The Ramanbhai Foundation 5th International Symposium
Current Trends in Pharmaceutical Sciences

"Advances in Translational Research & Medicine"

Feb 1-4, 2011
Zydus Research Centre, Ahmedabad, India

Scientific Abstracts

Advancing Translational Research

Zydus Research Centre
INNOVATION IN LIFE SCIENCE

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Advancing Translational Research

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 alleviating

human sufferings.

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Message from the Chief Patron

Dear Delegates,

It's a pleasure to welcome you all to the Ramanbhai Foundation 5th International Symposium.

A new decade has begun and it brings with it newer approaches and more promising ideas in research to predict, prevent, diagnose, and treat diseases. There is a need to look at newer ways to treat or prevent heart attacks, stroke, multiple sclerosis, cancer, diabetes and other diseases, including rare diseases and lessen the disease burden.

Whether its through a breakthrough, incremental or marginal innovation – the focus of pharmaceutical research will be on delivering solutions, that are safe, effective, provide meaningful health outcomes and have a positive impact on the quality of life.

The Ramanbhai Foundation 5th International Symposium, looks at one such new approach in research which is gaining importance the world over and that is : "Advances in Translational Research and Medicine".

Translational Medicine (TM) is an emerging field which focuses on using what is learned in pre-clinical studies and translating the findings in basic research more quickly and efficiently into medical practice and, thus creating meaningful health outcomes. Translational Research will help in understanding diseases, drug targets, therapeutic index in humans and enhance cost-effective decision-making in drug development.

The RBF symposium, over the past several years, has been looking at new trends in disease management. It's a journey that began in the year 2003 with an aim to create a knowledge sharing platform for exchanging thoughts amongst the scientists engaged in pharmaceutical research.

The Zydus Research Centre had first organized the international research symposium in 2003 on the theme 'Recent Trends in Pharmaceutical Sciences'. Since then, it has been held every two years. Scientists, academicians and experts from across the world converged once again in 2005 and then in 2007 to share their thoughts on the 'Role of Genomics and Proteomics' and 'Advances in Diabetes Therapy' respectively. In 2009, the theme was 'Advances in Cardiometabolic Research - Basic Science and Clinical Aspects' with a focus on research in the area of cardiovascular and metabolic diseases such as atherosclerosis, hypertension, dyslipidemia, thrombosis, heart failure, diabetes and obesity.

It's with your support and involvement, that we have been able to create a knowledge sharing platform through this biennial symposium. We hope to continue with this endeavour as we look at promising approaches in research through the coming decade.

With warm regards,

Pankaj R. Patel
Chief Patron

Advancing Translational Research

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 endeavours taking place across the world and create a platform for knowledge sharing, tracing the development of new molecules from the laboratory to the market.

Zydus Cadila

- 5th largest player in the domestic pharma market with a turnover of Rs. 3700 crores.
- A strong base in the regulated markets of U.S., Europe (France & Spain), Japan and high profile markets of Latin America, South Africa and 25 other emerging markets worldwide.
- Strong positions in key therapeutic segments - Cardiovasculars, Gastrointestinals, Women's Healthcare, Respiratory, Pain Management and Antiinfectives.
- 16 of our brands feature amongst the top 300 pharma brands in India (ORG IMS November 2010)
- Launched India's first indigenously developed H1N1 vaccine - VaxiFlu-S.
- A Partner of Choice for research-driven pharma majors like Nycomed, Abbott, Hospira, Bayer Schering Pharma, Madaus AG, Boehringer Ingelheim, to name a few.
- Declared the 'Emerging Company of the Year' by the Economic Times Awards for Corporate Excellence 2010.
- Received the 'Social and Corporate Governance Awards 2008' instituted by the BSE, NASSCOM Foundation and the Times Foundation, for the innovative and measurable impact of the group's CSR programme.
- Over 11,000 Zydans across the world unleashing value as an innovation research-driven global pharma company.

Zydus Research Centre (ZRC)

The Zydus Research Centre is the dedicated research arm of the Zydus Group. With its team of over 450 research professionals, ZRC spearheads the group's quest of creating healthier and happier communities globally. Spread over an area of over 4,87,000 sq ft, ZRC is working on cutting edge technologies in 14 different scientific disciplines.

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

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

Project	Target	Indication	Drug Discovery	Lead Optimisation	Pre-Clinical Development	IND	Phase I	Phase II	Phase III	NDA
ZYH1	PPAR alpha;gamma	Dyslipidemia								
ZYH2	PPAR alpha;gamma	Diabetes								
ZYH7	PPAR alpha	Dyslipidemia								
ZYI1	Multi-modal	Pain								
ZYO1	CB-1 antagonist	Obesity, Diabetes								
ZYT1	TR-beta agonist	Dyslipidemia								
ZYD1	GLP-1 agonist	Diabetes, Obesity								
ZYOG1	Oral GLP-1 agonist	Diabetes, Obesity								
Undisclosed	Oral GLP-1 agonist	Diabetes, Obesity								
ZYGK1	Glucokinase Activator	Diabetes								
Undisclosed	Oral PTH agonist	Osteoprosis								
Undisclosed	Undisclosed	Atherosclerotic Plaque								
Collaborative program	PEG-EPO	Anemia of Chronic Renal Failure	with Prolong Pharma							
Collaborative program	Selective GR agonist	Inflammation	with Karo Bio							
Collaborative program	Undisclosed	CVS	with Eli Lilly							
Collaborative program	Rabies MAb	Rabies	with World Health Organisation (WHO)							

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

Ramanbhai Foundation 5th International Symposium
"Advances in Translational Research and Medicines"

Program Schedule

Day 1: February 1, 2011

07.00-08.45 hr	Registration	
09.00 hr		Inauguration ceremony Keynote Address **A Nobel Prize by Chance!** Prof. (Dr.) Rolf Zinkernagel, Nobel Laureate (Medicine) Zurich, Switzerland
11.00 hr	**Tea/Coffee Break**	
	Session I **Chairpersons** **Dr. Kapil Dhingra** Retired Vice President, Head, Oncology Disease Biology Leadership Team, Roche **Dr. Y. K. Gupta** Professor & Head, Dept of Pharmacology, All India Institute of Medical Sciences, Delhi, India	
12.00 hr		**Therapeutic Science and Medicine: New Models for Academic--Industry Interactions** **Dr. William W. Chin, MD, PhD** Executive Dean for Research,Professor of Medicine,Harvard Medical School, Retired Senior Vice President, Discovery Research & Clinical Investigation, Eli Lilly, USA
12.45 hr		**State of Oncology Therapeutic Research : A look ahead** **Dr. Kapil Dhingra** Retired Vice President, Head, Oncology Disease Biology Leadership Team, Roche, USA KAPital Consuting LLC, USA.
13.10 hr	**Lunch Break / Poster Session**	
14.30 hr		**Synthetic Lethality in Cancer Treatment: Current status of PARP Inhibitors** **Dr. Hilary Calvert, MD** Director of Cancer Drug Discovery and Development, UCL Cancer Institute, London, UK
15.15 hr		**DNA repair dysfunctionality in lung cancer** **Dr. Jean-Charles Soria, MD** Institut Gustave Roussy, Head of the Early Therapeutics Innovations Service (SITEP), Villejuif, France
16.00 hr	**Tea/Coffee Break / Poster Session**	
16.30 hr		**Outliers, Invisible Gorillas, and Fellow Travelers-Understanding the Difference for Molecularly Targeted Drug Development** **Dr. Anthony W. Tolcher, MD** Director of START (South Texas Accelerated Research Therapeutics) and Clinical Professor of Medicine in the Division of Medical Oncology, University of Texas Health Science Center, San Antonio, USA

17.15 hr		**PI3 Kinase inhibitor for the treatment of cancer** **Dr. Pablo Cagnoni, MD** SVP Global Head, Clinical Development, Novartis Pharmaceuticals, Switzerland
18.00 hr		**Panel Discussion** • Dr. Kapil Dhingra • Dr. Rolf Zinkernagel • Dr. Willam W. Chin • Dr. Hilary Calvert • Dr. Jean-Charles Soria • Dr. Anthony W. Tolcher • Dr. Pablo Cagnoni

Day 2: February 2, 2011

	Session II **Chairperson** **Dr. Hilary Calvert, MD** Director, Cancer Drug Discovery and Development, UCL Cancer Institute, London, UK **Dr. S. D. Seth** Advisor, Indian Council of Medical Research, Delhi, India	
09.00 hr		**Harnessing the immune system to treat cancer – A reality at last** **Dr. Kapil Dhingra** Retired Vice President, Head, Oncology Disease Biology Leadership Team, Roche, USA KAPital Consuting LLC, USA.
09.45 hr		**Manipulating the Inhibitory Arm of the Immune System, a Needed Strategy for Cancer Therapy** **Dr. Samir N. Khleif, MD** Head, Cancer Vaccine Section, Investigator, National Cancer Institute Bethesda, USA
10.30 hr		**T cell-engaging BiTE antibodies for cancer therapy** **Dr. Patrick Baeuerle, PhD** Chief Scientific Officer, Micromet, USA.
11.15 hr	**Tea/Coffee Break / Poster Session**	
11.45 hr		**Oncology Clinical Research : India** **Prof. Vinod Raina, MD, FRCP.** Head Dept of Medical Oncology & Head Delhi Cancer Registry, Institute of Rotary Cancer Hospital, All India Institute of Medical Sciences (AIIMS)
12.30 hr		**Targeting Multiple Myeloma: Use of Translational Research to Inform a Development Path for the KSP inhibitor ARRY-520** **Dr. Duncan Walker, PhD** Senior Director, Translational Medicine, Array Biopharma, USA
13.15 hr	**Lunch Break / Poster Session**	
	Session III **Chairperson** **Dr. Pankaj Shah** Director, Gujarat Cancer Research Institute, Ahmedabad, India. **Dr. J. S. Yadav** Director, Indian Institute of Chemical Technology, Hyderabad, India.	
15.00 hr		**Estrogen receptor beta-selective compounds and their potential role in cancer therapy** **Dr. Anneli Hallgren** CSO, Karobio, Sweden

15.45 hr		**Cancer Metabolism: The Warburg Effect Revisited** **Dr. Rajesh Chopra MD, PhD** Vice President Translational Development, Celgene, USA
16.30 hr	**Tea/Coffee Break / Poster Session**	
17.00 hr		**From Fragment to clinic: Translational biomarkers for clinical candidates derived from fragment-based drug design.** **Dr. John Lyons, MSc PhD,** VP Translational Research & Development, Astex Pharma
17.45 hr		**'Innovation management in drug discovery'** **Dr. Mikio Arisawa** Retd. Head of Discovery, Chugai (Roche Group), Japan
18.30 hr		**Panel Discussion** • Dr. Kapil Dhingra • Dr. Samir N. Khleif • Dr. Patrick Beauerle • Dr. Anneli Hallgren • Dr. Duncan Walker • Dr. Rajesh Chopra • Dr. Mikio Arisawa • Dr. Vinod Raina
19.00 hr	**Workshop by Cambridgesoft Corp.** **Informatics solution for Research,** Cambridgesoft Corp, USA	
19.30 hr	**Workshop by Biotron Healthcare** **HTRF chemistry and applications in drug discovery** Roderick Haroutunian, CIS BIO, France **BMG omega / PHERAstar: new standard for multi label detection** John Abbenante, BMG Lab Tech Australia	
20.00 hr	**Workshop by GE Healthcare** **Modern Bioanalytics- Getting closer to understanding your product** Mr. Lalith Kishore, GE Healthcare.	

Day 3: February 3, 2011

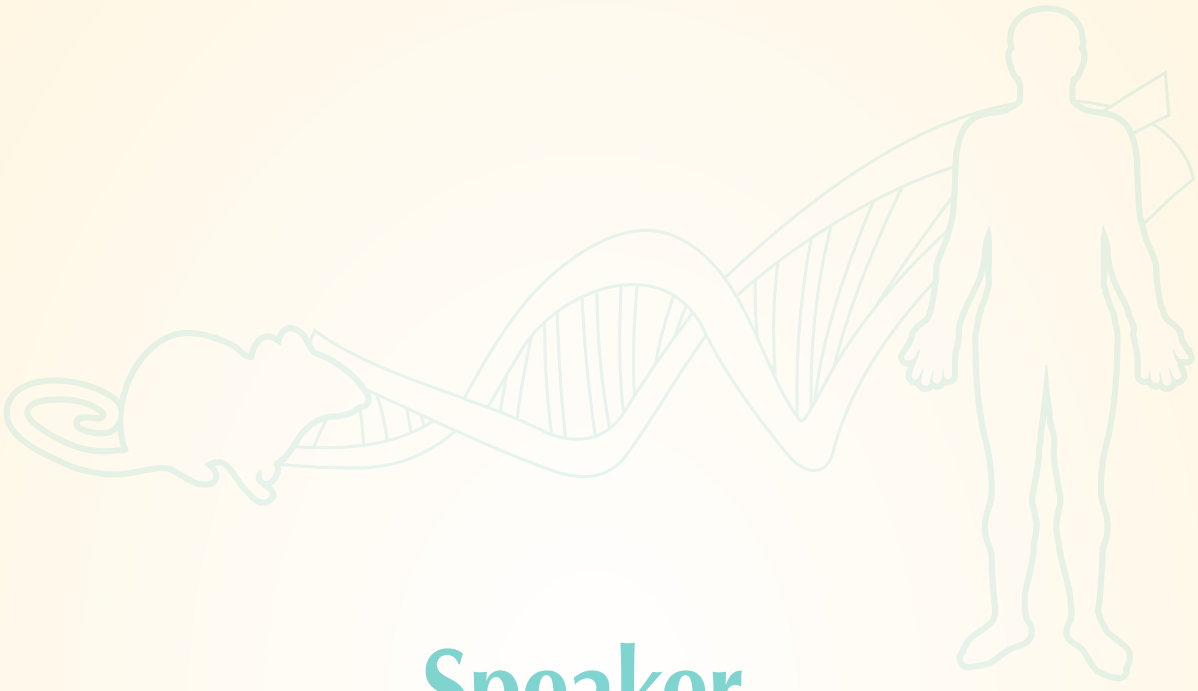
	Session IV **Chairperson** **Dr. Richard DiMarchi, PhD** Gill Professor of Biochemistry, Indiana University, USA **Dr. John Amatruda, MD,** Retired Merck Sr. VP & Franchise Head, Diabetes/Obesity, USA	
09.00 hr		**New Therapies for the Treatment of Type II Diabetes: Challenges and Opportunities** **Nancy Thornberry** Sr. VP, Metabolic Franchise Head, Merck Research Labs, USA
09.45 hr		**CNS Integration of Systems Metabolism: Target Opportunities for Diabetes Prevention and Therapy** **Dr. Matthias Tschoep, MD** Professor of Endocrinology, University of Cincinnati, USA
10.30 hr	**Tea/Coffee Break / Poster Session**	
11.00 hr		**MicroRNAs: Function in metabolism and therapeutic opportunities** **Dr. Markus Stoffel, MD** Professor, ETH Zurich Institute of Molecular Systems Biology Zurich, Switzerland
11.45 hr		**Insights into insulin resistance from metabolomics analysis following bariatric surgery** **Dr. Charles Burant, MD, PhD** Atkins Professor of Metabolism, University of Michigan, USA
12.30 hr	**Lunch Break / Poster Session**	
	Session V **Chairperson** **Nancy Thornberry** Sr. VP, Metabolic Franchise Head, Merck Research Labs, USA **Dr. Gianni Gromo** Sr. VP and Global Head, Metabolic & Vascular Disease Area, Roche, Switzerland	
14.00 hr		**Dissecting Hypothalamic Signaling: Targeting Metabolic Disease** **Dr. Jens C. Bruning, MD** Institute of Genetics, University of Cologene, Germany
14.45 hr		**The dynamic interaction between food, brain and body mass index** **Dr. Dana Small, PhD** Associate Professor, Department of Psychiatry Yale University School of Medicine and Associate Fellow, The John B Pierce Laboratory, USA
15.30 hr	**Tea/Coffee Break / Poster Session**	

16.00 hr		**ZYOG1: A Novel Oral GLP-1 agonist for treatment of Type 2 Diabetes** **Dr. Mukul R. Jain, PhD** Sr. VP, Zydus Research Center, Ahmedabad, India
16.45 hr		**Structure-based design of biotherapeutics with enhanced solubility and bio-stability** **Dr. Faming Zhang, PhD** CEO, Waterstone Pharmaceuticals Inc., USA.
17.30 hr		**Expectations of India from global scientific community** **Dr. V. M. Katoch** Secretary, Department of Health Research, Government of India & Director-General, Indian Council of Medical Research, India
17.50 hr	**Panel Discussion** • Dr. Richard DiMarchi • Nancy Thornberry • Dr. Matthias Tschoep • Dr. Markus Stoffel • Dr. Charles Burant • Dr. Jens C. Bruning • Dr. Dana Small • Dr. Mukul R. Jain • Dr. Faming Zhang • Dr. V. M. Katoch	
19.00 hr	**Cultural Program** Venue : Hotel Courtyard Marriot Ramdev Nagar Cross Roads, Satellite, Ahmedabad	

Day 4: February 4, 2011

		Session VI **Chairperson** **Dr. Charles Burant, MD, PhD** Atkins Professor of Metabolism, University of Michigan, USA **Dr. T. K. Chakraborty** Director, Central Drug Research Institute
09.00 hr		**The past, present and the future of Cardiovascular translational medicine research** **Dr. Gianni Gromo** Sr. VP and Global Head, Metabolic & Vascular Disease Area, Roche, Switzerland
09.45 hr		**Should Safety, Drug Exposure and Clinical Efficacy of Diabetes Drugs Be Assessed in Patients or in Healthy Volunteers?** **Dr. Marcus Hompesch,** CEO, Profil Institute for Clinical Research Inc., USA
10.30 hr		**"A prospective, multi-centric, open-label, single arm study to evaluate the safety and efficacy of 4mg of ZYH1 in hypertriglyceridemia in HIV associated lipodystrophy"** **Dr. Dhiraj Gambhire, MD** Cadila Healthcare Ltd, Mumbai, India
11.15 hr	**Tea/Coffee Break/ Poster Session**	
11.45 hr		**Big Pharma: Leveraging for an Efficient R&D Organization** **Dr. John Amatruda, MD,** Retired Merck Sr. VP & Franchise Head, Diabetes/Obesity, USA
12.30 hr		**Development of Prodrug Chemistry Suitable for Application to Therapeutic Peptides** **Dr. Richard DiMarchi, PhD** Gill Professor of Biochemistry, Indiana University, USA, Retired Executive VP, Lilly Research Labs., Indianapolis, USA
13.15 hr	**Lunch Break / Poster Session**	
14.30 hr		**Treatment of Metabolic Diseases with Proteins Site-Specifically Optimized for Pharmacological Use** **Dr. Douglas W. Axelrod, MD, PhD** Chief Medical Officer, Senior Vice President, Development, Ambrx, Inc. USA
15.15 hr		**Liver Selective Glucokinase Activation for Treating Type 2 Diabetes: Translation from Mouse to Man** **Dr. Kasim A. Mookhtiar, PhD** Chief Scientific Officer and EVP, Drug Discovery, Advinus Therapeutics Pvt Ltd, Pune, India

16.00 hr	**Panel Discussion** • Dr. Richard DiMarchi • Dr. John Amatruda • Dr. Gianni Gromo • Dr. Marcus Hompesch • Dr. Douglas W. Axelrod • Dr. Kasim A. Mookhtiar
16.30 hr	**Best Posters Award** • Three selected posters will be announced for prize presentation. • Time of 10 mins each will be provided to the 3 best posters for podium presentation.
17.00 hr	**Wrap-up session**



Speaker Profiles & Abstracts

Speaker Profile

Rolf M. Zinkernagel

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Born and raised in Basel, Rolf Zinkernagel studied at the Medical School of the University of Basel, obtaining his MD degree in 1968, and graduating to become a surgeon.

After working as a surgeon for a little over a year, Rolf Zinkernagel chose to focus on immunological research, undertaking a postgraduate course in experimental medicine at the University of Zurich; and subsequently spending two years in the Institute of Biochemistry of Lausanne working on immunity against infections. From 1973-1975 he became a PhD student, and later a post-doctoral researcher, at the John Curtin School of Medical Research of the Australian National University, Canberra, where Peter Doherty and he made seminal observations on how cytotoxic T cells recognize virus infected cells in an infected host (Nobel Prize for Physiology or Medicine 1996). Rolf Zinkernagel moved to the Scripps Clinic and Research Foundation in La Jolla, United States, from 1975 to 1979, where he studied T cell maturation and development of the T cell repertoire, dependent on the transplantation antigen expression in the thymus. In 1980 he joined the Department of Pathology, University of Zurich, as an associate professor where, together with Hans Hengartner, he has been studying immune protection and immunopathology caused by virus infections. Over the past 25 years within the Experimental Pathology group, and after 1992 the Institute of Experimental Immunology, he studied the role of antigen dependent beneficial immune protection or detrimental immunopathology, and compared these mechanisms with theories of immunological memory and immunological tolerance. He has retired from the University in Spring 2008.

Besides his interest in solving uncertainties and discrepancies in immunology, Rolf Zinkernagel tries to further biomedical research and its application in Zurich, in Switzerland and Europe. He has supported gene technology and animal experimentation in various locations in Switzerland and Europe, has been member of the Swiss Science Council, is now a member of the European Research Council and of the Executive Council of the International Union of Immunological Societies. He has also helped to popularize science in tabloid newspapers.

Keynote Address

A Nobel Prize by Chance!

The role of chance observations leading to key discoveries versus the rational of careful analysis of hypotheses is analysed. Once we know all details from the molecular to the physiological level of all things knowable, we will be able to ask reasonable questions and get answers that can be properly placed. Until then we probably have to rely heavily on observations that yield unexpected results. A few examples will be presented, including MHC restricted T cell recognition, the lack of an immune response against many self antigens without T cells or B cells having been eliminated by classical tolerance mechanisms, the role of immunopathology in explaining not only chronic or degenerative types of diseases, but also of so called autoimmune diseases, or so called immunological memory. Which is in fact antigen-driven.

These examples illustrate, that reasonable questions trigger experimental analyses with distinct potential outcomes: Either the hypothesis is supported - i.e. the result is not very interesting - or something unexpected can be observed, that often opens up truly new insights.

Notes:

Session I:

Introduction to Chairpersons:

Kapil Dhingra, MBBS
KAPital Consulting LLC, NJ, USA

Kapil Dhingra has served as a member of Micromet's Board of Directors since February 2009. In June 2008, Dr. Dhingra founded KAPital Consulting, LLC, a healthcare consulting firm. From 1999 to 2008, Dr. Dhingra served in positions of increasing responsibility at Hoffmann-La Roche, including Vice President, Head, Oncology Disease Biology Leadership Team, and Head, Oncology Clinical Development. Prior to joining Hoffmann-La Roche, Dr. Dhingra worked as a Senior Clinical Research Physician with Eli Lilly and Company. From 1989 to 1996, he served as a Clinical Instructor, Assistant Professor of Medicine at the University of Texas MD Anderson Cancer Center. Throughout his industry career, Dr. Dhingra maintained an active faculty appointment, initially at Indiana University School of Medicine from 1997 to 1999 as Clinical Associate Professor, and, more recently, at Memorial Sloan Kettering Cancer Center in New York from 2000 to 2008. Dr. Dhingra holds an MBBS degree from the All India Institute of Medical Services, and has performed postgraduate work at the All India Institute of Medical Services, the Lincoln Medical and Mental Health Center (New York Medical College), Bronx, NY and Emory University School of Medicine. Dr. Dhingra is currently an advisor to several biotechnology and pharmaceutical companies and serves on the board of directors of Micromet, Algeta ASA, Biovex, Inc., and Coferon.

Y. K. Gupta, MD
All India Institute of Medical Sciences (AIIMS) India.

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

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

Speaker Profile

William W. Chin, MD

Executive Dean for Research
Bertarelli Professor of Translational Medical Science
Professor of Medicine
Harvard Medical School
Boston MA 02115 USA

Born in New York, Chin received his A.B. in chemistry summa cum laude from Columbia College and his medical degree from Harvard Medical School. He then completed a residency in internal medicine at the Beth Israel Hospital and a fellowship in endocrinology and metabolism at the Massachusetts General Hospital, Boston, Massachusetts.

Chin served on the faculty of Harvard Medical School for 25 years and was professor of medicine, and professor of obstetrics, gynecology and reproductive biology at Harvard Medical School; investigator of the Howard Hughes Medical Institute; and chief of the division of genetics and senior physician at the Brigham and Women's Hospital, Boston. Chin then joined Eli Lilly and Company in 1999, and served most recently as senior vice president of discovery research and clinical investigation, with overall responsibilities for the therapeutic areas, chemistry, toxicology, ADME and early clinical development. He serves as a member of the company's senior management council. He previously was vice president of discovery biology research and clinical investigation. In 2010, he returned to academia as the Executive Dean for Research and Professor of Medicine at Harvard Medical School.

