecule and protein design.

Philip Larsen, M.D., Ph.D.

Global Head of Diabetes Research and Translational Science, Sanofi Aventis, France

Philip J Larsen MD, PhD is Global Head Diabetes Discovery and Translational Medicine. Dr Larsen joined Sanofi in August 2012, and his responsibilities encompass strategic and organizational leadership of Sanofi's diverse portfolio of preclinical and early clinical assets in the field of diabetes and related dysmetabolic complications. Dr. Larsen has 20 years of pharmaceutical and biotechnology industry experience in the field of diabetes and obesity. After few years of work at NovoNordisk and Zealand Pharma, Philip co-founded the Danish biotechnology company Rheoscience in 2001 also concentrating on obesity and diabetes. In 2008, Philip took up a position as chief scientific officer for diabetes research at Eli Lilly, Indianapolis, USA, before returning to Europe as VP for early clinical development in CVM at AstraZeneca. Dr. Larsen holds and MD from the University of Copenhagen and a PhD in neuroendocrinology also from University of Copenhagen".

Topic

In search of novel therapeutic approaches to improve insulin sensitivity

Naga Chalasani, M. D., FACG

Professor of Medicine, Professor of Cellular & Integrative Physiology, Division of Gastroenterology and Hepatology, Indiana University School of Medicine, Indianapolis, USA

Dr. Chalasani currently serves as David W. Crabb Professor of Medicine and Cellular &Integrative Physiology at Indiana University School of Medicine and is the Director of its Division of Gastroenterology and Hepatology. He completed his medical education in India and subsequently completed internal medicine residency and gastroenterology and hepatology subspecialty training at Emory University in Atlanta. Two broad themes to his research focus are nonalcoholic fatty liver disease and idiosyncratic drug induced liver injury, and he has made several important contributions to both of these areas. He is the Associate Editor for Gastroenterology and he has previously served or currently serving on the editorial board of many journals including Gastroenterology, Hepatology, Clinical Gastroenterology and Hepatology, American Journal of Medicine, Journal of Clinical Gastroenterology, and Nature Reviews Gastroenterology & Hepatology. He has been funded by the National Institutes of Health since 1998 for conducting investigations related to liver disease. Currently, he is the PI for two NIH U01 awards and one NIH K24 award, Co-PI for one NIH U01, and co-investigator for two NIH R01 awards. He has published over 170 original publications, 30 text book chapters and 26 editorials and commentaries. He is the lead author for the multisociety practice guideline for the diagnosis and management of nonalcoholic fatty liver disease published simultaneously in Gastroenterology, Hepatology, and American Journal of Gastroenterology in 2012.

Topic

Cardiovascular risk milieu in nonalcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD) is a major public health problem throughout the world. In the Western World, it currently is the second most common cause for listing for liver transplantation. NAFLD is broadly categorized into nonalcoholic fatty liver (NAFL) which generally benign hepatically and nonalcoholic steatohepatitis (NASH) which can progress to cirrhosis and liver failure. Adverse hepatic consequences of NAFLD (primarily from NASH) such as cirrhosis, liver failure, and liver cancer are well recognized, but non-so-well recognized is fact that the cardiovascular disease is the single most common cause of death in patients with either NAFL or NASH. Patients with NAFLD are heavily enriched with traditional cardiovascular risks such as obesity, type2 diabetes, and dyslipidemia. Recent publications highlighted the high prevalence of atherogenic dyslipidemia which is characterized by marked abnormalities in the characteristics of various lipoproteins. It is now evident that NAFLD and NASH are associated with a procoagulant state characterized by abnormal levels of clotting factors such as factor VIII, vWF, protein C, and antithrombin III. Additionally, there is clear cut evidence for high prevalence of significant endothelial dysfunction in individuals with NAFLD and NASH. Combined, these atherogenic dyslipidemia, procoagulant and proinflammatory state, and endothelial dysfunction create a milieu that is very high risk for cardiovascular morbidity and mortality in individuals with NAFLD and NASH. Improving these abnormalities may improve cardiovascular outcomes in patients with NAFLD and NASH

Mukul Jain, Ph. D.

Senior Vice President - Pharmacology, Zydus Research Centre, Cadila Healthcare Limited, Ahmedabad, Gujarat, India

Dr. Jain is heading the nonclinical research & development efforts at ZRC and is involved in discovery & development of NCEs. Dr. Jain obtained his B.Pharm, M.Pharm (Pharmacology), PhD (Medicine) and DBM from Nagpur University and a Certificate in Executive Management from IIM, Ahmedabad. After completing his PhD, he worked briefly at Wockhardt and then at Ranbaxy Research Center before moving to University of Florida at Gainesville in USA. After spending three years in US, he returned to India & joined NIPER at Mohali as Assistant Professor. In the year 2000 he came to Ahmedabad and joined Zydus Research Centre. Dr. Jain is the key person responsible for discovery & development of Saroglitazar / LipaglynTM, the first new drug from an Indian Pharmaceutical Industry and also the first approved 'Glitazar' class drug in the world. Besides Saroglitazar, his group has also developed 12 other NCEs that received IND approvals in India or abroad. His group is also responsible for conducting preclinical safety & toxicity studies for NCEs, Biologics, Vaccines & generic compounds. His facility has been accredited by GLP Authority of India, AAALAC, NABL, CAP, ISO and OHSAS etc.

He has guided 10 PhD students and several masters' students and has more than 215 research publications to his credit, which include 112 full length research papers in peer-reviewed International journals. He has also contributed to more than 38 patents as co-inventor. Dr. Jain is associated with various International Societies like ADA, ASPET, AACR, ACS, AAAS, IBRO, EASD, IPS etc. and is a Fellow of Academy of Sciences for Animal Welfare.

Topic

Saroglitazar: a potential new drug for Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH)

Non-alcoholic fatty liver disease (NAFLD) comprises a cluster of liver disorders with hepatic lipid accumulation (steatosis) as the key feature. NAFLD is commonly associated with dyslipidemia and insulin resistance and can progress to NASH (non-alcoholic steatohepatitis), which is characterized microscopically by steatosis, inflammation, ballooning and pericellular fibrosis. NAFLD and NASH are probably underestimated as a cause for liver cirrhosis and hepatocellular carcinoma. Although numbers of therapeutic options have been explored for management of NAFLD/NASH, no pharmacological treatment is yet approved. PPAR agonists are known to affect liver lipids and show pleotropic benefits. Saroglitazar is a novel PPARα/γ agonist having predominant PPAR alpha activity. Saroglitazar shows anti-hyperlipidemic, anti-hyperglycemic and insulin sensitizing effects in various preclinical models and has been approved for treatment of diabetic dyslipidemia and hypertriglyceridemia in humans.

We have evaluated the potential of saroglitazar in management of NAFLD and NASH using C57BL/6 mice, which were fed a choline-deficient, L-amino acid-defined, high-fat diet (CDAHFD) consisting of 60 kcal% fat and 0.1% methionine. CDAHFD is known to develop human-like NASH condition in mice. When CDAHFD-fed animals were treated with saroglitazar (0.3, 1 and 3 mg/kg) for 8 weeks, they presented significantly lower levels of liver dysfunction markers such as serum ALT, AST and MCP-1. Saroglitazar also prevented accumulation of lipid in hepatocytes as indicated by lower triglycerides and cholesterol levels in liver tissues. Furthermore, expression of pro-inflammatory genes such as MMP9, TNFα and pro-fibrotic marker genes such as TIMP1, Col1α1, CTGF and α-SMA were also suppressed in liver of saroglitazar-treated animals. Histological investigation of liver revealed suppression of steatosis, ballooning, inflammation and fibrosis in animals treated with saroglitazar. When administered after establishment of NASH, saroglitazar (1 and 3mg/kg per day) was found to reverse liver steatosis, inflammation and fibrosis, which was confirmed by reduction in serum MCP-1 levels and down regulation of various pro-inflammatory (MMP9, TNFα) and pro-fibrotic (TIMP1, Col1α1 and α-SMA) genes. Pioglitazone (25mg/kg/day) and fenofibrate (300 mg/kg/day) showed effects on circulating markers but were ineffective in controlling liver lipids and histological alterations.

The results of preclinical studies together with positive findings in an exploratory Phase-2 clinical trials in biopsy-proven NASH patients, indicate that saroglitazar appears to be a promising drug for the management of NAFLD & NASH.

Markus Hompesh, M. D.

President, CEO and Founder, Profil Institute for Clinical Research, Inc, San Diego, California, USA

Dr. Marcus Hompesch is an expert in the field of metabolic diseases, and clinical metabolic research methodology.

Dr. Hompesch established Profil Institute for Clinical Research in San Diego, CA in 2004. Over the past 10 years under Dr. Hompesch's leadership, Profil has become the leading institute in providing services focused on the early phase clinical develop- ment of new diabetes and obesity treatments.

Profil Institute has been involved with almost every clinically promising drug and device development in diabetes in more than 220 clinical studies. Dr. Hompesch received his M.D. from the University of Duesseldorf, Germany he spent eight years as a practicing physician and academic clinical researcher receiving his training in internal medicine and diabetology. Dr. Hompesch has also been a sci- entific associate at the department of Biostatistics and Medical Informatics at the Ruhr University of Bochum, Germany.

Between 2000 and 2003, prior to establishing the Profil Institute for Clinical research in San Diego, Dr. Hompesch had executive management responsibilities at a contract research institute in Germany. Dr. Hompesch was also the founder of Med.IQ, a company that developed electronic patient records and electronic disease management tools for patients with diabetes. Based on his research Dr Hompesch has extensively published in peer reviewed journals and is the editor of a textbook on translational research methods for diabetes, obesity and cardiometabolic drug development published by Springer.

Topic

Non-Alcoholic Fatty Liver Disease / Non-Alcoholic Steato-Hepatitits Biomarkers: Are we stuck with biopsies? Diagnostic Tools beyond Biopsies

Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steato-hepatitis (NASH) are disease modalities of increasing prevalence and therefore relevance for health care systems. NAFLD is the most common cause of chronic liver disease (CLD) in the United States where it affects 80-100 million Americans of whom 10%-22% may have nonalcoholic steatohepatitis (NASH). NAFLD/NASH preva- lence rates in other geographies are similar, with reported peaks of >50% in some geographies. NASH as the progressive form of the disease may lead to cirrhosis and hepatocellular carcinoma.

NAFLD is associated with obesity, insulin resistance, hypertension, diabetes, and dyslipidemia. Currently the diagnostic gold standard to diagnose advanced fibrosis is liver biopsy, however in looking at the increasing incidence and prevalence of NAFLD/NASH it is quite obvious that liver biopsies aren't a suitable tool to diag- nose or to monitor progression of a disease as prevalent as NAFLD/NASH.

While stringent regulatory guidance on acceptable biomarkers beyond biopsies, that are suitable for disease staging, assessment of disease progression or monitor- ing of therapeutic interventions are missing, there has been remarkable progress in developing diagnostic tools both imaging biomarkers and circulating biomarkers, that may have the potential to become acceptable surrogates and that may even re- place liver biopsies in the future.

This review will present recent developments in liver imaging (e.g. MRI-PDFF, MRS-PDFF, MRE) and in identifying specific metabolites (e.g. lipid metabolites like poly-unsaturated fatty acids) indicative of progression of NAFLD / NASH.

Paul Zimmet, AO, MD, PhD, FRACP, FRCP, FTSE

Director Emeritus, Victor Smorgon Diabetes Centre, Baker IDI Heart and Diabetes Institute, Adjunct Professor, Monash University, Honorary President, International Diabetes Federation, Chair, Programme Committee, World Diabetes Congress 2013, Melbourne, Australia

Paul Zimmet is Director Emeritus, Baker IDI Heart and Diabetes Institute, Adjunct Professor, Monash and Pittsburgh Universities and an Honorary President of the International Diabetes Federation (IDF). He has an outstanding international record in diabetes and obesity research, particularly in epidemiology and public health. His research has been a major trigger in predicting and then charting the evolving global type 2 diabetes epidemic. He has published over 800 papers in peer reviewed journals. He has been listed recently in the Thomson Reuters "Worlds-most-influential-scientific-minds-2014" as only one of only seven Australians of the 400 scientists in the "Clinical Medicine" category.

His many international and national awards include the Kelly West and Harold Rifkin Medals (American Diabetes Association), the IDF Lilly Award, the Banting Award (Diabetes UK), the Kellion Award (Australia) and the Global Novartis Award for long standing contributions in the field of diabetes that have had a major impact. In 2010, he received the Grand Hamdan International Prize for Medical Sciences. In 2013, he was made a Member of the Spanish Royal National Academy of Medicine and was awarded the Peter Wills Medal from Research Australia. This recognises an Australian who has made an outstanding contribution to building Australia's international reputation in the area of health and medical research. He has recently been appointed as Co-chair of the Federal Government's National Diabetes Strategy Advisory Committee to develop a new diabetes strategy for the nation. He holds Honorary Doctorates from the Complutense University (Spain), Monash University (Melbourne) and Tel Aviv University (Israel).He is an Officer of the Order of Australia (AO) for distinguished services to medicine, nutrition, and the biotechnology industry

Topic

Diabetes: The Greatest Epidemic in the 21st Century?

The number of people with diabetes mellitus has more than doubled over the last few decades. It has become one of the most important public health challenges faced globally. One of the most concerning aspects of the rapid increase has been the emergence of type 2 diabetes among children, adolescents and young adults. While there has been significant attention to traditional risk factors for type 2 diabetes – genetic, lifestyle and behavior, more recently attention has focused on epigenetic mechanisms and the impact of the intra-uterine environment as a future driver of this epidemic. The epidemiological data foreshadow an inexorable and unsustainable increase in global health expenditures attributable to diabetes making prevention a high priority. Prevention of type 2 diabetes requires an integrated approach recognizing its multiple pathophysiological origins and its heterogeneity. Thus research needs to be directed at a better understanding of the potential role of determinants such the maternal environment and other early life factors to help shape prevention programs as well as novel therapies.

Shaukat M. Sadikot, M. D.

President-Elect, International Diabetes Federation 2013-2015, President of DiabetesIndia, Consultant Endocrinology, Jaslok Hospital and Research Center, Mumbai

Dr. Shaukat M. Sadikot from India is the President-Elect of the International Diabetes Federation 2013-2015, and President of DiabetesIndia. Presently working as a Consultant in Endocrinology at the Jaslok Hospital and Research Center, Mumbai, he has been actively involved with the cause of diabetes and associated metabolic disorders for the past 30 years.

He has been closely associated with the activities of IDF for many years and is a member of the IDF Task Force on Insulin, Test strips and Other Diabetes Supplies, the IDF Consensus Group on the Prevention of Prediabetes, Diabetes and the Metabolic Syndrome, and the IDF Consensus group on Diabetes and Obstructive Sleep Apnoea. Presently, he is working on the interactions between phytochemicals and chemokines on the endothelium.

Dr. Sadikot is the editor of the upcoming International Scientific Journal "Diabetes and the Metabolic Syndrome: Clinical Research and Reviews". He has written four books and has 87 publications to his credit.

Topic

Controlling the Tsunami: In our "Stars" or in our "Hands"

Viren Mehta, Ph.D.

Chairman, Gather Health Limited, Founder, Mehta Partners, LLC, USA

Viren Mehta founded and is managing member of Mehta Partners, LLC. His analytical insights on global health care have influenced bio-pharmaceutical strategy and investments worldwide. Educated at the University of Southern California (Doctor of Pharmacy) and UCLA (MBA in international finance and marketing), he has worked with senior BioPharma leaders and investment managers for over 30 years.

Gather Health is Viren's new initiative to empower patients while enhancing physician productivity. Gather Health brings together providers (physicians, nurses, dietician, exercise therapist and others) and patients' social network (other patients, friends and family), enabling patient to get real-time and active resources and motivation from this team that improves outcomes. Physicians are able to see more patients due to the efficiencies fostered by the GH triage engine. Gather Health is headquartered in Hong Kong, with operations in Beijing, Mumbai and New York.

Viren's biopharma strategic advisory work focuses on refining the business model to expand global healthcare access, and to help the bio-pharmaceutical industry succeed globally. Viren's philanthropic work in ecology and education through viram foundation includes an active board role with Project Hope (Washington DC) and the Venice Family Clinic (Los Angeles, CA).

Viren began with Merck & Co. in international strategic planning and competitor analysis. This foundation prompted Wood MacKenzie & Company Inc. to invite him to establish a pharmaceutical research function in New York. This effort was expanded at S.G. Warburg & Company, and led to the formation of the BioPharma investment advisory group Mehta and Isaly. Now known as Mehta Partners, with a 30-year record, Viren continues to focus on helping refine investment strategy to achieve superior growth while enhancing access to healthcare innovations.

Topic

Achieving better research and clinical outcomes in mHealth age

Mobile technology, though at the beginning of its development, is already proving to be a great enhancer across the medical system. Our healthcare systems must adopt the efficiency and efficacy improvements offered by mobile health, from companion diagnostics, to recruitment of patients for clinical studies, to achieving better clinical outcomes more efficiently. If we are to meet the needs of our patients and expand our understanding of disease, mHealth offers revolutionary opportunities. Diabetes is an obvious illustration, as 387 million people have diabetes, over half of whom live in Asia-Pacific—but the challenges cut across all chronic diseases. These patients feel alone, depressed, and often have only their physician for any support. They struggle to maintain diet, exercise, medication adherence, and all that is good for them. The widespread adoption of mobile phones can help create a more robust support systems for patients, resulting in improved outcomes, but early studies have shown mixed results due to the heterogeneity of approaches. It is becoming clear that simple, one-directional informational messages are not enough to support sustained behavior change. Instead, the richer and multifaceted platform that gives all stakeholders right tools and support can be transformative. A platform that puts the patient in the center of a holistic system empowers patient's team—all the providers plus patient's own network—to motivate the patient on a sustained and continuous basis. As the majority of interaction can be automated, and many other tasks can be shifted to appropriate junior professionals or patient's social network so that physicians and other highly trained providers can focus on specialized tasks, raising the efficiency of the entire system. In addition to clinical applications, mobile health systems provide fascinating opportunities to researchers, ranging from speeding up patient enrollment, to collecting more robust datasets, opening up new research areas which were previously logistically and financially prohibitive to explore. The presentation will illustrate these principles and first round of data around a new platform being tested in Asian countries.

Chairpersons: Session V

Naga Chalasani, MD, FACG

Professor of Medicine, Professor of Cellular & Integrative Physiology, Division of Gastroenterology and Hepatology, Indiana University School of Medicine, Indianapolis, USA

Dr. Chalasani currently serves as David W. Crabb Professor of Medicine and Cellular &Integrative Physiology at Indiana University School of Medicine and is the Director of its Division of Gastroenterology and Hepatology. He completed his medical education in India and subsequently completed internal medicine residency and gastroenterology and hepatology subspecialty training at Emory University in Atlanta. Two broad themes to his research focus are nonalcoholic fatty liver disease and idiosyncratic drug induced liver injury, and he has made several important contributions to both of these areas. He is the Associate Editor for Gastroenterology and he has previously served or currently serving on the editorial board of many journals including Gastroenterology, Hepatology, Clinical Gastroenterology and Hepatology, American Journal of Medicine, Journal of Clinical Gastroenterology, and Nature Reviews Gastroenterology & Hepatology. He has been funded by the National Institutes of Health since 1998 for conducting investigations related to liver disease. Currently, he is the PI for two NIH U01 awards and one NIH K24 award, Co-PI for one NIH U01, and co-investigator for two NIH R01 awards. He has published over 170 original publications, 30 text book chapters and 26 editorials and commentaries. He is the lead author for the multisociety practice guideline for the diagnosis and management of nonalcoholic fatty liver disease published simultaneously in Gastroenterology, Hepatology, and American Journal of Gastroenterology in 2012.

Paul Zimmet, AO MD PhD FRACP FRCP FTSE

Paul Zimmet is Director Emeritus, Baker IDI Heart and Diabetes Institute, Adjunct Professor, Monash and Pittsburgh

Universities and an Honorary President of the International Diabetes Federation (IDF). His research has been a major trigger in predicting and then charting the evolving global type 2 diabetes epidemic. He has published over 800 papers in peer reviewed journals. He has been listed recently in the Thomson Reuters "Worldsmost-influential-scientific-minds-2014" in the "Clinical Medicine" category. His many international and national awards include the Kelly West and Harold Rifkin Medals (American Diabetes Association), the IDF Lilly Award, the Banting Award (Diabetes UK), the Kellion Award (Australia) and the Global Novartis Award for long standing contributions in the field of diabetes that have had a major impact. He has recently been appointed as Co-chair of the Federal Government's National Diabetes Strategy Advisory Committee to develop a new diabetes strategy for the nation. He holds Honorary Doctorates from the Complutense University (Spain), Monash University (Melbourne) and Tel Aviv University (Israel). He is an Officer of the Order of Australia (AO) for distinguished services to medicine, nutrition, and the biotechnology industry.

Y. K. Gupta, MBBS, MD, FAMS, FNASc, FIPS, FIAN

Professor and Head, Pharmacology, AIIMS, India

Dr. Y.K. Gupta M.B.B.S (1974), M.D (Pharmacology, 1979) from King George's Medical College, Lucknow, is Professor and Head, Department of Pharmacology and Spokesperson, All India Institute of Medical Sciences (AIIMS), New Delhi. He earlier served as Sub Dean, A.I.I.M.S (1996 - 2001) and Director, Indian Institute of Toxicology Research (IITR, CSIR), Lucknow from 2003 to 2005.

Dr.Gupta is incharge of National Poison Information Centre and is also National Scientific Co-coordinator of Pharmacovigilance Program of India (PvPI). He has been honored with Fellowships of 7 National Scientific bodies wiz: National Academy of Medical Sciences (FAMS), National Academy of Sciences (FNASc), Indian Pharmacological Society (FIPS), National Academy of Science (FNASc), Indian Academy of Neurosciences (FIAN), Society of Toxicology (India) (FST), Academy of Environmental Biology (FAEB), and International Academy of Cardiovascular Sciences (FIACS). He has more than 230 publications in International and National journals with total impact factor of over 780 and several chapters in books to his credit.

Dr Gupta is recipient of several awards including Young Scientist Medal from Indian National Science Academy (INSA) , Shakuntala Amirchand Prize (Indian Council of Medical Research (ICMR) , Chandrakanta Dandiya Prize, G. Achari Oration Award (Indian Pharmacological Society (IPS), Major General S. L. Bhatia Oration Award (Association of Physiologist and Pharmacologist of India : APPI), AEB Honours Award (Academy of Environmental Biology), C. L. Malhotra Prize (Association of Physiologist and Pharmacologist of India : (APPI) etc.

Dr. Gupta is currently President of Society of Toxicology, India and Dean Indian Society for Rational Pharmacotherapeutics, and was President of the Indian Pharmacological Society (2005-2006). He was the Editor of the Indian Journal of Physiology and Pharmacology 1999 -2011) (Pharmacology Section) and member editorial board of several International and Indian journals.

He is the Chairman of National Committee of IUPS-IUPHAR of Indian National Science Academy (INSA), Member of IUPHAR –IOSP committee and was member of Advisory Committee on Safety of Medicinal Products (ACSoMP) of WHO,(2009-2012) chairman of Equivalence Committee and member Ethics Committee of Medical Council of India.(2011-2013). He has been member of Project Advisory Committee / Research Council / Scientific Advisory Committee and Task force of CSIR, ICMR, DST and DBT and Chairman, SAC of National Institute of Occupational Health (NIOH-ICMR). He is chairman of national GLP technical committee of DST, member of the Scientific Body of Indian Pharmacopoeia (IP) and Chairman of Expert Committee on Clinical Medicine and Pharmacology of IP.

He was the Governing body member of Indira Gandhi Postgraduate Institute of Medical Education and Research, Patna. He was the Chairman of National Essential Medicine List Committee 2011 of Ministry of Health & Family Welfare, Government of India and also the Chairman of the working group of High Powered Inter-Ministerial Coordination Committee to look into the matters of implementation Government commitment to provide quality medicine at affordable prices.

Topic

Discovering and Developing Drugs in India: A Scientific and Regulatory Perspective

Susanne Mandrup, Ph.D.

Professor, Department of Biochemistry and Molecular Biology, University of Southern Denmark

Susanne Mandrup has been Professor at Department of Biochemistry and Molecular Biology, University of Southern Denmark since 2008. She obtained her PhD in Biochemistry from Odense University in 1992 and worked among others as a post doc in Prof. M. Daniel Lane's group, Department of Biological Chemistry, Johns Hopkins University, Baltimore 1995-96. In 1996 she was recruited back to Odense as Assistant Professor. The research in the Mandrup group (http://www.sdu.dk/mandrupgroup) focuses on understanding the molecular cross-talk between transcriptional regulation and metabolism in adipocytes and pancreatic β-cells, and in the transcriptional network regulating adipocyte differentiation. Her group runs its own sequencing platform and combines genome-wide studies of transcription factor binding, epigenetic marks and chromatin structure with detailed molecular analyses of the cross-talk between transcriptional regulators.

Susanne Mandrup recently received a Sapere Aude Advanced Grant from the Danish Independent Research Council and is one of the leading figures in the newly established Danish Diabetes Academy (http://www.danishdiabetesacademy.dk/) supported by the Novo Nordisk Foundation and the Villum Center for Bioanalytical Sciences at University of Southern Denmark. She is member of AcademiaNet Expert Database for Outstanding Female Scientists and Scholars and of Academia Europeaea and is currently member of the Medical and Natural Science Committee of the Novo Nordisk Foundation as well as European Research Council panel for Genetics, Genomics, Bioinformatics and Systems Biology.

Topic

Reprogramming of PPARγ super-enhancers during browning of human adipocytes

The emergence of brown in white (brite)/beige adipocytes in white adipose tissue (WAT) is associated with protection against obesity and metabolic dysfunctions in rodents. Recent results indicate that brite adipocytes also play an important role in human energy metabolism, and strategies to induce such browning in humans therefore hold promise as future means to alleviate obesity. Using genome-wide technologies we have investigated the transcriptional processes underlying browning of human multipotent adipose-derived stem cells (hMADS). Rosiglitazone-induced browning of these cells activates a comprehensive gene program that is linked to increased mitochondrial function. Once induced this gene program is maintained independently of rosiglitazone, suggesting that additional browning factors are activated. Browning is associated with reprogramming of PPARγ binding to form brite-selective PPARγ super-enhancers that appear to play a major role in activation of key brite-selective genes. Based on the association with a brite-selective PPAR super-enhancer, we have identified an evolutionarily conserved metabolic regulator, KLF11, as a novel browning transcription factor in human adipocytes required for rosiglitazone-induced browning. KLF11 is directly induced by PPARγ and appears to cooperate with PPARγ in a feed forward manner to activate and maintain the brite-selective gene program.