Chin is a world-renowned molecular endocrinologist who has pioneered the understanding of the mechanisms of nuclear receptor action with a focus on thyroid, estrogen, and other hormones, as well as various aspects of hormonal regulation of pituitary hormone gene expression. As the leader of the genetics program at the Brigham and Women's Hospital, he was responsible for the establishment of genomics, bioinformatics, and clinical genetics in the practice of medicine. He is author or co-author of more than 270 original papers, invited chapters or books, and he has served on numerous editorial boards and private and governmental review panels.

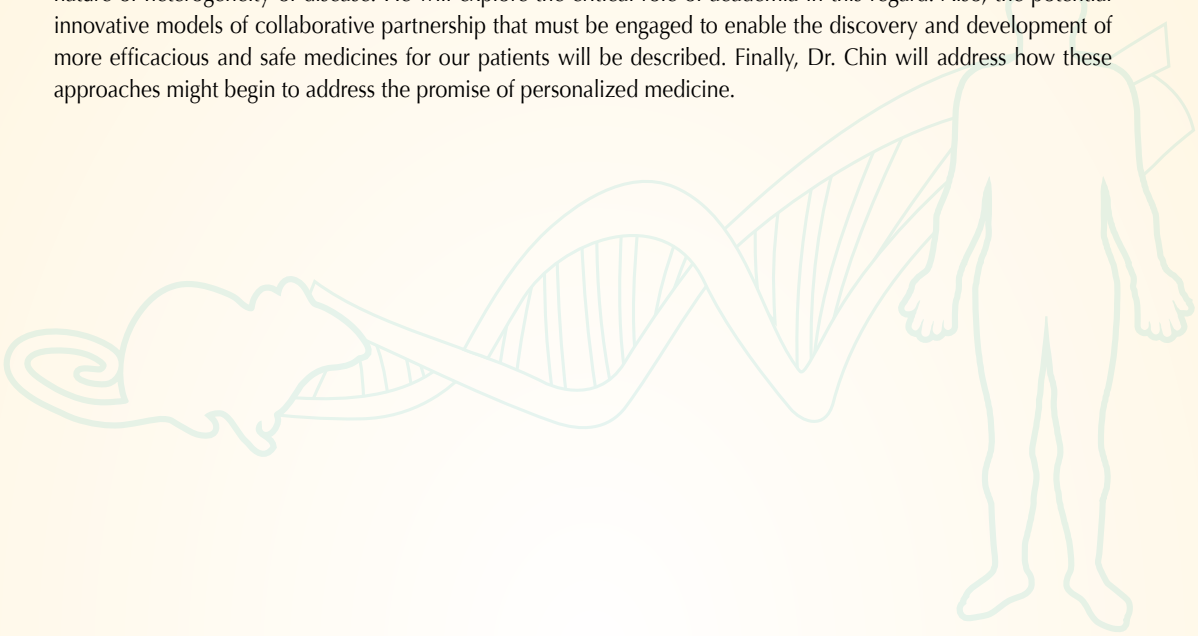
He has received many accolades, including the Robert H. Williams Distinguished Leadership Award from the Endocrine Society, the Sidney H. Ingbar and Van Meter Awards from the American Thyroid Association, the Bowditch Award from the American Physiological Society, and the AFCR Young Investigator Award, and election to the American Society for Clinical Investigation and the American Association of Physicians. Chin has been a member of the board of scientific counselors of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH), and chair of the NIH endocrinology study section. He has also provided leadership on the council of several key professional societies, including service as president of the American Thyroid Association and the Interurban Clinical Club.

Chin is a member of the Board of Directors at the Indianapolis Museum of Art and the Indianapolis Prize [the largest monetary prize for wildlife conservation in the world] Jury. He has also been an overseer of the New England Conservatory of Music and a co-chair of Project Success, a science program for underprivileged secondary students in Boston.

Topic

Therapeutic Science and Medicine: New Models for Academic—Industry Interactions.

Dr. Chin will discuss the challenges that the "therapeutics ecosystem," which includes academia, healthcare centers, pharma and government, faces. One of the key issues is the lack of knowledge of disease pathogenesis and nature of heterogeneity of disease. He will explore the critical role of academia in this regard. Also, the potential innovative models of collaborative partnership that must be engaged to enable the discovery and development of more efficacious and safe medicines for our patients will be described. Finally, Dr. Chin will address how these approaches might begin to address the promise of personalized medicine.



Notes:

Speaker Profile

Hilary Calvert, MB, BChir, MSc, MD, FRCP, FMedSci

Director, Cancer Drug Discovery and Development, UCL Cancer Institute, London, UK

Hilary Calvert, trained in Medicine, Mathematics and Biochemistry, was recently appointed the Director of Anticancer Drug Discovery and at the UCL Cancer Institute, London.

His work on new drugs for treating cancer started in the Institute for Cancer Research and the Royal Marsden Hospital, London (1977-89) where he established the use of Carboplatin for the treatment of Ovarian Cancer and devised a formula which allowed the dose to be optimised for each individual patient. He also introduced a new family of drugs based on the vitamin, folic acid. The first of these is called Raltirexed and is in clinical use for Colon Cancer, and later work around the world led to the development of Pemetrexed, a drug used for treating Lung Cancer. Pemetrexed is also the only drug licensed for treating the asbestos-induced cancer, Mesothelioma. Between 1989 and 2009 he led a team at Newcastle University where the first of another new class of drugs, PARP Inhibitors, was developed. PARP Inhibitors are particularly useful in treating familial Breast and Ovarian Cancers.

In 2005 he was awarded the Pfizer Research Innovation Award – an award made annually within Europe but encompassing all areas of science – for his work on developing new anticancer drugs. In 2009 he was the recipient of the British Oncological Association / Pfizer Lifetime Achievement Award."

Topic

Synthetic Lethality in Cancer Treatment: Current status of PARP Inhibitors

Inhibitors of poly(ADP-ribose)polymerase (PARP) may be applied to cancer treatment in a number of different ways.

They may be used as single agents in the treatment of cancers arising in patients who are carriers of a BRCA1 or BRCA2 mutation. Since PARP is involved in the repair of single strand breaks in DNA, treatment with a PARP inhibitor leads to an accumulation of such breaks. Cancers arising on a background of a BRCA mutation lack the homologous recombination repair pathway and are uniquely unable to survive single strand breaks. This mechanism is known as "synthetic lethality" in which two molecular lesions combine to have a lethal effect on the cell, although neither of them is harmful individually. Clinical "proof of principle" for this mechanism has been demonstrated using olaparib in an expanded Phase I study and in two Phase II studies where response rates in the region of 40% were seen in breast and ovarian cancer[1,2,3].

In vitro, and in experimental animal models, PARP inhibitors have been shown specifically to potentiate monomethylating agents and topoisomerase I inhibitors regardless of their BRCA status. A Phase I and Phase II study of AG014699 in combination with temozolomide has shown promising response rates in patients with metastatic melanoma[4,5]. PARP inhibitors have also been shown to potentiate chemotherapy treatment in patients whose tumours are expected to have a BRCA-like phenotype – that is to have a reduced ability to undertake homologous recombination repair. BSI 201 has been the subject of a randomised Phase II study in combination with gemcitabine and carboplatin in triple negative breast cancer. PARP inhibitors also have potential as radio-sensitising agents and are a new class of drugs with potential in this area, since previous trials have focussed on hypoxic cell sensitisation. Finally there is the possibility that PARP inhibitors might be given prophylactically to known BRCA mutation carriers, who have a very high lifetime probability of developing various cancers.

There are currently at least nine PARP inhibitors in development, listed below. We can expect to see extensive applications of PARP inhibitors with the major ones probably focussing on patients with tumours that are deficient in homologous recombination repair.

Agent	Company	Route	Clinical Status
AG014699	Pfizer	IV (oral)	Phase I/II combos
Olaparib (AZD2281)	AstraZeneca	Oral	Phase II/III combos
ABT888	Abbott	Oral	Phase I/II combos
BSI-201	BiPar / Sanofi-Aventis	Iv	Phase II/III combos
INO-1001	Inotek	Iv	Phase 1b complete
GP121016	Eisai / MGI Pharma	Oral	Phase I
CEP-9722	Cephalon	Oral	Phase I
MK4827	Merke	Oral	Phase I
BMN-673	Biomarin / LEAD		Preclinical

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2. Tutt et al. J Clin Oncol 27:15s, 2009 (suppl; abstr 5500)
3. M. W. Audeh et al, 2009 ASCO Annual Meeting Proceedings 27 abstract 5500
4. Plummer R, et al. Phase I Study of the Poly (ADP-Ribose) Polymerase Inhibitor, AG014699, in Combination with Temozolomide in Patients with Advanced Solid Tumors. Clinical Cancer Research 14(23):7917-7923, 2008
5. Plummer R, Lorigan P, Evans J, et al. J Clin Oncol 2006;24:456S

Notes:

Speaker Profile

Jean-Charles Soria, MD, PhD

Institut Gustave Roussy, Villejuif, France

Professor Jean-Charles Soria is Professor of Medicine and Medical Oncology at Paris University XI. He is a tenure-track and full time cancer specialist at the Institute Gustave Roussy. Professor Soria trained as a medical oncologist and obtained a Silver medal from Paris Medical School in 1997. He gained a PhD degree in the fundamental basis of oncogenesis in 2001, and completed his training with a two-year post-doctoral fellowship in the Department of Thoracic Head and Neck Medical Oncology at MD Anderson Cancer Center, Houston, USA. Professor Soria is currently Head of the phase I program at the Institute Gustave Roussy and member of the lung cancer unit with a focus on targeted therapies. His main research interests are in early clinical development, phase I trials across solid tumors, pharmacodynamic biomarkers, early phase II trials and lung cancer. He is also involved in translational research aspects related to tumor progression, notably in lung cancer models. Professor Soria has been the Principal Investigator on ten phase I trials during the past 3 years as well as half a dozen phase II trials in lung cancer. He is currently the Chair of the French Scientific National Program on Lung Cancer (PNES), launched by the French NCI. Professor Soria is Member of ASCO, AACR, ESMO and IASLC. He also founded the Flims Alumni Club (FAC) in 2001. Professor Soria is a current member of the ESMO educational committee, as well as an ASCO committee member. He is on the editorial board of the Journal of Clinical Oncology, the Lancet Oncology, the American Journal of Clinical Oncology and Bulletin du Cancer. He has contributed to over 100 peer-reviewed publications, including publications as first or last author in the New England Journal of Medicine, the Journal of the National Cancer Institute, Cancer Research and Clinical Cancer Research.

Topic

DNA repair dysfunctionality in lung cancer

DNA repair dysfunctionality is related to genomic instability, an important hallmark of cancer cells. The study of DNA repair mechanisms (regulation, efficiency, and associated biomarkers…) in lung cancer will allow a better comprehension and prediction of the clinical evolution of this disease. Differential degrees of DNA repair dysfunctionality between patients might explain why some DNA-damaging anticancer agents yield highly heterogeneous therapeutic responses. We previously showed that long-term survival benefit derived from chemotherapy is different according to both MSH2 and ERCC1 expression (chemotherapy strongly prolonged long-term survival in the combined MSH2-negative/ERCC1-negative subgroup compared to observation (adjusted hazard ratio for death, 0.65; 95%CI, 0.47 to 0.91; P=0.01). This observation suggest that lung cancers presenting high expression of DNA repair biomarkers might be a different disease compared to cancers with low expression profiles.

There are at least 6 major pathways of DNA repair in a cell, each processing a particular type of DNA damage: DR (Direct Repair), NER (Nucleotide Excision Repair), BER (Base Excision Repair), MMR (mismatch repair, or mismatch repair), HRR (Homologous Recombination Repair,) and NHEJ (Non-Homologous End-Joining). Despite a high complexity of DNA damage signalling and connexions between different DNA repair pathways, it is generally possible to highlight one or two (MMR), BRCA1/2 (HRR) and DNA-PKcs (NHEJ). We are actually pursuing our investigations using an integrated approach to characterize DNA repair dysfunctionality in lung cancer cells and in patients. This is achieved by means of CGH and measurement of the aberrant genome index in tumor samples, and also by a functional test allowing the dynamic measure of the global number cisplatin induced DNA adducts IHC evaluation of ERCC1, BRCA1, MSH2 and PARP1 clearly demonstrate that loss or low protein expression of these proteins is observed in 38% to 53% of around 650 resected NSCLC samples. Further, using an independent cohort of lung cancer patients, we also found a significant association between the level of ERCC1 immunohistochemical status and genomic instability measured by CGH arrays. In conclusion, DNA damaging-based therapy could be chosen according to individual tumor evaluation of DNA repair dysfunctionality.

Notes:

Speaker Profile

Anthony W. Tolcher, MD, FRCP(C)

Director of START (South Texas Accelerated Research Therapeutics) and Clinical Professor of Medicine in the Division of Medical Oncology, University of Texas Health Science Center, San Antonio, USA

Dr. Anthony W. Tolcher is the Director of Clinical Research at START (South Texas Accelerated Research Therapeutics) in San Antonio, Texas.

He is a graduate of the University of British Columbia in Vancouver, Canada. He performed his residency in internal medicine at the University of Toronto and his fellowship in oncology at the University of British Columbia. He followed this with a research fellowship at the National Cancer Institute, Bethesda, Maryland. Dr. Tolcher was the Director of Clinical Research at the Cancer Therapy and Research Center (CTRC) in San Antonio from 2003 until April, 2007, and prior to that served as the Associate Director at the CTRC from 1999 to 2003.

Dr. Tolcher's major interest is in the development of new anticancer agents, with a special interest in molecular genetic targets for cancer therapy.

He was a Fogarty Fellow at the National Institute of Health, and received the Murray Muirhead Award for humanitarian and academic excellence, and the Goel Prize in Medicine for excellence in the Clinical Disciplines.

He is a Fellow of the Royal College of Physicians of Canada; a Diplomate of the American Board of Internal Medicine and Medical Oncology; a Fellow of the American College of Physicians, and a member of the American Association for Cancer Research, the American Society of Clinical Oncologists, and the European Society for Medical Oncology. He also serves as a member of the American Society of Clinical Oncology Scientific Program Committee and the Cancer Education Committee.

He is an Associate Editor of the The Journal of New Anticancer Agents; and he is a scientific grant reviewer for the National Cancer Institute of Canada. Dr. Tolcher has authored numerous publications, including 89 peer reviewed publications, 143 Conference Proceedings, and 9 book chapters. He serves as a reviewer for the following journals: Anti-Cancer Drugs, Journal of Clinical Oncology, Annals of Oncology, Cancer Research, Clinical Cancer Research, Clinical Lung Cancer, Clinical Prostate Cancer, Human Gene Therapy, and the Journal of Cancer.

Topic

Outliers, Invisible Gorillas, and Fellow Travelers-Understanding the Difference for Molecularly Targeted Drug Development

Notes:

Speaker Profile

Pablo J. Cagnoni, MD

Sr. VP and Global Head, Oncology Clinical Development, Novartis Pharmaceuticals. Switzerland

Pablo J. Cagnoni, MD was appointed Senior Vice President and Global Head, Oncology Clinical Development with Novartis Pharmaceuticals Corporation as of October 2009. He is responsible for leading nearly 300 employees working in Oncology Clinical Development to ensure successful clinical development plans and to establish a Center of Excellence for all clinical activities, including the development of talent within Oncology. In this position, Pablo continues to help find ways to expedite Oncology Global Development trials in order to bring more new therapies to patients faster, leveraging his many strong external relationships with key stakeholders, as well sharing new and innovative ideas to strengthen the clinical function. He also partners closely with the Novartis Oncology Global Program heads to provide expertise on clinical strategies and actively manages and ensures the quality of all clinical programs.

Pablo joined Novartis from Allos Therapeutics, Inc. where he served as Senior Vice President and Chief Medical Officer, responsible for clinical research, biometrics and data management, regulatory affairs, project management and pre-clinical development. Pablo led the team that recently obtained the accelerated approval of FolotynTM (pralatrexate) for the treatment of peripheral T-cell lymphoma.

Prior to that, Pablo was Chief Medical Officer and Vice President, Clinical Research and Medical Affairs at OSI Pharmaceuticals, where he had oversight for all translational and clinical development activities for Tarceva® (erlotinib), OSI-930 (Kit/KDR inhibitor), OSI-817 (Kit/KDR inhibitor) and OSI-906 (IGFIR inhibitor). Pablo led the team responsible for the successful submission and approval of Tarceva for pancreatic cancer indication. Prior to OSI Pharmaceuticals, he served as Vice President and Head of Clinical Development at Allos Therapeutics, Inc. and previous to his industry experience, Pablo was Assistant Professor of Medicine and Assistant Director, Pharmacology Laboratory, University of Colorado, Bone Marrow Transplant Program.

Pablo earned his Medical Degree from University Buenos Aires School of Medicine. His postgraduate training includes a residency in internal medicine at Centro de Educacion Medica e Investigaciones Clinicas (CEMIC), Buenos Aires, a fellowship in Hematology and Oncology as well as serving as Chief Fellow, Division of Hematology, Department of Medicine at Mount Sinai Medical Center, New York, in addition to other appointments. Pablo is widely published, with more than 70 publications and abstracts.

Topic

PI3 Kinase Inhibitors for the Treatment of Cancer

The superfamily of PI3 kinases is characterized by primary sequence homologies within the catalytic domain of these enzymes. Currently, 8 members of this family are known, belonging to three classes (I-III). At structural level, the enzyme PI3K is composed of a 110-kDa catalytic subunit and an 85-kDa adaptor subunit. PI3K signaling regulates diverse cellular functions, including protein synthesis and glucose metabolism, cell survival and growth, proliferation, cellular resilience and repair, cell migration, and angiogenesis (Katso, et al 2001).

Multiple components of the PI3K pathway are often dysregulated in cancer cells and over-activation of PI3K signaling is implicated in many aspects of tumor growth and survival. Activation of this pathway can be the result of: i) Amplification and/or overexpression of the p110α catalytic subunit; ii) Presence of activating mutations in the PIK3CA gene encoding the p110α catalytic subunit; iii) Constitutively active mutants or overexpression of some receptor tyrosine kinases (e.g. EGFR, ErbB2) leading to constitutive recruitment and activation of PI3K; iv) Constitutive recruitment and activation by mutant forms of the Ras oncogene; v) Loss or inactivating mutation of the tumor suppressor gene PTEN, a endogenous negative regulator of the PI3K pathway; or vi) Overexpression of the downstream kinase Akt.

Preliminary data suggest that activation of the PI3K pathway may be a predictor of poor prognostic outcome in many cancers. Several lines of evidence suggest that inhibition of the PI3K signaling pathway might provide benefit for the treatment of many cancers: solid tumors (breast cancer, prostate cancer, glioblastoma multiforme, colon cancer, lung cancer, etc.) and tumors of the hematopoietic system (Kim 1994, Ram 1996, Ma 2000, Fry 2001, Roymans 2001, Bachman 2004, Broderick 2004, Samuels 2004, Ohgaki 2005, Zeng 2006).

Therapeutic interventions can impact PI3K signaling and the activation of the pathway could contribute to the therapeutic resistance of tumors or could alternatively increase the efficacy of chemotherapy/radiation. Exposure of tumor cells to cytotoxic agents, treatment with trastuzumab or with tamoxifen or letrozole can also lead to constitutive activation of the PI3K pathway (Brognard 2001, Clark 2002, Campbell 2004, Ellis 2004). In the case of trastuzumab/lapatinib treatment, preliminary evidence suggested that activation of the PI3K signaling pathway may play a role in the development of resistance (Fujita 2006, Nahta 2006a, Nahta 2006b, Dieras 2007). For example, PTEN activation is important for the growth inhibitory effect of trastuzumab, whereas loss of PTEN function is predictive of trastuzumab and gefitinib resistance (Nagata 2004, She 2005). Together these insights suggest that many cancers, either treatment naïve or following exposure to anti-cancer treatment, exhibit a 'genetic dependency' to PI3K pathway activation, which can be exploited for biomarker guided therapeutic gain from PI3K inhibition.

Notes:

Session II:

Introduction to Chairpersons:

Hilary Calvert, MB, BChir, MSc, MD, FRCP, FMedSci

Hilary Calvert, trained in Medicine, Mathematics and Biochemistry, was recently appointed the Director of Anticancer Drug Discovery and at the UCL Cancer Institute, London.

His work on new drugs for treating cancer started in the Institute for Cancer Research and the Royal Marsden Hospital, London (1977-89) where he established the use of Carboplatin for the treatment of Ovarian Cancer and devised a formula which allowed the dose to be optimised for each individual patient. He also introduced a new family of drugs based on the vitamin, folic acid. The first of these is called Raltirexed and is in clinical use for Colon Cancer, and later work around the world led to the development of Pemetrexed, a drug used for treating Lung Cancer. Pemetrexed is also the only drug licensed for treating the asbestos-induced cancer, Mesothelioma. Between 1989 and 2009 he led a team at Newcastle University where the first of another new class of drugs, PARP Inhibitors, was developed. PARP Inhibitors are particularly useful in treating familial Breast and Ovarian Cancers.

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S. D. Seth, MD
Advisor, ICMR

Dr. S.D. Seth was Professor of Pharmacology at All India Institute of Medical Science, New Delhi. Currently, he is Advisor, Indian Council of Medical Research, New Delhi. He is on the panel of Government Advisory Board and has lot of publication to his credit.

Speaker Profile

Kapil Dhingra, MBBS
KAPital Consulting LLC, NJ, USA

Kapil Dhingra has served as a member of Micromet's Board of Directors since February 2009. In June 2008, Dr. Dhingra founded KAPital Consulting, LLC, a healthcare consulting firm. From 1999 to 2008, Dr. Dhingra served in positions of increasing responsibility at Hoffmann-La Roche, including Vice President, Head, Oncology Disease Biology Leadership Team, and Head, Oncology Clinical Development. Prior to joining Hoffmann-La Roche, Dr. Dhingra worked as a Senior Clinical Research Physician with Eli Lilly and Company. From 1989 to 1996, he served as a Clinical Instructor, Assistant Professor of Medicine at the University of Texas MD Anderson Cancer Center. Throughout his industry career, Dr. Dhingra maintained an active faculty appointment, initially at Indiana University School of Medicine from 1997 to 1999 as Clinical Associate Professor, and, more recently, at Memorial Sloan Kettering Cancer Center in New York from 2000 to 2008. Dr. Dhingra holds an MBBS degree from the All India Institute of Medical Services, and has performed postgraduate work at the All India Institute of Medical Services, the Lincoln Medical and Mental Health Center (New York Medical College), Bronx, NY and Emory University School of Medicine. Dr. Dhingra is currently an advisor to several biotechnology and pharmaceutical companies and serves on the board of directors of Micromet, Algeta ASA, Biovex, Inc., and Coferon.

Topic

Harnessing the immune system to treat cancer – A reality at last

The development of cancer is in part related to an inability of the immune system to recognize cancer cells as foreign and eliminate them. Commonly used cancer therapies, such as chemotherapy and radiotherapy are associated with significant toxicities, especially as their non-selective mechanism of action leads to adverse effects on normal tissues. The immune system has evolved during the course of evolution to selectively destroy noxious agents. However, most attempts at harnessing the immune system to target cancer cells proved to be mostly a fond hope. In particular, systemic administration of broadly acting cytokines such as alpha interferon and interleukin-2 showed significant toxicity with only modest efficacy, with few notable exceptions, e.g. CML, hairy cell leukemia and occasional patients with melanoma and renal cell carcinoma. Nearly all therapeutic cancer vaccines failed in pivotal phase III trials, even when the data from early clinical trials seemed quite promising.

The tide has started to turn over the last decade with several successes in late stage trials and with numerous new promising approaches in early development. Interestingly, a variety of diverse immunological approaches appear to be succeeding at the same time. Several monoclonal antibodies have been on the market for a decade to treat common tumors. While several of these inhibit signal transduction, there is clear and convincing evidence for the contribution of immune effector mechanism to the observed clinical efficacy of others, e.g. Rituxan/Mabthera. This has led to exploration of a variety of antibody engineering strategies to enhance their anti-cancer effects. Among the most promising approaches are those being pursued by Glycart and Micromet. A glycoengineered CD20 antibody optimized for ADCC and apoptosis has shown promising results in patients groups not expected to generally respond to rituximab. This is now in phase III trials. Bispecific T-cell engaging antibodies have been shown to be among the most potent anticancer agents in clinical development today and the first drug candidate from this platform has moved to pivotal trials.

Recently, the first therapeutic cancer vaccine has successfully completed phase III trials. Provenge (sipuleucel) demonstrated a 4 months improvement in survival in patients with castration refractory prostate cancer. An alternative proof of principle for breaking the tolerance of immune system to cancer has been provided by the survival benefit observed in patients with melanoma treated with iplimumab, an anti-CTLA4 antibody. Promising early results have also been observed with an anti-PD1 antibody.