Yoshihiro Ogawa, M.D., Ph.D.

Professor and Chairman, Department of Molecular Endocrinology and Metabolism, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Japan

Dr. Ogawa is Professor of Department of Molecular Medicine and Metabolism, Medical Research Institute, Tokyo Medical and Dental University. He received his M.D. and Ph.D. degrees from Kyoto University, Kyoto, Japan. While earning his Ph.D. degree, he worked with Hiroo Imura and Kazuwa Nakao at Kyoto University Graduate School of Medicine. He carried out his postdoctoral training as Research Fellow of Japan Society for the Promotion of Science at Kyoto University. Before joining Tokyo Medical and Dental University in 2003, he was an Assistant Professor of Department of Endocrinology and Metabolism, Kyoto University Graduate School of Medicine. His current research interest is the pathophysiologic and therapeutic implication of 1) chronic inflammation and 2) epigenetic modification in lifestyle-related metabolic diseases such as obesity, diabetes, and atherosclerosis.

Topic

Parenchymal-stromal Cell Interaction in Metabolic Diseases

Chronic inflammation may involve sustained interaction between parenchymal and stromal cells in response to a variety of cellular stresses, thereby leading to tissue remodeling and organ malfunction. In obese adipose tissue, saturated fatty acids, which are released as a danger signal from hypertrophied adipocytes, stimulates a pathogen sensor TLR4 in the infiltrating macrophages, thus establishing a vicious cycle that aggravates inflammatory responses. Histologically, macrophages aggregate to constitute crown-like structures (CLS), where they are considered to scavenge the residual lipid droplets of dead adipocytes. Macrophage-inducible C-type lectin (Mincle), a pathogen sensor for Mycobacterium tuberculosis, is induced in adipose tissue macrophages constituting CLS, the number of which is correlated with the extent of interstitial fibrosis. Our data suggest that Mincle, when activated by an as-yet-unidentified danger signal released from dead or dying adipocytes, plays a key role in adipose tissue inflammation and fibrosis.

Free fatty acids, when released from the obese visceral fat depots, are transported in large quantities to the liver via the portal vein, where they are accumulated as ectopic fat, thus leading to the development of non-alcoholic steatohepatitis (NASH). There is a unique histological feature termed “hepatic CLS (hCLS)” in the NASH liver, where macrophages aggregate to surround dead hepatocytes with large lipid droplets. Notably, the number of hCLS is positively correlated with the extent of liver fibrosis. Our data suggest that hCLS serves as an origin of hepatic inflammation and fibrosis during the progression from simple steatosis to NASH.

We postulate that CLS/hCLS represent the unique microenvironment for parenchymal-stromal cell interaction in metabolic diseases, thus providing a promising target of new drug discovery and development.

Ajay Chawla, M.D., Ph.D.

Professor, Cardiovascular Research Institute, University of California, San Francisco

Dr. Chawla received his B.Sc. from Johns Hopkins University in Biomedical Engineering in 1989, and his M.D., Ph.D. degrees from the University of Pennsylvania in 1996. He completed his graduate work in the laboratory of Dr. Mitch Lazar, and joined the laboratory of Dr. Ronald Evans at the Salk Institute for his postdoctoral studies. He became an Assistant Professor in 2003 at Stanford University, and is currently Professor of Physiology and Medicine in Cardiovascular Research Institute of the University of California San Francisco.

His laboratory focuses on innate mechanisms of tissue homeostasis. Work form his laboratory has contributed to our understanding of how innate immune cells and signals mitigate dietary and environmental stress to maintain metabolic homeostasis. Furthermore, recent work from his laboratory has elucidated the cellular and molecular pathways by which innate immunity orchestrates tissue regeneration after injury.

His awards include: NIH Director's Pioneer Award, AHA Innovative Science Award, NIDDK Young Investigator Award, Rita Allen Scholar, and Culpepper Medical Sciences Scholar. He is a member of American Society of Clinical Investigation and Association of American Physicians.

Topic

Innate Mechanisms of Metabolic Homeostasis

Macrophages take residence in nearly all tissues, where they function as sensors and integrators of environmental and metabolic stress. In metabolic tissues, tissue resident macrophages sense their local and systemic environment to coordinate parenchymal cell metabolism. Here, we present evidence that the innate immune system also regulates acclimatization to environmental cold. Previous work has demonstrated that prolonged cold exposure induces the growth of uncoupling protein 1+ brown adipocytes in the subcutaneous white adipose tissue of mice, termed "beige" fat, to provide a defense against cold and obesity. Although a cold environment is the physiologic stimulus for inducing beige fat mass in mice and humans, the events that lead from the sensing of cold to the development of beige fat had remained poorly understood. We identified the efferent beige fat thermogenic circuit, consisting of eosinophils, type 2 cytokines interleukin (IL)-4/13 and alternatively activated macrophages. Genetic loss of eosinophils or IL-4/13 signaling impairs cold-induced biogenesis of beige fat. Mechanistically, macrophages recruited to cold-stressed subcutaneous white adipose tissue undergo alternative activation to induce tyrosine hydroxylase expression and catecholamine production, factors required for browning of subcutaneous white adipose tissue. Conversely, administration of IL-4 to thermoneutral mice increases beige fat mass and thermogenic capacity to ameliorate pre-established obesity. Together, our findings have uncovered the efferent circuit controlling biogenesis of beige fat and provide support for its targeting to treat obesity.

Walter Wahli, Ph.D.

Professor, Center for Integrative Genomics, University of Lausanne, Switzerland, Professor of Metabolic Disease, Lee Kong Chian School of Medicine, Imperial College London & Nanyang Technological University, Singapore General Hospital, Singapore

Prof Walter Wahli is Professor of Metabolic Disease in Lee Kong Chian School of Medicine, Nanyang Technological University. Prior to this appointment, Prof Wahli spent most of his scientific career at the world-renowned University of Lausanne, Switzerland. He obtained his PhD in 1977 under the guidance of Prof. Weber at the University of Berne. He was appointed Full Professor and Director of the Institute of Animal Biology of the University of Lausanne in 1980. He is also the Founder Director of the Center for Integrative Genomics at Lausanne. He has been postdoctoral fellow at the Department of Embryology, Carnegie Institution of Washington in Baltimore, USA, and Visiting associate at the National Institutes of Health (NIH), Bethesda, USA.

Prof Wahli is internationally recognised for his contributions to the area of energy metabolism. He has provided fundamental insights into the functions of transcription factors (PPARs) activated by fatty acids and eicosanoids. His discoveries contributed in advancing our understanding of the molecular mode of action of these natural compounds, which signaling impacts most key biological processes in vertebrates. He has published close to 300 papers in top-ranking journals, book chapters and editorials. He was awarded several prizes and recently received the Lifetime Achievement Award from the Faculty of Biology and Medicine, University of Lausanne.

His professional experience includes evaluating research grants and fellowships for international funding bodies including the National Science Foundation (USA), Medical Research Council (UK), Human Frontier Science Program, The Wellcome Trust (UK) and many others. He has been the chair of the Division Biology and Medicine of the Swiss National Science Foundation and is a member of the Neslé Foundation Council. He has participated in many Evaluating and Advisory Committes of many European Institutions.

Topic

Multifaceted function of the transcription regulator PPAR

Among nuclear receptors, the peroxisome proliferator-activated receptors (PPARs) have emerged as sensors of fatty acids and fatty acid derivatives, translating modifications in the intracellular levels of these molecules into changes in metabolic activities. In mammals, many aspects of metabolism are under circadian control. This regulation is achieved by clock-controlled transcription factors whose abundance and/or activity oscillate during the day. In the liver, the clock-controlled proline and acidic amino acid-rich domain basic leucine zipper (PAR bZip) proteins play a key role in a cyclic release of fatty acids, which act as ligands for PPARα. Activated PPARα then stimulates the transcription of genes encoding proteins involved in the metabolism of lipids and glucose. Inborn errors of lipid metabolism illustrate the importance of proper milk fat oxidation in newborn mammals. Remarkably, the liver exhibits functional lipid catabolic competence at birth; however, it is unclear how this critical trait is regulated. Our present examination of mouse fetal liver reveals that the genes required for milk lipid catabolism are already stimulated during labor, rather than only after birth. Furthermore, this regulation is controlled by a fetal glucocorticoid receptor–PPARα axis. Fetal PPARα selectively regulates fatty acid oxidation genes without impacting adaptive effectors—like FGF21, which is apparently repressed by histone deacetylation. PPARα-null pups develop congenital steatosis, as well as increased anaplerosis that compensates for reduced energy gain from milk lipids. This study identifies a developmental axis regulating lipid catabolism gene expression and suggests that, apart from the known adaptive functions, PPARα also plays a proactive role in orchestrating lipid catabolism at birth.

Chairpersons: Session VI

Philip Larsen, M.D., Ph.D.

Global Head of Diabetes Research and Translational Science, Sanofi Aventis

Philip J Larsen MD, PhD is Global Head Diabetes Discovery and Translational Medicine. Dr Larsen joined Sanofi in August 2012, and his responsibilities encompass strategic and organizational leadership of Sanofi's diverse portfolio of preclinical and early clinical assets in the field of diabetes and related dysmetabolic complications. Dr. Larsen has 20 years of pharmaceutical and biotechnology industry experience in the field of diabetes and obesity. After few years of work at NovoNordisk and Zealand Pharma, Philip co-founded the Danish biotechnology company Rheoscience in 2001 also concentrating on obesity and diabetes. In 2008, Philip took up a position as chief scientific officer for diabetes research at Eli Lilly, Indianapolis, USA, before returning to Europe as VP for early clinical development in CVM at AstraZeneca. Dr. Larsen holds and MD from the University of Copenhagen and a PhD in neuroendocrinology also from University of Copenhagen".

Richard DiMarchi, Ph.D.

Standiford H. Cox Distinguished Professor of Chemistry, Linda & Jack Gill Chair in Biomolecular Sciences, Indiana University

Dr. DiMarchi is a retired Group Vice President at Eli Lilly & Company where for more than two decades he provided leadership in biotechnology, endocrine research and product development. He is recognized for discovery and development of rDNAderived Humalog® (LisPro-human insulin). As scientist and executive, Dr. DiMarchi also significantly contributed to the commercial development of Humulin®, Humatrope®, rGlucagon®, Evista®, and Forteo®. He is a co-founder of Ambrx, Inc., Marcadia Biotech, Assembly and Calibrium Biotech. He has served as a scientific advisor to multiple pharmaceutical companies and three venture funds; 5AM, TMP, and Twilight. Dr. DiMarchi is the recipient of numerous awards including the 2005 AAPS Career Research Achievement Award in Biotechnology, the 2006 ACS Barnes Award for Leadership in Chemical Research Management, the 2006 ACS Esselen Award for Chemistry in the Service of Public Interest, the 2007 Carothers Award for Excellence in Polymer Sciences, the 2009 Watanabe Award for Life Sciences Research, the 2011 Merrifield Award for Career Contributions in Peptide Sciences, the 2012 Phillip Nelson Innovation Award, the 2014 Erwin Schrödinger-Preis, and a 2014 inductee to the National Inventors Hall of Fame.

Anil Bhansali, DM

Head, Department of Endocrinology, PGIMER, Chandigarh, India

Prof. Anil Bhansali is the Professor and Head of the Department of Endocrinology at the Post Graduate Institute of Medical Education and Research, Chandigarh. He has been the Past President of Endocrine Society of India for the year 2012. He was the Chairman of the Organizing Committee for the ESICON 2014 held in Chandigarh. He is the Sectopm Editor of the ESI Manual of Endocrinology for Adrenals. He is also the Consulting Editor of Indian Journal of Endocrinology and Metabolism. He has more than 300 publications in reputed International and National Journals.

Topic

Non-HDL cholesterol in the management of CVD

Shashank R. Joshi, MBBS, MD, DM, FACP, FRCP, FACE

Consulting Endocrinologist, Lilavati Hospital in Mumbai, India

Prof Shashank Joshi is the President, API (Association of Physicians of India), President of Indian Academy of Diabetes and Past President of RSSDI (Research Society for Study of Diabetes in India).

He is a faculty at Grant Medical College and Sir JJ Group of Hospitals in Endocrinology. Dr.Shashank R. Joshi is practicing Endocrinologist and Diabetologist who has topped all years of MBBS, MD, and DM with Gold Medals. He is a Fellow of the American College of Endocrinology (USA), American College of Physicians (USA) and the Fellow of the Royal College of Physicians (Glasgow and Edinburgh). He has more than 600 research publications to his credit. He is the Hon. Emeritus Editor of JAPI (Journal of The Association of Physicians of India), Ex Editor of Indian Journal of Obesity, Indian Journal of Endocrinology and Metabolism and Indian Journal of Clinical Pharmacology and Therapeutics and several other leading medical journals. He is affiliated to several leading hospitals of the city including Lilavati & Bhatia Hospitals. He is the Past President, AIAARO (All India Association of Advancement for Research in Obesity, IASO Affiliate), Chapter Chair (India), American Association of Clinical Endocrinology (AACE). He is visiting faculty to several Indian and International Universities. He is actively involved with evidence based work in Endocrinology including Diabetes, Obesity, Thyroid, Osteoporosis and Growth. He was awarded "International Clinician of the year 2012" by the American College of Endocrinology. He has been conferred in 2014 "Padma Shri" by Government of India

Topic

Clinicians perspective into current and future therapies of type-2 diabetes mellitus

Rajendra Jani, Ph.D.

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Dr. Rajendra Jani is doctorate in pathology and bacteriology from faculty of medicine and more than 35 years' experience.

He worked as an Assistant Professor in Pathology & Bacteriology at Government Medical College, Surat, Scientist, Hoechst Research Center, Head, Regulatory Affairs, Rhone Poulenc India Limited and Director Medical Affairs & Research, German Remedies Limited,

Currently he is Senior Vice President & Head, Clinical R&D, Zydus Cadila.

He has conceptualized and conducted about 40 "first in man" (phase 1) studies for new chemical entities (NCEs), new biological entities (NBEs), biosimilars and vaccines. He also participated in more than 180 Phase II – IV clinical studies. He was responsible for clinical research and development of two new chemical entities; miltefosine and saroglitazar and adalimumab biosimilar.

Miltefosine was first orally acting drug, miltefosine, for the treatment of Kala Azar in collaborative public private partnership project of German Remedies Limited, Zentaris AG, ICMR, and WHO.

Saroglitazar (ZYH1/Lipaglyn), a first in class new anti-diabetic/anti-dyslipidemic drug and has approved for diabetic dyslipidemia in India. **Exemptia,** first biosimilar of adalimumab, which got approved in India Dr. Jani has numbers of patents and publication at his credit.

Topic

Clinical and Regulatory Challenges in New Drug Development Case Studies of Saroglitazar, ZYDPLA1 and ZYAN1

Drug discovery and development provides an opportunity to contribute to qualitative improvement in human health and longevity. Unfortunately, still we do not have any specific curriculum, which offers a student or a new investigator comprehensive drug and discovery development orientation.

Drug discovery and development involves identification of unmet therapeutic needs, identification of target receptor for achieving desired therapeutic effects and discovery of scaffold with structure activity relationship (SAR). The selected scaffold constructs possibilities of discovering a new chemical / biological entity (NCE/NBE). This is followed by preclinical activities such as formulations development, preclinical toxicity and pharmacological studies.

The results of preclinical studies guide the translational medicine experts to predict the human equivalent dose (HED). The challenges arise during conceptualization and conduct of clinical studies with new chemical entities (NCE) will be discussed.

ClinicalTrials.gov currently lists 176,056 studies with locations in 187 countries. Recruiting studies are 33,770, of which 43% are conducted only USA. India is listed for merely 2527 (1.44%) clinical studies. (As on October 6, 2014) Clinical development programs in India have more challenges than most of the developed and developing countries.

An archetypal of clinical development approaches with reference to saroglitazar, ZYDPLA1 and ZYAN1 in current research environment will be presented.

Charles F. Burant, M.D., Ph.D.

Dr. Robert C. and Veronica Atkins Professor of Metabolism, The Burant Lab, University of Michigan Medical School, USA

Charles F. Burant, MD, PhD is the Dr. Robert C. and Veronica Atkins Professor of Metabolism. Dr. Burant received his bachelor's degree from the University of Wisconsin and his graduate and medical degrees from the Medical University of South Carolina in Charleston. He completed his residency training at the University of California, San Francisco along with a fellowship in Endocrinology at the University of Chicago. He joined the faculty at the University of Michigan Medical Center in 1999. Dr. Burant's clinical interests are in the area of metabolic syndromes and management of Type II Diabetes. His research laboratory investigates the mechanisms of insulin resistance and utilizes animal models of diabetes to identify pathways important in understanding diabetes progression. Additionally, his lab also studies adult pancreatic progenitor cells and how they might be used to generate new insulin secreting β-cells.

Topic

Metabolism modulation by diet and drugs, insights into mechanisms of action by metabolomics profiling

The ability to understand in vivo metabolism has been enhanced in recent years by the introduction of high-throughput metabolomic profiling which allows the assessment of hundreds to thousands of metabolites. These metabolites can be assessed temporally through the use of heavy isotope tracer technology. These data can be integrated with other molecular and clinical phenotypes to understand I will present two case studies to demonstrate the insights that can be obtained. The degree weight loss that can be obtained through dietary interventions is variable in most clinical trials. We show that the variability may in part be due to underlying differences in oxidative capacity which is related to the accumulation of acyl-carnitine intermediates. The data suggests that the capacity to oxidize fatty acids, which are mobilized during caloric restriction, is elevated, but this may be accompanied by a lower efficiency, resulting in subtle differences in energy efficiency. In the second case, we use oral administration of fatty acids in Zucker fa/fa rats to demonstrate that the lipid lowering action of saroglitazar, a novel PPARα/PPARγ coagonist, is through an enhanced uptake into peripheral tissues. These studies will demonstrate the ability to perform dynamic measurements of a large number of metabolites to gain insights into metabolic alterations in animal models and people.

Poster Abstracts

P001:. Pharmacokinetic Issues of Novel Leads Targeting DPP-4 for the Treatment of T2DM.

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Dipeptidyl peptidase IV (DPP-4) is a widely distributed physiological enzyme that can be found solubilized in blood or membrane-anchored in tissues. The rationale for inhibiting DPP IV activity in type 2 diabetes is that it decreases peptide cleavage and thereby enhances endogenous incretin hormone (GLP-1 and GIP) activity. The journey of DPP-4 inhibitors in the market started from the launch of sitagliptin in 2006 to latest drug teneligliptin in 2012. A large variety of diverse chemical scaffolds are being discovered and developed as DPP-4 inhibitors globally. But despite of the many advantages of DPP-4 inhibitors over the conventional oral hypoglycemic therapies, many lead molecules are being dropped down during the development phase due to their pharmacokinetic issues or selectivity issues. So currently, pharmaceutical companies are interested in discovering selective inhibitors with long half-lives that are amenable for once-weekly dosing to improve patients compliance in T2DM. Two such drugs (Omarigliptin and Trelagliptin) are currently under development. Here we have summarized the examples of such fruitful as well as dropped out lead molecules and also discussed the few *in-silico* points correlating the physicochemical properties of leads with pharmacokinetic issues. Through this, a medicinal chemist can take care of the failure issues during designing of the molecules itself and can minimize the chances of pharmacokinetic failures.

P002: An Appraisal of HMPH for anti-diabetic and anti-inflammatory activity

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OBJECTIVES: To screen 1-H-Indole-3-carboxaldehyde phenylhydrazone (HMPH) for in vitro and in vivo anti-diabetic and anti-inflammatory property.

METHODS: Inhibition of LPS-induced ROS-generation and NO-release in macrophages (RAW-264.7). Augmentation of 2-NBDG-uptake by L6-myotubes and 3T3-L1 mouse-adipocytes in the presence/absence of palmitic acid-induced insulin-resistance and in presence/absence of wortmannin (PI3-kinase inhibitor) and compound-C (AMPK inhibitor). Acute inflammation in carrageenan-induced paw-edema. Neutrophil-infiltration in carrageenan-induced air-pouch and LPS-induced bronchoalveolar lavage. Ankle-distension and bone-erosion in Adjuvant-Induced Arthritis.

RESULTS: HMPH inhibited ROS-generation and NO-release in LPS-induced RAW-264.7 cells. IC_{50} of HMPH and α-tocopherol in lipid peroxidation was 33±5 and 31±0.1 µg/ml respectively. HMPH and metformin increased glucose-uptake by 186±22 and 191±19% in L6-myotubes and by 389±2% and 167±37% in 3T3-L1 mouse-adipocytes respectively. HMPH-induced increase in glucose uptake in L6-myotubes was attenuated by wortmannin and Compound-C by 18% and 29% respectively (similar pattern observed in AMPK phosphorylation) and by 70% each in 3T3-L1 adipocytes. HMPH and metformin increased glucose-uptake in L6-myotubes by 117±26% and 119±23% in palmitic acid-induced insulin-resistance. Neutrophil infiltration was considerably attenuated in carrageenan-induced air-pouch and LPS-induced bronchoalveolar-lavage. MPO, nitrite and TNF-α in air-pouch lavage were reduced significantly by HMPH. Both ipsilateral and contralateral paw inflammation were inhibited by HMPH in AIA-induced arthritis. HMPH prevented weight gain and attenuated Serum C-RP, RF and bone erosion in both paws.

CONCLUSION: Anti-inflammatory activity of HMPH might be mediated via activation of AMPK. Treating inflammation associated with metabolic syndrome by modulating a combination of oxidative, inflammatory and metabolic pathways, through pleiotropic outcomes that typically accompany AMPK activation, seems appropriate.

P003: Discovery of Nonsteroidal Selective Glucocorticoid Receptor Antagonist as Novel Antidiabetic Agents

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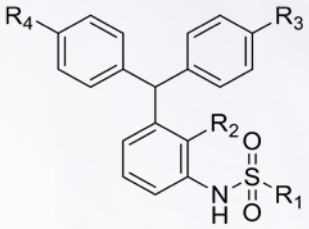
Non insulin-dependent diabetes mellitus (Type-2), is a debilitating disease characterized by abnormal elevation of blood glucose levels. It is driven by three factors: increased hepatic glucose production, inadequate clearance of glucose via insulin mediated pathways and decreased uptake of circulating glucose by tissue. Glucocorticoids have been shown to have major influence on glucose production. Excess of Glucocorticoid further aggravates diabetic condition. Steroid based GR Antagonist have been useful in glucose lowering effect but their utility is limited

because of side effect.Thus it would be important to develop non steroidal glucocorticoid receptor antagonist for the treatment of type-2 diabetes.

In the present communication, series of Triaryl methane sulfonamide derivatives (**12a-z**) are reported as non-steroidal glucocorticoid receptor antagonist with nanomolar affinity and has no detectable affinity for the highly related receptors MR, AR, ER, and PR. Among the compound tested Compound **12r** occupies the same hydrophobic pocket in the ligand binding domain as steroids and does not showing any binding which is necessary for agonistic activity. The lead compound **12r** exhibited significant oral antidiabetic and antihyperlipidemic effects (in vivo). These preliminary results confirm discovery of potent and selective GR antagonist for the treatment of T2DM.



12 (a-z)

P004: Design of GPR40 Modulators using Combiphore (Structure & Ligand Based Pharmacophores) Approach

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Human GPR40 receptor, also known as free fatty-acid receptor 1, is a G-protein-coupled receptor that binds long chain free fatty acids to enhance glucose-dependent insulin secretion. The new high-resolution GPR40 structure (4PHU) allows structural insight into the causes of ligand efficacy, biased signaling, and allosteric modulation. Present research work integrates computer-aided drug design methodology by utilizing crystal structure complex to produce structure- and ligand- based pharmacophores. The generation of ligand-based pharmacophore using the standard tools within Catalyst (Accelrys) from different training sets consisted of Hydrophobic, Hydrogen Bond Acceptor and Aromatic ring features as essential aspects. For Structure based pharmacophore generation crystal structures were retrieved from protein data bank. A sphere with a radius that comprises all the catalytically important residues has been created using Binding Site Analysis tool. The Interaction Generation protocol was used to identify features based on the active site residues that are inside the sphere. These features were then clustered and the most representative features were selected and included in the pharmacophore model. Thus generated models were then used as a query tool to search 3D databases. After applying drug-like and pharmacokinetic filters to the identified hit molecules, molecular docking can be carried out on the crystal structure of GPR40. Therefore such a methodology, whereby maximum structural information (from ligand and biological target) is explored, gives maximum insights into the plausible protein-ligand interactions and is more likely to provide potential lead candidates as exemplified from this study.

P005: Pharmacological Evaluation of *Prosopis cineraria* fruit extract in Triton Induced hyperlipidemic Rats

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The fruits extract of *Prosopis cineraria* (Fabaceae), herb has been used traditionally in India for medicinal purposes. The plant has been reported to treat hyperglycemia and associated hyperlipidemia. Hyperlipidemia and oxidative stress hastens coronary arterial diseases and develops atherosclerotic lesions. This study was to evaluate the hypolipidemic and antioxidant potential of *Prosopis cineraria*, in hyperlipidaemic rats. Experimental hyperlipidemia was induced by injecting a single dose of Triton (200 mg/kg, i.p.). Adult Sprague Dawley rats were divided into six groups; normal control, hyperlipidaemic control, standard (Simvastatin-4 mg/kg b.wt.), and three Et-PCF (doses 200, 400, 600 mg/kg b.wt. respectively) con-currently for 24 hrs. Serum lipid profile as well as antioxidant activity were determined. The result showed that increase in total cholesterol, LDL- cholesterol, VLDL-cholesterol, triglyceride, atherogenic index and decreased HDL- cholesterol were the significant features recorded in hyperlipidaemic control group. The Et-PCF supplements significantly reverted the levels of the studied lipid profile to near normal control values which were comparable with standard group. For antioxidant activity, IC_{50} value was found to be 58.33 µg/ml.

Key Words: *Prosopis cineraria*, Hypolipidemic activity, Triton WR-1339

P006: A Retrospective Study of the Effects of Angiotensin Receptor Blockers and Angiotensin Converting Enzyme Inhibitors in Diabetic Nephropathy

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SBKS Medical Institute and Research Centre, Sumandeep Vidyapeeth, Vadodara, Gujarat

Context: Till date, several studies have compared ACE Inhibitors and ARBs in terms of delaying the progression of diabetic nephropathy. But the superiority of one drug class over the other remains unsettled. This study has retrospectively compared the effects of ACE Inhibitors and ARBs in diabetic nephropathy.

Aims: Compare ACE Inhibitors and ARBs in terms of delaying or preventing the progression of diabetic nephropathy, association between blood pressure and urinary albumin and also blood pressure and serum creatinine with ACE Inhibitor and ARB., know the percentage of hyperkalemia in patients of diabetic nephropathy after taking ACE Inhibitor or ARB

Settings and Design: A total of 134 patients diagnosed with diabetic nephropathy during the years 2001 to 2010 and having a complete follow up were taken, out of which 99 were on ARB (63 patients of Losartan and 36 of Telmisartan) and 35 on ACE Inhibitor (Ramipril).

Methods and Material: There is atleast one month of interval between each observation made and also between the date of treatment started and the first reading i.e. the observation of the first month. In total, three readings have been taken i.e. of the first, second and third month after the treatment started. Comparision of the first and third month after the treatment started has been done. Mean $\pm$ SD, paired t-test and chi-square have been used for the analysis of the data.

Results: The results reflect that ARBs (Losartan and Telmisartan) when compared to ACE Inhibitor (Ramipril) are more effective in terms of delaying the progression of diabetic nephropathy and also in providing renoprotection. Also, ARBs have the property of simultaneously decreasing the systolic blood pressure and albuminuria when compared to ACE Inhibitor (Ramipril).

Conclusions: ARBs are more renoprotective than ACE Inhibitors and also provide cardioprotection simultaneously.

Key-words: Diabetes, Diabetic Nephropathy, Angiotensin Receptor Blockers(ARBs) and Angiotensin Converting Enzyme Inhibitors(ACE Inhibitors)

P007: Design, Synthesis and Biological Evaluation of Novel Aminomethyl-piperidones based DPP-IV Inhibitors

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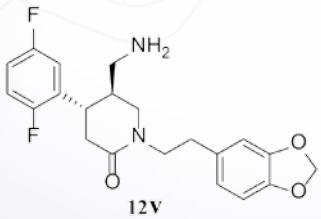
Dipeptidyl peptidase-IV (DPP IV) is a serine protease enzyme, which selectively cleaves the first two amino acids (His-Ala) of incretin hormones and thereby makes them inactive. Inhibition of DPP IV enzyme activity, using suitable DPP IV inhibitors likely to increase the levels of endogenous intact and bioactive incretins, thereby, it acts as antidiabetic agents. In this communication, novel DPP IV inhibitors were designed based on the piperidone skeleton, with anticipation that the aminomethyl and the amide groups of the piperidone ring may contribute improved potency and selectivity. Among 32 compounds tested in this series, test compound **12v** ((4S,5S)-5-(aminomethyl)-1-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-4-(2,5-difluorophenyl)piperidin-2-one) showed excellent potency and selectivity towards DPP-IV over various serine proteases, without exhibiting CYP inhibitory activity (*in vitro*).



12V

P008: Zinc oxide nanoparticles: A novel drug for the treatment of diabetes

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Zinc, an essential micronutrient, is associated with more than 300 enzymes, and plays a key role in diverse biological processes including glucose metabolisM. D.ecreased zinc in the pancreas may reduce the ability of the islet β-cells to produce and secrete insulin. Furthermore, knowing zinc's antioxidant role, reduced zinc may exacerbate the

oxidative stress-mediated complications of diabetes. Developing a zinc-based agent for treatment of diabetes thus becomes an attractive proposition.

Here, we have evaluated zinc oxide nanoparticles as a novel therapeutic agent in streptozotocin-induced Type 1 and 2 diabetic rats. The work is inspired from the traditional use of *Jasada bhasma* (zinc ash) in Ayurveda for the treatment of diabetes. Oral administration of zinc oxide nanoparticles (1, 3, 10 mg/kg) resulted in significant anti-diabetic effects – i.e. improved glucose tolerance, higher serum insulin (70%), reduced blood glucose (29%), reduced nonesterified fatty acids (40%) and reduced triglycerides (48%). Nanoparticles were systemically absorbed resulting in sustained serum zinc levels up to 24 h and selective tissue distribution was seen in the liver, adipose tissue and pancreas. Cytotoxicity, hemolysis, acute and sub-acute toxicity tests revealed that zinc oxide nanoparticles were safe up to 100-times the efficacy dose.

Our on-going mechanism of action studies indicate that increased insulin secretion, protection against oxidative stress and pancreatic beta cell proliferation are a few of the possible multiple mechanisms of the anti-diabetic action of zinc oxide nanoparticles. Overall, our results clearly show that zinc oxide nanoparticles are a highly promising anti-diabetic agent warranting further studies.

P009: Association between serum Matrix Metalloprotienases level and circulating Endothelial Progenitor Cells in Metabolic Syndrome: A Case-Control Study

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Matrix Metalloprotienases (MMPs) are tissue matrix enzymes and their activity is regulated by respective Inhibitory enzymes. The altered activity of MMPs causes pathogenic conditions. MMPs play significant role in pathophysiology of Metabolic Syndrome (MetS) and their consequences including diabetes and cardiovascular events. Endothelial progenitor cells (EPCs) are a subtype of bone marrow, are considered to be indicator of vascular integrity and involved in neovasculogenesis. MMPs plays pivotal role in homing of EPCs. An altered status of circulating EPCs represents a marker of endothelial dysfunction and vascular health.

Aim: This case control study emphasizes on the association of circulating EPCs with the components of MetS and serum MMP 2 and 9 level in MetS.

Material Methods: The age (20-60 years), sex matched 172 patients recruited for study, with 90 newly diagosed MetS cases according to NCEP-ATP-III criteria and 82 healthy controls. The serum MMP 2 & 9 level was analyzed by ELISA in all subjects. The enumeration of CD 34 $^{+}$ and CD 133 $^{+}$ and KDR $^{+}$ EPCs was done by flow cytometry while cell culture based CFU assays and migration assays were performed to evaluate the functionality of EPCs. SPSS software used for statistical analysis.

Results: Our study revealed the significant exhaustion of EPCs in MetS cases as compared to control group($p<0.05$). Serum MMP 9 level was significantly associated with number of circulating EPCs. Insuline resistance, hypertension were significantly associated with reduced EPCs level. EPCs number and functionality could serve a cellular biomarker of endothelial integrity and impaired neoangiogenesis in patients with MetS

P010: Iso-Steric Replacement of Thiazolidiene Dione to Imidazoline Dione (Hydantoin) as a Novel Scaffold, Synthesis and Pharmacological evaluation of PTP1B inhibitors

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Diabetes affects 12% of the total population in world. So it is very important to treat this fatal disease. There are many marketed preparation is available to treat diabetes but not a single medicine have the ability to cure it. A thirst in research area is more and more increased now a day. Novel pathways and targets are identified in current time that may be kill this dragon named diabetes. Inhibition of a novel target PTP1B is chosen for attack on diabetes. PTP1B inhibition reported as negative regulator of insulin signaling pathway which increased the insulin sensitivity on insulin receptor. The numerous scaffold are reported and still so much research task going on for PTP1B inhibition. We choose Hydantoin scaffold as novel inhibition of PTP1B and design molecule that binds with this enzyme and inhibit it. A series of substituted 2-[4-[(2,5-dioxo imidazolidin-4-ylidene) methyl] Aryloxy] -N-arylacetamide is decided to synthesized. The inhibition of PTP1B is in vitro tested over PTP1B enzymatic kit. Among all the tested compounds, two compound were found most potent activity 90.59% & 97.56 % inhibition respecively (N-(4-bromophenyl)-2-[4-[(2,5- dioxoimidazolidin-4-ylidene)methyl] phenoxy]acetamides) and 4.5 (2-[[2-[4-[(2,5- dioxoimidazolidin-4-ylidene)methyl] phenoxy] acetyl]amino]

benzoic acid) with compared to standard drug suramin

Thiazolidiene 2-4 dione imidazoline 2-4 dione

P011: Coagonism of GLP-1 and glucagon regulates lipid metabolism through bile homeostasis.

Vishal Patel, Amit Joharapurkar, Samadhan Kshirsagar, Kartik Patel, Rajesh Bahekar#, Gaurang Shah[1] and Mukul R. Jain

Department of Pharmacology &Toxicology, #Department of Medicinal Chemistry, Zydus Research Centre, Ahmedabad. [1]K.B. Institute of Pharmaceutical Education and Research, Gandhinagar.

Dyslipidemia is characterized by high concentrations of triglycerides and LDL-cholesterol, and low HDL-cholesterol is associated with persistent hyperglycemia. Hence, therapies that reduce LDL cholesterol and triglycerides should prevent and reduce cardiovascular disease. Despite many lipid-lowering drugs like the statins, there is a demand for new therapies to manage plasma lipids along with the treatment of type 2 diabetes. Dual agonism at GLP-1R and GCGR reduce body weight, improve insulin sensitivity and improves lipid profile independent of food consumption in diabetic models. In this work we investigated the role of coagonist on bile homeostasis in animal model. In acute study, animals received single injection of coagonist (0.5 mg/kg) or glucagon(2.5 mg/kg) or exendin-4 (8 µg/kg), following which bile was collected. In chronic study, high fat and high cholesterol diet-fed hamsters were treated with coagonist (0.3 mg/kg) or glucagon (2.5 mg/kg) or exendin-4(8 µg/kg) by subcutaneous route, twice daily for 14 days. After acute dosing, coagonist treatment increased bile flow rate better than exendin-4 treatment. On the other hand, coagonist treatment increased billiary cholesterol excretion better than glucagon treatment. In repeated treatment, coagonist reduced food intake, body weight, and hepatic as well as circulating lipids. Bile flow rate was increased, but cholesterol excretion in bile fluid reduced significantly after chronic treatment. It appears that coagonist modulates lipid metabolism in liver by increasing bile flow rate and lipid excretion in bile in hypercholesterolemic hamsters. Thus coagonist of GLP-1 and glucagon ameliorates dyslipidemia by modulating bile homeostasis.

P012: Novel 1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one analogues as DPP-IV inhibitors in diabetes

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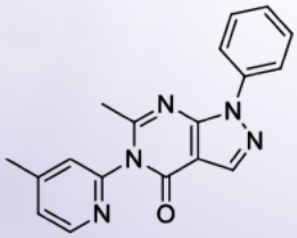
Dipeptidyl Peptidase-4(DPP-4) is one of the new emerging target in diabetes. DPP-4 inhibitors stabilize endogenous glucagon like peptide-1 (GLP-1) and induce insulin secretion in a glucose-dependent manner in contrast to insulin tropic agents which release insulin in glucose independent manners which manifest the hypoglycemia as a side effect. Inhibitors of DPP-4 enzyme improves pancreatic β-cell mass and its function. 1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one and its derivatives were synthesized. Structure elucidation of all the synthesized compounds was carried out by IR, ^{1}H NMR, ^{13}C NMR and MASS Spectroscopy. Molecular docking studies of all the compounds were performed. The protein model of DPP-4 was downloaded from the Protein Data Bank (PDB ID: 2RGU). Surflex Dock was facilitated through the Surflex Dock utility in Sybyl X 2.0. All the synthesized molecules were tested for their DPP-4 inhibitory activity. DPP-4 enzyme inhibition assay was performed for all the molecules. Further, synthesized compounds were tested for their *in vivo* anti-diabetic activity. High fat diet & low dose of streptozotocin model was developed in male *wistar* rats. Blood glucose level measurement was done before and after the treatment of synthesized molecules. Molecules were shown good DPP-4 inhibition as well as anti-diabetic activity. 6-methyl-5-(4-methylpyridin-2-yl)-1-phenyl-1H-pyrazolo[3, 4-d] pyrimidin-4(5H)-one showed promising activity in *in vitro* and *in vivo* studies.



6-methyl-5-(4-methylpyridin-2-yl)-1-phenyl-1H-pyrazolo[3, 4-d] pyrimidin-4(5H)-one

P013: Identification of Novel Orally Bioavailable TGR5 Receptor Agonist_

Brijesh Darji, Prashant Deshmukh, Santosh Sasane, Amit Patil, Umesh Aware, Kalapatapu V. V. M. Sairam, Priyanka Priyadarsiny, Harilal Patel, Suresh Giri, Mukul Jain, and Sameer Agarwal

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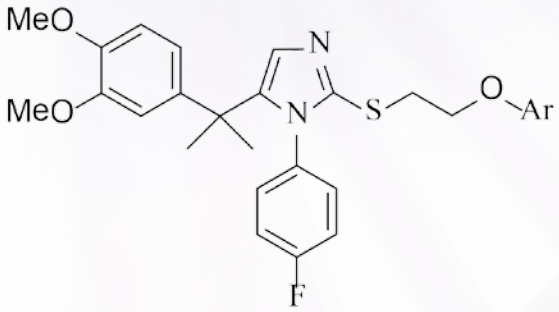
Takeda G-protein-coupled receptor 5 (TGR5), also known as GPR 131, GPBAR1, GPCR 19, M-BAR or BG37 activation plays a key role in pathways associated with diabetes, metabolic syndrome, and autoimmune disease. Novel classes of imidazole containing TGR5 agonists have been discovered and a comprehensive SAR studies resulted in the discovery of **1e** as a potent, selective, and bioavailable TGR5 agonist to test in preclinical metabolic disease models. Compound **1e** was able to stimulate cAMP against hTGR5 receptors with an EC_{50} of 14 nM in hTGR5 cAMP Assay and EC_{50} value of 57 pM & 63 pM against hTGR5 & mTGR5 receptor respectively in CRE directed Luciferase based RG Assay. Moreover, **1e** showed a favorable pharmacokinetic profile with the C_{max} of 9872 ng/mL in C57 mice at 30 mg/kg dose.



P014: Probiotics In Stress And High Fat Diet Induced Atherosclerosis In Rats

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Introduction: Stress and elevated levels of Low Density Lipoproteins (LDL) and free radicals generates an inflammatory response. Different strains of Lactobacillus in different doses and different forms are effective in decreasing lipid levels and inflammatory response.

Objectives: 1. Evaluating probiotics' efficacy on psychological stress and high fat diet induced atherosclerosis.
2. To study correlation between stress and development of atherosclerosis.

Materials and Methods: Wistar male rats (170-210g) were fed High Fat Diet (HFD) and subjected to Chronic Unpredictable Stress (CUS) for five weeks. Mixture of probiotics (L. acidophilus, L. rhamnosus, L. plantarum) either heat killed or live were administered either orally or intraperitoneally to these animals throughout the study period. Serum lipid profile, nitric oxide and urine valine mandelic acid (VMA) were measured on day 0, 14, 28 and 35. On day 35, brain noradrenaline, dopamine and serotonin levels were measured. Atherosclerotic lesions in carotid artery and histopathological examination of adipose tissue and liver were also carried out. Obtained results were compared with normal control, HFD control, CUS control and HFD+CUS subjected group.

Results: Probiotics treated animals showed normal lipid profile and nitric oxide levels. Interestingly, live probiotics treated animals showed less stained lesion area and normal hepatocyte structure; specifically those via oral route demonstrated more protective effect towards atherosclerosis development.

Conclusion: Stress and HFD together have a significant role in development of atherosclerosis; however, stress alone may develop atherosclerosis in long run. Probiotics , significantly reduce atherosclerosis development.

P015: Early Indications for Clinical Efficacy of Diabetes Drugs in Development in Phase 1 Studies: How?

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Based on the dramatically increasing number of patients with diabetes, and the need to find better treatments that can help to effectively battle the diabetes pandemic, the arsenal of drug candidates is growing dynamically. Picking up early indicators about a drug candidate's potential clinical efficacy is highly desirable in order to make the drug development process more effective. In looking at the early phase clinical research toolbox, the pharmacodynamic (PD) characterization of diabetes compounds is based on a number of different methods, with many of them being applied in different variations. PD profiling is done by means of

Oral Glucose Tolerance testing, Standardized Meal Challenges, Frequently Sampled Intravenous Glucose Tolerance testing, Glucose Clamps and others. The most relevant downsides of using different and variably applied methods to obtain information about a very limited number of relevant early phase clinical PD outcomes are obvious: a) a potential bias in selecting the method based on investigator awareness or preference; b) outcome data that aren't comparable between studies done on the same or similar compounds. Data from different studies performed by, and methods utilized by the authors will be discussed to identify methods that are more likely than others to provide meaningful and comparable gluco-metabolic outcome data in early phase clinical studies. Conclusions will be presented about the different methods regarding their potential utility.

P016: Effect of Discontinuing Anti-Diabetic Drugs (OAD) Prior to Enrollment in a Phase I Trial

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Subjects in Phase I trials of new OAD's typically stop current therapies ("wash off") 1 to 8 weeks prior to dosing with new compounds with risk of worsening glucose control. We retrospectively reviewed 48 T2DM subjects who successfully completed a phase I trial. Avg age 51±12 years, 25% female; BMI 32.2±4.6 kg/m2; screening HgBA1C 8.0%±1.0. Fasting plasma glucose (FPG) was recorded daily (glucometer) following wash off from metformin and/or sulfonylureas (SUs). Baseline OAD therapy discontinued on Day(D) -28. We compared FPG at D-28,-21,-14,-7,-2 prior to dosing, using a single factor analysis of variance.

FPG increased 13% in the first week after wash off from OAD's (Metformin and /or SU), and then plateaued over weeks 2 through 4 of the 28D wash off period ($p<.02$, single factor ANOVA). These data suggest that a one week wash-off is adequate prior to enrollment in a Phase I trial, and that withdrawing OAD therapy for longer than a week does not change FPG, but does expose the subject to unnecessary risk from poorly controlled blood glucose.

FBS (measured in days prior to enrollment; OAD withdrawn on day -28)

Day	-28	-21	-14	-7	-2
FBS ± SD	169.8 ± 41.9	192.3 ± 39.2	192.6 ± 43.2	195.3 ± 43.1	195.3 ± 41.3

Statistical Analysis

Source of Variation	SS	df	MS	F	P-value
Between Groups	19474.23	4	4868.557	2.773602	0.028081
Within Groups	379148.9	216	1755.319		

P017: TAK-875 (Fasiglifam) shows species difference in its pharmacological activity in rat and mice.

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TAK-875 (Fasiglifam) was identified as a potent and selective GPR40/FFA1 agonist for the treatment of type 2 diabetes mellitus (T2DM) developed by Takeda, recently discontinued due to hepatotoxicity. There are many reports showing its antidiabetic activity in rat but there is no report of its activity in most convenient and commonly use mice models. So, present study was aimed to compare the glucose lowering efficacy of TAK-875 in rat and mice models. In n-STZ rat model, TAK-875 has shown dose dependent AUC glucose reduction (upto 48% reduction at 10 mg/kg) and upto 3 fold increase in glucose stimulated insulin secretion (GSIS) after OGTT. TAK-875 has also improved glucose tolerance upto 36% at 10 mg/kg dose in Zucker fa/fa rats and showed 1.7-fold insulin secretion as compared to control. However, in db/db mice model it improved only 24% glucose tolerance and 1.6 fold GSIS at 30 mg/kg dose, it required high dose of 120 mg/kg to elicit 40% AUC glucose lowering. Further, in DIO mice model, TAK-875 could improve 34% glucose tolerance and 2.1 fold GSIS at high dose of 120 mg/kg dose. To understand this difference, we carried out pharmacokinetic analysis of TAK-875 at 3 mg/kg, p.o. dose and at 1 mg/kg, i.v. dose administration in mice and rats. At similar doses TAK-875 showed 3-fold less C_{max} (2.6 Vs 7.0 mg/ml) and 18-fold less AUC (4.8 Vs 84.6 µg.h/mL) in mice as compare to rats, which may be due to its 20-fold faster clearance (11.9 Vs 0.6 mL/min/kg) and 4-fold shorter elimination half -life $t_{1/2}$ (1.8 Vs 7.5 hr.) in mice Vs rats. Considering the general metabolic rate in mice is twice that of rats. These results shows that TAK-875 required almost 10-12 fold higher doses (as compare to rat) for its efficacy in mice; this may be primarily due to its difference pharmacokinetic parameters in mice and rats.

P018: Formulation and Evaluation of Pectin-Chitosan Composite Particles of an Anticancer Drug for Colon Targeting

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Pectin solution gelled with chitosan and calcium ion produced composite particles with a double layer structure, which may contribute to the undesirable premature and localized release of the drug. The aim of present study was to formulate pectin-chitosan composite particles of 5-fluorouracil and selection of most satisfactory formulation by in vitro evaluation. These multi particulate systems showing simultaneously specific biodegradability and pH dependent drug release were prepared based on chitosan, pectin, and calcium ions. Fourier transform infrared spectroscopic (FTIR) studies and Differential scanning calorimeter (DSC) studies were performed to study drug and excipients compatibility. The pectin-chitosan composite particles were prepared by complex coacervation from chitosan and pectin dispersions. Box Behnken Design was used to optimize three critical formulation parameters; concentration of chitosan, pectin and calcium chloride. The pectin-chitosan composite particles were characterized for particle size, % yield, swelling ratio and percent drug entrapment. Scanning electron microscopy was performed to study morphological behavior. In vitro drug dissolution was performed using dissolution apparatus (USP type I). Cytotoxicity study was performed on HCT-15 colon carcinoma cell line using MTT assay. Stability study was performed at room temperature and accelerated condition. FTIR and DSC study confirmed that the drug and excipients was found to be compatible. Particle size, %yield, swelling ratio and percent drug entrapment of optimized batch containing chitosan 0.1%w/w, pectin 10%w/w and calcium chloride 11%w/w were found to be 2.00±0,007mm, 87.57±0.05%, 357±2.45% and 96.77±0.90% respectively. SEM images of pectin-chitosan composite particles confirmed spherical shape and complexation. In vitro drug dissolution study confirmed that negligible drug was released from the Chitosan - pectin composite particles in pH 1.2 HCl. Pectin degrading enzyme increased the protein release from 31.15±0.005 to 92.84±0.007% within 12 h in phosphate buffer saline pH 7.4 . Cell line toxicity study had confirmed the better anticancer activity of pectin-chitosan composite particles against human colorectal adenocarcinoma cell line HCT-15. Hence, the developed 5-fluorouracil containing pectin-chitosan composite particles were effectively target the colon and shows better anticancer activity in colon cancer. These characteristics of the chitosan-pectin composite particles would be promising tool for targeting anticancer drugs to the colon.

P019: Design and Synthesis of Substituted Coumarin Derivatives as Antiinflammatory and Analgesic Agents

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Coumarin is classified as a member of the Benzopyrone family of compounds, all of which consist of a benzene ring joined to a pyrone ring. In this study various coumarin derivatives were synthesized using aromatic and heterocyclic amines, and tested the target compounds were tested for its analgesic and anti-inflammatory activity. The synthesized compounds were also docked on COX-2 enzyme to predict the binding affinity and orientation at the active site of the enzyme. All the compounds were synthesized in good yields and characterized using ^{1}HNMR, MASS and IR spectroscopy and purified using column chromatography. Most of the compounds showed significant *In-vivo* anti-inflammatory and analgesic activities. Comparing pharmacological activity and docking results, it was concluded that heterocyclic derivatives linked with nitrogen at 7-position of coumarin seem to be potentially active agents for anti-inflammatory, analgesic and ulcerogenic potential.

P020: Screening of tyrosine derivatives through computational methods intended for anti-inflammatory activity

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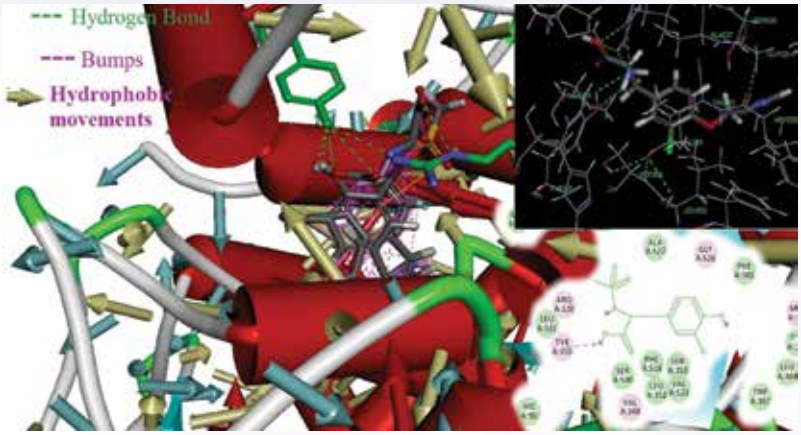
Cyclooxygenase-2 (COX-2)inhibitors are a class of drugs for treating the pain and inflammationthat do affect Cyclooxygenase-1 (COX-1)but selectively block COX-2 enzyme.The Coxib derivatives which selectively inhibitthe COX-2 enzyme possess a good anti-inflammatory activity with gastrointestinal, renal and cardiovascular side effects. In the present investigation, it was aimed to design novel COX-2 inhibitors with an enhanced COX-2 specific activity and fewer side effects. As a result, a library of 184 compounds was designed with tyrosine as core moiety. These molecules were generated by substitution at the -NH2,-OH and phenyl ring of tyrosine. The -NH2position was substituted with -SO2CH3, the-OH with diverse heterocyclic fragments and phenyl ring with electronegative groups. Molecular docking with COX-2 protein and toxicity prediction

were performed using Accelarys Discovery Studio software 2.5. The results of dockingagainst COX-2 protein were compared with standard celecoxib. Among the designed 184 compounds, the molecules 2, 95 and 160 showed good dock energy compared to standard. It was found that the above three molecules interacted with amino acid residues of Arg120 and Tyr-355 of COX-2 (3NT1) protein. In addition, cardiotoxicity and ulcerogenic property of thesemolecules wasperformed. Cardiotoxicity study was carried out using the human Ether-à-go-go-Related Gene (hERG) potassium channel and its interaction pattern with standard was calculated. Docking and toxicity results clinched that these moleculescould be effective as potent COX-2 inhibitor with negligible side effects.