Oncolytic viruses provide an innovative approach to achieve direct killing of antitumor cells with concomitant induction of anti-tumor immunity. A number of viral constructs are in development. The most advanced among these is Oncovex. This is a modified HSV that led to a 28% response rate in patients with metastatic melanoma. Importantly, the durable response rate was 20%. Even more significant was the observation of shrinkage of distant uninjected lesions in several patients, including those with deep seated lesions. This is presently in phase III trials with initial results expected in 2011.

The momentum provided by these successes has led to a resurgence of interest in exploring a diversity of next generation approaches. It is now realistic to expect that a number of immunotherapies will make it to routine clinical use to treat a variety of cancers in the near future.

Notes:

Speaker Profile

Samir N. Khleif, MD

Cancer Vaccine Section, Investigator, National Cancer Institute, USA

Biography

Dr. Khleif earned his MD from the University of Jordan in Amman in 1986. He completed his internal medicine residency at the Medical College of Ohio in 1990 and then joined the NCI as a medical oncology fellow. Currently, Dr. Khleif is head of the Cancer Vaccine Section, Vaccine Branch at the NCI; he also serves as a Special Assistant to the Commissioner of the Food and Drug Administration, leading the Critical Path Initiative for oncology. He also holds an adjunct academic appointment with the Medicine Department of the Uniformed Services University of the Health Sciences. Dr. Khleif serves on many local, national, and international committees and as a cancer vaccine expert for a number of national organizations. From 2002 to 2006, Dr. Khleif served as the Director General and CEO of the King Hussein Cancer Center as part of an agreement between the NCI and Jordan. During this time, Dr. Khleif led the development of the only cancer center in the Middle East into an internationally recognized comprehensive cancer center of excellence. In 2007, Dr. Khleif was appointed the Director of the King Hussein Institute for Biotechnology and Cancer. This appointment was the result of a new agreement between the NCI and Jordan to develop this new institute as a comprehensive cancer center and biotechnology research hub.

Research

Cancer Vaccine Development

Dr. Khleif's research focuses on integrating translational basic laboratory research and clinical trials to understand the interaction between tunor cells and the immune system and to develop cancer vaccines. His laboratory's emphasis is on the preclinical identification of potential new vaccine targets, the development of improved and more effective methods for vaccine delivery, an expanded understanding of the mechanism of immune response in vaccinated patients, and the incorporation of these findings into clinical trial development. His research has a special emphasis on viral and cellular oncogene antigenic potentials.

Topic

Manipulating the Inhibitory Arm of the Immune System, a Needed Strategy for Cancer Therapy

The scientific community has been working for more than 3 decades in developing effective targeted immune therapy and cancer vaccines with no notable major success. It has been shown clearly that the development process lacked the knowledge of a delicate interaction between the immune system and the tumor and of the ability of cancer cells to manipulate the immune system by promoting its inhibitory arm and suppressing its effector arm. This led to an apparent deficiency in the strategies addressing the development of effective immunotherapy and cancer vaccines. The inhibitory mechanism of the immune system play a major role in suppressing an infected immune response against tumors. The mechanisms by which the immune system is inhibited, now we know, are many. These include: inhibitory cells include both T and myeloid cells (T. regulatory cells and myelosuppressive cells); Co-inhibitory molecules that can be expressed on tumors sending suppressive and refill signals to T cells such as PDL1; and the secreted inhibitory cytokines and factors such as interleukin-10 and TGF-beta. Accordingly, developing strategies to inhibit these suppressive mechanisms would be crucial for the development of an effective immune response against cancer. Our laboratory has been working on addressing some of these mechanisms including the selective inhibition of T. regulatory cells and strategies combining blockade of co-inhibitory signaling with targeted vaccines to enhance their therapeutic effect. Some of immune suppressive mechanisms and strategies designed to inhibit those mechanisms will be addressed in the talk.

Notes:

Speaker Profile

Patrick A. Baeuerle, PhD

CSO, Micromet Inc., USA

Dr. Baeuerle has served as Micromet's Chief Scientific Officer since October 1998. From February 1996 to September 1998, Dr. Baeuerle headed the drug discovery activities of Tularik Inc. in South San Francisco, CA, as Director, Drug Discovery. From October 1994 to February 1996, Dr. Baeuerle served as a full Professor and Chairman of Biochemistry at the Medical Faculty of Freiburg University, Germany. In 1989, he was awarded a group leader position at the Gene Center in Martinsried, Germany, where he did seminal research on transcription factor NF-kappaB. According to a survey by the Institute for Scientific Information (ISI, Philadelphia, PA, USA), Dr. Baeuerle was Germany's most frequently cited biomedical scientist of the past decade, and 38th worldwide. He has published more than 200 scientific papers, and four educational children books on biology. In addition, Dr. Baeuerle is the first recipient of the Prix Européen de l'Avenir and an elected member of the European Molecular Biology Organization (EMBO). He was appointed Honorary Professor of Immunology at the University of Munich in 2000. Dr. Baeuerle performed his PhD work at the Max Planck Institute for Psychiatry in Martinsried and at the European Molecular Biology Laboratory (EMBL) in Heidelberg, obtained a PhD degree in biology from the University of Munich, and performed his post-doctoral research with David Baltimore at the Whitehead Institute of the Massachusetts Institute of Technology (MIT), Cambridge, MA.

Topic

T Cell Engaging BiTE Antibodies for Cancer Therapy

Bispecific antibodies can transiently link tumor cells with otherwise inactive polyclonal T cells for induction of a surface target antigen-dependent redirected lysis of tumor cells. One example is blinatumomab, a CD19/-CD3-bispecific BiTE for the treatment of human B cell malignancies. Blinatumomab and other BiTE antibodies were shown to activate T cells in a highly conditional manner that is strictly dependent on the presence of target cells. Blinatumomab is in phase 1 dose escalation study for the treatment of patients with therapy-refractory non-Hodgkin's lymphoma (NHL), and concluded a phase 2 study in patients with B-precursor acute lymphocytic leukemia (ALL). Centrally confirmed complete and partial responses have been observed with blinatumomab in 12 out of 12 NHL evaluable patients treated at 0.06 mg/m^2 per day, and a complete molecular response in 16 out of 20 evaluable ALL patients treated at 0.015 mg/m^2 per day.

MT110 is a novel BiTE antibody recognizing the pan-carcinoma antigen EpCAM (CD326), which is expressed on a large variety of human adenocarcinoma, and on cancer-initiating cells derived thereof. MT110 is a in phase 1 study with gastrointestinal, lung, breast, prostate, ovarian, and esophageal cancer patients. A murine EpCAM/CD3-specific version of the BiTE antibody, called muS110, has shown a robust therapeutic window in mice with no damage to EpCAM-expressing normal epithelia. Additional BiTE antibodies specific for EGFR, CD33, EphA2, CEA, Her-2/neu, FAP-alpha, IGF-1R and c-Met have been generated and shown to have a high potency of redirected target cell lysis. Conversion of anti-EGFR antibodies cetuximab and panitumumab into BiTE antibodies generated molecules engaging at high potency T cells for lysis of colorectal cancer cells expressing KRAS and BRAF mutations, and provided evidence for a therapeutic window in primate studies.

Four BiTE programs have been partnered with large biopharma companies including MedImmune, Bayer Schering Pharma, Sanofi-Aventis and Boehringer Ingelheim.

Notes:

Speaker Profile

Vinod Raina, MD, FRCP

Head Dept of Medical Oncology &
Head Delhi Cancer Registry Institute of Rotary Cancer Hospital
All India Institute of Medical Sciences (AIIMS), Delhi, India

Topic

Oncology Clinical Research : India

Notes:

Speaker Profile

Duncan Walker, PhD

Senior Director, Translational Medicine, Array Biopharma, USA

Dr. Walker is currently Sr Director for Oncology Translational Medicine at Array BioPharma in Boulder Colorado, working to support translational research and early development for Array's pipeline of clinical-stage cancer programs. In this capacity, he has worked to focus the early development of Array's cancer drugs on identifying and testing these compounds in the optimal indications and settings for early POC and establishing a path to registration. He has also participated in business development for Array's oncology programs. Prior to joining Array, he was VP Biological Sciences at Sunesis Pharmaceuticals in South San Francisco responsible for all Sunesis' biology activities in small molecule discovery and translational research in support of clinical trials. While at Sunesis, he was involved in the in-licensing and development of SNS-595, which is currently in Ph3 trials in AML. From 1998-2002 Dr. Walker had several roles at Hoffmann-La Roche in Nutley NJ, most recently VP Oncology leading a portfolio of preclinical oncology programs from target selection to entry into the clinic. Dr. Walker's pharmaceutical career started at Glaxo, where he led programs in cell cycle research in cancer. Dr. Walker received PhD degree in Biochemistry and B.S. degree in Molecular Biology from Washington University in St. Louis, Missouri.

Topic

Targeting Multiple Myeloma: Using Translational Research to Inform the Development Path for the KSP inhibitor ARRY-520

The discovery of novel mitosis-specific targets, such as the kinesin spindle protein (KSP, eg5), offered the promise of next-generation anticancer agents that could improve on the activity and safety profile of existing drugs. The clinical history of these agents, however, has not lived up to that promise: KSP inhibitors have shown disappointing activity in multiple clinical trials, predominantly in solid tumors.

ARRY-520 is a next-generation KSP inhibitor, with improved potency and superior preclinical activity. Given the poor clinical history of KSP inhibitors, it was critical to apply a rational approach to the identification of clinical indications that might enable successful development of ARRY-520.

By focusing on mechanisms of cell death in response to ARRY-520, we found that many cell lines require prolonged (>72h) and continuous exposure to ARRY-520 to elicit apoptosis. However, a subset of cell lines - predominantly hematological cells - underwent cell death within 24h of treatment. Investigation of the biological mechanisms underlying cell death in response to ARRY-520 showed that 1) cells undergoing rapid apoptosis express the short-lived survival protein Mcl1, a member of the BCL2 family and 2) the rapid degradation of Mcl1 following mitotic arrest by ARRY-520 is required for early cell death. These data suggest that tumors that rely on Mcl1 for survival may be clinically more sensitive to ARRY-520. Such tumor types include myeloma and lymphomas as well as subsets of other hematological and solid tumors. We have seen that in vivo myelomas are amongst the most sensitive models to ARRY-520. Further, the in vivo activity of ARRY-520 has shown striking additivity and synergy with both bortezomib and lenalidomide, which are standards of care in myeloma. In particular, the combination activity with bortezomib has been observed in several models that are resistant or poorly responsive to bortezomib as a single agent.

These data supported clinical investigation of ARRY-520 in multiple myeloma. In a phase 1 dose-escalation study of single agent ARRY-520 in relapsed and refractory multiple myeloma, ARRY-520 was well-tolerated, with reversible neutropenia the most common dose-limiting adverse effect. Clinical activity of ARRY-520, as evidenced by partial and minor responses and prolonged stable disease, have also been seen in this patient population, all of whom have been pretreated with both IMiDs (lenalidomide, thaldomid) and bortezomib. ARRY-520 is currently undergoing investigation in a phase 2 single agent study and a phase1b study in combination with bortezomib.

In summary, while multiple clinical studies of KSP inhibitors have shown negative data, by employing translational research, we have identified multiple myeloma as a preferred indication for development of KSP inhibitors and demonstrated a clinical proof-of-concept for ARRY-520 in this indication.

Notes:

Session III:

Introduction to Chairpersons:

Pankaj Shah, MD

Director, Gujarat Cancer Research Institute, India

J. S. YAdav, PhD, FNA, FASc, FTWAS

Director, Indian Institute of Chemical Technology, Hyderabad, India

Dr. Yadav is a director, Indian Institute of Chemical Technology, Hyderabad, India since 2003. Before taking up the present position, Dr. Yadav was heading Organic Chemistry division at IICT. Before joining IICT, Dr. Yadav was at National Chemical Laboratory, Pune. Dr. Yadav earned PhD from M. S. University, Baroda, India. He is widely published and in a span of two and half decades of research career, Dr. Yadav has been able to successfully carry out extensive basic and applied research investigations in the synthesis of complex Natural products of biological relevance. Dr Yadav is a member of prestigious scientific bodies like Department of Science and Technology, Technical Advisory Board (TAB) and a National representative of International Union for Pure and Applied Chemistry (IUPAC). He has received many academic and Industrial Awards viz., Shanti Swarup Bhatnagar Award (1991), Vasvik Award in Chemical Sciences & Technology (1999), Ranbaxy Research Award in Pharmaceutical Sciences (2000), Prof. Swaminathan 60th Birthday Commemoration Lecture Award (2002), Vigyan Ratna , Vigyan Gaurav Awards of Council for Science and Technology, Uttar Pradesh (2003)(2004), Goyal Award 2003, DOST Prof S K Sharma Medal and Chemcon Distinguished Speaker award 2006, CDRI oration award 2006, CHEMTECH award for Outstanding Achievement in R&D/Innovation Institutions in Pharma + Biotech 2007 to name few.

Speaker Profile

Anneli Hallgren, PhD

CSO & Vice President, Preclinical R&D, Karo Bio, Sweden.

- Master of Science in Pharmacy (Pharmacist), Uppsala University, Sweden
- PhD in physiology from the medical faculty, Uppsala University, Sweden
- Senior research scientist (safety pharmacology) and preclinical project manager at Astra Pain Control and, after the merger, AstraZeneca
- Various management positions at Swedish Biotech companies such as Melacure Therapeutics and Biolipox (now Orexo)
- Currently CSO and Vice President of Preclinical R&D at Karo Bio

Topic

Estrogen receptor beta-selective compounds and their potential role in cancer therapy

The two subtypes of the estrogen receptor may have different and opposing roles in certain cell types; ERalfa inducing proliferation and ERbeta acting as an anti-proliferative and pro-apoptotic regulator.

In contrast to some other cancer forms, where the ERbeta receptor is down-regulated as tumors progress, cholangiocarcinoma tumors retain the expression of both estrogen receptor subtypes. Karo Bio has, together with collaborators in Italy, investigated the effects of an ERbeta selective compound, both in vitro and in a chemically induced rat model of cholangiocarcinoma. The results demonstrated that selective activation of ERbeta reduced hepatic tumor infiltration and tumor volume. The findings open up for new treatment opportunities for this severe and rare cancer form for which very few therapeutic options exists today.

ERbeta is strongly expressed in cells of the immune system and together with collaborators at Karolinska Institute, Karo Bio has also investigated the anti-tumorogenic efficacy of agonist activated ERbeta in models of murine and human B- and T-cell lymphoma. Results demonstrated that selective activation of ERbeta inhibited lymphoma cell proliferation in vitro and the growth and progression of grafted lymphoma cells in vivo.

Notes:

Speaker Profile

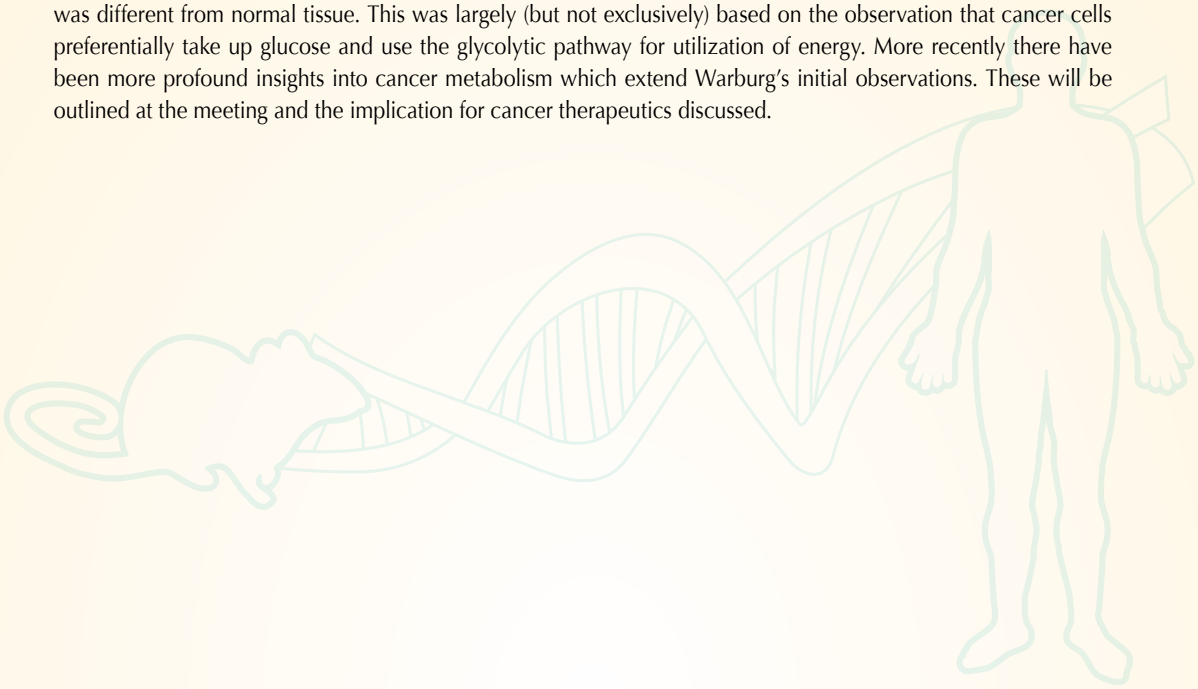
Rajesh Chopra, MD, PhD

Vice President Translational Development, Celgene, USA

Topic

"Cancer Metabolism: The Warburg Effect Revisited"

Otto Warburg, received the Nobel Prize in the 1920's, for the observation that the metabolic status of cancer cells was different from normal tissue. This was largely (but not exclusively) based on the observation that cancer cells preferentially take up glucose and use the glycolytic pathway for utilization of energy. More recently there have been more profound insights into cancer metabolism which extend Warburg's initial observations. These will be outlined at the meeting and the implication for cancer therapeutics discussed.



Notes:

Speaker Profile

John Lyons, MSc, PhD

Vice President Translational Research and Development, Astex Therapeutics Ltd, UK

John Lyons joined Astex as Director of Oncology in October 2003 and in 2007 was named VP of Translational Research with responsibility for the development of strategies for all of Astex's clinical oncology programmes. He has 19 years of industrial experience of cancer biology and clinical development and joined Astex from SuperGen Inc., where, as Senior Director of Scientific Development, he was responsible for the development of Dacogen™ approved for MDS, a form of leukemia. Prior to this, he spent 8 years at Onyx Pharmaceuticals were he led the team that discovered Nexavar, a molecule approved in the US and Europe for renal cell carcinoma and hepatocellular carcinoma. He also worked at Pierre Fabre Medicament in Castres, France and at Cetus Corporation in the US. Dr Lyons is a member of AACR and obtained his PhD in 1989 from the University of Ulm, Germany.

Topic

Fragment to clinic: Translational biomarkers for clinical candidates derived from fragment-based drug design

Heat Shock Protein 90 (HSP90) is a member of a family of molecular chaperone proteins which directs the folding of polypeptides into functional configurations affecting stabilisation and activation. AT13387 is a small molecule inhibitor of HSP90 discovered using fragment-based drug discovery. Pharmacokinetic studies in tumor bearing mice showed that AT13387 exhibits a much extended tumor half life compared to that in plasma.

We characterised the kinetics of pharmacodynamic (PD) activity in mouse models and how they may correlate with efficacy on a particular dose schedule. These data were then used to validate and translate a number of laboratory assays into a biomarker platform for use on clinical samples. Plasma and tumour samples from a phase I clinical study were used to develop and confirm a set of PD biomarker assays to assess the level of HSP90 inhibition in patient samples.

We show that a xenograft tumor half life of up to 72 hours results in the modulation of markers of HSP90 inhibition; including an induction of HSP70 and a reduction in the levels of client proteins for between 6 and 96h. This extended PD effect predicted efficacy on both once or twice weekly dose schedules and this was confirmed in a number of xenograft models. An HSP70 ELISA assay in peripheral blood mononuclear cells (PBMCs) was developed and again, in the mouse model, HSP70 induction was observed at between 1 and 6h, consistent with the plasma half life of AT13387 at 4 hours. There was a dose dependent effect of AT13387 on HSP70 induction resulting in a significant increase at doses above 60mg/kg. We confirmed that the HSP70 ELISA effectively monitored HSP70 in human PBMCs in an ex vivo assay and used the dose and time dependency data to design a sampling procedure for the phase I clinical study.

Finally, we attempt to correlate these effects in GIST preclinical models using a soluble c-Kit ELISA assay from culture media and plasma samples and extend these findings to clinical samples from a Phase I clinical trial.

Notes:

Speaker Profile

Mikio Arisawa, PhD

Executive Manager, Chugai Academy for Advanced Oncology
(Former head of R&D in Chugai Pharmaceutical Co., Ltd., Japan)

Mikio Arisawa is the Executive Director of Chugai Academy for Advanced Oncology (CHAAO), a wholly Chugai-sponsored non-profit organization. Before he retired from Chugai Pharmaceuticals in March 2010, he was a Senior Vice President responsible for Research and Early Development.

He joined research at Roche in 1972 and worked on infectious disease, biochemical screening, natural products, and development of antibiotics until 1987. Two years during this period, he worked in Basel Switzerland. In 1987 he became responsible for the operation of Roche Global Screening, in 1993 was assigned to the global Head of Antifungal Discovery, and in 1999 to Head of Oncology in Roche Discovery in Japan. He joined Chugai in 2002 as a Vice President when Nippon Roche and Chugai merged. Since then, he headed Chugai Research until 2010 together with additional responsibility for Technology Development (2004-2005) or Early Development (2005-2010). He held positions of Director of Roche Research in Japan and Executive Board Member of Roche Japan, and Roche Global Research Management Team for five years from 1997.

Dr. Arisawa received PhD in Pharmaceutical Science from The University of Tokyo and Master's degree in Molecular Biology from Nagoya University.

Topic

Innovation management in drug discovery

Discovering new drugs is not only the most useful approach to combat a disease for which available therapy is insufficient, but is also the only source for the sustainable growth of pharmaceutical industry. In drug discovery, we cannot stress more the importance of identifying innovative drugs with significant superiority to the available therapies at the time of launch. New drug targets with sound scientific evidence give a basis for an innovative therapy, but it takes several years before such scientific basis is proven in a clinical setting, and even longer until the drug is proven to provide significant overall benefit to patients. Management in drug discovery is therefore the management of such uncertainty over several years to achieve two apparently 'incompatible' aims; innovation and productivity.

Although scientific rationale should always be a platform, target setting of each project plays a role in drug discovery, since various aspects need to be taken into consideration for this process, such as expertise and experience in disease biology, therapy and discovery technology, level of science, resource availability, financial aspects, alliance strategy, capability in development and so on. Strength and weakness in each component vary from an organization to another, consequently making optimization of strategy and management critical for success. In this presentation, I am going to talk about our oncology discovery in a mid-sized research focusing on how we have managed drug discovery to differentiate ourselves from big competitors. A few examples will be shown.

Notes:

Session IV:

Introduction to Chairpersons:

Richard DiMarchi, PhD

Department of Chemistry, Indiana University, USA

Richard DiMarchi is the Linda & Jack Gill Chair in Biomolecular Sciences and Professor of Chemistry at Indiana University. He 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 currently serves as a co-founder and Board Chairman of Ambrx, Inc. He previously served as a board member to the biotechnology trade group BIO and the American Peptide Society, as well as such companies as Millennium Biotherapeutics and Inproteo. He currently serves as Board member to Isis Pharamceuticals, and scientific advisor to Alba Inc., Epitome Biosciences, Kai Pharmaceuticals, Semafore Biotechnologies, 5AM Ventures, and Twilight Ventures.

John Amatruda, MD

Retired Merck Sr. VP & Franchise Head, Diabetes/Obesity, USA

Most recently Dr. Amatruda was Senior Vice President and Franchise Head for Diabetes and Obesity and a member of the Research Management Committee at Merck. Dr Amatruda graduated from Yale University, received his MD degree from the Medical College of Wisconsin and did his internship and residency in Internal Medicine and Fellowship in Endocrinology and Metabolism at The Johns Hopkins Hospital. He is board certified in internal medicine and Endocrinology and Metabolism. Dr. Amatruda was a Professor of Medicine at The University of Rochester School of Medicine where he was head of the Clinical Research Center, fully funded as principle investigator on two NIH grants and acting Head of the Endocrine Metabolism Unit. He left the University of Rochester to start and run a drug discovery group at Bayer Corp where he was Vice President and Therapeutic Area Research Head as well as a Professor of Medicine Adjunct at Yale University School of Medicine. He assisted in the approval of Acarbose and his group put several compounds into clinical development including the first glucagon receptor antagonist. Dr. Amatruda left Bayer to become the Vice President and Therapeutic Area Head for Metabolism and Atherosclerosis at Merck. He was also acting Therapeutic Area head for Cardiovascular. Most recently Dr. Amatruda was Senior Vice President and Franchise Head for Diabetes and Obesity and a member of the Research Management Committee. Dr. Amatruda's group filed VItorin, Januvia and Janumet. Dr. Amatruda is an author on 150 papers, abstracts, reviews and book chapters. Dr. Amatruda continues to see patients.