P021: 1*H*-imidazo[4,5-c]quinolin-2(3*H*)-one derivatives as PI3Kδ inhibitors for the treatment of leukemia

Rajendra Chopade*, Dipam Patel*, Pradip Jadav*, Jignesh Pethani*, Bhushan Dave*, Hardik Shah*, Amitgiri Goswami*, Darshan Joshi*, Abhijit Chatterjee#, Mukul Jain# and Rajesh Bahekar*

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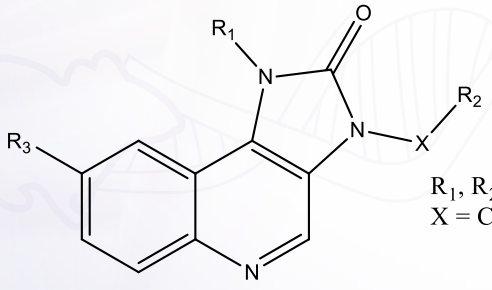
The Phosphoinositide-3 kinases (PI3Ks) are lipid kinases responsible for various inflammatory processes. Especially, PI3Kδ is most discretely expressed and confined to leukocytes and has been implicated as a therapeutically useful target in the treatment of certain forms of cancer & inflammation. In the present study we have synthesized heterocyclic compounds of the general formula (I) and evaluated their PI3Kδ inhibitory activity. The derivatives of 1H-imidazo[4,5-c]quinolin-2(3H)-one has showed excellent PI3Kδ inhibitory activity and selectivity over other kinases.

The synthesis of titled compounds (9a-j) was carried out by appropriate synthetic scheme. The in vitro testing of these compounds were carried out by PI3K ELISA assays of p110α/p85α, p110α/p85α, p110d/p85α and p110γ: Among the compounds tested (9g) & (9h) showed good in vitro PI3Kδ inhibitory activity. Further these test compounds were subjected for selectivity in isoform specific in vitro assay & compound (9h) exhibited remarkable PI3Kδ selectivity.



R_1, R_2, R_3 = H, alkyl, aryl, heteroaryl
X = CO, alkyl

(I)

P022: Studies on ATR kinase: A novel and potential drug target for cancer therapy

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UV/IR irradiation along with chemotherapy have been traditionally used as part of combinatorial therapy for the treatment of cancer cells. However, DNA damage through such treatment simultaneously leads to the activation of certain checkpoint kinases which help in the survival of treated cancer cells. ATR (Ataxia telangiectasia and Rad3-

related) is one such essential protein kinase involved in cell cycle checkpoint activation and triggers Chk1 kinase to regulate DNA damage response. Due to its inherent role in DDR, inhibition of ATR can serve as a potential target in enhancing the effect of radiation and chemo-therapy.

Torin 1, one of the potent mTOR1 inhibitors, is reported to have an IC_{50} value of 2 nM in HCT-116 cell line along with strong inhibitory action against ATR, ATM and DNA- PKs in the kinativ scan. Here, we present a systematic design of inhibitors for ATR as well preliminary molecular biology of the kinase.

P023: *Taraxacum Officinale* Inhibits Cisplatin-Induced Nephrotoxicity In Rats

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The protective effect of *Taraxacum officinale* mother tincture (*TO*) and its administration with Amifostine (AMF) was evaluated against cisplatin (5 mg/kg *i.p.*) induced nephrotoxicity in rats. The AMF was administered at 90 mg/kg *i.v.*, 30 minutes prior to CP injection. *TO* (0.1 ml/rat/day *p. o.*) was administered for 5 days post CP. On 5th day, blood samples were collected through retro-orbital puncture and rats were kept in metabolic cages for urine collection for subsequent 24 hours. Afterwards, the rats were sacrificed, and their kidneys were isolated. The CP induced rise in creatinine, BUN and ALP along with significant fall in the GSH, catalase and SOD levels in the kidney homogenates. Both *TO* and AMF treatments inhibited CP-induced deterioration of kidney function however, the protective effect of AMF was better. The protective effect of AMF against CP-induced nephrotoxicity was potentiated due to administration of *TO* for 5 days following it.

P024: Cardioprotective Effect of Oleanolic Acid and Urosolic Acid against Doxorubicin Induced Cardiotoxicity in Rats

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Oleanolic acid (3/3-hydroxy-olea-12-en-28-oic acid) and its isomer, Ursolic acid (38-hydroxy-urs-12-en-28-oic acid) are triterpenoids compounds which exist widely in plant kingdom in the free acid form or as glycosidic triterpenoids saponins. The aim of the study is to evaluate intravenously administered Oleanolic acid and Ursolic acid in doxorubicin induced cardiotoxicity. Cardiotoxicity was induced in albino wistar rat with single intravenous injection of doxorubicin at dose of 67.75mg/kg i.v for 48 hrs at 12 hrs interval following doxorubicin administration in the same model cardioprotective effect of Amifostine (90mg/kg i.v, single dose prior to 30 mins before doxorubicin administration) was evaluated as standard treatment. Induction of cardiotoxicity was confirmed by rise in cardiac markers in serum such as CK–MB, LDH and also by electrocardiographically. The doxorubicin treated group significantly increased in QT interval, serum CK-MB, serum LDH, SGOT, SGPT and antioxidant parameter. Oleanolic acid and Ursolic acid showed significant protective effect on biochemical anti oxidant and ECG parameters. The Oleanolic acid and Ursolic acid shows slight protection in histological lesions in doxorubicin induced cardiotoxicity. Hence, the results indicate that Oleanolic acid has more cardioprotective potential than Ursolic acid against doxorubicin induced cardiotoxicity in rats.

P025: Amelioration of oxazolone induced contact dermatitis by *Barringtonea racemosa* in mice

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The *Barringtonea racemosa* is used as a traditional remedy in India for treating various diseases including the immuno-inflammatory conditions. Triterpenoids and saponins are found to be the important constitutents of this plant. The active constituent called as Bartogenic acid is reported to possess anti-arthritic and alpha glucosidase inhibitory activity. The present study highlights ability of *Barringtonea racemosa* fruit extract fractions to delay the mainifestations and reduce the severity of delayed type hypersensitivity (DTH) in oxazolone induced contact dermatitis model. The DTH was induced in C57BL6 mice through the epicutaneous application of oxazolone and subsequent challenged on both the sides of ear on sixth day. The ear thickness was measeured after 24 and 48 hrs of challenge and intensity of DTH was calculated. The *Barringtonea racemosa* fruit extract fraction had effectively reduced the intensity of DTH reaction in treated mice at various time intervals. The reduction in the weight of thymus and spleen was observed as as compared to control animals. The histopathological changes associated with DTH were also effectually normalized by the *Barringtonea racemosa.* The inhibitory effect of plant on DHT reaction may be due to its ability to inhibit arachidonic acid metabolites such as postragrandines and leukotriens. Ability to decrease the weight of thymus gland implies potential of *Barringtonea racemosa* to suppress the immune response. Further investigations in this direction can clues the discovery of novel leads from this traditional plant which may be useful for the treatment of various immuno-inflammatory and allergic conditions.

P026: Ponatinib increases platelet counts and decreases bleeding time in Baf/3 xenograft mice

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Background: Ponatinib is an orally active BCR-Abl WT and T315I mutant kinase inhibitor, approved for the treatment of Philadelphia positive CML patients. Recently, Ponatinib treatment has shown adverse events like, life threatening blood clots resulting in artrial thrombosis and narrowing of blood vessels in CML patients. Platelet aggregation and thrombus formation at sites of atherosclerotic plaque rupture is a dynamic process that can lead to intermittent or permanent obstruction to blood flow, resulting in ischemic tissue injury and organ dysfunction. The current study was to evaluate the platelet related adverse changes in preclinical models which can be helful in screening novel BCR-Abl inhibitors.

Methods: Balb/c, nu/nu mice and nu/nu mice xenografted with BaF3 (T315I) cells were treated orally with ponatinib (3, 10 and 30 mg/kg) for 7 days. At the end of the experiment, blood was collected for analysis of platelet count followed by bleeding time experiments. In the xenograft study, tumor volume was recorded every alternate day as efficacy measurement.

Results: Platelet count was lower in nu/nu mice compared to Balb/c mice which were reflected in bleeding time experiment. Treatment with Ponatinib at 10 and 30 mg/kg doses increased platelet count irrespective of the strain of mice and its disease condition. There was also decrease in bleeding time in dose dependent manner. There was no significant change in PT or aPTT in Ponatinib treatment.

Conclusions: Treatment with Ponatinib significantly decreased bleeding time as a result of increased platelet count in the preclinical models which may be predictive of its clinical adverse events.

P027: Asiatic Acid Prevents the Doxorubicin Induced Cardiac and Hepato-Renal Toxicity and Protect Microstructures of Vital Organ in Wistar Rats

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Objectives: To study the organ protective effect of asiatic acid in doxorubicin induced toxicity

Methods: Organ toxicity cause by oxidative stress is one of the salient side effects of doxorubicin (DXR) at a dose of at a single dose (65.75 mg/kg, i.v. 48 hrs prior to end of study). The toxicity was observed by aberrant changes in the biomarker enzyme like CK-MB, LDH, BUN, Creatinine, SGPT, SGOT and antioxidant enzyme levels like SOD, Catalase and LPO. NrF2 stimulation by asiatic acid was done by docking study.

Results: Pentacyclic triterpenoid asiatic acid has been browbeaten revert the oxidative stress induced by the DXR at a single dose in heart, liver and kidney tissues of rats. Oxidative stress injury were evaluated biochemically and histopathologically, at 48 hrs after DXR administration. Rats pre-treated with asiatic acid at the dose of 5, 10 and 20 mg/kg p.o. shows revert the peroxidative damage in heart, liver and kidney tissues. It revert aberrant changes in CK-MB, LDH, creatinine, BUN, transaminase like SGPT and SGOT. Heart, liver and kidney tissues from DXR treatment was showed peroxidative lesions and depletion of GSH and SOD which restore by asiatic acid. Asiatic acid shows good docking score for the stimulation of NrF2 transcriptional factor.

Conclusion: Asiatic acid is food supplement having tissue repairing capacity which exerts the cytoprotective activity in dose dependant manner. Moreover, mechanism by which asiatic acid shows protection is might be through NrF2 stimulation. These results suggest that asiatic acid can be explored as organotropic adjuvant to chemotherapy

P028: Taraxacum officinale and L-arginine pre-treatment protects rats from cisplatin-induced nephrotoxicity.

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Objectives: In present study, Taraxacum officinale (TO) (mother tincture, 3cH, 6cH and 30cH) and a combination of TO mother tincture with ARG were evaluated for protective effects against CP induced nephrotoxicity in rats. Protective effect of L-arginine (ARG) against Cisplatin (CP) induced nephrotoxicity is well known.

Design: The study included eight groups: Naïve control, CP control, four groups receiving dilutions of TO, ARG treated group and combination treated group. The respective treatments were given for 14 days prior to CP injection. All groups except naïve control received CP (8 mg/ kg i. p.) on 15th day. Blood samples were obtained from all the rats at 24 hours after CP administration. Individual rats were kept in metabolic cages for urine collection. Afterwards, rats were sacrificed and kidneys were isolated for biochemical and histopathological examinations.

Results: CP group showed significant rise in serum and urine creatinine and depletion of antioxidant and increased lipid peroxidation. Treatment with TO and ARG protected rat kidneys from CP induced biochemical and histological changes. The combination treatment significantly protects rat kidneys than ARG or TO given alone.

Conclusion: The results indicate that dilutions of TO and combination of TO with ARG may be investigated for therapeutic efficacy in CP nephrotoxicity.

P029: Evaluation of antioxidant potential of *Lagerstroemia speciosa* against dextran sulfate sodium (DSS) induced ulcerative colitis in C57BL/6 mice.

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The herbal product form natural resources have been a divine key therapy from ancient time against numerous critical disorders. On the basis of this fact, *Lagerstroemia speciosa* (LS) commonly known as 'Pride of India' has evaluated in the present study for antioxidant activity. The administration of DSS (2.5% in drinking water *ad libitum*) induced ulcerative colitis in 7 days. The DSS-induced ulcerative colitis was assessed in terms of marked reduction in the levels of glutathione, catalase activity, superoxide dismutase and induction of oxidative stress and lipid alteration. The histopathological study revealed the inflammation in colon cells and marked impairment in the integrity of the mucosal lining. These functional changes were noted to be correlated with ulcerative colitis as observed in histopathological studies. However, treatment with different doses of methanolic extract of LS (100 mg/kg, 200mg/kg and 400 mg/kg, p.o., 7 days) just before one hour of DSS administration, partially but significantly prevent ulcerative colitis. Interestingly, the proportional inhibition of different oxidative parameters has been found with increased dose of LS up to 200 mg/kg but not for 400 mg/kg. In conclusion, it may be suggested that LS in low-dose comparative (100 mg/kg and 200 mg/kg) prevents DSS-induced ulcerative colitis by anti-oxidant activity. Moreover, LS at high dose (400 mg/kg) shows intermediate anti-oxidant potential and that may be due to saturation or down regulation of receptor.

Key words: Dextran sulfate sodium, ulcerative colitis, Lagerstroemia, 5-amino salicylic acid.

P030: Standardisation of Homeopathic Mother Tincture of Toxicodendron Pubescence by HPTLC and Correlation of Flavanoid Markers with Biological Activity

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Background and objective: Homeopathic formulations are standardized according to the homeopathic pharmacopoeial monographs. Standardisation of homeopathic mother tinctures by Thin layer chromatography (TLC) and High performance thin layer chromatography (HPTLC) for qualitative determination of chemical markers are recommended in recent pharmacopoeial editions. In the present work, a homeopathic mother tincture of Toxicodendron pubescence (Rhus tox) was standardised using a quantitative HPTLC method.

Methods: Five mother tincture formulations of Rhus tox obtained from different manufacturers was standardised by a validated HPTLC method. Precoated silica gel plates were used as stationary phase and mixture of methylene chloride: methanol: water: glacial acetic acid (15:1.5:1:8 v/v/v) was used as mobile phase. Quercitrin and rutin flavanoids were used as markers. After separation, the developed plates were scanned at 365nm.

Results: Resolution of quercitrin and rutin were Rf-0.63 and Rf-0.41 respectively. The minimum detectable concentration of the two flavanoids was 5ng/spot and showed a linearity range between 100-2000ng/spot. Later, the anti-inflammatory activity of these formulations was determined by carageenan induced paw edema in rats. Pain threshold and paw withdrawal latency was measured using electronic von-frey apparatus and Eddy's hot plate respectively. All the five formulations showed anti-inflammatory and analgesic activity. Anti-inflammatory effect, paw withdrawal latency and pain threshold at 3rd hour post carageenan injection correlated with flavanoid content in the formulations.

P031: Structural analysis of Toll-Like Receptor 4 (TLR4) as anti-inflammatory target: An *in silico* study

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Toll-Like Receptor 4 (TLR4) has been proven as potential target for chronic inflammatory disorders such as septic shock, rheumatoid arthritis, and cancer etc. TLR4 is a member of Toll-Like Receptors (TLRs) family, considered as pattern-recognition receptors (PRRs) and responsible for initiating immune responses

via recognizing both pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs). Targeting the TLR-4 mediated inhibition of inflammatory signaling has important therapeutic intervention. Before synthesizing the inhibitors, in silico approach is valuable method to validate for drug designing and facilitate the drug discovery process by hit identification, hit-to-lead selection, and optimization of the pharmacokinetic features such as absorption, distribution, metabolism, excretion and toxicity profiling for avoiding drug safety issues in later pre-clinical/clinical trials. There are a number of TLR4 complexes available in Protein Databank (PDB); therefore it becomes a mandatory step to evaluate the targets before proceeding towards computational drug discovery task. Evaluation process is very specific to the target structure and can be measured in terms of evaluation of binding pocket of target(s), their interaction with the ligand(s), their druggability measurement, and their interaction with the other accessory proteins, etc. Any of these evaluating parameters can modulate the binding affinity of drug(s) towards target. In present study we have performed the target evaluation for identifying better target among the available human TLR4 complexes in PDB. Targets were evaluated in terms of their binding pocket(s), their druggability prediction towards small lead molecules, protein-protein interaction of TLR4-MD2 complex and their mode of action for the range of ligand recognition.

P032: *In vitro* and *In vivo* targeted delivery of shRNA through ligand-targeted bacterial minicells in cancer

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The aim of this study was to explore the efficacy of folate-conjugated bacterial minicells as a novel targeted delivery system for shRNA. shRNA against VEGFA (psNIPERDU6A2) was packaged in bacterial minicells and minicells were linked with folic acid. *In vitro* delivery was studied by delivering 10^9 minicells from each the group, 1) $^{FA}minicells_{pSUPERneo}$ 2) $minicells_{psNIPERDU6A2}$, 3) $^{FA}minicells_{psNIPERDU6A2}$ in selected cell lines (A549, LNCaP, HeLa and KB) and expression of VEGFA was analysed by RT-PCR. Expression of VEGFA did not changed in any of the groups in A549 cell line. In contrast, expression of VEGFA reduced significantly in $^{FA}minicells_{psNIPERDU6A2}$ treated group when compared with other two groups in remaining cell lines. *In vivo* delivery of $^{FA}minicells_{psNIPERDU6A2}$ was studied in tumor xenograft of A549, LNCaP and KB cells where the animals of each group were treated with 1) Saline, and 10^9 of respective minicells, i.e. 2) $^{FA}minicells_{pSUPERneo}$, 3) $minicells_{psNIPERDU6A2}$, 4) $^{FA}minicells_{PSNIPERDU6A2}$ intravenously. There was a gradual increase in the tumor volume till the end of treatment in all four groups of A549 xenograft. Whereas in case of LNCaP and KB xenograft, there was a significant decrease in tumor volume in $^{FA}minicells_{psNIPERDU6A2}$ treated group as compared to other groups. Similarly, expression of VEGFA was found to be same in all the groups in A549 xenograft. On the contrary, significant downregulation of VEGFA was found in $^{FA}minicells_{PSNIPERDU6A2}$ treated LNCaP and KB xenograft. *In vivo* biodistribution study revealed that majority of $^{FA}minicells_{PSNIPERDU6A2}$ were localized in the tumor followed by liver and heart.

P033: Fabrication, Characterization, and Anticancer Potential of Niclosamide Encapsulated Albumin Nanoparticles

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Keywords: Albumin nanoparticles, niclosamide, cancer therapy, drug delivery, apoptosis

Niclosamide, an anthelmintic drug has potent anticancer properties and it has been demonstrated in various human cancer cells. However, the widespread clinical application of this proficient agent in cancer and other diseases has been limited by its poor aqueous solubility and bioavailability. An ongoing effort in the field of nanomedicine is to develop potent drug delivery system which overrules the drawbacks associated with this hydrophobic drug. In this work, a highly biocompatible niclosamide encapsulated albumin nanoparticles has been developed through desolvation method. Field emission scanning electron microscopy (FE-SEM) and dynamic light scattering (DLS) investigation confirmed that the as-prepared nanoparticles are spherical, highly monodispersed, and stable in aqueous system with a narrow size distribution in the range of 200-250 nm. Furthermore, nanoparticles showed much greater water solubility than free drug and on storage, the biological activity of drug loaded nanoparticles was preserved with negligible activity loss. These drug encapsulated albumin nanoparticles unlike free drug exhibits better *in vitro* therapeutic efficacy against human cancer cell lines, as assessed by cell viability assay and morphological analyses. Further, the efficient induction of apoptosis by these nanoparticles was confirmed by semi-quantitative RT-PCR. Hence our studies open up new facet for an existing anthelmintic drug as a potential anticancer agent.

P034: Anti-nociceptive activity of aliskiren in mouse models of pain: possible mechanism

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In the present study, anti-nociceptive activity of aliskiren was investigated on acetic acid induced writhing test and formalin test in mice. Mechanism for anti-nociceptive activity of aliskiren was also evaluated in acetic acid-induced writhing model using various antagonists of various pathways/receptors involved in pain mechanism. In acetic acid induced writhing test, vehicle, aliskiren (1, 3 and 10 mg/kg, i.p.) were administered intraperitoneally and 30 min later writhing response was elicited by intraperitoneal (i.p.) injection of acetic acid. Numbers of writhes were counted for 15 min. In formalin test, vehicle and aliskiren (10, 30 and 50 mg/kg, i.p.) were injected 30 min before injection of formalin into plantar surface of right hind paw. Animals were observed from 0 to 5 min represents early phase (neurogenic phase) and 15-40 min represents late phase (inflammatory phase), for time spent in licking and biting of the injected paw. In writhing test, aliskiren (1, 3 and 10 mg/kg, i.p.) produced significant anti-nociceptive effect by inhibiting the number of writhes as compared to vehicle in dose dependent manner. In formalin test, aliskiren (50 mg/kg, i.p.) produced anti-nociceptive effect in mice as indicated by reduced licking duration as compared to the vehicle control group, but this effect was non-significant as compared to vehicle. However, aliskiren (30 and 50 mg/kg, i.p.) produced significant anti-nociceptive effect in late phase of formalin test (15–40 min) as compared to the vehicle. The mechanistic study using various pharmacological agents indicated that anti-nociception caused by aliskiren was unaffected by atropine, prazosin, propranolol, pindolol, ondansetron, glibenclamide and rimonabant, whereas yohimbine and caffeine reversed the anti-nociceptive effect of aliskiren in acetic acid induced writhing test. This data suggests that aliskiren may have the potential to be used as an anti-nociceptive agent. The results of mechanistic study indicate that aliskiren might modulate pain transmission via $\alpha 2$ adrenergic and adenosine receptors.

P035: Evaluation of antibacterial and anticancer potential of drug loaded Ag/PEO/PCL blend composite nanofibers

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Keywords: Nanofibers, niclosamide, anticancer, antibacterial, silver nanoparticles

In the present study, synthesis of novel composite nanofiber scaffold was done in two steps. Firstly, the PEO/PCL blend was used for in situ synthesis of silver nanoparticles followed by incorporation of hydrophobic drug niclosamide into it. Electrospinning technique was used for fabrication of composite nanofibers. Field emission scanning electron microscopy (FE-SEM), Transmission electron microscopy (TEM), X-ray diffraction (XRD) and Fourier-transform infrared spectroscopy (FTIR) techniques were done to confirm the formation of niclosamide loaded Ag/PEO/PCL composite nanofibers. Thermal properties of fiber were assessed using thermogravimetric (TGA) analysis. Antibacterial efficacy of these nanofibers was assessed using Gram positive and Gram negative bacterial models. Nanofibers were further evaluated for their anticancer potential using various cell based assays. Thus the above fabricated nanofibers could be used as an effective antibacterial and anticancer agent.

P036: Quinuclidinone derivatives as potential anti-cancer agents

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Keywords: 3-quinuclidinone hydrochloride, anti cancer activity, SAR, MTT assay, DNA ladder assay, Hemolytic assay.

The molecule 3-quinuclidinone hydrochloride possesses wide variety of biological spectrum and is part of many existing drugs. A series of novel esters were synthesized from 3-quinuclidinone hydrochloride. The compounds were well characterized by various spectroscopic techniques. Synthesized compounds were screened for their cytotoxicity and possible implications of its anti-cancer potential .The structure activity relationship (SAR) revealed interesting results. Cell viability assay performed on lung carcinoma cells (A549) and normal lung cells (L132) via MTT assay revealed their IC50 value at <250µg. The compounds were found to be more cytotoxic to the A549 cells as compared to L132 cells at comparable doses. AO/EB and DAPI staining further revealed dose dependent cytotoxicity. Hemolytic assay performed using normal human erythrocytes to assess blood compatibility of the compounds showed that all the compounds studied herein were biocompatible at <250µg dose. Further investigation is underway to establish the alterations in expression of apoptotic genes and mechanism of cell death.

P037: Intercalator bearing cyclic phosphoramidates to understand targeting and enhancement of activity against cancer

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Cyclophosphamide, a phosphoramidate mustard, is a FDA approved alkylating prodrug used to treat solid tumors. It is metabolized and activated in liver and forms the toxin acroline which is one of the major

disadvantages of the drug. It is also known that due to its dependence on liver metabolism the drug dose is limited for cancer patients with acute liver problems. We design and synthesize cyclphosphamide analogues that may have less or no dependence on liver for its activation and since the targets of cyclphosphamide is not clearly known we also use fluorescent moieties to probe upon its target and investigate if the target gets changed on change of the auxiliary fluorescent ligand. Two planner cyclic phosphoramidate mustard has been synthesized and characterized. Fluorescent substituents provide an additional tool by which we can trace the drug inside the cell. The lipophilicity is ca. 1.88-2.22. They are found to be active *in vitro* against MCF-7 without the need of activation by liver enzymes. **1** and **2** kill cells via apoptosis. Compound **2** is also active under hypoxic conditions and the dose for IC_{50} rather shows improvement. Both compounds, show enhanced activity in presence of excess glutathione and ascorbic acid. Compound **1** arrests cell cycle at S phase whereas **2** arrests in G2/M phase. Compound **2** is traceable by Fluorescence inside the cell and changes the mitochondrial transmembrane potential signifying a probability of intrinsic pathway for apoptosis. It has been observed that **2** localizes in cytoplasmic compartment and produces ROS *in vitro*.

P038: Hypoxia active Ru^{II}(*p*-cymene) based anticancer agents of a sterically hindered Schiff base ligand

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The success of Platinum based anticancer agents in clinic is overwhelming however, so are their side effects. The alternative Ga(III) and Ru(II/III) based complexes seems to promising based on their activity so far. Our interest in Ru(II) complexes arise from their ability to slow hydrolyze as compared to Pt(II). We are interested to probe if slow hydrolysis can have an effect on the cytotoxicity of the anticancer agent. So far the investigations have revealed that it is difficult to ascertain a relationship between hydrolysis and cytotoxicity. We have synthesized a series of structurally related imidazole based Ru^{II}-arene complex $[(L1\text{-}L3)Ru^{II}(h^6\text{-}p\text{-cym})(Cl)](PF_6)$ (**1-3**) (where, L = N-((1H-imidazol-2-yl)methylene)-2,6-diialkylaniline, L1-L3 has changes in the alkyl groups) probed their hydrolysis and DNA binding. We found that these complexes bind to DNA with moderate affinity although they are very slow hydrolyzing complexes. Each of them is highly stable in 110 mM saline solution and shows no hydrolysis upto ten days and no binding was found to one of the major cellular the drug deactivating agent, glutathione (GSH). Their *in vitro* IC_{50} and cell cycle arrest studies against breast adenocarcinoma (MCF-7) and lung adenocarcinoma (A549) cell line show that their toxicity is comparable to cisplatin in normoxia and much better than cisplatin in hypoxia. pH dependent hydrolysis study shows that the rate of hydrolysis increases with decrease in pH**.** They arrest the cell cycle in sub G1 and G2/M phase and leads to apoptosis.