Speaker Profile

Nancy A. Thornberry

Senior Vice President and Franchise Head, Diabetes and Obesity, Merck & Co. Inc., USA

Nancy A. Thornberry is Senior Vice President and Franchise Head, Diabetes and Obesity, for Merck & Co. Inc. In this role, she leads discovery and clinical research in metabolic disorders such as diabetes and obesity. Nancy initiated and led Merck's dipeptidyl peptidase 4 (DPP-4) project, which resulted in the discovery of JANUVIA® for the treatment of Type 2 diabetes.

Nancy began her career with Merck Research Laboratories in 1979 as a biochemist and has served in many roles of increasing responsibility. She has held her current position since November 2009. In her tenure at Merck, she has achieved many notable scientific accomplishments, including the identification of the first caspase, interleukin-1β converting enzyme (ICE/caspase 1) as the cysteine protease responsible for IL-1β processing in monocytes.

She has also developed a novel approach involving positional scanning substrate combinatorial libraries for analysis of protease specificities.

Nancy has been awarded the Merck Presidential Fellowship for her outstanding achievements in drug discovery and development. In 2007, she received the Merck Directors Award, the highest and most prestigious award at Merck, for her role in the Januvia project.

Topic

New Therapies for the Treatment of Type 2 Diabetes: Challenges and Opportunities

The pathogenesis of type 2 diabetes (T2DM) involves a set of three primary defects: insulin resistance, insulin secretory dysfunction, and hepatic glucose overproduction. These defects are the principal targets of both current and future therapy. Currently available classes of oral antihyperglycemic agents include biquanides (hepatic glucose production), PPARg agonists (insulin resistance), sulfonyureas /meglitinides (insulin secretion), and DPP-4 inhibitors (insulin secretion/hepatic glucose output). These agents are used either in monotherapy or, increasingly, in combinations to lower glucose levels. Injectable therapies, typically used after failure of oral therapies, include insulin analogs and GLP-1 agonists. Despite the availability of a range of agents for the treatment of T2DM, there remain critical unmet medical needs, including increased efficacy in monotherapy and/or combination, improved durability, excellent safety/tolerability, and/or simultaneous control of glucose and comorbidities. Therapies that have the potential for a cardiovascular benefit are a particularly high priority. Several new approaches for the treatment of T2DM are currently being explored in clinical studies: oral approaches include SGLT2 inhibitors and glucokinase activators. New insulin analogs and a number of GLP-1 agonist peptides are also in clinical development. The limitations of existing therapies, and the potential of new classes for the treatment of this disorder, will be discussed.

Notes:

Speaker Profile

Matthias H. Tschöep, MD, PhD

Arthur Russell Morgan Chair of Medicine, Metabolic Disease Institute & Diabetes and Obesity Centre, University of Cincinnati, USA

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

Topic

CNS Integration of Systems Metabolism: Target Opportunities for Diabetes Prevention and Therapy

Numerous gut hormones have been reported to affect food intake, metabolism and body weight, mostly via modulation of specific target circuitry in the CNS. Bariatric surgery interventions represent still the only curative approach for morbid obesity and show promise for the treatment of diabetes. Efficient types of bariatric surgeries cause considerable changes in gut hormone patterns, which are thought to be at least in part of mechanistic relevance for metabolic benefits. We are working toward utilization of several afferent gut hormones as an indirect way of modulating CNS control centers of metabolism and ultimately design new combination therapy approaches. Recently we described a series of potent single molecule glucagon-GLP1 co-agonists with a molecular weight and structure similar to glucagon. These drug candidates were sufficiently potent to eliminate obesity and insulin resistance in diet-induced rodent models of obesity. In separate studies, we developed a similar sized single molecule co-agonist with full potency at the GLP1 and the GIP receptor. As expected, this molecule impressively increased insulin sensitivity in DIO rodent models. Unexpectedly, GLP1-GIP single molecule co-agonists also cured obesity using this pre-clinical model, in spite of earlier reports that GIP-R agonism may have anti-lipolytic effects. In parallel we tested new activation blockers of the adipogenic stomach hormone ghrelin, novel combinations of adipokines with liver factors or gut hormones as well as previously unexplored combinations of cannabinoid and opioid system components with promising results. In summary, our results provide encouraging support for the notion that indirect targeting of key CNS control centers via afferent hormone signals may offer a superior, safe and effective way to prevent and treat the metabolic syndrome.

Notes:

Speaker Profile

Markus Stoffel, MD, PhD

ETH Zurich, Institute for Molecular Systems Biology, Wolfgang-Pauli Str. 16, 8093 Zurich, Switzerland

Prof. Markus Stoffel is the Professor of Metabolic Diseases at the Institute of Molecular Systems Biology at the ETH Zürich since 2006. After studying Medicine in Cambridge, UK and Bonn, Germany, he performed postdoctoral studies on the genetics of type 2 diabetes at the Howard Hughes Medical Institute at the University of Chicago. In 1995 he joined the faculty of the Rockefeller University, New York, as Assistant Professor and Head of Laboratory of Metabolic Diseases and was promoted to full Professor in 1999. His major research interests focus on molecular mechanisms regulating glucose and lipid homeostasis, insulin secretion and insulin signaling and controlling of gene regulatory networks through transcription factors and small non-coding RNAs. His major contributions have been the identification and characterization of genes responsible for genetic forms of early-onset type 2 diabetes, the identification of growth-promoting genes and networks in pancreatic β-cells, the characterization of transcriptional networks responsible for the molecular switches between fasting and postprandial metabolism and the discovery and characterization of microRNAs in the control of pancreatic beta cell growth and metabolism. He has received numerous awards, including the Pew Award in the Biomedical Sciences (1996), the Bristol Myers Award in Metabolism (2002), the Irma Hirschl Award (1996), the Wieland Prize (2008) and the Outstanding Scientific Achievement Award (ADA) in 2006 and the Minkowski Price (EASD) in 2007, ERC Grant Award in 2010.

Topic

MicroRNAs: Function in metabolism and therapeutic opportunities

MicroRNAs (miRNAs) are an abundant class of short non-coding RNAs that have been identified in the genomes of a wide range of multi-cellular life forms as well as viruses. Like conventional mRNAs, miRNAs are transcribed by polymerase II as long primary transcripts that are capped, polyadenylated and spliced. Unlike mRNAs, miRNAs are processed into 19-22-nt duplexes by a two-step process involving nuclear and cytosolic RNase III-type endonucleases, known as Drosha and Dicer, to yield the 'mature' miRNA. In a final step this RNA duplex is loaded into the RNA silencing complex (RISC) where the functional strand engages in imperfect base pairing with specific sequences in a target mRNA, thereby inducing either degradation of its target transcript or translational repression. This mechanism resembles the process of RNA interference triggered by double-stranded RNA and utilizes similar molecular machinery. We have identified miRNAs that play essential roles in integrating metabolism by regulating the function of pancreatic β-cells, liver and adipocytes. I will discuss three microRNAs, miR-122, miR-375 and miR-103, which play essential roles in cholesterol synthesis, pancreatic β-cell growth and insulin sensitivity, respectively. Furthermore, the concept of pharmacologically targeting miRNAs to regulate protein networks that are involved in disease etiologies will be discussed.

Notes:

Speaker Profile

Charles F. Burant, MD, PhD

Dr. Robert C. and Veronica Atkins Professor of Metabolism
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

Insights into insulin resistance from metabolomics analysis following bariatric surgery.

Significant improvement in insulin resistance, cardiovascular risk factors and resolution of diabetes can found following weight loss. Roux-en-Y (RY) gastric bypass is more effective than either Gastric Banding (GB) or the institution of Very Low Calorie Diets (VLCD). We have conducted a series of metabolomic studies to understand the alteration in plasma metabolite levels in obesity and changes following weight loss and their relationship to improvement in metabolic parameters. In initial experiments, we assessed the levels of plasma and cerebral spinal fluid levels of amino acids and fatty acids in overweight and obese individuals at baseline and following 10% weight loss. We found that the fall in most amino acids in the CNS paralleled the expected fall in the plasma, but the relative reduction in CSF amino acids was greater in the more obese individuals.

We next used directed metabolomics to profile plasma amino acid levels in 3 groups of non-diabetic women during a mixed meal challenge: 4 lean (BMI=21.1±1.5), 6 before (BMI=53.3±11.0) and after (BMI=36.6±3.8) Roux-en-Y (RY) bypass, and 5 before (BMI=40.8±5.0) and after (BMI=34.5±5.2) Gastric Banding (GB). Fasting BCAA were higher at baseline in the RYGB and LAGB subjects compared with lean (17 and 24%, respectively), consistent with previous observations and decreased following wt loss in both groups. We find a linear relationship between BCAA (and the individual branched chain amino acids) and insulin resistance, in lean and obese pre- and post-surgery. In contrast, there was an inverse relationship between fasting glycine levels and HOMA. We also assessed the dynamic changes in plasma amino acid levels in response to Optifast challenge, before and following surgical weight loss. A consistent alteration in the amino acid curves post-RYGB was seen, with a sharper and higher rise in most amino acids compared to the profiles in LAGB patients after surgery (Figure 8A). This unique profile is likely due to the Roux-en-Y operative procedure and not due to alteration in body weight as final weight was identical in following surgery in both groups. A simple but potentially physiologically important explanation is that the diversion of nutrient absorption past the duodenum results in upregulation of intestinal transporters causing more rapid absorption.

In an initial analysis to identify additional metabolites that may contribute to satiety signals and glucose homeostasis following RYGB, we analyzed fasting and 30 min post-prandial plasma from individuals at baseline and 12 mos following RYGB (24.5% wt loss). When fasting samples were compared we found 24 (out of 239) metabolites were statistically different. Notable decreases were fatty acids, glucose and ketone bodies and vitamin D metabolites. Significant increases were seen in arginine, which is not detected in our standard amino acid assay and the catecholamine metabolite vanillylmandelic acid which has previously been reported to fall following wt loss induced by diet (74). Interestingly, vanillylmandelic acid was reduced 30 minutes following RYGB-induced weight reduction. When we compared the levels of metabolites 30min after meal in presurgical subjects, we found a significant change in a number of metabolites (Table). Additional data from GB patients suggest a procedure-specific change in metabolite dynamic. The data show that we will be able to further elucidate the relationship between amino acids and other metabolites with body wt, insulin resistance, wt loss and modality of weight loss. These data also emphasize the importance of examining post-meal changes after surgery that have not been previously reported.

	Number	UP	Down	Comment
Baseline Pre vs post	24	7	17	Down primarily fatty acids and derivatives.
Baseline 0 to 30 min MMTT	52	25	27	Increases in amino acids, glucose, lactate, bile acids; decreases in fatty acid species
Wt Loss 0 to 30 min MMTT	75	21	54	Increases in amino acids, glucose, lactate, bile acids; decreases in fatty acid species, catacholamines

Notes:

Session V:

Introduction to Chairpersons:

Nancy A. Thornberry

Senior Vice President and Franchise Head, Diabetes and Obesity, Merck & Co. Inc., USA

Nancy A. Thornberry is Senior Vice President and Franchise Head, Diabetes and Obesity, for Merck & Co. Inc. In this role, she leads discovery and clinical research in metabolic disorders such as diabetes and obesity. Nancy initiated and led Merck's dipeptidyl peptidase 4 (DPP-4) project, which resulted in the discovery of JANUVIA® for the treatment of Type 2 diabetes.

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She has also developed a novel approach involving positional scanning substrate combinatorial libraries for analysis of protease specificities.

Nancy has been awarded the Merck Presidential Fellowship for her outstanding achievements in drug discovery and development. In 2007, she received the Merck Directors Award, the highest and most prestigious award at Merck, for her role in the Januvia project.

Gianni Gromo, MD, PhD

Global Head Metabolic & Vascular Disease Area, Roche, Switzerland

Gianni Gromo joined Roche in 1998, as Head of Global Cardiovascular Research (to include Metabolic Research from 2001) and in 2002 became Head of Discovery Research, Basel and in 2006 Head of Discovery Research and Non Clinical Development, Basel.

Before joining Roche, Gianni Gromo was Acting Vice President for the Cardiovascular Division of Eli Lilly in Indianapolis, USA, having been first Medical Advisor and then Research Director for Lilly from 1995. Between 1988 and 1994, he was Immunology Section Leader and then Research Director for Italfarmaco in Milan, Italy.

Gianni Gromo trained in medicine and gained his PhD in Clinical and Experimental Haematology at the University of Milan, followed by a Fellowship in Experimental Oncology at the University of Pavia, Italy. From 1980 to 1984 he was Associate Medical Doctor, University of Milano, Divisione di Medicina II, San Raffaele Hospital, Milano, Italy. From 1984 to 1988 he was first Postdoctoral Associate and then Assistant Professor, at the Immunobiology Research Center, Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota, US

Gianni Gromo is married with Paola, they have two daughters Giulia & Martina. He has a long standing interest in modern art, tennis, skiing, hiking and scuba diving.

Speaker Profile

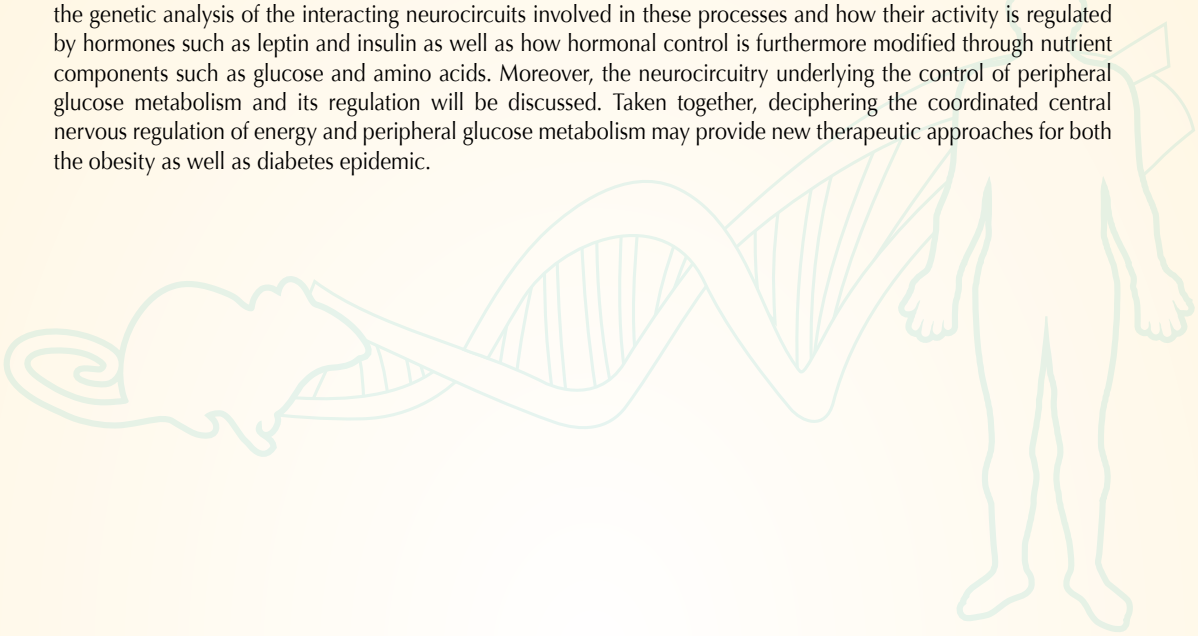
J. C. Brüning, MD

Institute for Genetics, University of Cologne, Germany

Topic

Dissecting hypothalamic signaling: Targeting metabolic diseases

The central nervous system serves as a central regulator of energy homeostasis by integrating signals from the periphery of the organism such as hormones as well as nutrient components to adapt food intake, energy expenditure as well as locomotor activity to the degree of peripheral energy sources. The presentation will focus on the genetic analysis of the interacting neurocircuits involved in these processes and how their activity is regulated by hormones such as leptin and insulin as well as how hormonal control is furthermore modified through nutrient components such as glucose and amino acids. Moreover, the neurocircuitry underlying the control of peripheral glucose metabolism and its regulation will be discussed. Taken together, deciphering the coordinated central nervous regulation of energy and peripheral glucose metabolism may provide new therapeutic approaches for both the obesity as well as diabetes epidemic.



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Speaker Profile

Dana M Small, PhD

Associate Professor, Yale University School of Medicine and The John B Pierce Laboratory, New Haven, Connecticut, USA

Dr. Small is an Associate Professor in Psychiatry at Yale University and an Associate Fellow at the John B Pierce Laboratory. She completed her graduate work in Neuroscience and Clinical Psychology at McGill University in Montreal, Canada in 2001. Her research focuses on understanding the psychology and neurophysiology of taste, flavor and feeding in humans. Dr. Small has received numerous international awards for her work including the Ajinomoto award for research excellence in gustation, The Mosckowitz-Jacobs award for research in the psychophysics of taste and smell, and the Ruth Pike award her contributions to the field of nutrition. Her work has been covered by Scientific America, Science Now, Good Morning America, Nightline, National Public Radio and The Nature of Things. She is especially honored to have been included as an expert muggle scientist in the book "The Science Behind Harry Potter". Dr. Small has delivered over 50 invited lectures and serves on the executive committee for the Association for Chemoreception Sciences and on the editorial board of several scientific journals. Her laboratory is currently funded by the National Institute on Drug Abuse, National Institute of Diabetes and Digestive Kidney Diseases, and National Institute on Deafness and Other Communication Disorders.

Topic

The dynamic relationship between brain response to food and body weight: Teasing apart cause and consequence

There is now strong evidence that body weight influences brain response to the sensation of food. However, the extent to which these differential responses reflect cause or consequence of obesity is unknown. For example, a brain region that responds differently in obese compared to healthy weight individuals may represent a biomarker for weight gain susceptibility or it may reflect a neural adaptation that occurs as a consequence of the metabolic and physiological alterations that are known to accompany obesity. In this lecture I will present data to support the working hypothesis that the relationship between brain response to food and body weight is dynamic and accompanied by cognitive correlates. It will be argued that overeating leads to down regulation of dorsal striatal response to a palatable and energy dense food and that this down regulation is associated with increased impulsivity that may confer further risk for overeating. Genetic influences on this neural adaptation will also be discussed. Finally, preliminary evidence will be presented suggesting that amygdala-dependent learning and memory mechanisms may promote eating in the absence of hunger and that these mechanisms may also undergo adaptation in the face of increased body weight.

Notes:

Speaker Profile

Mukul R. Jain, PhD

Senior Vice President - Pharmacology, Zydus Research Centre, Ahmedabad, India

Dr. Mukul Jain is associated with Zydus Research Centre as Senior Vice President - Pharmacology. He is also leading the New Chemical Entities (NCE) program at this R&D Centre of Zydus Cadila Group. Dr. Jain obtained his B.Pharm., M.Pharm. and PhD degrees from Nagpur University, Nagpur, India. He also has a diploma in Business Management from Nagpur University and a certificate in Executive Management from Indian Institute of Management (IIM), Ahmedabad. Dr. Jain has over 20 year's total research experience. After completing his PhD in Faculty of Medicine of Nagpur University, he worked as Research Scientist at Wockhardt Research Centre, Aurangabad and then at Ranbaxy Research Laboratories at New Delhi before moving to USA as Post-doc Associate at University of Florida at Gainesville. After spending three years as a Post-doc in the area of Molecular Neuroendocrinology, he returned to India & joined NIPER as Assistant Professor of Pharmacology. In the year 2000, Dr. Jain joined Zydus Research Centre, when this Centre had just started the NCE Research Program and since then he has been associated with ZRC in various capacities. At ZRC, he has remained a key person for all the 9 NCEs that have been designed & developed at this Centre and undergoing human clinical trials. His group has also developed preclinical dossier for 7 recombinant therapeutic proteins and the H1N1 vaccine developed by Zydus Cadila. Currently, about 20 different NCE discovery & development programs are ongoing at ZRC including 3 in collaboration with MNCs. Under his supervision, ZRC has received various national & international accreditations including GLP, NABL & AAALAC. Dr. Jain has contributed to more than 25 patents as co-inventor and more than 120 research publications, including 54 full-length research papers in reputed International Journals. Dr. Jain is connected with various academic institutes and has guided research work of several Masters & Ph.D students. He is a Fellow of Academy of Science & Animal Welfare and the Chairman of the Institutional Animal Ethics Committee at ZRC. He is also a member of several International Scientific Communities including American Chemical Society, American Diabetes Association, European Association for Study of Diabetics, Indian Pharmacology Society, American Association for Advancement of Sciences, International Brain Research Organization and Who's Who of Professionals.

Topic

ZYOG1: A Novel Oral GLP-1 agonist for treatment of Type 2 Diabetes

Incretins have recently emerged as a new class of therapeutic agents for type 2 diabetes mellitus. GLP-1 is the major incretin hormone secreted by the L cells of intestine. Apart from beneficial effects on hyperglycemia, GLP-1 agonists are known to reduce weight and show potential for the improvement of the beta cell function. Currently available GLP-1 agonists are all injectables and are associated with immunogenicity & side effects such as nausea.

We have developed a novel, orally bioavailable, short-chain peptidomimetic GLP-1 agonist, ZYOG1 for the treatment of type 2 diabetes mellitus. ZYOG1 forms similar secondary structure to native GLP-1 peptide under physiological conditions. ZYOG1 is stable at room temperature and in various biological matrices including GI fluids, plasma, and blood.

ZYOG1 showed potent GLP-1 agonistic activity in CHO cells overexpressing hGLP-1R. Oral administration of ZYOG1 showed good antihyperglycemic and anorexic effects in various animal models of type 2 diabetes. ZYOG1 showed oral bioavailability & desirable PK profile. It is eliminated mainly via non-renal pathways. The 28-day repeated-dose toxicity studies in Wistar rats and Beagle dogs revealed good safety profile, and absence of any immunogenicity. ZYOG1 was devoid of any nausea or vomiting effects in relevant models including Beagle dogs.

Phase-I human trials of ZYOG1, using oral dosage form, revealed dose-dependent pharmacokinetics and favorable pharmacodynamic and safety profile.

In conclusion, ZYOG1 represents a novel and orally bioavailable GLP-1 agonist for the safe and effective treatment of T2DM.

Notes:

Speaker Profile

Faming Zhang, PhD

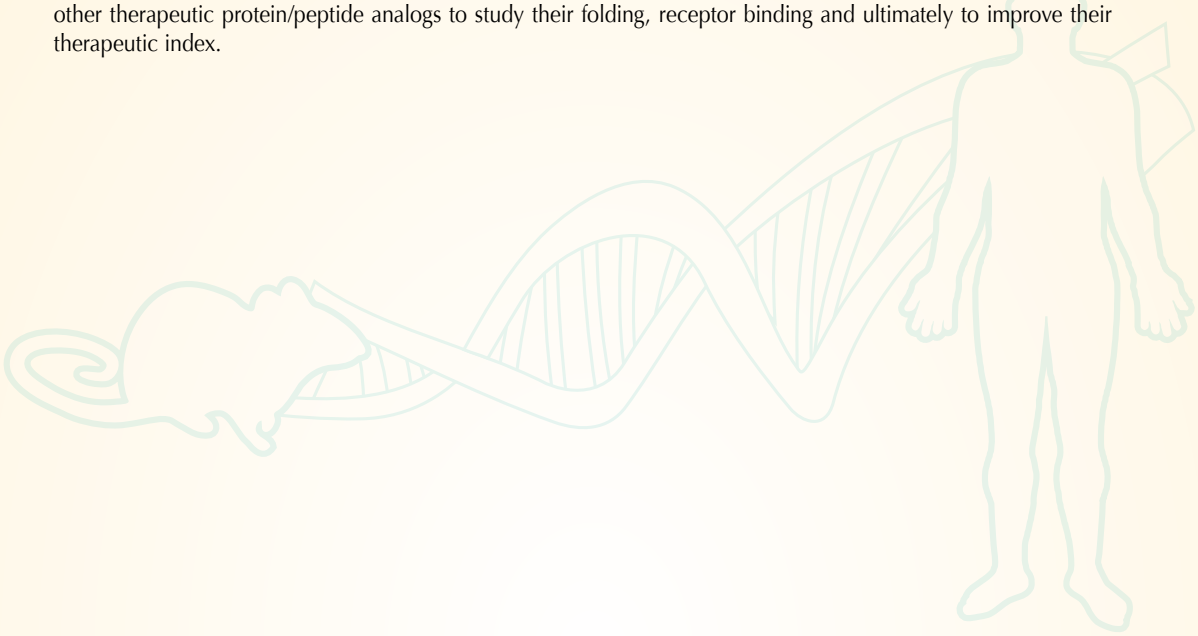
CEO, Waterstone Pharmaceuticals Inc., USA.

Dr. Faming Zhang is the co-founder and CEO of Waterstone Pharmaceuticals and CBO of Crown Biosciences Inc. Prior to co-founded Waterstone and Crown Bioscience, Dr. Zhang was an Associate Professor of Chemistry at Indiana University. Dr. Zhang spent 12 years at Eli Lilly & Co. served from a senior research scientist to Global Head of Drug Discovery and Development Information Sciences. While at Lilly, Dr. Zhang led the company's protein kinase crystal structure platform. He is the co-inventor of several patents in the area of kinase inhibitors and novel anti-obesity protein therapeutics. He also played a major role in the progression of cell cycle kinase inhibitors to the clinic. Dr. Zhang received his Ph.D in Biochemistry and Molecular Biology from Inst. of Biophysics, Chinese Academy of Sciences and an MBA from Indiana University Kelly School of Business. He had a 4 year postdoctoral training from the University of Texas Southwestern Medical Center in Dallas. Dr. Zhang has authored more than 30 scientific publications.

Topic

Structure-based design of biotherapeutics with enhanced solubility and bio-stability

We have solved the crystal structures of Leptin, PTH, and Glucagon analogs. These structures elucidated the correlation of key amino acids on the surface of the peptide and proteins with their solubility and biophysical stability. Using protein crystallography and other biophysical methods, we designed some new Insulin, GLP-1, and other therapeutic protein/peptide analogs to study their folding, receptor binding and ultimately to improve their therapeutic index.



Notes:

Speaker Profile

Vishwa Mohan Katoch, MD

Secretary, Department of Health Research (DHR),
Ministry of Health and Family Welfare, Government of India
Director General, Indian Council of Medical Research (ICMR),
V. Ramalingaswami Bhawan, Ansari Nagar, New Delhi

Former Director of National JALMA Institute for Leprosy & other Mycobacterial Diseases, an Institute of ICMR at Agra, Dr Katoch is a distinguished scientist who has won several accolades as well as awards for his research work on Leprosy, Tuberculosis and HIV-AIDS.

His scientific achievements were development of molecular methods of rapid diagnosis of TB, leprosy, DNA chips; DNA fingerprinting methods; viability determination methods like ATP bioluminescence etc. He has 25 years of experience working on microbiology and molecular biology of mycobacterial diseases and has contributed 247 research papers (147 national and 100 European, American and other foreign journals). Studies carried out by his research group at and with collaborators from other institutes, universities and medical colleges have led to important new findings and new technologies such as enzyme based methods in 1980s, molecular biology based techniques in 1990s and genomics based methods in the recent past. These studies have resulted in identification of new genotypes, new diagnostic techniques / molecules for better understanding of molecular basis of drug resistance and mechanisms of pathogenesis of TB, leprosy and other mycobacterial infections.

Among his other achievements are awards such as Young Scientist Award of IAMM 1985; Shere-I-Kashmir Shiekh Abdulla Memorial Oration Award 1989; Dr. G S Iyer Oration Award of ICMR 1990; Erwin Stindl Memorial Oration Award of German leprosy Relief -Organization 1991; Dr.S. C. Agarwal Oration Award of IAMM 1994; Dr.Manu Patel Prize of IADVL 1999; JALMA Trust Fund Oration Award 1999 of ICMR, IAMM Endowment Award 2003; Ranbaxy Science Foundation Award 2004; 10th Major General Sir Sahib Sokhey Memorial Oration Award,2009; 34th Mellanby Memorial Oration, 2009; IAMM (UP) UC Chaturvedi Life Time Achievement Award,2009 etc. Fellow of all prestigious academies of country: National Academy of Sciences (FNASc); Fellow of National Academy of Medical Sciences (FAMS); Fellow of Academy of Sciences, Bangalore (FASc); Fellow of Indian Academy of Science (FNA).

Topic

Expectations of India from global scientific community

Notes:

Session VI:

Introduction to Chairpersons:

Charles F. Burant, MD, PhD

Dr. Robert C. and Veronica Atkins Professor of Metabolism
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.

Tushar Kanti Chakraborty, PhD, FNA, FASc, FNASc

Director, Central Drug Research Institute, Lucknow, India

Dr. Chakraborty is the Director of Central Drug Research Institute, Lucknow, India. Before moving to CDRI, Dr. Chakraborty was Head and Deputy Director at Indian Institute of Chemical Technology, Hyderabad, India. Dr. Chakraborty is specialized in organic synthesis, especially asymmetric synthesis and total synthesis of natural products; Peptides and peptidomimetics; Drug design and Molecular Modeling. His interest also lies in total synthesis of other biologically active natural products. He has obtained his PhD from Indian Institute of Technology, Kanpur, India. Dr. Chakraborty is widely published with more than 100 publications. Dr. Chakrabortry is recipient of many awards including Shanti Swarup Bhatnagar Prize in Chemical Sciences in 2002 and J C Bose Fellowship in 2008 .

Speaker Profile

Gianni Gromo, MD, PhD

Global Head Metabolic & Vascular Disease Area, Roche, Switzerland

Gianni Gromo joined Roche in 1998, as Head of Global Cardiovascular Research (to include Metabolic Research from 2001) and in 2002 became Head of Discovery Research, Basel and in 2006 Head of Discovery Research and Non Clinical Development, Basel.

Before joining Roche, Gianni Gromo was Acting Vice President for the Cardiovascular Division of Eli Lilly in Indianapolis, USA, having been first Medical Advisor and then Research Director for Lilly from 1995. Between 1988 and 1994, he was Immunology Section Leader and then Research Director for Italfarmaco in Milan, Italy.

Gianni Gromo trained in medicine and gained his PhD in Clinical and Experimental Haematology at the University of Milan, followed by a Fellowship in Experimental Oncology at the University of Pavia, Italy. From 1980 to 1984 he was Associate Medical Doctor, University of Milano, Divisione di Medicina II, San Raffaele Hospital, Milano, Italy. From 1984 to 1988 he was first Postdoctoral Associate and then Assistant Professor, at the Immunobiology Research Center, Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota, US

Gianni Gromo is married with Paola, they have two daughters Giulia & Martina. He has a long standing interest in modern art, tennis, skiing, hiking and scuba diving.

Topic

The past, present and the future of cardiovascular translational medicine research

In preparing this presentation on the nature, scope and development of cardiovascular translational medicine (TM), it has been rather difficult to focus on those current aspects of TM that are likely to contribute to improvements in cardiovascular health in the future. The difficulty arises from the considerable span of TM, depending upon the context within which the clinical scientist researcher is working.

The question naturally arises as to which disease, if any, is likely to benefit from TM in the foreseeable future. One might ask: does the concept of TM really work in practice, and how might it be further improved? Most scientific leaders in this field recognise the need for major changes, both in attitudes and structures, in order for interdisciplinary teams to be truly effective.

The potential benefit of making this complex process effective includes:

1) Improving disease understanding 2) Improving confidence in human drug targets 3) Understanding the therapeutic index in humans 4) Enhancing cost-effective decision making.

In essence, we have to move from our current research philosophy, which is dominated by a reductionist approach, illustrated by our current major focus on genes, proteins and pathways, with far less emphasis on organs and organisms. Another way of looking at this problem is to capture in more detail the complex relationships between biological systems at the molecular level and the complex integrated systems Whilst this concept is exciting, I believe there are significant hurdles to be overcome before the new paradigm for innovative discoveries is implemented. The main hurdles are firstly cultural, and secondly intellectual. Cultural hurdles include what I term sub-discipline introspection. By this I mean: can a TM team composed of bioengineers, mathematicians, biologists and clinicians really sustain long-term effective collaboration? The intellectual hurdles which I anticipate include that abandoning a predominantly reductionist research philosophy may prove very difficult;

So in looking to the future of cardiovascular TM , we firstly must keep in mind the salutary advice that the great Nobel physicist, Richard Feynman, stated: “for a successful technology, reality must take precedence over public relations, for nature cannot be fooled”.

Notes:

Speaker Profile

Marcus Hompesch, MD

President - CEO, Profil Institute for Clinical Research, San Diego, USA.

Dr. Marcus Hompesch is an expert in the field of metabolic diseases, clinical metabolic research and the glucose clamp methodology, a licensed physician and entrepreneur.

Dr. Hompesch established Profil Institute for Clinical Research in San Diego, CA in 2004.

Under Dr. Hompesch's leadership, Profil has become a leading institute providing services focused on the early phase clinical development of new diabetes and obesity treatments. Profil has been involved with almost every clinically promising drug and device development in diabetes in more than 140 clinical studies.

Dr. Hompesch received his MD from the University of Duesseldorf, Germany. He spent eight years as a practicing physician receiving his training in internal medicine and diabetology at the Klinikum Wuppertal Medical Center, has actively been involved in designing, performing and publishing many clinical studies on metabolic diseases, in particular early phase diabetes studies. Based on their research Profil authors have published a substantial number of original research articles in peer reviewed medical journals.

Dr. Hompesch has also been a scientific associate at the department of Biostatistics and Medical Informatics at the Ruhr University in Bochum, Germany.

Between 2000 and 2003, prior to establishing the Profil Institute for Clinical Research in San Diego, Dr. Hompesch held various management roles, including executive positions at a contract research institute in Germany. Dr. Hompesch was also the founder of Med.IQ, a company that developed electronic patient records and disease management tools for patients with diabetes, which he led as CEO until completing the sale of the company in 2000.

Positions and Honors

Since 1992, principal investigator for numerous clinical studies, many related to metabolic disorders and evaluating new drug therapies or new devices.

1996 – 1998 Scientific Associate, Department of Medical Informatics, Biometry and Epidemioiogy, Ruhr University, Bochum, Germany
1998 – 2000 Founder & CEO, MKD GmbH, Neuss, Germany; and Founder & President - CEO, med.iq AG, Neuss, Germany
2000 – 2001 Director Clinical Research, Profil Institute for Metabolic Research GmbH, Neuss, Germany
2000 – 2002 General Manager (CEO), Profil Outpatient Trials GmbH, Neuss, Germany
2000 – 2004 General Manager (CEO), Profil Obesity GmbH, Neuss, Germany
2001 – 2003 CFO, Profil Institute for Metabolic Research GmbH, Neuss, Germany
2003 – 2004 COO, Profil Institute for Metabolic Research GmbH, Neuss, Germany
2003 – 2004 Vice-President - COO, Profil Institute for Clinical Research, Inc., Chula Vista, CA, USA
2004 – present President - CEO, Profil Institute for Clinical Research, Inc., Chula Vista, CA, USA

Topic

Phase 1 Clinical Research: Should Safety, Drug Exposure and Clinical Efficacy of Diabetes Drugs Be Assessed in Patients or in Healthy Volunteers?

Based on the dramatically increasing number of patients with diabetes, and the urgent need to find better treatments to effectively battle the diabetes pandemic, the arsenal of drug candidates is growing rapidly. Picking up early indicators about a drug candidate's safety and potential clinical efficacy is highly desirable in order to make the drug development process more effective; in particular, providing robust data much earlier should improve or enable the decision-making about candidates that should be failed early. Looking into the early phase clinical research toolbox, one sees that the pharmacodynamic (PD) characterization of diabetes compounds has historically been based on a number of different methods, with many of them being applied in different variations. A question of growing relevance is that of the appropriate target population in which to assess safety, tolerability and efficacy in the early phases of the clinical development process.

It appears that adhering to the historical approach of moving from the preclinical development into the clinical development with a first-in-human study in healthy volunteers may not necessarily be the most appropriate approach, neither from a safety, tolerability, drug exposure (pharmacokinetics) nor from an efficacy perspective (pharmacodynamics). Based on ethical considerations, the current regulatory environments and on a science-driven, high quality approach to clinical design and clinical execution, it seems appropriate to challenge the current dominant early phase approach. In light of the above, the key regulatory perspectives will be summarized, safety and tolerability considerations will be discussed, and opportunities to include pharmacodynamics (efficacy) profiling into phase 1 clinical research will be presented. Data from studies performed, and methods utilized by the author will be discussed to identify methods that are likely to provide meaningful safety and glucometabolic outcome data in early phase clinical research studies.

Notes:

Speaker Profile

Dhiraj Gambhire, MD

Sr. Scientist, Clinical Research, Cadila Healthcare Ltd., Mumbai, India

Dr. Dhiraj Gambhire is associated with Cadila Healthcare Ltd. as Senior Scientist – Clinical Development. Dr. Gambhire obtained his MBBS, MD (Medicine) degrees from Maharashtra University of Health Sciences, Nashik, India. He is part of the team for the New Chemical Entities (NCE) clinical development program at R&D Centre of Zydus Cadila Group. He has contributed in Phase I – III development programs in areas of Endocrinology, Oncology and Inflammation.

Topic

A prospective, multi-centric, open-label, single arm study to evaluate the safety and efficacy of 4mg of ZYH1 in hypertriglyceridemia in HIV associated lipodystrophy

Background**:** Potent antiretroviral therapy of HIV infections has recently been associated with lipid and glucose metabolism abnormalities and lipodystrophy. Most of patients suffer from hypertriglyceridemia, decrease HDL and hypercholesterolemia. The aim of this open label single arm prospective study was to evaluate the role of ZYH1, a PPARα/γ agonist, in the management of HIV-associated hyper triglyceridemia in HIV associated lipodystrophy.

Patients and Methods: Fifty subjects with HIV lipodystrophy, on highly active antiretroviral therapy (HAART) for at least 18 months and having triglyceride (TG) between 200-500 mg/dl were enrolled in this study after obtaining informed consent. They were treated with ZYH1 4mg for 12 weeks. A primary efficacy criterion was percentage change in TG levels from baseline. Secondary efficacy criteria were correction of lipid profile.

Results: Treatment with ZYH1, 4mg OD for 12 weeks, has reduced triglyceride upto ~44.8% at week 6 and 44.01% at week 12. During the study HDL increased upto ~28.91% at week 6 and ~31.95% at week 12. ZYH1 has demonstrated favorable tolerability profile.

Conclusion: ZYH1 4 mg found to be safe and effective in treatment of hypertriglyceridemia in HIV associated lipodystrophy.

Notes:

Speaker Profile

John Amatruda, MD

Retired Merck Sr. VP & Franchise Head, Diabetes/Obesity, USA

Most recently Dr. Amatruda was Senior Vice President and Franchise Head for Diabetes and Obesity and a member of the Research Management Committee at Merck. Dr Amatruda graduated from Yale University, received his MD degree from the Medical College of Wisconsin and did his internship and residency in Internal Medicine and Fellowship in Endocrinology and Metabolism at The Johns Hopkins Hospital. He is board certified in internal medicine and Endocrinology and Metabolism. Dr. Amatruda was a Professor of Medicine at The University of Rochester School of Medicine where he was head of the Clinical Research Center, fully funded as principle investigator on two NIH grants and acting Head of the Endocrine Metabolism Unit. He left the University of Rochester to start and run a drug discovery group at Bayer Corp where he was Vice President and Therapeutic Area Research Head as well as a Professor of Medicine Adjunct at Yale University School of Medicine. He assisted in the approval of Acarbose and his group put several compounds into clinical development including the first glucagon receptor antagonist. Dr. Amatruda left Bayer to become the Vice President and Therapeutic Area Head for Metabolism and Atherosclerosis at Merck. He was also acting Therapeutic Area head for Cardiovascular. Most recently Dr. Amatruda was Senior Vice President and Franchise Head for Diabetes and Obesity and a member of the Research Management Committee. Dr. Amatruda's group filed VItorin, Januvia and Janumet. Dr. Amatruda is an author on 150 papers, abstracts, reviews and book chapters. Dr. Amatruda continues to see patients.

Topic

Big Pharma: Leveraging for an Efficient R&D Organization

Big Pharma is on a "Burning Platform". R&D expenditures are rising, new drug approvals are not keeping pace with R&D expenditures, patent expirations are leading to decreased revenues, price and regulatory pressures are increasing and late stage failures are becoming more common. This has resulted in a wave of acquisitions, cost cutting, increasing reliance on external innovation and new ways of developing pharmaceuticals to improve the probability of success including an increased reliance on early decision making, biomarkers and early proof of concept studies. Diversification to reduce pipeline risk includes modalities, biosimilars, best in class, and diversification to things other that patented pharmaceuticals. Various organizational models to drive innovation are being used including attempts to incorporate a more entrepreneurial atmosphere. Some solutions to Big Pharmas' issues will be discussed including the importance of translational medicine and innovation outside of Big Pharma, all of which are opportunities for the biotech sector.

Notes:

Speaker Profile

Richard DiMarchi, PhD

Department of Chemistry, Indiana University, USA

Richard DiMarchi is the Linda & Jack Gill Chair in Biomolecular Sciences and Professor of Chemistry at Indiana University. He 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 currently serves as a co-founder and Board Chairman of Ambrx, Inc. He previously served as a board member to the biotechnology trade group BIO and the American Peptide Society, as well as such companies as Millennium Biotherapeutics and Inproteo. He currently serves as Board member to Isis Pharamceuticals, and scientific advisor to Alba Inc., Epitome Biosciences, Kai Pharmaceuticals, Semafore Biotechnologies, 5AM Ventures, and Twilight Ventures.

Topic

Development of Prodrug Chemistry Suitable for Application to Therapeutic Peptides

Bioactive peptides constitute a rich source of new drug candidates. They typically display unique pharmacology, appreciable potency and molecular specificity. The most notable limitations are the parenteral nature of most peptide-based drugs and their relatively short duration of action, as a function of susceptibility to protease degradation and rapid renal clearance. Employment of prodrug chemistry is an attractive approach to minimize the undesirable pharmaceutical properties. While medicinal prodrug chemistry is a well developed field its application has been largely directed at conventional small molecule drugs and approaches to enhancing oral bioavailability. Our work focuses on the development of prodrug chemistry suitable for peptides and proteins with a specific emphasis on pharmacokinetics. A prodrug method divorced from secondary elements such as protease-cleavage is deemed most desirable as a means to maximize reproducible inter- and intra-patient pharmacology. We describe here the use of a prodrug strategy to reversibly inactive peptide hormones at active site amines through site specific formation of reversible amides. The peptide synthesis of such prodrugs is suitable to conventional solid-phase chemical methodology. A set of model peptides were synthesized and their intramolecular degradation to the parent peptide was studied by HPLC and MS methods under physiological conditions. The speed of reaction was observed to be a function of intramolecular chemical cyclization which is controlled by structure of a terminal dipeptide. The observed results with model peptides provide a basis for application to bioactive peptides to study the rate of cleavage in biologically relevant solvents such as plasma in ex vivo and in vivo settings.

Notes:

Speaker Profile

Douglas W. Axelrod, MD, PhD

Chief Medical Officer, Senior Vice President, Development, Ambrx, Inc., USA

Prior to Ambrx, Dr. Axelrod served as Vice President of R&D for Discovery, Early Development and Product Development at Procter & Gamble Pharmaceuticals. In this role, he accelerated the discovery process, improved the discovery to early development transition and led efficiencies in product development. Earlier in his career at P&G Pharmaceuticals, he led the Worldwide Clinical Bone group, stewarding drugs such as Didronel™ and Actonel™ through late clinical development and regulatory approvals, where they became among the leading osteoporosis therapies worldwide. Dr Axelrod was also a major architect of the Genome Research Institute at the University of Cincinnati School of Medicine and served as its Professor of Genome Sciences. Dr. Axelrod obtained his PhD in the Department of Cell Biology at Baylor College of Medicine. He obtained his MD at the same institution, where he completed his Residency in Internal Medicine, Fellowship in Endocrinology and Metabolism and served as Visiting Scientist in the Department of Cell Biology at MD Anderson Tumor Institute before joining P&G Pharmaceuticals in 1990.

Topic

Treatment of Metabolic Diseases with Proteins Optimized for Pharmacological Use

Therapeutic proteins confer great target specificity, while minimizing off-target toxicity. Despite these salutary attributes, many potentially useful proteins display suboptimal pharmacokinetics, requiring high parenteral dosing, frequent administration, or both. These limitations are particularly acute in metabolic diseases such as obesity and diabetes, where the modulating endocrine signals are often tonic and the therapy chronic. Many approaches have been advanced toward improving time of action for proteins. Depot and liposomal formulations, fusions with long-acting protein fragments, or conjugation with polymers to reduce clearance, have significant limitations. In particular, the use of conventional pegylation while successful is unable to exactly specify the location or stoichiometry of chemical modification. We have developed means of pegylating therapeutic proteins with exact stoichiometry and unrestricted in site selection, thereby optimizing pharmaceutical and pharmacological properties. The application of these methods in the treatment of obesity and diabetes will be presented.

Notes:

Speaker Profile

Kasim A. Mookhtiar, PhD

CSO and EVP, Drug Discovery, Advinus Therapeutics Pvt Ltd, Pune, India

Kasim A. Mookhtiar, PhD, is a co-founder and the Chief Scientific Officer of Advinus Therapeutics Pvt Ltd, India's first innovative pharmaceutical research and development company, a Tata Enterprise, based in Bangalore and Pune. At Advinus, he is the Head of Drug Discovery, which is located in Pune. He has over 18 years of experience in Drug Discovery and innovative pharmaceutical research and has progressed from laboratory science to managing a large scientific team. A unique feature of his training is his in depth experience in both chemistry and biology of drug discovery.

Kasim was born and raised in Mumbai, India. After securing admission to the Indian Institute of Technology, Bombay, he pursued a 5-year integrated MS in Chemistry, where he worked with Prof. A.M. Mehta in the area of Synthetic Organic Chemistry. Following his Master's, Kasim traveled to the US to further his education and undertook a doctoral degree with Professor H. E. Van Wart at the Institute of Molecular Biophysics, Florida State University, Tallahassee, Florida. His graduate work encompassed biochemistry, protein chemistry, enzyme kinetics and inhibition and resulted in a dissertation entitled "Purification, Inhibition and Mechanistic Studies of Clostridium histolyticum and Human Neutrophil Collagenases". Kasim followed up his graduate work with a postdoctoral fellowship at the Yale University School of Medicine, where he investigated the basic mechanism of transcription in the process learning molecular biology and structural biology by two dimensional NMR. This very diverse training has developed in him a mindset that solutions to problems are not based in specific area expertise but in taking diverse approaches which would yield the best solution. He is fascinated by the application of non-traditional technologies to solving challenging problems.

Kasim began his professional career by joining the Metabolic Diseases Drug Discovery group at the Bristol-Myers Squibb Pharmaceutical Research Institute in Princeton, NJ, USA, where he worked from1992 to 2003. Early in his career he pioneered the Diabetes and Obesity programs at BMS and was then entrusted with the task of forming the Department of Aging Research in Drug Discovery, a very novel and cutting edge area for both basic and applied research. As Director, he was responsible for the strategic planning of this area and was also involved in numerous strategic efforts in the wider BMS activities.

In 2003, Kasim returned to India as Vice President, New Drug Discovery Research, at Ranbaxy Laboratories Limited. In two years, Kasim built a team of over 200 scientists from multiple disciplines to form a productive and creative group of drug hunters with a culture of innovation and teamwork. This tenure gave Kasim the experience of working in India, which contributed to his successful co-founding of Advinus.

Besides Drug Discovery, Kasim is fascinated by the world around him. His interests are wide and varied, from playing the guitar and writing poetry to traveling and gardening. He reads and watches movies or just "hangs out" with people to relax.

Topic

Liver Selective Glucokinase Activation for Treating Type 2 Diabetes: Translation from Mouse to Man

Glucokinase (GK), the physiological glucose sensor in glucose responsive tissues, plays a pivotal role in plasma glucose homeostasis through control of insulin secretion in pancreatic beta cells and hepatic glucose production in the liver. Small molecule GK activators have been shown to be effective antihyperglycemic agents. However, these molecules have revealed hypoglycemia as an unwanted mechanism-based effect. Previous studies in transgenic mice have shown that liver selective increase in GK has an antihyperglycemic effect without hypoglycemia. In this study, we describe a liver selective small molecule GK activator, GKM-001, that recapitulates the benefits seen in the transgenic mouse model published earlier.

GKM-001 allosterically activates GK in vitro. When dosed in mildly diabetic diet-induced obese mice, the compound dose dependently improves glucose tolerance in an oral glucose tolerance test. However, in fasted normal mice the compound has little effect on plasma glucose levels even at doses ten fold higher than those that show efficacy in the DIO mice. Pharmacokinetic studies showed that the compound had10-fold higher levels in liver compared to plasma. These studies suggest that greater safety may be obtained with liver selective GK activation.

Notes:

Scientific Poster Presentations

P-001: Anti-inflammatory activity of a marketed ayurvedic formulation.