P039: An Efficient Approach on Guanidium Appended Molecular Transporter For Targeted Delivery of Doxorubicin Towards Malignant Cells: A Future Prospect in Cancer Therapy

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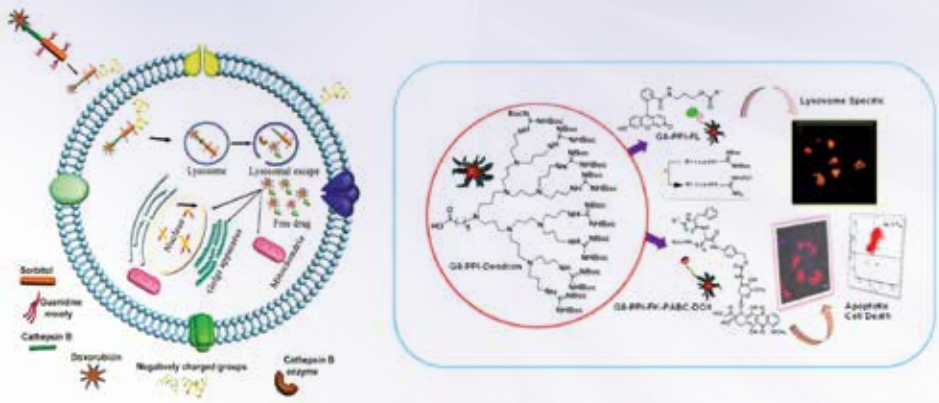
Over the last decades target specific drug delivery of anticancer drugs have wide interest in pharma industries because some of them successfully delivered at the right target with required doses, which minimizes dose limiting toxicity. Most of the widely used anticancer drugs are highly hydrophobic in nature and lack of specificity to particular tumour site, causes severe toxicity to normal tissues and organs. It is therefore a challenging task of pharmaceutical and medicinal chemistry researcher to come up with a unique targeted drug delivery system (TDDS) which selectively ferried the cargo molecule to the diseased cells and tissues in order to achieve maximum therapeutic effect. Keeping this in mind we have developed a straightforward synthetic approach for the construction of two guanidium rich molecular transporters such as i) sorbitol scaffold and ii) poly propenyl imine dendron conjugated to cathepsin B peptide substrate for lysosome targeted delivery of doxorubicin. The second carrier we have introduced newly which has octa-guanidine moiety attached on poly- (propylene imine) dendron starting from aminocaproic acid as the focal point, G8-PPI. Interestingly, transporter alone is found non-toxic, showed higher cellular uptake compared to Arg-8-mer and exhibited excellent selectivity towards lysosome in cathepsin B expressing HeLa cells. However, Dox-conjugate showed significant cytotoxicity compare to free Dox against HeLa cell, while insignificant cytotoxicity (< 5%) against normal cell (WI-38).



P040: Simultaneous quantification of atenolol and chlorthalidone in human plasma by ultra performance liquid chromatography-tandem mass spectrometry

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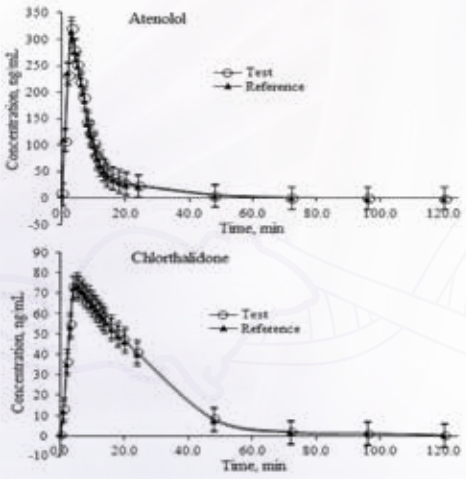
A simple, sensitive and reproducible ultra performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) method has been developed for the simultaneous determination of atenolol and chlorthalidone in human plasma using atenolol-d7 and chlorthalidone-d4 as the internal standards (ISs). Following solid phase extraction on Phenomenex Strata-X cartridges using 100 µL human plasma sample, the analytes and ISs were separated on Acquity UPLC BEH C18 (50 mm × 2.1 mm, 1.7 µm) column using a mobile phase consisting of 0.1 % formic acid: acetonitrile (25:75, v/v). A tandem mass spectrometer equipped with electrospray ionization was used as a detector in the positive ionization mode for both the analytes. The linear concentration range was established from 0.50-500 ng/mL for atenolol and 0.25-150 ng/mL for chlorthalidone. Extraction recoveries were within 95-103 % and ion suppression/enhancement, expressed as IS-normalized matrix factors ranged from 0.95-1.06 for both the analytes. Intra-batch and inter-batch precision (% CV) and accuracy values varied from 2.37-5.91 % and 96.1-103.2 % respectively. Stability of analytes in plasma was evaluated under different conditions like bench top, freeze-thaw, dry and wet extract and long term. The method was applied to support a bioequivalence study of 50 mg atenolol + 12.5 mg chlorthalidone fixed dose formulation in 28 healthy Indian subjects.

Pharmacokinetic Profile



Mean plasma concentration-time profile of atenolol and chlorthalidone after oral administration of test and a reference formulation to 28 healthy subjects.

P041: UPLC-MS/MS method for the simultaneous determination of losartan, losartan carboxylic acid and hydrochlorothiazide in human plasma

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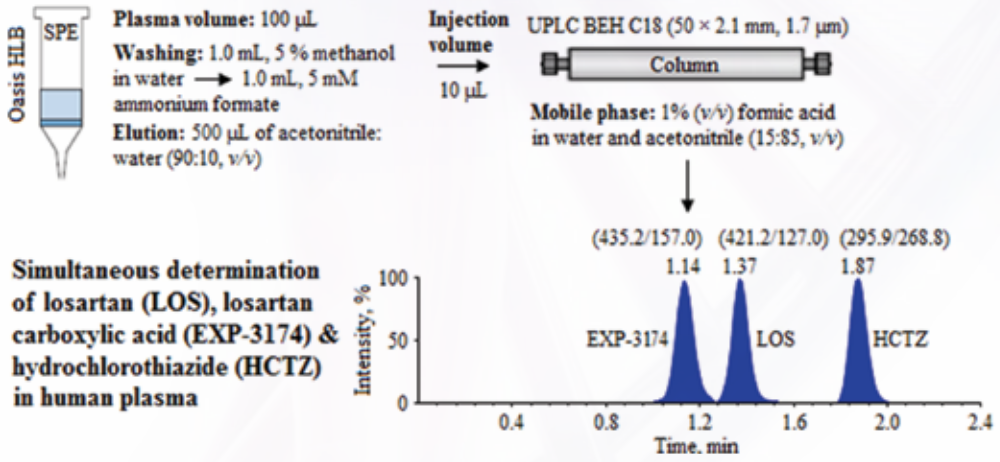
A selective and sensitive ultra performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) method is developed for the simultaneous determination of losartan, its active metabolite losartan carboxylic acid (EXP-3174) and hydrochlorothiazide in human plasma. Candesartan was used as an internal

standard for losartan and EXP-3174, while hydroflumethiazide was used for hydrochlorothiazide. Solid-phase extraction was carried out on Oasis HLB cartridges with 100 µL plasma to give an extraction recovery in the range of 88.5-102.5 % for the three analytes. Chromatography on BEH C18 (50 × 2.1 mm, 1.7 µm) column afforded baseline separation of all the analytes within 2.4 min using 1.0 % formic acid in water and acetonitrile (15:85, v/v) as the mobile phase. Quantitation was performed with multiple reaction monitoring in the negative ionization mode. The response of the method was linear over a dynamic range of 0.5 - 500, 1.0 - 750 and 0.25 - 150 ng/mL for losartan, EXP-3174 and hydrochlorothiazide respectively. The method was validated to demonstrate its selectivity, linearity, accuracy and precision, recovery, stability, dilution reliability, stability and ruggedness. Extent of signal suppression/enhancement was examined through post-column infusion technique. The effect of matrix components was evaluated by post-extraction spiking and calculation of slope of calibration lines. The method was successfully applied to a bioequivalence study of 50 mg losartan potassium and 12.5 mg hydrochlorothiazide hydrochloride fixed dose tablet formulation in 65 healthy human subjects under fasting. Reproducibility of the method was shown by reanalysis of 213 incurred samples.



P042: A novel UPLC-Q-ToF mass spectromery method for the reaction monitoring and determination of isotope labelled lamotrigine drug substance

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An ultra-performance liquid chromatography-quadrupole time of flight mass spectrometry (UPLC-Q-ToF) method was developed to determine deuterium labelled lamotrigine (D3). The method has capabilities to determine the amount of deuteration as well as it is useful for the reaction monitoring of labelling process. Non-labelled and labelled lamotrigine-D3 was separated over Waters Acquity BEH C_{18}(50 X 2.1 mm, 1.7 µm) column using mobile phase 3 mM ammonium acetate pH = 6.0 and acetonitrile with gradient elution. The detection was performed by UV and the Q-ToF MS detector. UV wavelength was set at 220 nm while MS operated under scan-resolution mode using electrospray ionization technique with positive polarity in the range over 50-1200 Da. The high resolution mass spectrometer was used to get the exact mass difference between the isotopically labeled compound and non-lablled drug substance. The High Resolution Mass Spectrometer detection is resourceful to identify the number of hydrogen atom replaced in the molecule, which is very important in the controlled labelling process.

P043: Selective and Sensitive Liquid Chromatography Tandem Mass Spectrometry Method for Simultaneous Determination of Propaphenone and its Metabolites in Human Plasma

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Propafenone is indicated for prophylaxis and treatment of ventricular arrhythmias. I t works by slowing the influx of sodium ion into the cardiac muscle cells, causing a decrease in excitability of the cells. Propafenone is primarily metabolized in liver where it rapidly converts into two active metabolites, 5-hydroxypropafenone and N-

depropylpropafenone. The objective of this study was to develop a selective and sensitive liquid chromatography tandem mass spectrometry (LC-MS/MS) method for the simultaneous determination of propafenone and its metabolites in plasma for a bioequivalence study. The mass transitions for propafenone, 5-hydroxypropafenone, N-des propyl propafenone and the internal standard (Carbamazepine) were 342.3 →116.2 m/z, 358.3 →116.2 m/z, 300.3 →74.2 m/z and 237.2 →194.1 m/z, respectively. Samples were extracted by solid phase extraction (SPE) using Strio-E 1cc, 30 mg cartridge, and chromatographic separation of propafenone and its metabolites was performed on an ACE5 C8, 50*4.6 mm column using gradient elution. The calibration curve range was 1 to 500 ng/mL for propafenone and 5-hydroxypropafenone, and 0.1 to 25 ng/mL for N-depropyl propafenone. The absolute recovery for propafenone, 5-hydroxypropafenone, N-depropylpropafenone and internal standard were 89.24% to 92.34 %, 73.90% to 75.38%, 78.35% to 83.44% and 95.40 %, respectively. The between run precision and accuracy was found within the 15% of the acceptance range for propafenone and its metabolites. The matrix effect was assessed at low and high quality control samples and internal standard normalized matrix factor at low and high QC was 1.1 with precision (%CV) of 4.22% to 2.21. The validated was applied for evaluation of comparative bioequivalence study of Propafenone 300 mg table with Innovator drug (RITMONORM) in healthy human volunteers.

P044: Estimation of Iloperidone in rabbit plasma using high performance liquid chromatography: Application to a pharmacokinetic study.

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In order to investigate the pharmacokinetic of Iloperidone, a rapid, simple, sensitive and reproducible high performance liquid chromatography (HPLC-UV) method has been developed and validated for iloperidone from rabbit plasma. After SPE with cartridge, celerity deluxe the analysed and internal standard (paliperidone) separated on Hypersil MOS-I C_8 (4.6 mm×250 mm, 5 µm) using mobile phase (pH 5.0) composed of acetonitrile, water and 5mM phosphate buffer along with 0.1% triethylamine in the ratio of 80:5:15(v/v/v) at flow rate of 1ml/min, in isocratic mode. Analyte were analyzed at 285 nm using UV detector. The method was validated in terms of specificity, matrix effect, recovery, accuracy, precision and solution stability in concentration range of 2-100 ng/ml. The correlation coefficient of linearity was 0.9996 and lower limit of quantitation was 2 ng/ml. The recovery of ILO and IS was more than 95% and 99 % respectively. Precision and accuracy was determined on three quality control level with % CV of less than 6 % in precision and accuracy was between 92.3 to 99.5 %. Stability of Iloperidone was established in storage, processing and analysis conditions by performance of bench-top, processed sample, stock solution, long term storage as well as freeze/ thaw cycle studies. The validated HPLC-UV method was applied for the evaluation of pharmacokinetic parameter of ILO after an intramuscular administration of 18.6 mg/kg to three newzeland white rabbits.

P045: Pharmacokinetics of ARS-MG-34 following a single intravenous and oral dose administration to male Sprague Dawley rats

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OBJECTIVE: ARSMG-34 is a novel patented molecule isolated from *Yucca gloriosa* L (Family- Aspargaceae). The objective of this study was to investigate the pharmacokinetics of ARS-MG-34 in male Sprague Dawley rats following a single intravenous and oral dose administration.

METHODS: Animals in Group 1 and Group 2 were administered with ARS-MG-34 solution formulation prepared in 7.5% NMP, 5% solutol HS, 10% PG, 10% PEG-400 in 67.5 % normal saline intravenously via tail vein at a dose of 2 mg/kg and oral solution formulation prepared in 7.5% NMP, 5% DMSO, 5% solutol HS, 10% PG, 10% PEG-400 in 62.5 % normal saline orally at 10 mg/kg respectively. The blood samples were collected from set of jugular vein cannulated rats at each time point. Plasma samples were separated by centrifugation of whole blood and stored below -70ºC until bioanalysis. All samples were processed for analysis by protein precipitation using acetonitrile and analyzed with fit-for-purpose LC-MS/MS method (LLOQ = 50.39 ng/mL). Pharmacokinetic parameters were calculated using the noncompartmental analysis tool of Phoenix WinNonlin® (Version 6.3).

RESULTS: Following a single intravenous dose administration, plasma concentrations were observed only up to 0.5 hr while, following a single oral dose administration, plasma concentrations were observed up to 0.5 hr (2 animal). These low concentrations and early elimination suggest high clearance compound could be due to high first pass metabolism. PK parameters were not calculated due to insufficient data.

P046: *In vitro* and *In vivo* Correlation of Gender Differences in Pharmacokinetics of Olaparib in Rats

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Olaparib is a novel, selective and potent inhibitor of poly adenosine diphosphate-ribose polymeras-1 (PARP-1) and PARP-2. It has been reported to be extensively metabolized, in particular by cytochrome P450 3A4. Significant gender-related differences occur in the expression of certain CYPs in rats, due mainly to the different patterns of growth hormone secretion (pulsatile in male rats and continuous in female rats). Therefore, olaparib metabolism in male and female rat and human liver microsomes was studied in-vitro. Metabolism by recombinant human isozymes was also studied in-vitro. In-vivo, the pharmacokinetics of olaparib was studied in male and female Wistar rats (IV dose 1 mg/kg and oral dose 3 mg/kg). All samples were quantitated using an specific and sensitive LC-MS/MS method. Studies with recombinant human isozymes in-vitro confirmed that olaparib is a substrate of CYP3A4 ($T_{1/2}$ 1.9 min), and fractional contribution of CYP3A4 to the total metabolism was estimated to be 93%. In rat liver microsomes in-vitro, olaparib was metabolism was 6.5 times higher in male compared to female liver microsomes. In-vivo, the intravenous plasma clearance (CL) of olraparib was 86.4 ± 11.3 mL/min/kg and 14.7 ± 0.7 mL/min/kg in male and female rats, respectively. The steady state volume of distribution (Vss) was 1.3 ± 0.1 L/kg and 2.6 ± 0.2 L/kg, respectively. The much higher plasma clearance in male rats was reflected by a shorter plasma $T_{1/2}$ in male rats (0.3 ± 0.1 h) compared to female rats (2.8 ± 0.3 h). The oral bioavailability of olaparib was 99% in female rats and 23% in male rats, likely reflecting first pass effects. Thus, in rats the gender differences in the in-vitro metabolism of olaparib in liver microsomes correlates with gender differences in its pharmacokinetics in-vivo.

P047: pH-Dependent Passive and Active Transport of Roxadustat (FG-4592) Across Caco-2 Cell Monolayers

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Roxadustat (FG-4592) is a hypoxia-inducing factor alpha-subunit prolyl hydroxylase inhibitor.with an ionizable acid functional group. In a screening CaCo-2 permeability study, FG-4592 showed an efflux ratio (ER) of 21, suggesting that it may be a substrate for an active efflux transporter expressed in CaCo-2 cells (e.g. P-glycoprotein, P-gp;, and breast cancer related peptide, BCRP). Despite the high efflux ratio in CaCo-2 cells, FG-4592 showed excellent oral absorption across species in-vivo. The aim of this study was to characterize this finding in CaCo-2 cells by measuring bidirectional flux of FG-4592 in the presence of the P-gp inhibitor ketoconazole, and also under altered physiologic pH conditions. Twenty-one day old cultures were used for the study, and flux of the FG-4592 (5 µM spiked concentration) was monitored in both apical→basolateral and basolateral→apical directions. Samples were analyzed using a specific and sensitive LC-MS/MS method. With buffer pH 7.4 in both apical and basolateral compartments (pH 7.4 / pH 7.4), FG-4592 showed very low apical→basolateral permeability (Papp: 14 nm/sec) and a very high basolateral→apical permeability (Papp: 290 nm/sec, ER = 21). Under these conditions, in presence of ketoconazole (P-gp inhibitor; 50 uM), the ER was decreased to 3. In contrast, with pH 5.5 in the apical compartment and pH 7.4 in the basolateral compartment and in the absence of inhibitors, FG-4592 showed a much higher apical→basolateral permeability (Papp: 321 nm/sec; 23-fold higher relative to pH 7.4 / 7.4; ER = 0.3). The marked reduction in the ER of FG-4592 seen at pH 7.4 / pH 7.4 conditions in presence of ketoconazole are consistent with its transport being mediated in part by an efflux transporter such as P-gp. The results seen at the pH 5.5 / pH 7.4 conditions suggest a possible pH-dependent interaction of substrate with a transporter in CaCo-2 cells, or more simply passive diffusion-mediated transport of FG-4592 where the unionized/membrane-permeable species of FG-4592 predominated at acidic pH, and the ionized/less-permeable species predominates at pH 7.4. The excellent oral absorption of FG-4592 in-vivo across preclinical species likely occurs from the mildly acidic conditions in the lumen of the jejunum and major part of the small intestine.

P048: Development of SPR based methods for biologocal characterization of Monoclonal antibody therapeutics and its applications in Biosimilars

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Monoclonal antibodies (mAbs) are rapidly growing class of highly specific therapeutics. Till date there are around 32 monoclonal antibodies approved for various indications and many more are in various phases of development. They have become effective treatments for immunological, oncological, transplantation and cardiovascular and infectious diseases. The therapeutic efficacy of the monoclonal antibodies is dependent on 2 major interactions. The interaction of the mAb with its target and the effector molecules such as FcRs and C1q are essential for the final bioactivity of the mAb. Following the binding of the antibody to the target, the subsequent binding of the FcRs is a critical step for the initiation and control of the cell mediated effector functions and determination of the half-life of

the drug. The glycan structure of the Fc Domain of the mAb is a critical determinant of Fc-FCgR binding.

Current state of the art cell based assays to determine the effector functions of mAbs are time consuming and have inherent variability. Robust Protein-protein interaction assays using SPR have proven to be valuable orthogonal tool for monitoring structural integrity during upstream and downstream process development of therapeutic mAbs. These assays can also be used to establish the biosimilarity between products after process change / site change.

We here report the development of robust and reproducible SPR based methods to study the critical FcR interaction. The method was used to compare one of the Zydus Biosimilar mAB product with the innovator product. Our results show that the Zydus mAb is highly biosimilar to Innovator mAb in terms of critical Fc receptor binding affinities.

P049: Development of ELISA based methods with improved Drug tolerance for assessment of HAHA

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Generation of Anti Drug antibodies (Immunogenicity) is a major concern in clinical and preclinical studies for biotherapeutics, since it can lead to potentially serious side effects, changes in drug exposure (PK) and loss of efficacy (PD). Therefore, it is very important to develop reliable approach for immunogenicity assessment.

Monoclonal antibodies (murine, chimeric, humanized, fully human) are widely developed for various therapeutic purpose. Anti-drug antibodies (ADA) are known to be produced for all these classes of Antibodies including the humanized monoclonal antibody or even fully Human monoclonal antibody therapeutics administration. Therapeutic monoclonal antibodies usually have longer half-life and high therapeutic dose. The detection of antibodies is difficult while the drug is present in the blood at high concentrations as it tends to bind ADA forming ADA-Drug complexes, masking the detection of anti-drug antibodies (ADAs) in immunogenicity (IM) analysis using the traditional ligand binding assays (ELISA, RIA and other modern platforms etc.). Hence drug tolerance is critical parameter to consider during method development.

Acid treatment of samples has been successfully used to improve drug tolerance in ADA assays. We describe a sensitive and selective method with better drug tolerance using an acid dissociation step incorporated for evaluation of immunogenicity.

P050: Development and Evaluation of Amino Acid Based Lyophilized Dry Powder Inhalers of Theophylline and Montelukast for Treatment of Asthma

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The aim of present investigation was to develop and evaluate amino acid based lyophilized dry powder inhaler of theophylline and montelukast for treatment of Asthma. Asthma is a chronically inflammatory lung disease having significant impact worldwide. Montelukast is the drug-of-choice which act as anti inflammatory and theophylline is act as bronchodilator. This both drug in combination produces synergistic effect and reduces chronic symptoms and prevent asthma attacks if given by pulmonary route as dry powder inhaler dosage form. Lyophilization using crystalline amino acids such as Phenylalanine/ Valine/ L-Leucine/ Arginine rendered a dose independent three-fold increase of the fine particle fraction (FPF). This is possibly due to enhanced fracture properties of the lyophilisates upon impact of the air stream and reduced particle agglomeration/cohesion caused by a rougher surface. FTIR have been employed to study drug-drug and drug-excipient compatibility. Analytical method was developed using Q absorption ratio method by UV visible spectroscopy. 32 Factorial Design was applied for Optimization of Amino acid to carrier Ratio. Flow properties, particle size, percent drug content and Surface morphology by Scanning Electron Microscopy (SEM) and aerosol performance using Anderson Cascade impactor were evaluated for developed formulation. The in-vitro drug release study was performed using dialysis bag. Stability study was performed at accelerated conditions as per ICH. Drug-drug and drug-excipient were found to be compatible with each other. Developed analytical method was compatible for quantitative analysis of both drugs. Lyophilized dry powder inhaler of both drugs was successfully prepared with montelukast (0.1 mg), theophylline (0.2 mg), respitose SV001 (30% w/w), phenylalanine (40% w/w). Particle Size and percent drug content of and theophylline and montelukast were found to be 3.30 ± 1.33 µm and 98.02 ± 1.65% and 98.34 ± 1.24 % respectively for optimized batch. Scanning Electron Microscopy (SEM) study indicates that the particles were found to be highly creased, raisin-like. Carr's index, Hausner's ratio and angle of repose were found to be 11.46 ± 0.56 %, 1.12 ± 0.45 and 32.76 ± 0.16 °respectively which show good flow property of lyophilized dry powder inhaler. In-vitro drug release of theophylline and montelukast of optimized batch was found to be 96.42± 0.53 % and 96.78 ± 0.62 % up to 4 hrs. A fine particle fraction (FPF), fine particle dose (FPD) and mass median aerodynamic diameter (MMAD) were found to be 65.54 %, 252.3 µg, 2.26 µm respectively for optimized batch. Dry powder Inhaler containing montelukast and theophylline were stable at accelerated condition. The present

investigation demonstrated that lyophilized dry powder inhaler is suitable for respiratory deposition and hold great potential for treating diseases that require direct lung delivery. Thus we can conclude that the prepared DPI's may be consider as promising carrier for delivery of drug such as montelukast and theophylline in combination.

KEYWORDS: Montelukast, Theophylline, Asthma, Dry Powder Inhaler, 32 Factorial Design, Lyophilization.

P051: Formulation Development and Acute Eye Irritation Study of Cyclosporine Ophthalmic Microemulsion

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Dry eye disease is one of the most frequently encountered ocular morbidities with available treatments only providing limited temporary symptomatic relief. Cyclosporine is an immunosuppressive agent, indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. An ophthalmic microemulsion formulation of Cyclosporine 0.05% w/v may provide advantages over the currently available formulations Restasis® ophthalmic emulsion, Allergan Inc. through easy instillation and clear vision. The purpose of this study was to develop a unique, efficacious and safe formulation for the treatment of keratoconjunctivitis sicca. *In-vivo* acute eye irritation study for Cyclosporine ophthalmic microemulsion was performed on New Zealand white rabbits. One day prior to treatment; both the eyes of each rabbit were examined for ocular lesions to confirm that there were no pre-existing eye diseases, corneal damage or any other defects. After instillation of samples, the eyes of all the rabbits were observed for signs of ocular irritation at 1, 24, 48 and 72 hours. The mean eye irritation scores of conjunctival redness, corneal opacity, iritis and chemosis graded after instillation. No abnormalities were detected in the control eye of the rabbits during the course of this study. No treatment related clinical signs were observed in the rabbits. Cyclosporine ophthalmic microemulsion is found to be non-irritating to the eyes as it is being classified under category 1, 2A and 2B as per OECD Harmonized system.