Rohini A., Mahander Maheshwari

Pacific College of Pharmacy, Udaipur, Rajasthan, India

Inflammation is the underlying mechanism in several chronic diseases such as asthma, arthritis, coronary artery disease and some cancers. The current therapy is associated with many side effects such as gastric ulcers (NSAIDs) and heart attacks (COX-2 inhibitors). In the present study, an ayurvedic polyherbal formulation containing the plant and mineral origin was chosen to evaluate the anti-inflammatory activity in wistar rats. The animals were divided into four groups i.e. (i) Saline treated (ii) Positive control (Ibuprofen 10 mg/kg) (iii) Formulation (125 mg/kg) (iv) Formulation (250 mg/kg). The in vivo anti-inflammatory activity was carried out by Cotton pellet granuloma and Freund's adjuvant induced arthritis. In Cotton pellet granuloma method, 125 mg/kg and 250 mg/kg showed significant inhibition of 20.74 % and 43.98 % respectively. In Freund's adjuvant induced arthritis model, the 125 mg/kg and 250 mg/kg showed significant activity ($P < 0.001$) by the end of twelth and ninth day respectively in terms of paw thickness. The *in vitro* anti-inflammatory activity was also carried out by assessing the mast cell stabilization activity and the results show significant activity ($P<0.05$) at 10 and 100 µg/ml. Thus, it can be concluded that this ayurvedic formulation can be used as complementary medicine for the ant-inflammatory activity

P-002: A novel process for the preparation of cis-diamminediiodo platinum (II) and its use in the synthesis of highly pure Carboplatin (Antineoplastic)

Nikhil Singh, Chetan Vasava and Kumar K Singh

Zydus Research Centre, Ahmedabad, India

A novel process for the preparation of an intermediate cis-diamminediiodoplatinum (II) has been generated which is being utilize for the synthesis of Antineoplastic drug in the class of alkylating agent Carboplatin, use to treat non-small cell lung cancer (NSCLC) and ovarian cancer. Process includes reaction of an aqueous solution of potassium tetrachloro platinate (II) (PTCP) with an aqueous buffer of Ammonium iodide (NH_4I) and Ammonium hydroxide (NH_4OH) in mole ratio of 1:1.5 with pH range of 7 to 11 for 4H at ambient temperature provides the pale yellow to yellow coloured solid compound cis-diamminediiodoplatinum (II) in excellent yield (≥ 94 %) with good quality which meets with well defined spectral criteria. This intermediate on further reaction with Silver sulphate in stochiometric amount in water in dark provide an intermediate diaquo complex which on further treated with Barium salt of cyclobutane dicarboxylic acid at ambient temperature provided the crude Carboplatin in excellent yield (≥ 98 %) and purity. Purification of the crude Carboplatin by utilizing water gave us the highly pure Carboplatin as white crystalline powder in good yield (≥ 72 %) with 99.9 % purity and 99.9 % assay by HPLC with silver and barium less than 10 ppm. It meets with all parameters of US pharmacopoeia and European pharmacopoeia. The beauty of our process for the synthesis of Carboplatin includes novelty of process for synthesis of intermediate cis-diamminediiodoplatinum (II), excellent yield and quality and utilization of water as solvent in complete process (green chemistry).

P-003: Protection against schistosomiasis-induced hepatic fibrosis by modulating the immune system.

El-Sisi A, Awara W, El-Masry T, El-Kowrany S, El-Gharbawy R

Tanta University, Egypt.

Hepatic Schistosomiasis is one of the most prevalent forms of chronic liver diseases, resulting in the morbidity from infection due to its complications of liver fibrosis. However, there are few medicines or means available to control and treat fibrosis in Schistosomiasis. The aim of this study was to assess the possible disturbance in immune system and mechanism through which immunomodulating agents can produce their beneficial effects in hepatic schistosomal fibrosis. Three hundred male Swiss albino mice infected with Schistosoma mansoni live cercariae were divided into seven groups: Control; infected (Schistosoma mansoni live cercariae); Praziquantel (500 mg/kg/day); Rosiglitazone (4 mg/kg/day); Propolis (250 mg/kg/day); Bisphenol A diglycidyl ether (BADGE) (30 mg/kg/day); combination of Praziquantel plus Propolis, Praziquantel plus Rosiglitazone, Praziquantel plus BADGE, Rosiglitazone plus BADGE. Blood samples, Liver and intestine were taken for determination of serum interleukin-2, interleukin-10, immunoglobulin E (IgE), immunoglobulin G (IgG) , Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) , hepatic hydroxyproline, immunohistochemical examination of liver tissues and tissue egg count (in liver and colon). Serum

level of IL-2 showed significant increase in mice treated with Praziquantel and Praziquantel plus Propolis, plus Rosiglitazone or plus BADGE and decrease in Rosiglitazone group. Serum IL-10 showed significant decrease in all treated groups except Rosiglitazone and BADGE showed no significant change. Serum IL-10 showed significant decrease in all treated groups except Rosiglitazone and BADGE showed no significant change. Serum IgE, IgG, ALT, AST and hepatic hydroxyproline, showed significant decrease in all treated groups except BADGE showed no significant change. Results showed that combination of chemotherapy plus immunomodulating agents modulate cellular and humoral immune responses led to significant reduction in hepatic hydroxyproline content and liver pathology in schistosomal infected mice

P-004: Characterization of a novel cannabinoid agonist against CB2 receptor for treatment of neuropathic pain

Purvi Vyas[1], Hitesh Bhayani[1], Pravin Kadam[2], Shivaji Gugale[2], Sandeep Shedage[2], Umesh Mali[2], Praveenkumar Singh[2], Siddartha Kar[2], Rahul Salunke[2], Rakesh Patel[3], Brijesh Kumar Srivastava[2], Vishwanath Pawar[3], Mukul Jain[3], Pankaj Patel[1] and Priyanka Priyadarsiny[1].

1 Dept. of Cell Biology; 2 Dept. of Medicinal Chemistry; 3 Dept of Pharmacology. Zydus Research Centre, Ahmedabad, India

Cannabinoid Receptor 2 agonists are being developed as potential therapeutics in management of neuropathic pain. In this study, we characterized the In-vitro efficacy and specificity of ZY8794 against human CB2 receptors using various functional assays like cAMP & [S-35] GTPgammaS Assay. In-vitro specific agonist activity of ZY8794 as agonist was confirmed in presence of CB2 antagonist. In-vivo efficacy of ZY8794 was assessed in different in-vivo models of neuropathic pain.

Inhibition of cAMP in CB2 expressing CHO-K1 cell line identified the NCEs as CB2 agonists. ZY8794 significantly inhibited cAMP in hCB2 receptors with an EC_{50} of 0.67nM compared to that of 40.22nM in hCB1 receptors. In [S-35] GTPgammaS functional assay ZY8794 behaved as a CB2 agonist with EC_{50} value of 2.87nM. The effect of ZY8794 was reversed even at lower concentration of the CB2-R selective antagonist indicating that the effect of ZY8794 is mediated through CB2 receptors. ZY8794 showed a dose dependent anti-allodynia effect in spinal nerve ligation neuropathic pain model and in the chronic constriction injury model of neuropathic pain. These results suggest that ZY8794 is a potent CB2 agonist, which may be beneficial in chronic inflammatory as well as neuropathic pain conditions.

P-005: Investigation in to the immunomodulatory and adaptogenic activity of Trapa bispinosa in myelosuppressed experimental animals

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The objective of the present study was to investigate the immunomodulatory potential of various fractions of aqueous extract of fruits of *Trapa bispinosa* (TBAE) in experimental immune inflammation. The immunomodulatory effect was assessed in mice against sheep red blood cells (SRBC) as an antigen by studying humoral immunity response, cell-mediated delayed type hypersensitivity reaction (DTH), macrophase phagocytosis by carbon clearance method. Histopathological studies of hind paw, lymphoid organs and other vital organs of mice were examined for pathological and morphological changes in D- penicillamine induced immunodeficient mice after induction of DTH reaction. Percent change in neutrophil count by neurophil adhesion test was performed using cyclophosphamide induced immunosuppressed rats. Further to evaluate antistress activity, fresh Wistar rats were subjected to forced swimming endurance test and chronic cold restraint stress. The present investigation suggests that TBAE showed a promising immunostimulatory activity and further its ethanol fraction (TBEtOH) was found a more superior as per designed models of immunostimulatory activity. Further, histopathology studies of mice demonstrated that TBEtOH treated group produced remarkable hypertrophy of dermis and subcutaneous tissue, hyperplasia, leukocyte infiltration, congestion, multiple calcification, presence of macrophase and histiocytes. This is in turn to stimulate leukocyte, fibroblast activation, inflammatory cells migration and chemokines secretions. The anti-stress and adaptogenic activity exhibited by its ethanol fraction in the study suggests that TBEtOH may useful in the treatment of several disorders caused by stress by its immunostimulating and immunomodulating properties and also enhancing the homeostasis mechanism.

P-006: Anti-proliferative effect of Metformin in MCF7 Cells depends on the critical level of expression of CD44, CD24 and P53

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Metformin is a well-tolerated hyperglycemic drug prescribed to type 2 diabetes. Recent reports on the role of metformin suggest that lack of p53 is critical in sensitizing the cancer cells to the metformin treatment. To unravel if identical mechanism exists in the metformin-mediated cytotoxicity observed in MCF7 cells, the MCF7 cells were treated with different concentration of metformin and the effect on cell proliferation was measured by MTT assay. Expression of specific marker genes was measured by realtime RT-PCR and the P53-expression in metformin-treated cells was visualized by specific immunohistochemistry analysis. MCF7 cells treated with 1, 5 and 10mM metformin produced 4, 25 and 42% cytotoxicity at 24 hours post treatment, respectively. Analysis of specific markers indicated that cells treated with 10mM metformin produced 44% decrease in the expression of CD44, whereas the level of CD24 was decreased by 43% compared to the control. However, the relative expression of CD24 was enhanced by 17% when the level of expression was compared with MCF7 cells treated with 1mM metformin. Interestingly the level of expression of P53 remained un-altered in MCF7 cells treated with all three concentration of metformin. To unravel if metformin resistant cells were positive for the expression of P53, metformin-treated cells were probed with anti-P53 antibody and observed to express P53 in almost all surviving MCF7 cells. The results indicated that metformin-induced anti-proliferative effect of MCF7 cells depend on the expression of P53 and balanced level of both CD24 and CD44. The study further affirmed that any MCF7 cells defective in P53 expression or produced enhanced CD44 expression are sensitive to metformin-mediated cytotoxicity in vitro. Such observations open up novel indications for metformin to be used as potential anticancer therapy for cancer cells possessing a defective P53 expression or signaling.

P-007: Evaluation of Antiasthmatic activity of Leptadenia reticulata (Retz.) (Fam. Asclepiadaceae)

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Introduction: Asthma is a complex syndrome that is characterized by mucus hyper-secretion, bronchial hyper-responsiveness. smooth muscle hypertrophy and airway obstruction. Antigen chalange resulting in significant increase in number of inflammatory cells like eosinophils, neutrophils, lymphocytes, monocytes in BALF fluid, increase serum IgE and degranulation of mast cells.

Leptadenia retculata(Retz.) (Fam.Asclepiadaceae) is a plant known as JIVANTI. Plant leaves are used in asthma, skin infections, wounds, nose and ear disorders. It alleviates 3doses vata, pita and kapha. Leaves contain hentriacontanol, α-amyrin, β-amyrin, stigmasterol, ϒ-sitosterol, flavonoids (diosmetin, luteolin) etc.

Material & Methods: The antiasthmatic activity of ethyl acetate fraction of *L.reticulata* (3 different concentration) was studied on the active and passive anaphylaxis in albino rats & ovalbumin sensitized rat bronchoalveolar lavage fluid analysis. Mast cell stabilizing activity using rat mesentary and serum IgE assay was carried out in anaphylaxis rat model which is sensitized by horse serum and triple antigen. WBC and Differential cell count (eosinophils,lymp hocytes,neutrophils) in rat BALF was estimated.

Result: *L.reticulata* treatment showed dose dependent mast cell stabilizing activity and significantly reduced the elevated serum IgE level of actively and passively sensitized rats when compared with sensitized group. *L.reticulata* treatment significantly reduced the elevated WBC, eosinophils, neutrophils, macrophases when compared with sensitized control.

Conclusion: Antiasthmatic and antianaphylactic activity of ethyl acetate fraction of *L.reticulata* may be possibly due to its mast cell stabilizing potential, suppression of IgE antibody level, normalizing the elevated leukocytes and differential leukocyte count and inhibition of antigen induced histamine release.

P-008: Pre Clinical Safety Evaluation of a Novel Topical Nanogel NSAID in Wistar Rats

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Lornoxicam is a member of oxicam group of non-steroidal anti-inflammatory drugs (NSAIDs). Oxicams have potent anti-inflammatory and analgesic effects, but their use is associated with a high risk of adverse gastro intestinal and renal effects by oral route. To understand the toxicity profile of Lornoxicam by dermal application, a novel topical nanogel preparation was made and evaluated for its safety in Wistar rats by dermal application in the strengths of 0.1, 0.5 and 1.0 % concentration for a minimum period of 28 days with 14 days recovery period. There were no signs of gastro intestinal and renal toxicity upto 0.5% concentration of this novel preparation for dermal application. However, drug related toxicity in gastrointestinal tract and kidney were observed at the highest concentration of 1.0% and these lesions were found to be largely reversible over a period of 14 days. The toxico-kinetic data revealed good absorption trend in both the

sexes. It may be concluded that Lornoxicam to have a better safety profile by dermal route in terms of GI and renal toxicity over oral route at a dose of ≤0.5 % to treat post operative pain and rheumatoid arthritis in humans.

P-009: Evaluation of antiasthmatic activity of *Amaranthus spinosus* linn. (Fam. Amaranthaceae)

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Introduction: Asthma is a complex clinical disease characterized by airway obstruction, airway inflammation and airway hyperresponsiveness to a variety of stimuli. The development of allergic asthma exists of three phases, namely the induction phase, the early-phase asthmatic reaction (EAR) and the late-phase asthmatic reaction (LAR). Each phase is characterized by the production and interplay of various cell-derived mediators.

Amaranthus spinosus linn. is a plant belonging to Amaranthaceae family. Plant contains terpenes, flavonoids and isoflavonoids, saponins, sterols, tannins, alkaloids and cardiac glycosides. In Ayurveda, plant is used in bronchitis.

Material & Methods: Antiasthmatic activity of ethyl acetate fraction of leaves of *A.spinosus* was investigated using active and passive anaphylaxis in rats and bronchoalveolar lavage fluid (BALF) model. Anaphylactic study was carried out on rat mesentries sensitized with horse serum to induce mast cell degranulation, were mast cell count and IgE assay was carried out. In BALF model, rats were sensitized by ovalbumin and total leukocyte and differential leukocyte count were estimated.

Result: Treatment with *A.spinosus* showed significant protection against mast cell degranulation and reduction in serum IgE levels in actively and passively sensitized rats and also showed significant decrease in total leukocyte and differential leukocyte count in BALF of ovalbumin sensitized rats.

Conclusion: It can be concluded from the results obtained in present investigation that ethyl acetate fraction of leaves of *A.spinosus* possess significant antianaphylactic and antiasthmatic activity, may be due to the membrane stabilizing potential, suppression of IgE antibody level and normalizing the elevated leukocyte and differential leukocyte count.

P-010: A rare case of dysplasia with adenocarcinoma and foveolar type metaplasia of hepatic and extrahepatic bile ducts in ICR Mice.

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A construction of historical tumor data is of prime importance in justifying the species specific spontaneous tumor data in the carcinogenic or tumorigenic effect of drugs in humans via animal models. As part of routine health activity, mice of age 7 – 8 month old were subjected to clinical pathology and histopathology evaluation. In these review we came across a rare case of dysplasia with adenocarcinoma and foveolar type metaplasia of hepatic and extrahepatic bile ducts in ICR female mice. Although clinical pathology and urinalysis did not reveal altered function, grossly we noted dilatation of bile duct during necropsy. Microscopically, the sections of liver stained with H and E revealed dysplasia with adenocarcinoma and foveolar type metaplastic change with excess cytoplasmic mucin, reactive hyperplasia and multifocal hepatocellular hypertrophy. Bile duct and pancreas showed the same lesion as that of liver of dysplasia with adenocarcinoma and foveolar type metaplastic change with excess cytoplasmic mucin. The neoplastic tubular glands were lined by slender tall columnar cells with mucin containing cytoplasm and basal nuclei having small nucleoli. The glandular lumen showed presence of hemoglobin crystals. To the authors' knowledge, we claim that this is the first report of dysplasia with adenocarcinoma in bile duct in ICR mice.

P-011: Prognostic utility of Insulin like Growth Factor signaling in human breast cancers

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Insulin like growth factor family comprised of ligands, binding proteins and their receptors is known to have a role in the development and maintenance of normal cells and also in tumor cell proliferation, survival and resistance to anti-cancer therapy in breast cancer. IGF-1 and IGFR-1 are the major players of IGF signaling cascade and hence important to get evaluated as predictors of breast cancer prognosis. The current prospective study on 52 breast cancer patients estimated IGF-1 and IGF-1 receptor expression as copy numbers from total RNA extracted from synchronous primaries, malignant lymph nodes and adjacent normal tissues. The copy numbers of IGF-1 and IGFR-1 mRNA obtained with quantitative real time PCR were correlated to the known clinico-pathologic parameters using SPSS 13.0. Downregulation of IGF-1 was seen in 65.38% tumors whereas IGFR-1 was upregulated in 76.92% as

compared to synchronous normal tissues. A trend of increasing mean copy number of IGF-1 and IGFR-1 was seen with advancement of the disease stage. Up-regulation of both IGF-1 and IGFR-1 was evident in 32.69% patients that stamped augmented functionality of IGF-signaling cascade and points the utility of these biomarkers in breast cancer prognostication and stamping of a subset of patients likely to respond to anti IGF-1 therapeutic modalities.

P-012: Anti-Psoriatic effect of TAK-715, a p38 MAP Kinase inhibitor, in an Imiqimod induced Psoriasis model

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Psoriasis is an autoimmune disorder associated with increased cellular infiltration into skin. TLR7/8 ligand imiquimod (IMQ) a potent immune activator can induce and exacerbate psoriasis, a chronic inflammatory skin disorder after topical application. There is growing evidence that the p38 inhibitors play essential role in the modulation of several types of inflammatory condition, however, the exact physiological and pathophysiological roles of the p38MAP Kinase enzyme has not yet been evaluated in imiquimod induced psoriasis. We aimed to investigate effects of prednisolone and TAK-715 a p38 inhibitor on inflammation and cytokine levels after imiquimod application. Imiquimod was applied for 6 days on the shaved back of mice and ear. Ear thickness was monitored daily. On day 7 animals were sacrificed, ear weight were recorded and tissues were frozen for cytokine estimations. The Topical application of Imiquimod cream was sufficient to increase ear thickness along with erythema and scaling. IMQ induced psoriasis also exhibited systemic inflammation with marked leukocytes in blood associated with higher levels of proinflammatory cytokines. Cytokine levels were also elevated in the ear homogenates after IMQ challenge. Both treatments resulted in a significant ($p<0.01$) inhibition of lymphocyte, monocyte and neutrophils. Interestingly, both the treatments exhibited distinct cytokine regulation. Prednisolone treatment showed inhibition of both the serum and tissue cytokine levels whereas p.o. p38 treatment, either showed no effect or up-regulation of certain cytokines. This clearly indicates that although there was partial anti-psoriatic effects observed in p.o. p38 treatment, a local application might yield better results.

P-013: Vascular Endothelial Growth Factor Expression in Human Breast Carcinoma

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Breast cancer is a tumor type in which VEGF is known as a key mediator of angiogenesis. VEGF and its receptor VEGFR are the most important proximal factors that are employed to select the potential candidates likely to respond to anti-angiogenic newer treatment modalities. The functionality of VEGF and its receptor was analyzed at two different levels to determine their role by estimation in a cohort of 50 breast cancer patients. The levels were compared with age matched controls and correlated to known clinico-pathologic prognostic features by multivariate analysis. Moreover, VEGF and VEGFR mRNA from synchronous primaries and malignant lymph nodes were quantitated from the same set of patients with real-time quantitative RT-PCR by absolute quantitation and were correlated to the circulatory levels. Circulating VEGF was significantly elevated in breast cancer patients than controls. Tumor tissues expressed a significantly higher VEGF mRNA in tumor tissues than adjacent normal tissues while VEGF receptor levels were similar in both the sample types. However, VEGF was significantly higher than its receptor at both the levels. VEGF was up-regulated in 86.53% of tumors whereas VEGFR was upregulated 53.84% tumors. A significant linear correlation was observed between VEGF and VEGFR. Prognostic utility of VEGF signaling was evident both at translational and transcriptional level from the present study similar to the other studies and stamp them as surrogate biomarkers for breast cancer. The results of the current study demonstrate the utility of numerous anti-VEGF agents in a subset of our breast cancer patients.

P-014: Aminoguanidine improves anti-asthmatic effect of glucocorticoid agonist dexamethasone: Possible role of HDAC2

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Corticosteroids are the most effective anti-inflammatory therapy for many inflammatory diseases, such as arthritis and asthma; but their chronic treatment produces resistance in asthmatic patients. Glucocorticoids suppress multiple inflammatory genes that are activated in chronic inflammatory diseases. Glucocorticoids reverse histone acetylation of activated inflammatory genes through recruitment of histone deacetylase-2 (HDAC2) to the activated transcription complex. COPD and

asthmatic patients who smoke, have markedly reduced HDAC2 levels as a result of oxidative/nitrative stress and they develop resistance to corticosteroids. We hypothesized that a nitric oxide synthase inhibitor aminoguanidine may reverse this corticosteroid resistance by activating HDAC-2. In the present study, BALB/c mice were challenged with Ovalbumin (i.p.) on days 0 and 14 followed by 14 days of aerosolized OVA exposure. Day-21 onwards animals were treated with dexamethasone, aminoguanidine or their combination. Upon study completion, BAL fluid was collected for haematological analysis and lung tissues were collected for histopathology and snap frozen for gene expression profiling. We found that, cytokines (TNF-α, IL-6, IFN-γ) levels were significantly lower in animals treated with dexamethasone-aminoguanidine combination as compared to dexamethasone alone. Histopathological data showed combination treatment completely resolved the infiltration of inflammatory cells and reduced goblet cell hyperplasia as well as collagen deposition in alveoli. All these phenomenon are closely associated with TGF-β1 cytokine which was markedly inhibited by this combination therapy. The pharmacological mechanism responsible for improved activity of the combination may be elevation of HDAC2 activity due to aminoguanidine. Our results revealed that aminoguanidine may act as a novel 'add-on therapy' with low dose of dexamethasone which may enhance the clinical efficacy of glucocorticoid agonists and help overcome development of resistance to these drugs

P-015: Effects of *Clerodendrum serratum* Spreng. and *Premna herbacea* Roxb. on Concanavalin-A stimulated spleenocytes proliferation

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Root of *Clerodendrum serratum* Spreng. and *Premna herbacea* Roxb. (*Verbanacea*) known under common name Bharangi, which is important constituent of well known formulation Dashmularistha used for the various aliments of disease. Phytocompounds from *C. serratum* (CSM) and *P. herbacea* (PHM) roots were methanol fractioned and used for *in vitro* and *ex vivo* concanavalin A (Con A) stimulated splenocyte proliferation assay. In *in vitro* assay, splenocytes, when incubated with increasing concentrations (20-80 µg/ml) of CSM and PHM, significantly ($p< 0.001$) increased the extent of Con A stimulated splenocyte proliferation in a concentration dependent manner, when compared to the control. In *ex vivo* assay, splenocytes prepared from animals pretreated with CSM and PHM (300 mg/kg) daily for 3 days showed a significant enhancement in the extent of Con A stimulated mitogenic response 28.80± 1.11 and 9.74 ± 0.05 respectively, as compared to control group (9.31 ± 0.29). The ensemble of results indicates that both CSM and PHM were able to produce immunostimulatory action. In both the *ex vivo* and *in vitro* experiments, CSM showed more immunostimulatory effect as compared to PHM.

P-016: A phase II Open label Multicentric Randomized trial to determine the safety and efficacy of Non-pegylated Liposomal Doxorubicin (Nudoxa®) in metastatic breast cancer

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Background: Pegylated Liposomal Doxorubicin (PLD) is one of the treatment options for metastatic breast cancer (MBC). Although, PLD demonstrated reduction in anthracyclines related cardiotoxicity, PLD, at 50mg/m^2 every month, has shown Palmar-Plantar Erythrodysesthesia (PPE), dose limiting adverse events. New non-pegylated liposomal doxorubicin (NPLD) formulation developed by Zydus BSV has shown favourable toxicity profile and reduced potential for PPE in preclinical studies and in Phase I clinical study

This phase II study was designed to establish safety and efficacy of NPLD at 60 and 70 mg/ m^2 every 21 days upto 8 cycles among the MBC subjects.