P052: Development and Evaluation oof Boronate-Dextran Based an Acid Responsive Biodegradable Nanoconstructs for Cancer Targeting

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Stimuli responsive smart polymers have great potential to deliver drug on demand and to a specific location for targeting within the human body. Acid responsive drug carries can release the incorporated drug specifically in the acidic microenvironments of tumor cells or in the lysosomes. In present investigation, an approach to modify vicinal diols of dextran with hydrophobic boronate esters in order to produce a water insoluble boronate-dextran polymer was described. Fourier transform infrared study was performed to confirm the modification of dextran. The polymer spontaneously forms acid responsive nanoparticles. Hydrophilic anticancer drug, topotecan hydrochloride was incorporated in nanoparticles by nanoprecipitation method. Analytical method was developed by UV spectrophotometer. Boronate-dextran nanoparticles of topotecan hydrochloride was successfully prepared by 1:20 weight ratio of drug and modified dextran 10 and evaluated for percent drug entrapment, percent drug loading, particle size, zeta potential and polydispersity index. In vitro particle degradation study and in vitro drug release study was performed at pH 5.0 and pH 7.4. Stability study was preformed at two different temperature conditions, i.e., 4-8 ± 2° C/45±5% RH (Refrigerator; RF) and 25 ± 2° C/ 65 ±5% RH (Room temperature; RT) for 1 month. Percent drug entrapment and percent drug loading for optimized batch was found to be 54.62 ± 0.007 % and 2.60 ± 0.008 % respectively. Particle size, zeta potential and polydispersity index was found to be 258.7 ± 43.90 nm, -0.191 ± 0.053 mV and 0.102 ± 0.062 respectively. Particle degradation at acidic pH was confirmed by optical transmittance and particle size measurement. It was Biodegradable Nanoconstructs found to be 50.4 ± 3.842 % and 99.2 ± 8.708 nm at 20 h . In vitro drug release was found to be 90.85 ±0.183 % and 21.87 ± 0.738 % at pH 5.0 and pH 7.4 up to 96 hrs respectively. Sterilization of optimized batch was performed by dry heat sterilization method and confirmed to be sterile by sterility testing. Stability study shows that boronate-dextran (B-Dex) nanoparticles containing topotecan hydrochloride are stable on storage. The present study demonstrated that B-Dex based an acid responsive biodegradable nanoparticles hold great potential for the targeting of cancer cells.

KEYWORDS: Topotecan hydrochloride; Dextran; Boronate ester; Stimuli Responsive polymer; Nanoprecipitation

P053: Formulation and Development of Dronedarone HCL Nanoparticle by Solvent Evaporation for Dissolution Enhancement

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Atrial fibrillation (AF) is the most common sustained heart rhythm disorder, which affects more than 10% of cases diagnosed in people over the age of 75 years. Dronedarone HCL (DNH) is used as an Anti arrhythmic agent in AF.

As compared to Amiodarone HCl, DNH is better because Amiodarone HCl has complex pharmacokinetics with serious extra cardiac side effects, due to the presence of an iodine moiety where DNH is an iodine-free molecule and widely used to reduce adverse effects. DNH is BCS Class – IV drug so it has low solubility and low permeability which requires to enhance by solubility and permeability enhancement techniques. Nanotechnology is newer and well known technique to improve solubility and permeability by increasing surface area of the particle. The main objective of the present investigation is to prepare & evaluate nanoparticles of DNH to increase Solubility and/or Bioavailability. The comparison of solvent evaporation method was done with anti solvent method which resulted Solvent Evaporation Method with better Particle size and Entrapment Efficiency (EE). By 3^2 Full factorial design, the formulation was optimized and for that Particle size, Entrapment Efficiency (EE), Drug Loading, TEM (Transmission Electron Microscopy), In Vitro study were Performed which showed the Compliance of nanoparticles. Therefore it is concluded that DNH nanoparticles can be prepared by Solvent Evaporation method and it may also show better stability and bioavailability.

P054: Formulation Development and Efficacy Evaluation of Clobetasol Propionate and Salicylic Acid NanoLotion

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Psoriasis is a skin condition that causes red, flaky, crusty patches of skin covered with silvery scales. Clobetasol propionate is a corticosteroid used to treat eczema and psoriasis. Salicylic acid is known for its ability to ease aches and used as an anti-inflammatory drug. A new and unique formulation of Clobetasol Propionate 0.05% and Salicylic Acid 6% (CLOP S® Lotion) may provide advantages over the currently available formulations (Topisal Lotion, Systopic Lab) through easy application and skin friendly. The purpose of this study was to develop better formulation and more efficacious and safe CLOP S® Lotion to Marketed formulation in the treatment of moderate to severe plaque-type psoriasis. In-vivo study on CLOP S® Lotion formulations in Oxazolone induced psoriasis model conducted. Animals were randomized to receive sensitization phase followed by challenge test after 5 days interval at the same time it receive either test product CLOP S® Lotion, Topisal Lotion and control for 21 days. Before challange and 24 hours after every challenge, ear thickness and at the end of the experiment ear weight were measured. Ear thickness was measured after every challenge application and ear weight & cytokines level after end of the treatment as an Efficacy tool. CLOP S® Lotion reduce ear thickness and ear weight significantly to reference product and very significant to control treatment. Cytokines levels also observed significantly less in CLOP S® Lotion treated group. Overall, CLOP S® Lotion showed better efficacy compared to Marketed preparation.

P055: Development of Silver Nano articles Based Formulation for Topical Drug Delivery

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Silver nanoparticles is one of the paramount example in the gamut of nanotechnology materials due to its insurmountable properties like antimicrobial agents, catalysts etc. which provoked intensive research interest to researchers to use it in various applications. The current research is focused to augment the wound healing and antioxidant activity of aqueous extract of Tridax procumbens in combination of broad anti-bacterial activity of silver nanoparticles. Green synthesis of silver nanoparticles has proven to be better alternate over chemical methods which render product with bio compatible attributes whilst giving a cost effective and environmental friendly process. In the present research, silver nanoparticles were prepared using aqueous extract of Tridax procumbens. It is having polysaccharides constituents which causes stepwise reduction of silver ions to synthesize silver nanoparticles. Nanoparticles were characterized using UV-spectrophotometry (surface plasmon resonance) and dynamic light scattering (DLS) methods. The developed nanoformulations was converted to stable nanogel with carbopol as gelling agent and optimized. The effect of amount of the reducing extract, amount and concentration of silver solution and concentration of stabilizers were observed on particle size and %yield. The results were found within acceptable limits. In conclusion, developed nanogel was found stable and effective for wound healing.

P056: Development of Modified Release Venlafaxine HCl Capsules

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The purpose of this research work was to develop venlafaxine hydrochloride capsules for obtaining zero order drug release. Granules were prepared by wet granulation technique using combination of ethyl cellulose & hydrophilic polymers and were filled into hard gelatin capsule. The *in-vitro* dissolution study was performed in distilled water. Capsule containing ethyl cellulose and hypromellose were coated by different ratio of ethyl cellulose and dibutyl phthalate at different levels. 3^2 full factorial design was applied for optimization of the formulation. Model independent approach was used for comparison of drug release profile of selected batch with reference release profile. Kinetics of drug release was studied and the dissolution of

the optimized batch was carried out in 0.1N HCl and phosphate buffer. Burst drug release was exhibited by the uncoated capsules, probably due to high aqueous solubility of the venlafaxine hydrochloride. The coated capsules showed sustained drug release without burst effect. The optimized batch showed similarity with the proposed release profile, the drug release was best explained by zero order release model. The optimized batch showed identical drug release in 0.1 N HCl and phosphate buffer. This study demonstrate that it is a challenge to develop sustained release capsule for highly water soluble drug venlafaxine hydrochloride and burst drug release could not be controlled without coating of granules or capsule as a whole.

P057: Enhanced Bioavailability of ZY3925 molecule using Hot Melt Extrusion Technique

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In recent years, more than 50% of new drug candidates are speculated to be highly lipophilic and thus, poorly bioavailable. One very successful approach to increase bioavailability of such poorly water-soluble drugs is the formation of amorphous solid dispersions (ASD).

A novel selective antagonist of cannabinoid type 1 (CB 1) receptor molecule ZY3925 which having poor water solublity has been selected to make novel solid dispersion based formulation. Hot melt extursion techqniue was used to improve the solubility and hence the bioavability of ZY3925. A combination of ZY3925 and polymer (Eudragit EPO) at 1:5 was proessed through the Hot melt extrusion at 180 °C and the pellets obtained were milled to obtain the particle size between 100 to 250 micron. DSC and XRD data of the milled poweder showed complete amouphous conversion of drug and the solubility of same in 0.1 N HCl increased to 75.6 µg/ml from 5.5 µg/ml of crystalline API. Directly compressible tablets of the ZY3925 of strength 40 mg were prepared using common tableting excipients and the dissolution compared with the tablet prepared using crystalline ZY3925 in 0.1 N HCl. A significant improvement in the dissolution of ZY3925 formulated with HME was observed compared to conventional tablet formulation with drug release upto 90 % achieved within 1 hr. Based on results of dissolution studies, a pharmacokinetic studies of both the formulation were carried out in beagle dogs. A significant increase in the Cmax of 9.14 fold and AUC (0-24 hr) 4.30 fold in AUC was observed in Hot melt extrusion formulation compared to conventional tablet.

P058: Eudragit coated microspheres for the targeted delivery to brain using full factorial design

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Rivastigmine tartrate (RIVA), an anti-cholinesterase inhibitor and used in the treatment of Alzheimer's disease, has poor oral bioavailability due to extensive hepatic first pass metabolism. The potent nature with shorter half-life and GIT side effects associated with drug indicate there is a need to develop an alternate route to oral route. The lipophilic and low molecular weight properties facilitate the absorption of drug from the nasal mucosa. The intranasal route allows absorption of drug by olfactory bulb of nasal cavity and allows drug to go directly into brain bypassing Blood Brain Barrier. Hence, an attempt was made to prepare intranasal microspheres of RIVA by using chitosan and span 80 by emulsion crosslinking method. The prepared batches were evaluated for % entrapment efficiency (% EE), particle size, in-vitro drug release, in-vitro drug permeability, % drug loading and % mucoadhesion. 2^3 full factorial design was used to optimize the critical quality process parameters. From the optimization of designed batches, it was found that the results of optimized batch were well within the acceptable range. To prepare once a day formulation, it was decided to coat the microspheres by emulsion solvent evaporation method using Eudragit RS PO to sustain the drug release. The evaluation of coated microspheres showed that the drug release was controlled up to 24 hr. Scanning electron microscopy studies of coated and uncoated microspheres of optimized batches indicated microspheres were of smooth surface and good sphericity. Prepared microspheres should be stored in cool and dry place to maintain their quality.

P059: Generation of new leads as HIV-1 integrase inhibitors: 3D QSAR, docking and molecular dynamics simulation

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HIV-1 integrase (IN) enzyme play a pivotal role (viral replication) in the HIV-1 life cycle and is recognized targets for the development of anti-HIV-1 drugs. Combination of ligand and structure-based approaches along with activity and toxicity predictions provides best lead compounds in the drug discovery process. In this study seventy one IN inhibitors were used for the development of 3D QSAR models. The generated contour maps were used for the design of novel IN inhibitors and their activity and toxicity were predicted. Molecular docking study was performed to known the binding mode of designed compounds. The designed compounds showed interactions with active

site amino acids, which are already proved to be important for catalysis. Then, molecular dynamics (MD) simulation studies of ligand-enzyme complex were carried out. Designed compound **4d** was stable in the catalytic core domain of IN during the MD simulations

P060: Pharmacological evaluation of boswellic acid on ovarectomized rat model for post menopausal osteoporosis.

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Osteoporosis is a major health problem affecting post menopausal women worldwide. Therefore the objective of our study is to evaluate the anti-osteoporotic effect of boswellic acid in Ovarectomized (OVX) rat model of Osteoporosis. The female rats were divided into 4 groups: Sham operated, OVX control, OVX treated with boswellic acid (34.2 mg/kg, p.o), OVX treated with estrogen (0.0563 mg/kg, p.o). Osteoporosis was induced by removal of ovaries bilaterally. The treatment was carried out for 42 days. At the end of treatment, the blood and urine samples were collected. The serum was separated and subjected to analysis of calcium, phosphorus and alkaline phosphatase. Immediately, after collecting the urine and blood samples, uterus was carefully removed and weighed. The femur and lumbar vertebrae were isolated and used for the measurement of weight and biochemical and mechanical properties. Right femur was subjected to the histopathological evaluation. It was observed that serum calcium, phosphorous and alkaline phosphatase levels were increased significantly with boswellic acid as well as estrogen treated group as compared to OVX control group. In present study significant ($p<0.05$) increase in uterine weight in estrogen treated and boswellic acid treated group was observed as compared to OVX control groups. Following the administration of boswellic acid and estrogen it was observed that there was an significant ($p<0.05$) increase in length and the weight of femur when compared with disease control group. The histopathological results also confirmed the protective effect of boswellic acid**.** The present findings strongly suggest that boswellic acid possess the potent antiosteoporotic activity in OVX rats and substantiates the ethnic use in treatment of postmenopausal osteoporosis

P061: CoMFA, CoMSIA and Molecular Docking studies of Indomethacin derivatives

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Classical nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit both COX-1 and COX-2 to varying extents. Inhibition of COX-1 leads to side effects such as gastrointestinal ulceration and bleeding, renal damage, and platelet dysfunction etc. So selective COX-2 inhibitors are needed since COX-2 clearly associated with inflammation but not with the physiological synthesis of PGs. Selective inhibitors of COX-2 offered the possibility of inhibition of inflammatory PGs without affecting PGs generated by COX-1 in the stomach, kidney or platelet and thus GI side effects developed by classical NSAIDs can be avoided. Comparative molecular field analysis (CoMFA) and Comparative molecular similarity indices analysis (CoMSIA) was performed for 49 indomethacin analogues which includes aliphatic and arylalkyl amide derivatives of indomethacin in order to design selective COX-2 inhibitors using SYBYL-X-1.2 from Tripos Inc. St. Louis, MO, USA. The models were validated for their statistical significance by means of Partial least square (PLS) analysis. The studies produced models with good correlation coefficients and predictive ability were used to predict the activity of the designed compounds. Molecular docking study was also performed on Surflex-Dock of SYBYL-X-1.2 for designed compounds to analyze receptor-ligand interactions that confer the selectivity for COX-2. There are some strong hydrogen-bonding interactions observed between amino acid residues Arg120, Tyr355, His90, Ser530 and Leu352. Based on docking study as well as CoMFA and CoMSIA analysis indomethacin analogues were designed.

P062: Influence of estrous stage on electrocardiography, clinical pathology and ovarian weight of experimental beagle dogs.

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Estrous cycle is a repetitive phenomenon occurring during the reproductive life of a female dog. The duration of the canine estrous cycle is considerably longer than that of most other animals and is broadly grouped into follicular phase (proestrus and estrus), luteal phase (diestrus) and non-seasonal anestrus. Dogs in the same stage of cycle can be inadvertently assigned to one group during routine toxicity studies, leading to possible erroneous interpretation. The retrospective analysis was conducted by analyzing data from 86 female beagle dogs to correlate any possible effect of estrous stage on electrocardiography, clinical pathology and ovarian weight. Beagles in different stages of estrous cycle were confirmed histologically by evaluating

ovary, uterus and mammary glands. The incidence of different stages of estrous was 33.73% in diestrus, 26.51% in anestrus and proestrus, 4.82% in estrus and 8.43% were immature. No significant effect was noticed on heart rate, P-A, P-D, RR, QRS, QT and PR intervals. However, significant variation was observed in PQ interval in proestrus dogs (high) as compared to dogs in anestrus and proestrus. Significant variation was observed in differential leucocyte counts among different stages of estrous. Immature animals exhibited low triglycerides, HDL cholesterol, total protein, globulin which resulted in significant variation with dogs in anestrus and or diestrus and high serum inorganic phosphorous. Relative ovary weight was significantly higher in diestrus dogs. Considering these variations, interpretation of data from toxicity studies should be performed with due consideration given to stage of estrous in female dogs.

P063: Synthesis and BACE-1 inhibitory activity of Tetrahydrobenzo[b]pyrans

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One-pot synthesis of tetrahydrobenzo[b]pyrans was carried out by condensing aromatic aldehyde, malononitrile and 1,3-cyclohexanedione using ionic liquid 1-butyl, 3-methyl imidazolium chloride([bmIm]Cl) in hydro-alcohol media. The compounds were characterized by using IR, NMR (^{1}H & ^{13}C) mass data. The compounds were subjected to BACE1 inhibitory assay using Ð-secretase activity detection kit. Only six compounds, KVB-4, KVB-5, KVB-6, KVB-8, KVB-9, KVB-17 have shown significant IC_{50} values at micromolar level. Among these six active compounds, KVB-5 was a potential inhibitor with its IC_{50} value in nanomolar range. All the synthesized compounds were docked onto the active site of β-Secretase enzyme by using Glide module of Schrodinger suite-2012. The more active compounds were found to be KVB-9, KVB-4, KVB-7 and AKB-9, where their glide score went below -4.1 and came close to the glide score of standard inhibitor 4L7G was -5.88. The moderately active compounds were found to be KVB-15, AKB-18, AKB-19, KVB-5, AKB-11, KVB-16, AKB-14, AKB-17, AKB-16, AKB-4, AKB-5, AKB-4, AKB-2 and KVB-6, where their score fell in the range of -2.54 to -3.57. The remaining compounds were considered as low active compounds due to their higher Glide score (more than -2.0). In the moderately active compounds, namely KVB-15, AKB-18, AKB-19, KVB-5, AKB-11, KVB-16, AKB-14, AKB-17, AKB-4, AKB-5, AKB-4, AKB-2 and KVB-6, only one or two hydrogen bond formations were observed with water and there were no proper interactions with certain key amino acid residues. Low active compounds neither showed any hydrogen bonding with key amino acid residues nor occupied the crystal ligand active sites.

P064: Lowe Syndrome: cellular phenotypes and therapeutic opportunities

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Lowe Syndrome (LS) is a developmental disease characterized by congenital cataracts, mental retardation and renal dysfunction. Although this lethal disorder was first described almost 60 years ago and linked to deficiencies of the lipid phosphatase Ocrl1 in the early nineties, no LS-specific therapy is yet available. This unacceptable situation reflects the lack of knowledge of the mechanism(s) by which Ocrl1 deficiency causes the developmental abnormalities leading to LS.

We recently established that cells from LS patients display severe defects in cell spreading/migration and primary cilia (PC) assembly. Further emphasizing the relevance of these findings for the disease, we observed developmental abnormalities due to cell spreading/migration and PC defects in a zebrafish animal model of LS. In addition, our investigations indicate that the RhoGTPase biochemical pathways are affected in LS patient cells. We utilized the above mentioned phenotypes as a readout of the ability of different pharmacological agents to alleviate LS-specific phenotypes. Our results indicate that RhoGTPase-modulating agents are capable of significantly reverting LS-cell spreading defects, but was unable to suppress the PC phenotype. In a similar manner, we found that drugs able to counteract other ciliopathy phenotypes were competent to alleviate LS-cell PC-assembly defects, but ineffective at rescuing cell-spreading deficiencies. These results suggest that the cellular phenotypes seen in LS cells reflect two independent functions of Ocrl1 that may be better targeted by a combination therapy.

P065: Effect of oryzanol on Intraoccular glaucoma

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Gamma Oryzanol (OZ) is a component of rice bran oil, containing mixture of ferulic acid, esters of tri-terpene alcohol, reported for its free radical scavenging, anti-inflammatory, immunosuppressive, neuroprotective, anti-ulcer, and anti-cancer activity. The present study was undertaken to evaluate effect of OZ in acute and chronic models of glaucoma. New Zealand white rabbits (either sex) were used for study. Effect of OZ was evaluated in 5% dextrose induced acute model of occular hypertension in rabbit eye. Chronic model of glaucoma was induced with

subconjunctival injection of 5% of 0.3 ml phenol in almond oil in four different quadrants of the eye to produce scarring in the aqueous humor (AH) pathway. Treatment with OZ was given for next two weeks. AH was collected from anterior chamber of rabbit eye from all groups to assess various biochemical parameters. Histopathological evaluations were performed in rabbit eye. In acute model of occular hypertension OZ and FOR-X did not produce effect on the raised intra ocular pressure (IOP). In chronic model of glaucoma treatment with OZ exhibited significant decrease in IOP as compared to disease control eye. It showed significant decrease in levels of protein, MDA and NO in comparison to disease control group. SOD, GSH and CAT levels were significantly increased in the aqueous humor of eye after treatment with OZ. The changes were also observed in the levels of TNF and IL-6 levels. These reduction in oxidative stress resulted in reduced levels of inflammatory responses which subsequently resulted in reduced IOP.

P066: Compatibility of N-Methyl-2 Pyrrolidinone (NMP) as vehicle for in vitro genotoxicity testing

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Bacterial reverse mutation (Ames) assay and chromosome aberration assay are most widely used in vitro genotoxicity assessment tools in the drug development program. The goal for selection of highest test concentration for these both the assay is either to achieve precipitation in test medium or to achieve meaningful cytotoxicity. For water insoluble compounds organic solvents are permissible to use as vehicle for test item. As routinely being used, DMSO is first choice of organic solvent for poor water soluble compounds. Other solvents being used are dimethly formamide, tetrahydro furan, ethanol, dioxane, ethyl methyl ketone, acetone, acetonitrile and ethylene glycol. Some compounds are so poor soluble in DMSO and other organic solvents as at soluble concentration they neither form precipitate in final treatment medium nor show sign of toxicity to the test system. In such cases it is difficult to justify the rationale for highest test concentration. N-Methyl-2 Pyrrolidinone (NMP), a water miscible organic solvent, is least known to use as vehicle for in vitro genotoixicity testing. We have proved that up to certain concentrations, NMP is fully compatible with test systems being non-cytotoxic, non-clastognic and non-mutagenic in nature and does not compromise the effect of S9.

P067: Structural and functional characterization of Inosine-5′-Monophosphate Dehydrogenase (IMPDH): A novel therapeutic gateway for Helicobacter pylori infection

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Helicobacter pylori (H. pylori) colonizes in the gastric mucosa of more than 50% of the world's population with infection rates much higher (~80%) in developing countries. It is a major risk factor for peptic ulcer, stomach and upper small intestine ulcers, and is an important cause for gastric cancer and gastric mucosa-associated lymphoid tissue lymphoma. Due to increased resistance to the current antibiotic based triple and quadruple therapies, there is urgent need to identify new drug target to overcome the drug resistance in H.pylori infection therapy.

IMPDH catalyzes the first important step in the de novo biosynthesis of purine (guanine) nucleotide catalyzing oxidation of IMP to XMP, which is further converted into GMP-by-GMP synthase. Inhibition of IMPDH could stop expansion of the guanine nucleotide pool that is needed for the microbial proliferation. Here we present our initial efforts for making potent and selective inhibitors both in silico as well synthetic ones. Also the efforts towards structural studies of Hp IMPDH will also be discussed.

P068: Structural insight into plasmepsin V, an aspartic protesae from Plasmodium falciparum

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Plasmodium falciparum is a protozoan parasite, one of the species of Plasmodium that cause malaria in humans. The parasites survive inside the human red blood cells by exporting hundreds of proteins into the red blood cell to remodel it. The majority of exported proteins contain the Plasmodium export element (PEXEL; RxLxE/Q/D) in their N-terminus, which is proteolytically cleaved in the parasite endoplasmic reticulum by Plasmepsin V, and is necessary for export. As a consequence plasmepsin V could be a potential target for antimalarial drugs. Plasmepsin V contain two distinct domains and the protease active site patterns were recognized in both the domain. There is no three-dimensional structures reported for this protein. An approach to understand the molecular structure, a threading based homology modeling was performed on I-Tasser and the model was validated using protein structure checking tools PROCHECK and WHAT IF. Insilico analysis of the model plasmepsin V may provide an insight for experimentally derived crystal structures.

Reference:

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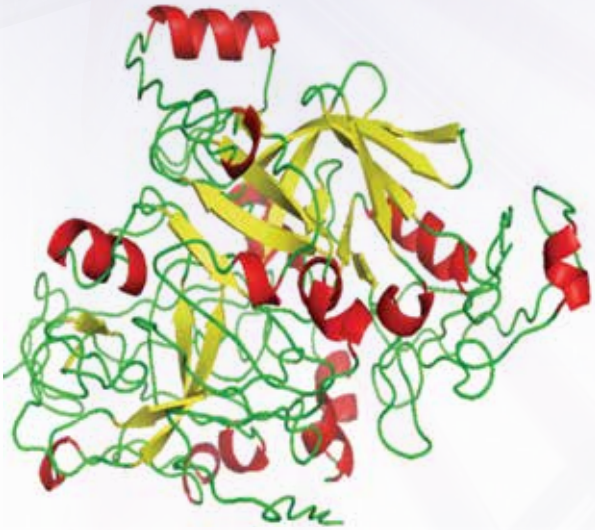
Figure: Modeled three dimensional strucutre of plasmepsin V



P069: Reproductive and Developmental Toxicity Studies Demonstrate that Hepatitis B (rDNA) Vaccine, is neither a Reproductive Toxicant nor a Teratogen

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Hepatitis B is a significant public health issue worldwide, and Cadila Healthcare (CHL) is working to make its chronic hepatitis B medicines accessible to patient population, as quickly as possible. Hepatitis B (rDNA) vaccine is produced by recombinant DNA technology and they are formulated with Alum hydroxide as final vaccine in liquid form. The nonclinical, reproductive and developmental toxicity studies (fertility and teratogenicity) were conducted to support the inclusion of women of child bearing potential (WOCBP) in the clinical trials via intramuscular administration. In fertility study Hepatitis B (rDNA) vaccine was administered in male (Day 1, 14 & 28) and female (Day 1 & 14) before mating. Treatment was continued in females from on gestation day 10 and on lactation day 7. In fertility study sperm analysis and male and female fertility indices were evaluated. In teratogenicity study vaccine was administered to female rats once prior to pregnancy and during pregnancy (on gestation day 10). The pregnant females were sacrificed about one day prior to expected date of parturition (on gestation day 20) to evaluate the uterine contents and the fetuses for external, visceral and skeletal abnormalities. No effects on mating and fertility in male or female rats or Caesarean sectioning and litter parameters of female rats were observed. Based on the results obtained from the reproductive and developmental toxicity studies in rat, Hepatitis B(rDNA) vaccine is not a reproductive toxicant or teratogenic agent, and serum antibody titer provide adequate immunogenicity and inclusion of WOCBP in clinical trials via intramuscular administration.

P070: Gamma Secretase Activating Protein as a potent drug target for Alzheimer's disease

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Alzheimer's disease (AD) is a neurodegenerative disorder, mainly caused due to misfolding of Aβ- peptide fragments, leading to progressive mental deterioration. Approximately 36 million people are suffering from Alzheimer's disease worldwide, out of which 5.2 million are Americans while 2.7 million people are Indians. According to the reports, Beta amyloid pathway leading to AD involves cleavage of amyloid precursor protein by β-secretase and then γ-secretase, giving rise to a 4 kD peptide fragment that aggregates to form β-amyloid plaques and causes AD. γ-secretase involved in cleavage of C-99 peptide fragment acts only in the presence of an activator protein known as gamma secretase activating protein or GSAP. GSAP in humans is encoded by the PION gene.

There are no macromolecular structures of GSAP reported till now. Our ultimate goal is to elucidate the crystal structure and design potent inhibitors against AD via X-Ray crystallography. Further, structural understanding of their molecular mechanism and function, will lead to possible breakthrough in the field of Alzheimer's disease.

P071: Effect of sylimarin on cardiac hypertrophy and its mechanism

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Aim: Study of effect of sylimarin on cardiac hypertrophy and determine its mechanism of action.

Materials and Methods: Cardiac hypertrophy was induced by partial abdominal aortic constriction (PAAC) in wistar rats. PAAC was induced by ligating abdominal aorta by 4-0 silk thread along with 7.0mm diameter blunt needle. Then needle was removed to leave aorta partially constricted for 9 weeks. Sylimarin was given in the dose of 50mg/kg/day and 100mg/kg/day orally for 9 weeks. At end of 9 weeks, we evaluated hypertrophic, hemodynamic and oxidative stress parameters, and mitochondrial DNA concentration. We also carried out docking studies and determined mRNA expression.

Results: PAAC produced significant cardiac hypertrophy as evident from increase in hypertrophic indices, cardiomyocyte diameter, LV wall thickness and collagen levels. Treatment with sylimarin prevented cardiac hypertrophy. PAAC also produced dyslipidemia, oxidative stress, hypertension, bradycardia, decreased rate of pressure development and decay, increased serum biomarkers and decreased mitochondrial DNA concentrations. Treatment with sylimarin controlled dyslipidemia, improved hemodynamic functions, prevented oxidative stress and increased mitochondrial DNA concentration. The mechanism of action was determined by docking and mRNA expression studies which revealed that sylimarin acts through MAP kinase p38.

Conclusions: Silymarin produces beneficial effects on cardiac hypertrophy as evident from reduction in hypertrophic indices, preserving of hemodynamics and increase in mitochondrial DNA concentration. These effects of silymarin are mediated through inhibition of MAPK p38.

P072: Protective Effect of Intravenously Administered Oleanolic Acid and Ursolic Acid against Cisplatin-Induced Nephrotoxicity in Rats

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Objective: The aim of the study was to investigate protective effect of intravenously administered oleanolic acid and ursolic acid in chemotherapeutic agent cisplatin induced nephrotoxicity in rats. Induction of nephrotoxicity was confirmed by rise in toxicity markers like creatinine, urea, blood urea nitrogen.

Method: Nephrotoxicity was induced in albino wistar rat with single intra-peritoneal injection of Cisplatin at dose of 5mg/kg i.p. oleanolic acid and ursolic acid at 0.5(low), 1.0(medium), and 1.5 (high) mg/kg dose given for 5 days following Cisplatin administration on first day single dose. In same model, nephroprotective effect of Amifostine alone was also evaluated as standard treatment. At termination of study, urine albumin excretion, urine output, serum creatinine/urea clearance and glomerular filtration rate were measured. The renal oxidative stress marker malondialdehyde, glutathione, levels and anti-oxidant enzymes and catalase were measured in kidney homogenate.

Result: In toxicant group urine creatinine, serum creatinine, blood urea nitrogen, urinary ALPase activity, urine albumin, protein and weight of rat kidneys were found to be increased and GFR decreased. Treatment with oleanolic acid and ursolic acid was found to restore the alterations induced by cisplatin also found to be effective.

Conclusion: Oleanolic acid and ursolic acid can be used in treatment of chemotherapeutic agent induced nephrotoxicity. As both acids are also having anticancer activity, it can be said that the further study can be carried out to evaluate nephroprotective activity of oleanolic acid and ursolic acid without altering anticancer activity.

P073: Study of *In-vitro* Immunomodulatory Activity of Certain Antipsychotic Agents

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The study aimed to examine the effect of some typical and atypical antipsychotic drugs on cellular and humoral immunity in the experiment animal models. The different generations of antipsychotic drugs were tested for sheep red blood cells (SRBCs) induced delayed type hypersensitivity (DTH) and antibody titer. Also these drugs were further tested for in vitro effect of human polymorph nuclear (PMN) cells on phagocytosis, chemotaxis and NBT dye reducing assay. Typical drugs like Chlorpromazine and Haloperidol show potent suppressive effect on humoral and cellular immunity as compared to atypical drugs Risperidone and Aripiprazole in animal models. The antipsychotic drugs also show significant inhibitory effect on nonspecific immune function like phagocytosis of *Candida albicans*, Chemotaxis, as well as Nitro blue tetrazolium (NBT) dye reduction by normal PMN cells. The result indicate that out of the four antipsychotic drugs we studied, Chlorpromazine and Haloperidol show the most potent immunosuppressive effect, while Risperidone and Aripiprazole produce a moderate effect both in vivo and in vitro. These findings suggest that the choice of antipsychotic drugs also depends on disturbance of immune system activity, in particular, those occurring in several forms of psychosis.

P074: A process of stable and highly pure Dasatinib amorphous (Antineoplastic)

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A process for the preparation of stable and highly pure antineoplastic drug Dasatinib in amorphous form. It is an oral multi- BCR/Abl and Src family tyrosine kinase inhibitor approved for first line use in patients with chronic myelogenous leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia. Process includes condensation of 2-Amino-N-(2-chloro-6-methylphenyl) thiazole-5-carboxamide with 4,6-dichloro-2-methyl pyrimidine in presence of sodium tertiary butoxide in tetrahydrofuran at ambient temperature provides the off white solid compound N-(2-chloro-6-methylphenyl)-2-[(6-chloro-2-methyl-4-pyrimidinyl) amino]-5-thiazole carboxamide in good yield (≥80 %) with good quality which meets with well-defined spectral criteria. This intermediate on further reaction with piperazines-2-ethanol and triethyl amine in stoichiometric amount in N-methyl pyrrolidone at ambient temperature provides the crude N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-Piperazinyl]-2-methyl-4-pyrimidinyl] amino]-5-thiazolecarboxamide in excellent yield (≥96 %). Purification of crude API by methanol and water provides us the highly pure white crystalline powder of Dasatinib in good yield (≥85 %) which is further milled as such and with premix to get a stable polymorphic form of Dasatinib as Amorphous having ≥99.9% purity by HPLC and is meeting with ICH guidelines. The beauty of Zydus's commerciable viable process for the synthesis of Dasatinib involves highly stable form, which is chemically stable upto six months and is suitable for global requirement.

P075: Effects of Hydroalcoholic Extract of *Cissus qudrangularis* (Family:Vitaceae) on Mercury Chloride Induced Nephrotoxicity in Rat.

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Objective: To evaluate the protective effect of hydroalcoholic extract of *Cissus quadrangularis* on mercuric chloride induced toxicity in rats.

Method: The animals were divided into 5 groups (n=6). Negative control group treated with normal saline, Diseased control group treated with mercuric chloride 5 mg/kg, i.p. Group 3 was treated with *Cissus quadrangularis* (CQE) (100 mg/kg, p.o) Group 4 was treated with mercuric chloride + CQE (200 mg/kg, p.o) Group 5 was treated with mercuric chloride + CQE (400 mg/kg, p.o). Animals were treated for 3 consecutive days. On the second day, animals were kept in metabolic cages for urine collection. Prior to urine collection blood samples were collected. On the third day, animals are sacrificed and bone marrow of each animal is collected, spleen thymus and kidney are isolated for biochemical estimation and histopathology.

Result: In Mercury chloride treated rats it was found that increased in body weight, urine creatinine, serum creatinine, blood urea, serum alkaline phosphatase and weight of kidneys where it was normalized by the hydroalcoholic extract of *Cissus quadrangularis*. Diseased control rats showed decrease in the urine volume, total protein, biochemical parameters and endogenous antioxidant level while treatment with *Cissus quadrangularis* normalized the level of total protein and endogenous antioxidant levels.

Conclusion: It can be concluded that *Cissus quadrangularis* showed nephroprotective activity due to its potent antioxidant mechanism.

P076: Pharmacological Screening of Saponin Fractions of Roots of *Eranthemum roseum* in a mouse models.

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The Steroidal Saponin rich fraction of *Eranthemum roseum* (SFER) was evaluated Neuropharmacological activity including Behavioural test batteries by Irwin method, Central analgesic, muscle coordination and hypnotic activity in mouse model. Experimented data observed for SFER 60mg/kg and 120mg/kg significantly ($P<0.05$) ($P<0.01$) alter the behavioral observation. Statistically significant reduction was observed in awareness, myorelaxant, Motor Activity, Locomotor activity, Hypnotic, gait, defecations. From the findings we can conclude that Saponin fraction of *Eranthemum roseum* presented depressant, analgesics and potentiate sleeping time.

P077: Protective effect of Agomelatine, a novel antidepressant against traumatic brain injury

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Traumatic brain injury represents the leading cause of morbidity and mortality in individuals under the age of 45 year in the world. Significant success has been achieved in improving short-term outcomes in severe traumatic brain injury victims; however, the functional recovery has been remained as limitation after severe traumatic brain injury. Agomelatine is a novel antidepressant. Agomelatine has synergistic action on melatonin MT_1 and MT_2 receptor agonist and serotonin $5HT_{2C}$ receptor antagonist. Aim of this study is to evaluate the protective effects of agomelatine against traumatic brain injury. Traumatic brain injury was induced by craniotomy in Sprague Dawley rats using dental drill with 0.8 mm diameter bur by creating 5 mm diameter cranium flap. Flap was removed and brain was exposed for 4 mins to normal environment, then bone flap was replaced with bone wax and incision site was sutured. 4 groups of animals were taken: Normal, Craniotomy, Craniotomy with 1 & 3 mg/kg Agomelatine (*p.o.*). Agomelatine was given after the surgery had been performed. As compared to normal, craniotomy animals showed alteration in oxidative stress and antioxidant levels. Craniotomy animals had reduced performance in behavioral tests (Beam walking test and Pole test). Histological assessment was done using Nissl staining. Agomelatine at the dose of 3 mg/kg decreased the oxidative stress and increased antioxidant parameters. Agomelatine improved the performance in behavioral parameters. Histopathological studies showed improvement with agomelatine. Thus, agomelatine may be effective in decreasing the brain damage in the traumatic brain injury.

P078: neuroprotective effect of ethyl pyruvate and andrographolide against neurotoxicity induced by aluminium chloride on primary neuro-glial mixed culture

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Neurodegeneration is the progressive loss of structure and function of neurons, including death of neurons which leads to several diseases. Aluminum chloride ($AlCl_3$) is a neurotoxic compound which causes neurodegeneration. Toll like receptor 4 (TLR4) is important in the activation of innate immunity and evidence supports that TLR4 play an important role in neuroinflammation and neurodegenaration by activation of microglial cells. The aim of present study is to evaluate the neuroprotective effects of ethyl pyruvate and Andrographolide which have TLR4 inhibitory properties against neurotoxicity induced by $AlCl_3$ on primary neuron-glial mixed culture. Primary neuro-glial mixed culture was prepared from 16-18 days old female pregnant mice fetuses. Animal was euthanized in CO_2 chamber and fetuses were removed from the uterine horns and placed them in petridish with ice cold Hank's balanced salt solution (HBSS). Brain cortices were isolated and dissociated with 1% trypsin solution. After 20 min, cells were suspended in DMEM containing 20% FBS. Dissociated cells were plated on Poly-L-lysine coated 24 well plates. After 10 days, cells were pretreated with different doses of ethyl pyruvate (10mM, 20mM, 30mM, 40mM) and Andrographolide (2.5µM, 5µM, 7.5µM, 10µM) and incubated for 2 days and then cells were treated with $AlCl_3$(1mM) and incubated for 48 hours. The cytotoxicity of $AlCl_3$ was evaluated by MTT assay. The % cell viability was significantly decreased in $AlCl_3$ treated cells when compared with cells which were pretreated with vehicle, ethyl pyruvate (20mM) and Andrographolide (10µM). Thus, ethyl pyruvate and Andrographolide showed neuroprotection against neurotoxicity induced by $AlCl_3$.

P079: Pentacyclic triterpenoids are the potent translocators of NrF2 transcriptional factor: A software assisted drug development study

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Objective: To study the computer assisted docking, toxicity and ADME parameters for pentacyclic triterpenoids for the translocation of nuclear factor erythroid-derived like 2 (NrF2)

Methods: Software based drug discovery is milestone for the hunting of multitargeted agents. Prior to start with actual docking the toxicity and the ADME are the important parameters which provide more valuation to the computational study. The Schrodinger with Quick-pro ADME prediction and the Discovery studio-3 with TOPKAT toxicity predictor were used. Multifunctional small molecules, pentacyclic triterpenoids (PT) are now emerging as the new era of naturally occurring medicine to treat the inflammation and cancer. Pt contain 30-carbon skeleton are secondary plant metabolites widely available in mediterranean plant at 0.1-3%. We had prepared structural library of more than 78 naturally occurring PT's. The authentic structures then screen from the Quick-pro and TOPKAT predictors. However, the parameter like LD_{50} in rat, carcinogenicity, mutagenecity and oral bioavailability in human are mainly analyzed. Afterward, the molecular target NrF2 to which the structural library with high throughput screening was performed.

Results: Glycyrrhizin, asiatic acid, ursolic acid and whithaferin-A was found to be good docking score to translocate the NrF2 along with better bioavailability, non-mutagenic, non-carcinogenic and less toxic as shows high LD_{50} value.

P080: Insights into host nuclear receptor TR4 - *M. tuberculosis* interactions and exploration of novel ligands for TR4: A step towards drug discovery

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Testicular Receptor 4 (TR4) belongs to nuclear receptor super family and has been shown to play an important role in brain development, metabolism, cancer and infection. It has been categorised as orphan because its true endogenous ligand has not yet been discovered. Pro-Mycobacterial role of TR4 has been reported recently by our group. As TR4 functions as fatty acid sensor, *M. tuberculosis* H37*Rv* cell wall lipid repertoire components were evaluated for their ability to transactivate Gal4-TR4. Only total lipids and total-mycolic acid were found to cause significant transactivation. In the total-MA pool, α-MA, methoxy-MA did not, while keto-MA showed quite significant activation of the luciferase reporter. This suggests the role of keto-MA as a heterologous ligand of TR4. However, our docking studies with keto-MA showed a high positive score of docking, where as its canonical ligand linoleic acid showed a good negative score, which indicates that, keto-MA may not be a canonical ligand for TR4. ITC, CD and dose dependent transactivation experiments showed ligand like properties of keto-MA. Further characterization of keto-MA binding site and designing small molecule inhibitors against the site may give new insights into drug development against *M. tuberculosis*. Apart from this, we have also identified synthetic ligands for TR4 by *in silico* docking studies and validated them by *in vitro* assays.

P081: Anemia is a risk factor for maternal-prenatal complications & pregnancy outcomes in pregnant women.

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Anemia is a global public health problem affecting both developing and developed countries with major consequences for human health as well as social and economic development. Anemia is most frequently observed nutritional disease in the world. Prevalence of anemia is higher among pregnant women in India, anemia is second common cause of maternal deaths.

The objective the study was to determine, the prevalence of anemia during pregnancy. We compare the maternal and prenatal complication and pregnancy outcomes between anemic and non anemic patients In this study we found that rate of complications was increase as the severity of anemia is increase we found the significant relationship between maternal and prenatal complications It was concluded from the study the prevalence of anemia among pregnant women in the rural area is relatively high.

P082: Evaluation of CNS activities of purified *Curcuma longa* in mice and rats.

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Background and objective: To observe and evaluate various central nervous activities like antinociceptive, anticonvulsant, motor in-coordination, hypnotic and anxiolytic effects of purified Curcuma longa in mice and rats.

Materials and methods: It was a quantitative experimental study done in the laboratory setting of the department of Clinical Pharmacology and Therapeutics, BPKIHS. For each test, respective animal models were used. Animals were divided into five groups of six each, group I as control, group II as standard control whereas groups I, II and III as test groups (three doses) .Control and the three test drug doses were given for 21 days. Data were presented as mean ± Standard Error of Mean. Statistical differences between the test drug and control groups as well as within the test drug groups were calculated using Mann-Whitney U test. A probability level less than 0.05 was considered significant.

Results: Significant effects were observed in antinociceptive, anxiolytic, motor co-ordination and antihypnotic-antisedative models. No significant effect as compared to control was observed in test of memory and learning.

Conclusion: This study showed that aqueous extract of purified Curcuma longa (CL) possesses antinociceptive, anxiolytic, motor- coordination improving and antihypnotic-antisedative effects. The mechanism(s) and active principle(s) behind the effects of CL could not be established.

P083: Newer technique for examination of soft tissue morphology (head razor sectioning) in rat fetus

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Despite the variety of modern molecular techniques available, examination of fetal anatomy is still a fundamental

part of teratology studies in the evaluating the developmental toxicity of xenobiotic or other non-chemical factors. This poster presents contemporary methods of embryo toxicity and foetotoxicity assessment. Soft tissue examination can be performed as a gross dissection of unfixed fetus or after bouin's fixation using the Wilson free hand head razor cross sectioning technique, performed under magnification or stereozoom microscope. As per recommended protocols 50% of the litter of rats and mice are evaluated for soft tissue alterations (malformations or variations) using Wilson's technique while 100% of rabbit fetuses are evaluated for visceral examination of which 50% are assigned for head razor examination. Due to manual artifacts in soft tissues while examination with aceto-alcohol formalin/ Davidson`s fixative and prohibited use of picric acid in bouin`s fluid alternate method for head-razor sectioning was essential. Out of liquid nitrogen and dry ice frozen heads, sectioning with dry ice frozen head is reliable method. This method can be used in conventional teratogenicity studies for head razor sectioning for visceral examination. Improving this is the only guarantee of reducing the risk of a tragedy similar to that of thalidomide.

P084: Novel synthesis of benzimidazole - thiosemicarbazones hybrid derivatives, biological screening, QSAR study and docking study.

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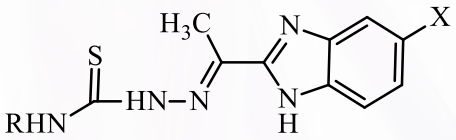
Synthesis of benzimidazole - thiosemicarbazones hybrid derivatives by green chemistry routes. The structures of synthesised compounds were conformed by analytical methods. The compounds were also screened for antimalarial as well as anticancer activity. Also we done the QSAR and docking study of the new compounds.



Where, R = various subsituents

X = Cl, H

P085: Microwave Assisted Synthesis Spectral and Biological Properties of GD (III) Complexes with Quinoline Derivatives

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The importance and versatility of derivatives of quinolines is well established in many forms of drugs, potential use of lanthanide complexes as diagnostic molecule have also been reported in literature but studies on biological aspects of complexes of lanthanides related with bioactive species are lesser.

The constructions and characterizations of lanthanide complexes are currently of great interest because of their unique physico-chemical properties and various applications in medical field. The present work describes the synthesis, spectral and biological investigations on the complexes of quinoline derivatives with Gd (III) ions. A method for the synthesis of complexes has been developed by the use of microwave irradiation which is in agreement to Green chemistry approach. All complexes have been characterized by various physico-chemical techniques. The magnetic moment of Gd (III) complexes showed slightly higher-values which originated due to low J-J separation leading to thermal population of next higher energy J levels and susceptibility due to first order Zeeman effect. Various energy and intensity parameters such as Racah (E^K), Slater-Condon (F_K), Lande' (z_{4f}), Oscillator strength (P) and Judd-Ofelt parameter (T_l) etc. have been computed using partial and multiple regression methods. The strong luminescence emitting peaks for Gd(III) can be observed, which could be attributed to the ligand have an enhanced effect to the luminescence intensity of Gd(III). A new peak has been observed in this work being reported first time. Antimicrobial activities of compounds were also carried out against bacteria, fungi and yeast and minimal inhibitory concentration (MIC) have also been also determined.

P086: Identification of novel phenyl butenonyl C-glycosides with ureidyl and sulfonamidyl moieties as antimalarial agents

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Malaria, the most severe parasitic disease, infects more than 500 million people and continues to kill around one million children each year. Most of the malarial infections and deaths are due to Plasmodium falciparum and Plasmodium vivax species. The recent emergence of resistance necessitates the search for new antimalarial drugs which overcome the resistance and acting through novel mechanisms. Very recently a class of hemoglobin degradation enzymes, plasmepsins has been discovered as a validated drug target and diphenyl ureas are known to inhibit this enzyme and display antimalarial activity.[1] Diphenyl propenones (chalcones) also exhibit antimalrial activity and malaria trophozoite cysteine protease has been proposed as possible target for this class of compound.[2] Inspired by the above facts we thought to design and synthesize compounds based on sugars having C-linked phenyl propenone moiety and diphenyl urea units together to get hitherto unreported antimalarial agents (Scheme 1).[3] In order to further analyze the feature requirement of these molecules in 3D space, we analyzed the common features through HipHop algorithm.

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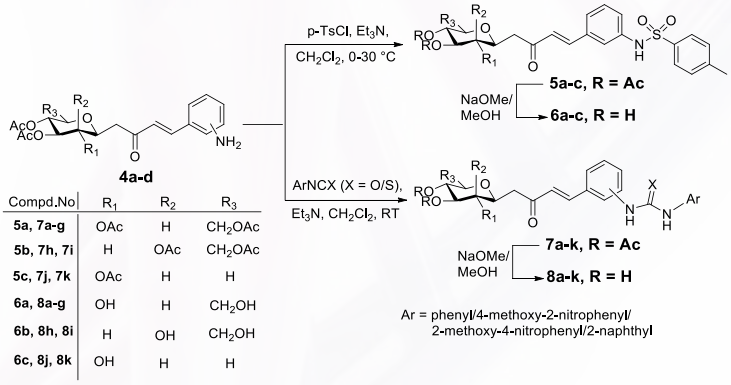

Compd.No	R_1	R_2	R_3
5a, 7a-g	OAc	H	CH_2OAc
5b, 7h, 7i	H	OAc	CH_2OAc
5c, 7j, 7k	OAc	H	H
6a, 8a-g	OH	H	CH_2OH
6b, 8h, 8i	H	OH	CH_2OH
6c, 8j, 8k	OH	H	H

Scheme 1: Synthesis of the N-sulfonylaminophenyl, ureido and thioureido glycopyranosides

P087: Development & Validation of the Surface Plasmon Resonance based Kinetic Assay for the Characterization of Biosimilar Molecule.

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Surface Plasmon Resonance (SPR) is a label free biosensor-based technology that has been widely used to study biomolecular interactions in real time, with high degree of sensitivity. It has been considered as a gold standard for the characterization of biosimilar molecule. By providing high-quality kinetic data and the unique ability to detect low-affinity between interacting partners, SPR technology can be used throughout the entire biosimilar drug development process from early screening of cell clones to clinical immunogenicity studies, as well as final product release testing.

Here, in this study we have developed and validated a SPR based method using innovator's drug (analyte) to evaluate its kinetic interactions with specific cell surface receptor (ligand). This method was used to access the biosimilarity between ZRC-3025 and innovator's drug in terms of binding kinetics. Since there are no clearly defined validation requirements for SPR-based binding/kinetic assay, the validation strategy was prepared based on guidelines stipulated by the International Conference on Harmonization for Analytical Method Validation to assess specificity, precision, linearity and robustness which included sample stability, variation between flow path as well as chips and immobilization level variation. Some degree of adaptation of these definitions was necessary in designing the validation protocol. For each kinetic run of validation, the ligand (recombinant receptor fused with Fc region of human IgG1), was captured freshly on protein A-immobilized surface and replicate concentrations of analyte were injected over it to acquire association-dissociation rates and equilibrium dissociation constant using 1:1 binding model for curve fitting.

P088: Identification of 1-[(4-Benzyloxyphenyl)-but-3-enyl]-1*H*-azoles as New Class of Antitubercular and Antimicrobial Agents

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Among chronic infectious diseases, tuberculosis (TB) a highly contagious, air-borne disease caused by Mycobacterium tuberculosis is a leading killer in the world and currently it represents the most threatening health problem globally. A series of 1-[(4-benzyloxyphenyl)-but-3-enyl]-1*H*-azoles has been identified as potent antitubercular agents against *Mycobacterium tuberculosis*. Synthesis of compounds involved acid catalyzed ring opening of cyclopropyl ring of phenyl cyclopropyl methanols followed by nucleophilic attack of the azoles on the carbocation intermediates. Several of the compounds, three are exhibited significant antitubercular activities with MIC value as low as 1.56 µg/mL, 1.56 µg/mL and 0.61 µg/mL respectively, comparable to many standard drugs. These compounds were also screened against other strains of bacteria and fungi and few of them showed good antifungal activity against *A. fumigatus,* responsible for lung infection. It has been shown that these compounds most likely target the CYP121 enzyme. These compounds have good *in-vitro* activity and ongoing studies are focused on improving the efficacy through further analogue generation.

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P089: Systemic administration of S1P improves adaptive responses in rats exposed to acute duration of hypobaric hypoxia.

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WHO estimates more than 35 million people travelling to high altitude (HA) for recreational/military activities annually, and being exposed to hypobaric hypoxia (HH, low ambient partial pressure leading to compromised oxygen bioavailability). Rapid ascent to HA can lead to fatal disorders such as acute mountain sickness, tissue edema, multiple organ dysfunction syndrome etc. Gradual ascent, practiced mainly by military personnel though confers the inherent adaptive responses to set in (acclimatization), is time-consuming. This study proposes a pharmacological intervention – sphingosine-1-phosphate (S1P) as an acclimatization/pre-conditioning agent, which shall trigger the adaptive mechanisms to set in before the actual hypoxia exposure, and conferring a "prepared phenotype" to the subject. S1P is a biological lipid, with physiological and pathological signaling functions emerging to overlap with hypoxia adaptive responses. In the present study, male SD rats were pre-treated systemically with S1P, and exposed to HH for 6 hours (acute exposure) at an altitude of 25,000 ft, along with suitable control animals. Post-exposure analysis of the S1P pre-conditioned animals indicated improved oxygen availability ($vSpO_2$ = 78 ± 1.41%) w.r.t. untreated hypoxia control animals ($vSpO_2$ = 55.67 ± 7.76%). This improved oxygen availability was an outcome of raised blood oxygen carrying capacity indicated by increased haemoglobin, haematocrit and RBC number. Raised oxygen carrying capacity could be attributed to increased haemoconcentration *via* renal S1P receptor 1 and raised Epo production (and erythropoieis) due to increased stabilization of Hypoxia Inducible Factor 1a (master transcriptional regulator of hypoxia adaptive response). S1P pre-conditioning also conferred protection from hypoxia induced oxidative stress and inflammation. Summarily, S1P pre-conditioning is a potent pharmacological strategy warranting further pre-clinical and clinical investigations in the field of HA medicine.