Patients and Methods: Thirteen patients with MBC were enrolled in this study after obtaining informed consent. They were treated with either Nudoxa 60 mg/m^2 or Nudoxa 70 mg/m^2 every 21 days upto 8cycles as single agent therapy. The primary efficacy criterion was overall response rate to NPLD (60 and 70 mg/m^2) in target lesions of MBC using RECIST criteria.

Results: This is an interim analysis after 5 cycles. Of 13 subjects, 12 were evaluable after cycle 3. One subject withdrew consent after first cycle and was not evaluable. Presented in the table are the investigators' evaluations based on RECIST criteria after cycle 3 and 5 cycles.

	Cycle 3		Cycle 5	
Nudoxa® Dose: mg/m^2 every 21 days	60	70	60	70
Complete Response	0	0	0	0
Partial Response	2	2	0	2
Stable	4	2	4	2
Progressive	0	2	0	2
Dropout	0	0	2	0

Most commonly reported adverse event was Grade I-III) neutropenia at 60 and 70 mg/m^2. No cardiotoxicity was reported in serial 2 D Echo and ECG analysis. No subject was withdrawn due to treatment related adverse events.

Conclusion: NPLD (Nudoxa), 60 and 70 mg/m^2 every 21 days, was well tolerated and also demonstrated efficacy among the MBC upto 5th cycle.

P-017: A novel animal model of non- alcoholic fatty liver disease (NAFLD) with psoriasis

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Psoriasis is an inflammatory disease, the relationship between the disease and co-morbidities are probably related to the underlying chronic inflammatory process. Non-alcoholic fatty liver disease (NAFLD) is one among the emerging co-morbidity diseases of psoriasis. Present investigation was aimed to develop an animal model of NAFLD with psoriasis.

Male C57BL/6 mice were fed either standard chow diet or high fat (60 Kcal%) diet with fructose (40%) in drinking water for 60 days to induce NAFLD. After the induction period the animals were further divided into three groups as NAFLD control, NAFLD+acetone treated (vehicle for oxazolone) and NAFLD+Oxazolone (topical) treated (1% for sensitization (one week) and 0.5% for induction (thrice a week for 2 weeks). Normal animals were also treated in same manner as mentioned above. Body weight and ear thickness were recorded. At the end of the experiment, animals were sacrificed ears, liver and fat pad collected and weighed. Liver and ear samples were subjected to histopathological analysis. Plasma glucose was analyzed by colorimetric method.

The NAFLD animals showed significant increase in body weight ($P<0.0001$), fasting plasma glucose ($P<0.01$) and hepatic steatosis ($P<0.01$). Upon Oxazolone treatment these animals showed substantial increase in ear thickness ($P<0.01$), weight ($P<0.01$) and histopathological features of psoriasis as compared to NAFLD control and normal+Oxazolone animals. The animals fed high fat diet with fructose in drinking water and oxazolon treatment develops features of both NAFLD and psoriasis. These animals represent a suitable experimental model for evaluating new therapeutic strategies for the treatment of NAFLD with psoriasis.

P-018: γ-Lactum hydroxamate based TACE inhibitors

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Tumor necrosis factor alpha (TNF-α) converting enzyme (TACE), a member of A Disintegrin and Metalloprotease (ADAM) family is responsible for the cleavage of membrane bound TNF-α in to soluble form. Compounds that inhibit TACE reduce the level of soluble TNF-α [inflammatory cytokine] and might be effective in controlling various inflammatory diseases. Several orally active small molecule TACE inhibitors are reported in the literature [DPC-333, TMI-005], but none of them hit the market, mainly due to hepatotoxicity and/or lack of efficacy. Earlier efforts were mainly directed to achieve selectivity over MMPs and limited attention has been paid to discriminate between TACE and other ADAM proteases, especially ADAM-10.

Herein we report the design, synthesis and biological evaluation of γ-lactum hydroxamate based TACE inhibitors. The synthesised compounds are more potent, non toxic and are selective towards TACE over MMPS and ADAM-10. Overall, these results demonstrated discovery of highly potent and selective

γ-lactum hydroxamate based TACE inhibitors which would be clinically useful for the safe and effective treatment of various inflammatory conditions.

P-019: A phase 1 comparative dose escalating toxicity and pharmacokinetic study of two intravenous liposomal Doxorubicin formulations in adult with solid tumors

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Background: A new non-Pegylated liposomal long circulating formulation of doxorubicin, Doxolip, is anticipated to have anti-tumor activity, as well as a better toxicity profile, as compared to pegylated doxorubicin. Objectives and Methodology: The study was a prospective, unicentric, openlabel, randomized, comparative dose-escalation study in adult patients with solid tumors that were refractory/resistant/relapsed/without any therapeutic option, to determine the MTD of intravenously administered Doxolip and compare the PKs of Doxolip with those of Caelyx® at 50 mg/m^2 administered as an i.v. infusion. The Doxolip treatment arm consisted of 5 cohorts of 3 patients each and Caelyx® treatment arm consisted of 1 cohort of 3 patients. Pharmacokinetic analysis was performed at pre-determined time-points. Results:The mean C_{max} and $AUC_{(0-\infty)}$ of doxorubicin increased with dosing from 40 mg/m^2 to 80 mg/m^2. However, the C_{max} values for Doxolip were not similar to Caelyx® 50 mg/m^2. In the study group, 7 SAEs were reported in cycle 1: 2 SAEs in 60mg/m^2, 1 SAE in 70mg/m^2 and 4 SAEs in 80 mg/m^2 as compared to 2 SAEs in 50mg/m^2 Caelyx® arm. No incidence of PPE was observed in Doxolip treated patients for subsequent cycles. There were two deaths, one in Doxolip 80 mg/m^2 cohort and other in Caelyx® 50 mg/m^2 study group.Conclusion: DLT was observed at 80 mg/m^2 dose and 70mg/m^2 was taken as the MTD. Data on dosage administered vs. number of cycles along with adverse events, establishes the safety of Doxolip as compared to Caelyx.

P-020: Novel Amino-Benzophenone Derivatives as Potential Anti-Inflammatory Agents

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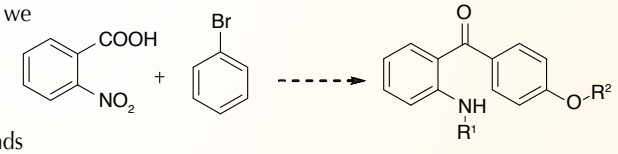
Benzophenones, the precursors for the synthesis of the title compounds are essential due to their diverse biological and chemical properties. The suitability of benzophenone analogues as chemotherapeutic agents, especially as anti-inflammatory, is well cited. Towards this end, we inspired and made an attempt to synthesize a series of nitrogen- containing benzophenone analogues as potential inhibitors of TNF-α and IL-6 and as antioxidant agents. The synthesized compounds contain a wide range of substitution pattern for establishing structure-activity relationship. Functional biological activity studies of these compounds are currently in progress and will be reported in due course.



P-021: Toxicological evaluation of new solid lipid nanoparticlulate dispersion of anti cancer drug Etoposide

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The present study was carried out to access the potential in-vivo tolerability of developed solid lipid nanodispersion system of etoposide (ET-SLN). Acute toxicity and repeated dose toxicity studies were carried out in Swiss albino mice for 3 and 5 days respectively and compared with a marketed etoposide injection (Et-MKT). Evidence of toxic effects was accessed by clinical observations, body weight and gross necropsy findings. In both the toxicity studies basal and terminal hematology and biochemistry of animals were recorded. Acute toxicity study revealed decrease in hemoglobin, RBC and hematocrit levels compared to control group because of cytotoxic nature of etoposide. However biochemical parameters showed almost normal values comparable to control group clearly signifying normal functioning of liver, kidney and heart. Histopathological findings indicated no major abnormalities in body organs even at dose double than the therapeutic dose.

Repeated dose toxicity studies suggested that Et-SLN and Et-MKT could be administered with daily dosing for 3 days only after which the mice showed severe toxicity. The levels of Hb, RBC and hematocrit were found to decrease significantly for all tested formulations as compared to control group at the end of day 7. As compared to Et-SLN, Et-MKT, showed much lower values for hematological parameters. Day 14 investigations for hematological parameters

clearly indicated slow reversal of the levels to normal value. The biochemical parameters almost remained constant. No abnormalities were detected in major organs after histopathological observations for Et-SLN group including kidney whereas Et-MKT group showed moderate diffused cloudy swelling in tubular lining of cortex in kidney.

Thus the above research findings suggested that the developed lipid based nanoparticle dispersion had better in-vivo tolerability in mice than the etoposide marketed injection.

P-022: Design and Synthesis of Novel Biologically Active Carbazole Derivatives

Amit Patil, Umesh Aware, Mayur Mukim, Prashant Deshmukh, Amitgiri Goswami, Kiran Shah, Pravin Thombare, Mukul Jain, Pankaj Patel and Sameer Agarwal

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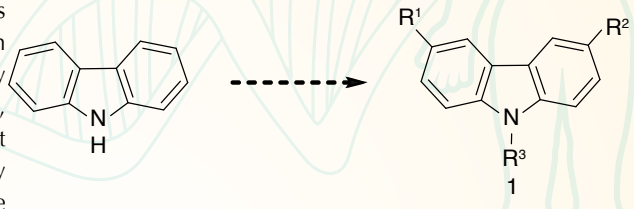
Nature offers a wide range of carbazole alkaloids with in many cases useful biological activities. Because of their pharmaceutical importance they induced the development of numerous medicinal products. Herein, we have described the synthesis of novel series of N-substituted-Carbazole derivatives 1, compounds 1(a-e), as the potential biological active agents. These compounds contain a wide range of substitution pattern for establishing meaningful structure-activity relationship. The biological activity studies, including anti-inflammatory and antioxidant properties of these compounds are currently under investigation and will be reported in due course.



P-023: Halogenation of Resiniferatoxin TRPV1 Agonists

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Resiniferatoxin (RTX), isolated from *Euphorbia resinifera*, is an extremely potent irritant tricyclic diterpene which is structurally related to phorbol-related diterpenes except for its homovanillyl ester group at C-20. RTX has proven to function pharmacologically as an ultrapotent agonist for the transient receptor potential vanilloid 1 (TRPV1) channel, displaying 10^3- to 10^4-fold greater potency than the prototypic agonist capsaicin.

Structure-activity relations for RTX derivatives have been investigated employing partial modifications starting from RTX or ROPA (resiniferonol orthophenylacetate) based on the three structural regions including the A-region (4-hydroxy-3-methoxyphenyl), B-region (C_{20} ester), and C-region (diterpene).

In the SAR of the A-region of RTX (4-hydroxy-3-methoxyphenyl), any modifications on the phenolic hydroxyl, such as methylation and 2-aminoethylation, led to the reduction in binding affinity and agonism in rat DRG. However, 5-Iodo RTX, prepared semisynthetically from RTX by iodination, displayed good potency in rat and human TRPV1 and shifted the activity from agonism to antagonism. Previously, we and other groups reported that the halogenation of the aromatic A-ring of TRPV1 agonists also shifted the agonism of the ligands toward antagonism.

On the basis of this SAR analysis, we have investigated the halogenated RTX analogues in which 5 position of the 4-hydroxy(or 4-amino)-3-methoxyphenyl group was halogenated with fluoro, chloro and bromo atoms, respectively. In this presention, the synthesis, receptor activities and SAR analysis of halogenated RTX will described.

P-024: Novel 1,4-Dihydro Quinoline-3-Carboxamide Derivatives as Potential Cannabinoid Modulators through CB2 Agonism

Shivaji Gugale[1], Pravin Kadam[1], Sandeep Shedage[1], Rina Soni[1,4], Purvi Vyas[3], Hitesh Bhayani[3], Rakesh Patel [2],Priyanka Priyadarsiny[3], Vishwanath Pawar[2], Mukul Jain[§2], Pankaj Patel[1] and Brijesh Kumar Srivastava[1].

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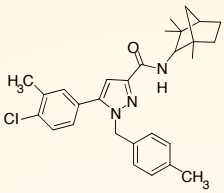
The CB2 receptor activation can be exploited for the treatment of diseases such as chronic pain and tumors of immune origin with no psychotropic activity. A series of novel substituted 1,4-Dihydro Quinoline-3-carboxamide derivatives (Fig. 2, 3-13) were rationally designed, synthesized and investigated for their affinities towards the human CB1 and CB2 cannabinoid receptors. This class of compounds shows

high affinity towards CB2 receptor and favorable selectivity over CB1 receptor. The compound 5 was further selected for evaluation against the in vivo CCI induced neuropathic pain and found to be a potent CB2 ligand.



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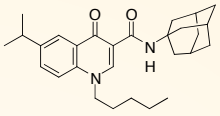

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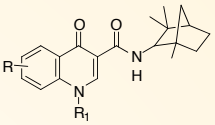

3-13

P-025: Phytosterols aiming the triad – Colon cancer, Inflammation and Oxidative stress

Amruta A. Tandel[1], Shaijesh S. Wankhede[2], Sateesh Belemkar[1]

[1] SVKM's NMIMS, Shirpur campus; [2]Oriental college of Pharmacy, Sanpada, NaviMumbai , India

Objective: To evaluate the efficacious Phytosterol combinations in treating Colon cancer and its correlation with inflammation and oxidative stress

Method: Two phytosterols - β-sitosterol and Stigmasterol in the ratios 25:75, 50:50 and 75:25 were screened for anti-cancer activity using in vitro and in vivo techniques. The MTT assay and the SRB assay were performed in vitro on human COLO 205 cell line. The murine colon cancer cell lines were injected *in vivo* in the mice to induce colon tumors & the phytosterol combinations were orally administered at 200 mg/kg once in a day. The inflammation was induced by the carrageenan model in mice and inhibitions were checked for the specified combinations at 200 mg/kg. Oxidative stress was monitored using ABTS antioxidant assay.

Result: The *in vitro* MTT and the SRB assay gave cytotoxicity of the human colon cancer cell lines with significant GI50 values NMT 70 µg/ml comparable with Adriamycin while the in vivo induced tumors reduced in the murine. The combinations showed 45%, 67% and 51% reduction respectively in paw edema after 5hrs of drug administration while the standard Indomethacin showed 78% reduction at the dose of 150 mg/kg. The results showed a concentration-dependent effect that reached an ABTS radical cation inhibition as high as 83% with the 50:50 combination for concentration of 640 µg/ml.

Conclusion: The combinations worked synergistically at aiming the colon tumors, inflammation & oxidative stress; which showed interlinking within the triad. Thus, affirming that the phytosterols can target the three interlinking diseases and show concerted efficacy with LD50 above 3000 mg.

P-026: Identification of a novel series of Cannabinoid CB2 Agonists for treatment of malignant lymphoma.

Purvi Vyas[1], Hitesh Bhayani[1], Dipali Sethi[1], Pravin Kadam[2], Shivaji Gugale[2], Sandeep Shedage[2], Umesh Mali[2], Praveenkumar Singh[2], Siddartha Kar[2], Rahul Salunke[2], Brijesh Kumar Srivastava[2], Mukul Jain[3], Pankaj Patel[1] and Priyanka Priyadarsiny[1].

1 Dept. of Cell Biology; 2 Dept. of Medicinal Chemistry; 3 Dept of Pharmacology. Zydus Research Centre, Ahmedabad, India

Cannabinoids have been reported to affect the multiple signaling pathways and biological processes involved in the development of cancer showing anti-proliferative, anti-angiogenic and pro apoptotic activity in both in-vitro and in-vivo model of cancers. In the current study a novel class of CB2 agonist benzoimidazole derivatives have been identified which showed dose dependently anti-proliferative effect in number of lymphoma cell lines. We have characterized the in-vitro efficacy and selectivity of these NCEs against CB2 receptor in cAMP Assay & [S-35] GTPgammaS functional assays. We examined number of lymphoma cell lines whether they are susceptible to cell proliferation induced by CB2 agonists. In-vitro potent CB2 agonists of this series showed dose dependent anti-proliferative effect in specific ARH77, HL60 and U937 lymphoma cell lines. Structure activity relationship studies identified one potent and selective CB2 agonist with IC_{50} value of 0.19nM and selectivity 200fold higher against human CB1 receptor which showed dose dependent anti-proliferative effect in ARH77 cell lines. We also investigated the possible involvement of mitogen activated protein kinase in CB2 receptor induced antitumor activity in human lymphoma cell line. These finding indicate the possible avenues for future development of cannabinoids as antitumor agents.

P-027: Evaluation of 5-FLUOROURACIL effects on tumor regression in a HCT116-LUC2 orthotopic colorectal cancer model in Mice

Laura Brullé[1,2] ,Eric Martel[1] , Anne Maurin[1] ,Pascal Champéroux[1] , Stéphanie Lerondel[2], Alain Le Pape[2] and Serge Richard[1]

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In testing novel anticancer therapies , models that most faithfully reflect the human disease must be used as much where possible. In this regard experimental orthotopic models are developed because the in vivo microenvironment surrounding cancer cells exerts a significant influence on the tumor's growth and metastasis as well as its response to treatment.

The purpose of the poster we would like to present is a validation study of an orthotopic model of colorectal cancer in nude mice . This validation is done by characterizing the behavior of a human colon cancer cell line, HCT116-LUC2 and evaluating effects of a standard chemotherapeutic 5- FLUOROURACIL (5-FU) using in vivo bioluminescence imaging.

P-028: Novel Substituted 1H-benzo[d]imidazole-2-carboxamide derivatives as CB2 Receptor Agonists: Synthesis and Biological Evaluation

Pravin Kadam[1], Shivaji Gugale[1], Sandeep Shedage[1], Umesh Mali[1] Praveen kumar Singh[1], Rina Soni[1£], Jayendra Patel[1] Rahul Salunke[1] Sidhartha Kar[1], Purvi Vyas[3], Hitesh Bhayani[3], Rakesh Patel[2], Priyanka Priyadarsiny[3], Vishwanath Pawar[2], Mukul Jain[2], Pankaj Patel[1] and Brijesh Kumar Srivastava[1].

1 Dept. of Medicinal Chemistry; 2 Dept. of Pharmacology; 3 Dept. of Cell Biology. Zydus Research Centre, Ahmedabad, India. £Present address- Dept. of Chemistry, University of Warwick, UK.

The CB2 receptor agonist is an attractive therapeutic target for the treatment of inflammation and neuropathic pain. There is growing interest among the medical fraternity from academia and pharmaceutical industries to explore the cannabinoid receptor 2 (CB2) agonists for the treatment of the neuropathic pain. Herein, we describe the discovery of a novel class of 1H-benzo[d]imidazole-2-carboxamide derivatives (Fig. 1, 3-14), their functional activity and selectivity against human CB2 receptors using cAMP assay. Structure-activity relationship studies of this class led into the identification 7-Chloro 1H- benzimidazole derivative 7 as a potent CB2 agonist in the CCI induced neuropathic pain and spinal nerve ligation (SNL) models.

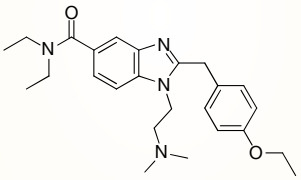

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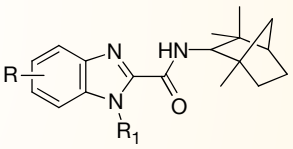
Figure 2



2-9

Figure 1

P-029: Effects of melatonin on NF-κB-Nrf2 axis in experimental diabetic neuropathy.

Geeta Negi, Ashutosh Kumar, Shyam S Sharma

Molecular Neuropharmacology Lab, Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research (NIPER), Sector 67, SAS Nagar, Mohali, Punjab-160062, India

Rationale & Hypothesis Melatonin exhibits an array of biological activities including antioxidant and anti-inflammatory actions. NF-κB is a central mechanism involved in genesis and resolution of inflammatory insult and is reported to play a crucial role in the pathophysiology of diabetic neuropathy.

Objective: In the present study, we investigated the role of nuclear factor-kappa B (NF-κB) and nuclear erythroid 2-related factor 2 (Nrf2) using melatonin as pharmacological intervention in streptozotocin induced diabetic neuropathy. Melatonin at doses of 3 and 10 mg/kg was administered daily in 7th and 8th week after 6 weeks of diabetes induction. Functional, sensorimotor and biochemical studies were performed at the end along with protein expression and immunohistochemical studies.

Findings: Motor nerve conduction velocity and nerve blood flow were improved in melatonin treated animals along with improvement in sensorimotor parameters. Melatonin also reduced the elevated expression of NF-κB and phosphorylated IκB-α. Further, melatonin treatment reduced the elevated levels of pro-inflammatory cytokines (TNF-α and IL-6), iNOS and COX-2 in sciatic nerves of diabetic animals. The capacity of melatonin to modulate Nrf2 pathway positively contributed to increased heme-oxygenase-1 (HO-1) expression which strengthens antioxidant defence. This fact was also established by decreased DNA fragmentation (due to excessive oxidant induced DNA damage) in the sciatic nerve of treated

animals. The results of the present study suggest the potential of modulating neuroinflammation by decreasing NF-κB activation cascade and oxidative stress by increasing Nrf2 expression, which might be provide beneficial strategy against development and progression of diabetic neuropathy.

P-030: Adjuvant effect of gabapentin with antiallodynic effect of diclofenac in post operative pain

Anushri Naik[1], Rakesh Patel[2], Vishwanath Pawar[2], Meena Chintamaneni[1], Mukul Jain[2]

1 Department of Pharmacology, Narsee Monjee Institute of Management Studies, Mumbai-400056, India; 2 Zydus Research Centre, Ahmedabad, India.

In the perioperative period, acute tissue injury results in intense nociceptor activation. Coupled with the signals initiated by nerve injury, this can result in either reversible or sustained changes (or both) in the peripheral and central nervous systems which can amplify post-operative pain and favour its persistence. The neuroplastic changes which follow an acute inflammatory stimulus tend to be short-lived; those that follow injury to peripheral nerves are longer-lasting. Gabapentin is an anti-epileptic drug which has also been used successfully to treat neuropathic pain. There are very few reports on its usefulness in treatment of postoperative pain. The objective was to assess the antiallodynic effect of gabapentin, diclofenac and co-administration of gabapentin and diclofenac in postoperative pain model using tactile allodynia. We evaluated the effect of gabapentin (50 mg/kg, po) diclofenac (15 mg/kg, po) and co-administration of gabapentin and diclofenac in post-operative pain model using von-Frey hairs for tactile allodynia. Gabapentin and diclofenac per se produced 62% and 27% maximal possible effect (MPE), respectively. The co-administration of gabapentin with diclofenac produced 88% MPE. The result of this study suggests that the co-administration of low dose gabapentin with agents like NSAIDs offer beneficial effects in management of incisional pain.

P-031: Crustacean lectin for Cancer Therapy and Diagnosis

Maghil Denis[1] and Ann Stevens[2]

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Crustaceans cannot synthesize sialic acid but they produce sialic acid specific lectin which has been purified and characterized from the hemolymph of lobsters, prawns'barnacles and the crabs. Sialic acids are sterically located on the cell surface and are implicated to act as receptors for certain toxins, viruses and hormones. Sialic acids comprise a group of over 20 derivatives based on N-acetylneuraminic acid (NeuAc) or N-glycolylneuraminic acid (NeuGc). Normally cell surface of human tissue contain NeuAc but O-acetylation of sialic acid may change with transformation or other alteration in the environment of the cell . Sialic acid specific lectins are useful to identify the transformed cells and a number of pathogenic strains of bacteria . Thereby lectins are used as tools for cell surface recognition, cell adhesion and localization. The present review is an attempt to bring out the role of lectins in as diagnostic and therapeutic tool for cancer.

P-032: Evaluation of role of cannabinoid receptor 2 (CB2) in sepsis.

Vishwanath Pawar[1], Jaimin Vaishnav[2], Anuj Kumar Singh[1], Bhavin Sonara[1], Rakesh Patel[1], Brijesh Srivastava[1] and Mukul Jain[1].

1 Zydus Research Centre, Ahmedabad, India; 2 L. M. College of Pharmacy, Ahmedabad– 380009, India.

CB_2 receptors are present on immune cells and may play a role in development of immune response. Thus we have evaluated role of CB_2 receptor by using CB_2 agonist (GW842166X) and CB_2 antagonist (SR144528) in Cecal Ligation and Puncture model of mice.

Mice were divided in three groups consisting of Vehicle, GW842166X (30 mg/kg, po) and SR144528 (30 mg/kg, po) and CLP surgery was performed. Bacteremia was significantly reduced at 6 hour with GW842166X [7350 ± 257.9 CFU/ml] and SR144528 [4520 ± 361.7 CFU/ml] compared to vehicle group [9360 ± 253.1 CFU/ml]. Plasma IL-6 was significantly reduced at 8 hour with SR144528 (4665.9 ± 677.9 pg/ml) compared to vehicle group [6494.7 ± 177.7pg/ml] which was not observed with GW842166X treatment [5815.7 ± 31.8 pg/ml]. Body weight and body temperature was decreased with GW842166X and SR144528 but not significant with vehicle group. Similarly no significant change in Plasma TNF-α (pg/ml) was observed by treatment with GW842166X or SR144528. % Survival was decreased in GW842166X treated mice [11.1%] but was not significant with vehicle treated mice [41.2%]. Similarly % Survival was increased in SR144528 treated mice [55.6%] but was not significant with vehicle treated mice. Conclusion: Taken together, our results establish that CB_2 receptors activation is important contributor to

septic immune dysfunction and mortality, indicating that CB_2 receptors may be therapeutically targeted for the benefit of patients suffering from sepsis.