P090: Hypoxia activates Mitogen Activated protein Kinase (MAPK) signalling cascade in lung epithelial cells to opt between life and death.

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Hypoxic stress causes several cellular and molecular changes in cells which can modulate the gene expression to kick off stress responses or stress adaptive responses. The aim of this study was to explore the hypoxia mediated responses in A549 cells. To investigate this, lung epithelial (A549) cells were exposed to 0.5% O_2 at 37 °C in hypoxia incubator for 24 hours and ROS, Nitric Oxide (NO), intracellular calcium level, cell cycle analysis, P27 level, Extracellular-signal-Regulated Kinase (ERK), AKT and Tumor Growth Factor β (TGFβ) levels were evaluated. Our results showed that, hypoxia exposure led to increased intracellular calcium levels and ROS

production whereas, decreased NO level. The increase in ROS and calcium levels may act as a signalling molecule to activate MAPK signalling pathway which may further activate redox sensitive transcription factors such as AP-1 and NFκB, playing significant role in cell proliferation, cell differentiation and apoptosis. Phosphorylated ERK, a member of Mitogen Activated Protein Kinase was increased in hypoxia (0.5% O_2) exposed A549 cells for 24 hours. In addition, Flow cytometry results for cell cycle analysis in hypoxia exposed cells showed that maximum cells were arrested in Go-G1 phase of cell cycle, which was confirmed by the increased expression of P27 protein, a cyclin dependent kinases inhibitor. At the same time the major protein AKT and TGFβ playing important role in cell survival, were also decreased. The decreased NO levels might be responsible for decreased level of AKT protein, as NO acts as a signalling molecule to activate AKT signalling pathway. In conclusion, hypoxia stress activates the MAPK pathway through ROS generation which inhibits cell proliferation in A549 cells by suppressing the AKT and TGFβ levels.

P091: Novel role of exogenous Sphingosine 1-Phosphate in repair and regeneration of hypoxia induced skeletal muscle damage: an exploratory study in hypoxia exposed C2C12 cells

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Hypobaric hypoxia is an environmental stressor to which increasing population is getting exposed upon visit to high altitude for occupational, recreational and pilgrimage reasons. The low ambient oxygen bioavailability is known to compromise physical performance, which is further a function of optimal skeletal muscle physiology. Hypoxia is known to restrict the myofiber area and decrease muscle mass along with interfering with energy metabolism and generation of reactive oxygen species. All these factors negatively affect the proliferation and differentiation of satellite cell, key players of repair and regeneration of myofibrils under hypoxia. Murine C2C12 cell line is a widely accepted *in vitro* model for studying satellite cell proliferation and differentiation.

Sphingosine-1-phosphate (S1P), is a biological lipid with pleiotropic signaling functions in cell survival, proliferation, motility and differentiation. In our previous studies we have shown exogenous S1P supplementation improves survival and physiological health of murine splenocytes during hypoxia exposure. In the present study, we aimed to study the effect of exogenous S1P treatment (1μM) in promoting myogenesis and energy metabolism in C2C12 cells following exposure to 0.5% oxygen up to 8 days. The study included evaluation of glucose uptake, anaerobic respiration and creatine kinase activity along with microscopic analysis of myogenesis at day 0, 2, 4, 6 and 8. It was observed that, hypoxia exposure delayed differentiation and myogenesis, however S1P pretreatment could restore myogenesis despite chronic hypoxia exposure. Interestingly, S1P boosted myogenesis in normoxic cells too as evident by longer myotubes in these cells compared with control cells. These effects were accompanied with S1P mediated efficient glucose uptake and utilization by C2C12 cells, potentially by boosting pasteur's effect as hinted by intracellular and secreted lactate levels as well as LDH and creatine kinase activities. The study is one of the pioneers to propose S1P as a novel pharmacological agent, worth further exploration, for boosting repair and regeneration skeletal muscle under hypoxia.

P092: Three-Dimensional Quantitative Structure-Activity Relationships Studies on a Series of N-[(2S,3R)-4-(-N-isobutyl-N-tosylamino)-3-hydroxy-1-phenylbutan-2-yl] amide as HIV-1 Protease Inhibitors.

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Ligand based drug design approach provides a advantage over methods performed individually. Present work represent a good assembly of ligand based pharmacophore generation concept. Ligand-oriented study was accomplished by employing the HypoGen module of Catalyst in which we have translated the experimental findings into 3-D pharmacophore models by identifying key features (four point pharmacophore) necessary for interaction of the inhibitors with the active site of HIV-1 protease enzyme using a training set of 20 compounds belonging to the of N-[(2S,3R)-4-(-N-isobutyl-N-tosylamino)-3-hydroxy-1-phenylbutan-2-yl] amide. The most predictive pharmacophore model (hypothesis 1), consisting of hydrogen bond donars, two hydrophobic and ring aromatic four features, shown a correlation (r) of 0.944 and a root mean square of 0.921 and cost difference of 60.33 bits between nullcost and fixed cost. The model was validated using CatScramble technique, internal test set prediction and external validation by comparision with marketed drugs naming Amprenavir and Ritonavir. This work has taken a significant step towards the full integration of ligand based drug design methodologies as pharmacophoric features retrieved from ligand-based study hence proving the accuracy of the developed models.

P093: Phytochemical analysis and Antioxidant Potential of water extracts of different parts of *Moringa oleifera*

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During last two decades, there is increasing interest in the field of free radical biology. Excessive generation of free radicals play damage cell structures including lipid membranes, proteins and nucleic acid. This leads to several degenerative disorders such as coronary heart disease, cancer and neurodegenerative diseases in human being. Recently much attention has been focused on plants due to their excellent potential to fight against the free radicals. Thus, keeping this thing in mind, a study was planned to evaluate the antioxidant potential various parts of *Moringa oleifera* of family Moringaceae, commonly known as "Drumstic". For this purpose, aqueous extracts of test plant were subjected to determination of antioxidant potential through total antioxidant activity (TAA), DPPH (1,1-diphenyl-2-picryl hydrazyl) radical scavenging test, hydroxyl radical scavenging test and ferric ion reducing antioxidant power (FRAP) test. High amount of phenolic and flavonoid were estimated in all extracts. The study depicts that antioxidant potential of test plants increased in dose dependent manner. Upon phytochemical analysis, high amount of phenolic and flavonoid were detected in all the extracts, indicating their role in providing antioxidant activity of the plant. It was thus clear from the study that *Moringa oleifera* possess good antioxidant potential and could be utilized by pharmaceutical companies.

P094: Evaluation of Hepatotoxicity Predictive Potential of HepG2 and Primary Hepatocyte Cell Systems Utilizing Surrogate Markers for Screening of New Chemical Entity

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Recognition of drug-induced hepatotoxic potential early in the drug development cascade creates opportunities for ranking and prioritizing, or developing alternatives with lower toxicity. The present study evaluated the ability to investigate the comparative hepatotoxicity-predictive potential of HepG2 cells and Primary Hepatocyte cell models for screening of NCEs and establishing the significance and applicability of surrogate markers in vitro which could play a key role in the detection of toxicity and the classification of compounds based on patterns of cellular injury.

Compounds with known hepatotoxicities were tested to validate the capabilities of this invitro system in identifying toxicities based on estimation of various surrogate toxicity endpoints. HepG2 cell line was obtained from ATCC and passaged in-house until the experiment. Male Wistar rat weighing 300 g was used for isolation of primary hepatocytes. The animal was anesthetized by intraperitoneal administration of a cocktail of ketamine and xylazine, followed by cannulation of hepatic portal vein and liver perfusion using HEPES buffer system. The liver was then digested with collagenase in situ and surgically excised to obtain primary hepatocytes. The cells were maintained in RPMI 1640 until the experiment. The cells were treated with vehicle/Acetaminophen/Aspirin/Cyclophosphamide/ Diclofenac.

The results were indicative of better reliability on primary rat hepatocytes model for predicting hepatotoxicity during lead optimization or candidate selection. Further assessment of multiparametric endpoints of xenobiotic toxicity using selected model is underway.

P095: Antioxidant Potential of wild *Prunus armeniaca:* An Underutilized Tree from Western Himalayas

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Prunus armeniaca L. (commonly chul; wild apricot) is an underutilized fruit tree growing wild in the dry temperate region of the Western Himalayas between 2000-3500 m. The fruit of the tree is sour, eaten raw, and alcoholic liquor is prepared from dried fruits used by the local tribal's. Traditionally, the different parts of the tree are used in treatment of various ailments by the people residing in these areas which include gynaecological disorders, skin hyper pigmentation, headache and rheumatic pain. The oil extracted from kernels is used for cooking and massage as it relieves arthritis pain. However, little study has been undertaken to validate/investigate its usefulness. The antioxidant properties of water extracts and oil of *P.armeniaca* were evaluated by determining radical scavenging activity. It was assessed in terms of scavenging of hydrogen peroxide, hydroxyl and DPPH radicals, FRAP activity and the content of phenolics and flavonoids. The leaf extract exhibited strongest activity against hydroxyl radical, hydrogen peroxide and FRAP; but, in case of the DPPH, the residue extract showed highest activity. The scavenging capacity of *P.armeniaca* oil was studied in the hydrogen peroxide, hydroxyl, DPPH and FRAP assay system had a good antioxidant power. The total phenolic and flavonoid content of different extracts of *P.armeniaca* varied from (5.9±0.11to 13.1±0.03 mg/g) and (16.6±0.06 to 62.6±0.12 mg/g). Further, the chemical composition of the oil was analyzed by GC-MS and it revealed that oleic acid (63.5%), linoleic acid (26.0%) and palmitic acid (5.09%) were its major constituents. The results suggest that *P.armeniaca* can be used as a source of natural antioxidant. 13.1±0.03 mg/g) and (16.6±0.06 to 62.6±0.12 mg/g). Further, the chemical composition of the oil was analyzed by GC-MS and it revealed that oleic acid (63.5%), linoleic acid (26.0%) and palmitic acid (5.09%) were its major constituents. The results suggest that *P.armeniaca* can be used as a source of natural antioxidant.

P096: Evaluation of Protective Effect of Phloroglucinol in an Experimental Model of Oxaliplatin Induced oxidative Stress in Neuro 2a Cells

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Oxaliplatin is primarily used in the treatment of colorectal cancer and occurrence of neurotoxicity up to 30% of patient is dose limiting for its successful usage. Involvement of oxidative stress and mitochondrial mediated apoptosis has been well established. In this study we have demonstrated the In vitro neuroprotective role of Phloroglucinol, a well-known antioxidant and mitochondrial protectant derived from the brown algae Ecklonia cava. Neuro 2a cell lines were exposed to the Oxaliplatin concentration of 25 µM and treated with Phloroglucinol at a dose of 25µM and 50µM to screen its antioxidant, antiapoptotic and mitochondrial protective activities. Treatment ameliorated the elevated malonaldehyde (MDA), nitrite levels and restored the glutathione content. Intracellular ROS levels were detected by DCFDA staining which were decreased significantly when compared to the levels in oxaliplatin insulted cells. Mitoprotective actions were revealed with the estimation of the levels mitochondrial superoxide by mitosox staining, mitochondrial redox activity by NADH assay and mitochondrial superoxide dismutase enzyme. In addition treatment also significantly increased the length of the neurites which was abolished by the oxaliplatin treatment. Further, western blotting confirmed the antiapoptotic activity Phloroglucinol by decreasing the levels of cleaved caspase-3 and p38 MAPK. These results suggest that Phloroglucinol possesses antioxidant, antiapoptotic and mitoprotective properties and further studies are warranted for studying its effect on preclinical models of oxaliplatin induced peripheral neuropathy.

P097: Rosmarinic acid attenuates oxidative stress and apoptosis In vitro and In vivo models of Oxaliplatin-evoked peripheral neuropathy

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Oxaliplatin a novel platinum based drug widely used for the treatment of several malignancies like colorectal, breast, lung ovarian cancers. Peripheral neuropathy which is one of the adverse effects associated with oxaliplain treatment many a time turn into dose limiting ADR. Nerve damage due to oxaliplatin treatment is well known to be an aftermath of oxidative stress and neuronal cell apoptosis. Therefore, in the current study we studied the in vitro and in vivo effect of Rosmarinic acid derived from the plant Rosmarinus officinalis. Neuro 2a cell lines were used as an in vitro model for Chemotherapy induced peripheral neuropathy (CIPN). Rosmarinic acid at 25µM and 50 µM were given as treatment to oxaliplatin insulted cells at a dose of 25 µM. D.ecreased levels of MDA, nitrite and restored levels of glutathione indicated its antioxidant property. Neuroprotection was revealed by neurite outgrowth. In addition, western blotting disclosed its antiapoptotic activity by decreasing the levels of Cleaved Caspase-3, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and p38 levels. Rosmarinic acid was administered at doses of 10 and 20 mg/kg for 4 weeks daily (i.p.) for Oxaliplatin (4 mg/kg twice weekly for 4 weeks, i.p.) treated animals. Protective effect was analyzed by subjecting rats to standard behavioral models of hyperalgesia and allodynia on alternate weeks. Rosmarinic acid treatment corrected the thermal, mechanical, chemically induced allodynia and hyperalgesia significantly by the end of the treatment. Electrophysiological examinations proved that treatment has restored control values of sciatic sensory nerve conduction velocity drastically reduced by oxaliplatin treatment. Elevations in the levels of oxidative-nitrosative stress markers were examined in both sciatic nerve and spinal cord. It significantly reduced the levels of elevated Malonaldehyde (MDA) and Nitrite and also improved the levels of antioxidant enzymes like glutathione and superoxide dismutase. Immunohistochemistry of rat sciatic nerve and spinal cord revealed the elevated expression levels of Cleaved Caspase-3, NF-κB, cyclooxygenase-2 (COX-2) and P^{38} in oxaliplatin treated rats and were attenuated by treatment. Collectively, these results suggest that rosmarinic acid can be one of the choices for managing CIPN. Further in-depth studies are required for establishing the molecular effects of the effects found in our study.

P098: Antibacterial Potency of Prosopis juliflora on Methicillin Resistant Staphylococcus aureus (MRSA)

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Objective: Antibacterial Potency of Prosopis juliflora was evaluated against nine isolates of Methicillin Resistant Staphylococcus aureus (MRSA) from cases of bovine mastitis.

Methods: Total nine Methicillin Resistant Staphylococcus aureus were isolated from milk collected from bovine suffering from mastitis and methicillin resistance were determined phenotypically with Kirby-Bauer disk diffusion

method and confirmed with detection of Mec A gene in each isolate. Water, methanol and chloroform extracts of Prosopis juliflora were prepared by using Soxhlet extraction and alkaloid rich fraction (ARF) was also isolated from crude extracts. Minimum inhibitory concentration of extracts and ARF was determined by Iodonitrotetrazolium chloride (INT) based microtiter dilution assay.

Results: Methanolic extract of Prosopis juliflora showed lowest minimum inhibitory concentration between 0.04-0.08 mg/mL against all isolates. Alkaloid rich fraction of Prosopis juliflora were found to be endowed with highest antimicrobial activity against all nine isolates with minimum inhibitory concentration of 0.04 mg/mL.

Conclusion: Alkaloid rich fraction of Prosopis juliflora could be potential reservoir of bioactive compounds. Post treatment analysis of proteome of test micro-organisms can explore potential anti-bacterial targets.

P099: Novel Class of Potent Cytotoxic Agents: Synthesis, Characterization, Molecular docking studies and in vitro Anti-proliferative Activity of Metallamacrocyclic Xanthate Complexes [M^{II}_2-μ^2-bis-{(κ^2S,S-$S_2COCH_2CH_2)_2N(R)$}]

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Pharmaceutical development is one of the prime concerns of current research in the battle against cancer wherein large-scale synthesis for lower cost of production of generic and proprietary products is a big challenge. The efforts in the evaluation of anticancer drugs have been shifted to non-platinum metal-based agents to avoid significant side effects and the emergence of drug resistance associated with platinum chemotherapeutics.1 Reports suggest on the use of binuclear transition metal complexes as bioinorganic replica, to investigate the mode of action of complex biological systems or to mimic metalloproteins featuring dinuclear active sites.2-3 Despite a great success of metallamacrocyclic complexes in supramolecular chemistry4-5, this structural class is surprisingly underexploited in medicinal chemistry, especially in anti-proliferative activity.

A facile one pot synthesis of metallamacrocyclic complexes [M^{II}2-μ^2-bis-{(κ^2S,S-$S_2COCH_2CH_2)_2N(R)$}] {R = Ts; M = Ni^{II} **1**, Zn^{II} **2**, R = Bz; M = Ni^{II} **3**, Zn^{II} **4**} containing tertiary amido groups in the backbone, will be presented. All the compounds are well characterized by standard spectroscopic methods, microanalysis, thermo-gravimetric study. Single crystal X-ray diffraction study has been performed to elucidate the molecular structure of some of the representative compounds. Most of the synthesized compounds appeared as potent cytotoxic agents against human HEP 3B and IMR 32 cancer cell lines.

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P100: Formulation, Optimization & Evaluation of Ethosomal gel of Maritime pine extract, USP

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The exposure of human skin to sun's UV radiation over a period of time causes chronic and acute effects. Skin generates oxygen and Nitrogen radical species which cause oxidative stress and damage to components of skin like collagen, Elastin and Glycosaminoglycans. Such damage to the skin creates undesired changes such as wrinkling and sagging. Many research studies suggest that Natural anti-oxidants such as Maritime pine extract (MPE) can effectively curtail this oxidative damage. Ethosomes (ET) as a novel drug delivery system would be of immense advance in carrying the MPE across the skin upon topical application.

This study aims to formulate and evaluate ethosomes containing MPE by using Ethanol (20-30%), Phospholipid (2-4%),Propylene glycol (10%), Cholesterol (0.25%) and Purified water. Ethosomal vesicles thus prepared were evaluated for vesicular size, Entrapment efficiency, in vitro release and Forced degradation. Scanning electron microscopic results uncovered that ethosomes were in spherical, unilamellar and micrometre size. The formulation ET/MPE showed highest entrapment efficiency of 74%. Then, optimized formulation of ethosomal vesicles was further formulated to gel by using Carbopol. The formulated gel was evaluated for drug content, viscosity, pH, Homogeneity, grittiness, skin irritation studies & in vitro diffusion studies. Stability studies for the gel was performed at 40°C for 75% RH. The drug content was found to be 92% & viscosity of gel was found to be 273.6 CP at 50 RPM. The gel was found to be homogenous & free from grittiness when

observed under microscope. The formulation was non irritating to the skin. It was found that, ET/MPE showed 56% of the drug release after 8 hrs. compared to gel containing free MPE.

Keywords: Ethosomes, Maritime Pine extract (MPE), Vescicular size, Entrapment efficiency, Scanning electron microscopy.

P101: Microemulsion based Gel of Eperisone Hydrochloride

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Eperisone hydrochloride is central muscle relaxant which is widely used for the treatment of plasticity to relieve muscle stiffness. Eperisone hydrochloride has been orally administered in the form of tablets. When administered orally, the drug absorbed by the intestines is being extensively decomposed through metabolism in the liver at a considerably high ratio before it exhibits a pharmacological effect at an affected part. Eperisone hydrochloride has bioavailability problems and the release in topical formulations was less than 30% in 7 hours. The microemulsion system seems to be a promising approach for targeting Eperisone hydrochloride through the skin. A large amount of drug can be incorporated in the formulation due to the high solubilising capacity that would increase thermodynamic activity towards the skin therefore developed a microemulsion based gel for Eperisone hydrochloride. The microemulsion system comprised of oil phase (5-20 %), lyophillic surfactant, a co-surfactant and water (40%) as aqueous phase was prepared. Oily phase with powerful permeation enhancing ability acted as the key role for the topical delivery of the drug from the microemulsion based gel system. Microemulsion have lower viscosity and are difficult to apply on skin so for the ease of application it was tried to be gelled. A microemulsion based gel containing 5% Eperisone hydrochloride with suitable viscosity for topical administration was formulated by using carbomer. Particle size of 246.4 nm and the zeta value of -16.8 indicated that the formulation was stable. Keywords: Microemulsion, Eperisone Hydrochloride, Microemulsion gelled system

P102: Engineered lipid-peptide nanoscale material for siRNA delivery

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The efficient cellular internalization of siRNA remains the most significant barrier to implement the widespread therapeutic application of siRNA. It has considerable potential to create a new class of therapeutics that can be harnessed to treat previously untreatable diseases. Exploiting the rich and diverse peptide conformational nowledge, we have designed improved lipid-peptide based siRNA delivery system with enhanced proteolytic stability and efficacy. Additionally, it can stabilize the siRNA-peptide complex and increase the siRNA payload. Our designed lipid-peptide based nanoscale siRNA delivery system can potentially offer substantial improvement in siRNA therapeutics.

P103: Protein phosphatase 3 links environmentally controlled mitochondrial fusion-fission dynamics with energy metabolism in flies and mice

Paul T. Pfluger[1], Dhiraj G. Kabra[1], Verónica Casquero García[1], Michaela Aichler[2], Sonja C. Schriever[1], Katrin Pfuhlmann[1], Maarit Lehti[3],Jon Weber[4], Maria Kutschke[1], Annette Feuchtinger[2], Axel Walch[2], Susanna M. Hofmann[1], Stephanie M. Rollmann[5], Timo D. Müller[1], Bruce J. Aronow[6], Jeff D. Molkentin[7], Diego Perez-Tilve[4], Martin Jastroch[1], Maria DeLuca[8] and Matthias H. Tschöp[1,9#]

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Canonical Protein Phosphatase 3 (Ppp3; calcineurin) signaling is central to numerous physiological processes and tissues. We here provide evidence that Ppp3 also plays a pivotal role in controlling systemic energy and body weight homeostasis. Piggy-bac transposon mediated knockdown of Ppp3 in flies led to a decrease in body weight, triglyceride content, glycogen content, and an increase in metabolic rates. In mice pharmacological inhibition of Ppp3 activity by injection of FK-506 decreased diet-induced obesity. Global deficiency of the catalytic subunit Ppp3cb as well as tissue-specific ablation of the regulatory subunit Ppp3r1 from skeletal muscle (Ppp3r1^{MlcCre} KO), but not adipose tissue or liver, led to protection from high-fat diet induced obesity and associated sequelæ. Mechanistically, we observed increased substrate oxidation kinetics in isolated mitochondria from muscle of Ppp3r1^{MlcCre} KO mice chronically exposed to high-fat diet, and hyperphosphorylation at the inhibitory serine 637 site of dynamin-related protein 1 (Drp1), a master regulator of mitochondrial fission. Transmission electron microscopy of skeletal muscle from HFD-fed Ppp3cb and Ppp3r1^{MlcCre} KO mice and indirect flight muscle of Ppp3 fly mutants confirmed the shift in mitochondrial dynamics towards fusion and the formation of elongated mitochondrial filaments. Enhanced

mitochondrial fusion and the formation of power-cable shaped filaments, but an overall decrease in exercise capacity, were observed in Ppp3cb and Ppp3r1^{MlcCre} KO mice after moderate treadmill exercise. Overall, our data suggest that Ppp3 acts as highly conserved pivot for the adaptive metabolic response to environmental changes such as high-fat diet feeding or exercise. The concomitant protection from obesity and its sequelae but impairment in exhaustive exercise capacity in Ppp3 mutant mice further highlights the importance of a physiologically intact mitochondrial network for muscle physiology and systemic body weight and energy homeostasis.

P104: Histone Deacetylase 5 Mediates Hypothalamic Leptin Action

Dhiraj G. Kabra[1], Ph.D., Veronica Casquero García[1*], M.Sc, Adam Fiseha Kebede[2*] M.Sc, Sonja C. Schriever[1], Ph.D., Cristina García-Cáceres[1,8], Ph.D., Esther Fuentew-Martin[1,8], PhD., Katrin Pfuhlmann[1], M.Sc., Chitrang Trivedi[3,6], Ph.D., Kristy Heppner[6], Ph.D., N. Henriette Uhlenhaut[1], Ph.D., Beata Legutko[1,8], Ph.D., Uma D. Kabra[1,8], M.Pharm., Dominik Lutter[1], Ph.D., Thomas Schwarzmayr[4,5], M.Sc., Yuanqing Gao[1,6], M.Sc, Chun-Xia Yi[1], M.D., Ph.D., Carmelo Quarta[1], Ph.D., Christoffer Clemmensen[1], Ph.D., Brian Finan[1], Ph.D., Timo D. Müller[1], Ph.D., Carola W. Meyer[1], Ph.D., Kerstin Stemmer[1], Ph.D., Tim M. Strom[4,5], M.D., Stephen C. Woods[6], Ph.D., Diego Perez-Tilve[6], Ph.D., Robert Schneider[2], Ph.D., Eric N. Olson[7], Ph.D., Matthias H. Tschöp[1,8#], M.D. and Paul T. Pfluger[1], Ph.D.

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Leptin-melanocortin (MC) signaling plays a key role in food intake and energy balance control and is often impaired in obese individuals, but exact molecular underpinnings for this dysregulation are incompletely understood. We here aimed to identify novel leptin-MC regulators, and revealed a clear association between leptin-MC signaling and hypothalamic histone deacetylase 5 (HDAC5) gene expression. Global HDAC5 KO mice displayed increased food intake and propensity for diet-induced obesity when chronically exposed to high fat diet. Pharmacological and genetic inhibition of HDAC5 activity in the mediobasal hypothalamus increased food intake and modulated pathways implicated in leptin-MC signaling such as POMC expression. Mechanistically, we identified direct interaction between Stat3 and HDAC5. Knockdown of HDAC5 led to increased Stat3 acetylation, but decreased Stat3 phosphorylation and diminished Stat3 binding to the POMC promoter. In consequence, leptin sensitivity was massively impaired in HDAC5 KD cells as well as in KO mice, compared to WT controls. Finally, hypothalamic overexpression of HDAC5 decreased food intake, attenuated HFD-induced leptin resistance, and ameliorated diet-induced obesity in mice. Overall, our data suggests that hypothalamic HDAC5 activity acts as essential regulator of leptin MC signaling to ultimately adapt food intake and body weight to changes in our environment.

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