P-033: Effects of mechanistically distinct NF-κB inhibitors on experimental diabetic neuropathy

Ashutosh Kumar, Geeta Negi, Shyam S Sharma

Molecular Neuropharmacology Lab, Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research (NIPER), Sector 67, SAS Nagar, Mohali, Punjab-160062, India

Rationale & Hypothesis: NF-κB is a central mechanism involved in genesis and promulgation of inflammatory insult and is reported to play a role in the pathogenesis of diabetic neuropathy.

Objective: To assess the role of NF-κB activation and inhibition we targeted the nuclear translocation of NF-κB using JSH-23(Nuclear translocation inhibitor) and MG-132 (Proteosome inhibitor).

Methodology: In a reversal paradigm JSH-23 and MG-132 was administered (n=8) for two weeks, after 6 weeks of STZ (55 mg/kg) diabetes in Sprague Dawley rats (240-250 g). Functional (MNCV and NBF), Behavioral (Thermal and Mechanical Hyperalgesia), and NF-κB translocation studies (western blot technique) were undertaken.

Findings: Development of diabetic neuropathy was evidenced from the functional, behavioral and biochemical deficits. JSH -23 ameliorated the nerve functions and sensorimotor alteration in diabetic rats but MG-132 failed to show any beneficial effect on these parameters. MG-132 did not show any effect on elevated NF-κB, IκB and p-IκB levels in treated groups. Nuclear translocation of p65/p50 subunit was inhibited by JSH-23 treatment as seen in protein expression studies. JSH-23 treatment also mitigated the elevated levels pro-inflammatory cytokines (TNF-α, IL-6) , and inducible enzymes (iNOS and COX-2) in the treated rats while MG-132 was unable to affect these parameters. JSH-23 also elevated the Nrf2/HO-1 levels thereby strengthening antioxidant status in sciatic nerve of diabetic animals. This study substantiates the role of NF-κB activation in the etiology of diabetic neuropathy. NF-κB inhibition with JSH-23 was effective in experimental diabetic neuropathy by inhibiting neuroinflammation and oxidative stress.

P-034: Probable replacement of Dexamethasone by a novel p38MAPK inhibitor for the treatment of Multiple Myeloma .

Mehul Raviya, Soma Srivastava, Shankar Shetty, Pankaj Patel and Ganes Chakrabarti.

Zydus Research Centre, Ahmedabad, India

Multiple myeloma (MM) is a bone marrow disease characterized by uncontrolled plasma cell proliferation and by various clinical manifestations such as hyperproteinemia, renal insufficiency, anemia, and skeletal destruction. Multiple myeloma is characterized by the clonal expansion of malignant plasma cells that commonly results in overproduction of large amounts of monoclonal immunoglobulins. Because multiple myeloma remains associated with a poor prognosis, novel drugs targeting specific signaling pathways are needed. Vincristine-Doxorubicin (Adriamycin)-Dexamethasone (VAD) regimen quickly became one of the most commonly used treatments for multiple myeloma. But extensively use of dexamethasone in VAD treatment cause serious side effects like diabetes, osteoporosis, muscle wasting, etc. Towards minimizing side effects, one of probable replacement of dexamethasone in VAD treatment may be p38MAPK inhibitor. The p38 MAPK is activated by cytokines and growth factors and plays a significant role in MM cell growth. Interleukin 6 (IL-6) is necessary for sustaining the *in vitro* growth of many MM cell lines and enhancing the proliferation of explanted human myeloma cells. Specific p38 inhibitors inhibit MM cell growth by blocking IL-6 secretion in U937 cells, thereby further inhibiting MM cell growth and survival. We have presented *in vitro* p38 MAPK (isofroms) enzymatic inhibition along with inhibition of LPS induced IL-6, TNF-α, IL-1β production by a known p38MAPK inhibitor (Scios-469) in human monocytic cell linage and also have tested the same p38MAPK inhibitor as a replacement of dexamethasone in VAD treatment against MM cell lines (RPMI8226 & U266b1) growth inhibition *in vitro*.

P-035: Optimization of DSS induced Colitis Mouse Model

Mahesh G. Jadhav, Jacqueline V. Trivedi, Prasad R. Tondare, Nilesh M. Dagia, and Ravindra D. Gupte

Department of Pharmacology, Piramal Life Sciences Limited, Mumbai, India

Inflammatory bowel disease (IBD) is a chronic, relapsing disease that affects the gastrointestinal tract. It is characterized by inflammation and tenderness of the intestines. IBD is a group of diseases, mainly consisting of ulcerative colitis and Crohn's disease, having the symptoms like weight loss, diarrhea and rectal bleeding/anemia. The animal models of IBD match with the human disease only symptomatically. Dextran sulfate sodium (DSS) induced murine colitis model is widely used experimental model of ulcerative colitis. Briefly, drinking water is replaced by aqueous DSS solution (2-10% w/v), for a period up to two weeks and the animals soon start showing the symptoms mentioned earlier. The experiment is terminated by sacrificing the animals; the colon is preserved for histology after length measurement. Initially, when these experiments were conducted using 3% DSS, administered for 10 days, animal to animal variations were observed intra and inter-experimentally. Moreover, the standard compounds never showed benefit. Hence, the study protocol was optimized. Previous experience suggested that the first parameter to get affected following DSS administration is colon length and hence the attention was concentrated only on colon length. The optimum concentration of DSS and the duration of its administration required to induce colitis in the shortest time was determined. 5% DSS administered for 4 days was found to induce colitis in mice. Thus this experimental protocol gives uniform and reproducible disease induction and efficacy of the standard compounds is consistently observed at macroscopic and histological levels.

P-036: Sensetive and selective liquid chromatography coupled with temdem mass spectrometry (LC-MS/MS) method for estimation of tacrolimus from human plasma

Chandrakant Bhatt, Arvind Shenoy, Jatin Patel , Anil Jha , Harilal Patel

Zydus Research Centre, Ahmedabad, India

Tacrolimus is an immunosuppressive drug whose main use is after organ transplant to reduce the activity of the patient's immune system and so the risk of organ rejection. It is also used in a topical preparation in the treatment of severe atopic dermatitis, severe refractory uveitis after bone marrow transplants, and the skin condition vitiligo. Tacrolimus is chemically known as a macrolide.

A sensitive and selective liquid chromatography coupled with electrospray ionization mass spectrometry (LC-MS/MS) method has been developed for the estimation of Tacrolimus (an immunosuppressant drug) from human plasma. Mass transition 826.6 m/z⇨616.4 m/z and 936.6 m/z⇨409.3 m/z were optimized for Tacrolimus and internal standard, respectively. The sample preparation was carried out by using liquid – liquid extraction (LLE). The Sirolimus was used as internal standard. The chromatographic separation was achieved on ACE5 CN, 50*4.6 mm analytical column using an isocratic mobile phase containing 0.1% v/v formic acid in water: acetonitrile (10: 90 % v/v) at a flow rate of 1 ml/min with split. The method was found to be linear over a dynamic range from 50 pg/ml to 20000 ng/ml, with a correlation coefficient (r) 0.9979. The lower limit of quantitation (LLOQ) was 50 pg/ml. Inter day precision and accuracy were range from 2.74 % to 9.57% and 102.22 % to 105.86 %, respectively. The absolute recovery for Tacrolimus and internal standard were 87.6 % and 64.5 %. The method was found to be selective, sensitive, precise and accurate for application of bioequivalence study in healthy human volunteers.

P-037: Antitumour and Antiangiogenic effects of green tea extract : could its administration time affects the tumor growth in albino mice?

Aliaa M. Issa Abdou.

Zoology Department, Faculty of Science, Cairo University, Egypt.

Antitumour and antiangiogenic effects of two different administration times of green tea extract on a subcutaneous Ehrlich solid tumour were studied. Swiss albino mice were divided into 3 groups: a)control-Tumour , b)"Tea-before" (mice received green tea extract before the Ehrlich tumour cells inoculation) and c)"Tea-after" (mice received green tea extract after the palpation of the tumour masses) groups. Growing subcutaneous tumour, animal survival, histopathological changes, necrotic areas percentage and blood vessels areas- as a marker of angiogenesis and detected by immunohistochemistry in the tumour masses- were studied in all groups, after 2 and 4 weeks from tumour inoculation. The results showed that in green tea extract-treated groups ("Tea-before" and "Tea-after") a delay in tumour growth was observed when compared to the control-Tumour group, with an increase in animal survival. The striking histopathological change was the abundance of giant multinucleated cells in the tea-treated

groups. Necrotic area percentage in the tumour masses was significantly increased in the green tea extract groups compared to the control-Tumour group. Whereas the group treated with green tea extract after tumour inoculation and studied after 2 weeks showed smaller necrotic area percentage than all other groups. Blood vessel areas were significantly decreased in animals treated with green tea extract before tumour cells inoculation and studied 4 weeks after tumour inoculation, while there was an inconsistent increase, in the same parameter, in the group treated with green tea extract after tumour inoculation and observed after 2 weeks. The significance of using both treatments was discussed.

P-038: A high throughput and sensitive liquid chromatography coupled with temdem mass spectrometry (LC-MS/MS) method for estimation of valproic acid from human plasma

Krunal Soni, Kanchan Singh, Anil Jha, Harilal Patel

Zydus Research Centre, Ahmedabad, India

Valproic acid is an antiepileptic drug with unique anticonvulsant properties and is used in the treatment of primary generalize seizures, partial seizures and myoclonic seizures. Valproic acid (VPA, 2-propylpentanoic acid), a branched C8 carboxylic acid, is commonly used for the treatment of seizures and as a mood stabilizing agent for variety of psychiatric disorders.

A rapid and selective gradient reversed-phase liquid chromatography–tandem mass spectrometry method equipped with turbo ion spray (TIS) source, operating in the negative ion and pseudo selective reaction monitoring (SRM) acquisition mode to quantify valproic acid. The extraction of valproic acid and internal standard from the plasma was performed by using plasma protein precipitation using acetonitrile (100%v/v). Sample Extraction using this method showed very good and consistent recovery ranging from 75.79 % and 73.18% for valproic acid and internal standard, respectively. The method was found linear over a dynamic range from 50.0–40000.0 ng/ml with a correlation coefficient (r) =0.9983. The lower limit of quantification was 50 ng/ml. Inter day coefficient of variance (CV %) and accuracy of the quality control samples were 2.44 % to 14.41% and 96.44 to 104.87 %. This method was fully validated for its accuracy, precision, recovery, matrix effect; carry over, ion suppression and analyte stability in plasma. This developed method proved selective, sensitive, precise and accurate for the application of bioequivalence study of valproic acid 250mg soft gelatin capsule in healthy human volunteers.

P-039: Synthesis, stereochemical investigations and in vitro evaluation of anti (±) 5-methyl-3-(substituted phenyl)-5-[(substituted phenyl)-hydroxyl methyl]-2-thiooxazolidin-4-ones on prostate cancer cell lines

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Many drugs/intermediates contain oxazolidinones and thiooxazolidinones as an integral part of their skeleton. Thiooxazolidinone scaffolds are known for various biological activities such as antidiabetics, potassium channel openers, and anticonvulsants. They are also employed as chiral directing agents in asymmetric synthesis. Our investigations on these substrates were mainly directed to study the aldol reactions, ascertain the extent of diasteroselectivity and evaluate the anti-prostate cancer activity. The synthesis carried out as follows. Aryl isothiocyanates were converted into 5-methyl-3-aryl-2-thiooxazolidin-4-ones with ethyl lactate in presence of $LiClO_4$ in DIPEA mediated cyclization. The 3-aryl-2-thiooxazolidin-4-ones were subjected to aldol reactions with 4-halobenzaldehydes by in situ generation of enolates using LHMDS to afford the anti (±)-5-methyl-3-(substituted phenyl)-5-[(substituted phenyl) hydroxy methyl]-2-thiooxazolidin-4-ones as a major product which was determined by the ^1H NMR and ROESY spectra, and confirmed by single crystal X-ray diffraction study. Anti isomers which were obtained as a major product were evaluated in vitro on PC-3 (androgen independent) and LNCaP (androgen dependent) cell lines using the Doxorubicin and Flutamide as positive controls respectively. We observed that some of compounds have shown good cytotoxicity on both cell lines with IC_{50} in the micromolar range. Further development of the thioxooxazolidinone pharmacophore may provide a lead molecule which may have the potential to serve as anti-prostate cancer agents.

P-040: A high throughput method to predict oral absorption by PAMPA using precoated filter membrane

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The Parallel Artificial Membrane Permeation Assay (PAMPA) is a well-accepted secondary screening assay used as an *in vitro* model of passive, transcellular permeation, avoids the complexities of active transport and allowing test compounds to be ranked based on a simple permeability property alone. In this study we have used pre-coated PAMPA 96-well filter plate (BD Gentest™ Pre-coated PAMPA Plate System) to access permeability of 9 commercially available drug compounds at 100, 150 and 200 µM concentration by incubation at room temperature for five hours without agitation. The final concentrations of compounds in both donor wells and acceptor wells were determined by LC-MS/MS, with standard curves ranging from 1 to 50 µM concentration. This technique has advantage over traditional PAMPA plate (manual coating of artificial membrane and 16 hr to 24 hr incubation time) in terms of more reproducibility and high throughput data. The observed permeability of all 9 compounds was in good (within 1.5 fold) correlation with human absorption.

P-041: Role of ligand mediated nanostructured lipid carrier in the management of osteoarthritis

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Number of NSAIDs have been tried in the management of the osteoarthritis. Most common mechanism of this class of drugs is the blocking of prostaglandin generation by inhibition of enzyme cyclooxygenase (COX). Most of the NSAIDs inhibit COX -1 and COX- 2 non selectively, thus the physiological house keeping function of COX-1 are also inhibited.

To over come these demerits of classical NSAIDs, Solid lipid nanoparticles(SLNs) are prepared for achieving higher concentrations of the drug at the arthritic joint and minimizing its distribution to the other tissues would minimize the side effects associated with the drug. Targeting drugs to the inflamed joints, in the treatment of osteoarthritis, would reduce the amount of drug required to control the disease, with possible additional reduction or even elimination of adverse side effects. Colloidal forms of chondroitin sulphate (CS) have been considered as potential carriers of drugs for their site-specific localization or their targeted approach. CS is able to diminish NF-kappa B activation and nuclear translocation in chondrocytes and synovial membrane, effects that may explain the benefits of CS in osteoarthritis. Increasing the circulation half-life of the formulation by reducing its uptake by the reticulo endothelial system has been shown to improve the targeting efficiency of the formulation to the arthritis. Hence the use of intravenously administered biodegradable solid lipid nanoparicles having CS ligand ,as a targeted drug delivery system for delivering NSAIDs to the arthritic joints is beneficial over conventional delivery systems. Hence, it will be beneficial to design SLNs with ligand CS,bearing NSAIDs for more efficiently effect on OA.

P-042: A novel approach to study drug-drug interaction of glibenclamide and losartan using freshly isolated rat hepatocytes

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The use of freshly isolated hepatocytes as an *in vitro* system for the prediction of *in vivo* clearance is widely accepted because it represents a more realistic physiological model than some other liver preparations, e.g., hepatic microsomes. In this study, the surgical method for isolating rat hepatocytes using two step enzymatic perfusion was established. The viability the freshly isolated rat hepatocytes was ~ 89 %. Enzymatic activity was assessed by incubation of Diclofenac (probe substrate of CYP 2C9) and Testosterone (probe substrate of CYP 3A4) with freshly isolated rat hepatocytes , which showed positive results and prove the effectiveness of the established isolation procedure. Drug-drug interaction study of Glibenclamide and Losartan were studied by incubation in freshly isolated rat hepatocytes in controlled aseptic condition for various time points (0, 30, 60, 120 and 180 minutes). The results of the study has shown that metabolism of Glibenclamide decreased on co-incubation with Losartan to ~ 40 % in freshly isolated rat hepatocytes on incubation over 180 min. The *in vitro* intrinsic clearance (Cl_{int}, *in vitro*) of Glibenclamide was reduced from ~ 1.6 µl/min/10^6cells to 1.0 µl/min/10^6cells in presence of Losartan. This indicate that Losartan has enzyme-inhibition property, which is thought to be mediated by inhibition of CYP 2C9 as major CYP enzyme involve in the metabolism of Glibenclamide.

P-043: Prohibitin (Phb1)-MEK-extracellular signal-regulated kinase 1/2 (ERK1/2) signaling pathway activate Bcl2 and Bclxl for mitochondrial dependent survival of rat granulosa cells (GCs).

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Prohibitin (Phb1) is a member of a highly conserved eukaryotic protein family containing the stomatin/prohibitin/flotillin/HflK/C (SPFH) domain [also known as the prohibitin (PHB) domain] found in divergent species from prokaryotes to eukaryotes. Phb1 is abundantly expressed in granulosa cells (GCs) and associated with GC differentiation and apoptosis. Ovarian GCs play an important physiological role in supporting the development and selection of the ovarian follicle by controlling oocyte maturation and by producing the steroid hormones, estradiol and progesterone, that are critical for maintenance of the ovarian cycle. We used a primary rat GC model to investigate the molecular mechanisms of Phb1 dependent survival of GCs. GCs were isolated from immature 23-25 days old female Sprague Dawley (SD) rats, were infected with adenovirus-GFP (Ad-GFP, control) or adenovirus Phb1-eGFP (Ad-Phb1-eGFP) or silence PHB1 expression using adenoviral micro interfering RNA (AdmirPHB1). Twenty-four hours later, cells were treated with the protein kinase C (PKC) inhibitor staurosporine (STS) in presence or absence of MEK-inhibitor PD-98059 for 2h. Ad-Phb1-eGFP infected GCs acquired a remarkable resistance to apoptosis. Using Affymetrix Gene-Chip System following STS treatment, we uncovered significant changes (50-80%) in several genes that are strong anti- or pro-apoptotic regulators, with forced-expression of Phb1 in GCs resulting in a profile of expression consistent with attenuated apoptosis when compared to control infected cells. Forced-expression of PHB1 in GCs increased more than two fold Bcl2, Bclxl and Erk transcription, whereas it decreased transcription of Bax, Bak, and caspase-3, results that were further confirmed by Western blot analysis. Forced-expression of PHB1 in GCs inhibits apoptosis associated with increased levels of the anti-apoptotic proteins Bcl2 and Bclxl, and reduced release of cytohrome c and stimulation of caspase-3 activity. Moreover, silencing of PHB1 expression using AdmirPHB1 or inhibiting Erk1/2 phosphorylation with the MEK-inhibitor PD-98059 blocked the protective effects Phb1 on STS-induce apoptosis in GCs. These findings shed new light on the PHB1-mediated apoptotic resistance mechanism of GCs through a Phb1⇨ Mek-Erk1/2⇨ Bcl/Bcl-xL pathway and may have important clinical implications. GRANT SUPPORT: This study was supported in part by National Institutes of Health Grants 1RO1HD057235-01A2, HD41749 and RR03034. This investigation was conducted in a facility constructed with support from Research Facilities Improvement Grant C06RR18386.

P-044: A rare case of dysplasia with adenocarcinoma and foveolar type metaplasia of hepatic and extrahepatic bile ducts in ICR mice.

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A construction of historical tumor data is of prime importance in justifying the species specific spontaneous tumor data in the carcinogenic or tumorigenic effect of drugs in humans via animal models. As part of routine health activity, mice of age 7–8 month old female mice from a historical control data study weighing 27.3 g at necropsy was housed and maintained for a historical control data. The mice were housed, maintained in standard individually ventilated cages and environmental conditions. They received commercial rodent diet and drinking water *ad libitum*. The mice were maintained according to the standard regulatory guidelines. No untoward changes were observed during the in-life phase. Clinical pathology and urinalysis did not reveal altered function. Gross lesion noted during necropsy was only dilatation of bile duct. Microscopically, the sections of liver stained with H and E revealed dysplasia with adenocarcinoma and foveolar type metaplastic change with excess cytoplasmic mucin, reactive hyperplasia and multifocal hepatocellular hypertrophy. Bile duct and pancreas showed the same lesion as that of liver of dysplasia with adenocarcinoma and foveolar type metaplastic change with excess cytoplasmic mucin. The neoplastic tubular glands were lined by slender tall columnar cells with mucin containing cytoplasm and basal nuclei having small nucleoli. The glandular lumen showed presence of hemoglobin crystals. To the authors' knowledge, we claim that this is the first report of dysplasia with adenocarcinoma in bile duct in mice.

P-045: Effect of catechin on ethanol induced hepatotoxicity and expression of Bcl-2, Bax and p53 levels.

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Background and aims: Oxidative stress plays a pivotal role in the pathogenesis and progression of alcoholic liver disease (ALD). Considering the antihepatotoxic property of catechin, a well known anti oxidant (flavonoid); we investigated the hepatoprotective effect of catechin and underlying mechanism(s).

Methods: Twenty four Wistar strain albino rats (180–200 g) of either sex were used. The animals were divided into three groups and treated for 60 days as follows: (1) normal control group received the vehicle (Sodium CMC 0.3%); (2) ethanol group was administered ethanol 3.6 g/kg (30% <v/v>, 10 ml/kg) 1 h after ingestion of Sodium CMC 0.3%; (3) ethanol plus catechin group received catechin 100 mg/kg 1 h prior to the administration of ethanol 3.6 g/kg; Animals received ethanol and catechin by oral route daily. Liver damage was evaluated by histopathology and liver function test. At molecular level, expression of p53, Bax and bcl-2 was determined by reverse transcriptase polymerase chain reaction (RT PCR).

Results: Catechin at 100 mg/kg each ameliorated ethanol-induced macrovesicular steatosis and parenchymatous degeneration in hepatocytes, and decreased serum aminotransferases level. Ethanol down regulated anti apoptotic Bcl-2, up regulated pro apoptotic p53 and Bax mRNA levels in liver hepatocytes, thus inducing apoptosis. However, this alteration in mRNA levels of p53, Bax and Bcl-2 was significantly prevented by catechin treated animals at a dose of 100 mg/kg.bt.wt.

Conclusion: Together, these results identify the biological efficacy of catechin against ethanol induced hepatotoxicity in rats. Hence, catechin merits further investigation in clinical trials to support its hepatoprotective effect.

P-046: Evaluation of Genotoxicity Potential of Metronidazole using In vivo Bone marrow Micronucleus Test in ICR mice

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Metronidazole, a synthetic, nitroimidazole antibacterial and antiprotozoal agent widely used in both human and animals. Metronidazole is converted to reduction products that interact with DNA to cause destruction of helical DNA structure and strand leading to inhibition of protein synthesis and cell death in susceptible organisms. It is also proven to be mutagenic in bacterial reverse mutation (AMES) test. Therefore the current approach is to evaluate the clastogenic potential of metronidazole under *in vivo* condition in mice. Dose levels were approximately 1X (130 mg/kg), 3X (390 mg/kg) and 6X (780 mg/kg) from recommended human dose based on body surface area was considered. Parallel positive and negative controls were maintained in this study. Animals were treated for two consecutive days and bone marrow was evaluated microscopically for the incidence of micro nucleus in polychromatic erythrocytes. Incidence of increase in micronuclei was not apparent up to dose of 780 mg/kg. Based on these findings it can be concluded that metronidazole has less potential to interact with the DNA in eukaryotic cell under *in vivo* conditions.

P-047: Identification of novel target genes of LMO4 by gene expression studies

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Cancer is caused by the accumulation of genetic and epigenetic changes which is due to the altered sequence or expression of cancer-related genes, such as oncogenes or tumor suppressor genes.

The LIM domain defines a conserved cysteine-rich structure comprising two tandemly repeated zinc fingers and is found in a large group of diverse proteins. LMO4 gene is found to be over-expressed in more than 50% of breast cancers and suggested to be involved in the causation and progression of breast cancer. Studies have shown that deletion of LMO4 impaired the function and development of mammary gland in LMO4 conditional knockout mice, indicating that LMO4 protein is necessary for maintaining the normal development of mice mammary gland. Hence if the genes involved in enhancing the activity of LMO4 oncogene, are identified it could prove as an insight to produce drugs to suppress these genes of LMO4 blocking its effects in the progression of the disease. Studies have also proven that BMP7 is bonafide target gene of LMO4 blocking its effects partially. In the present study role of

LMO4 in breast cancer was analysed using Genespring GX and R Bioconductor package to identify novel potential targets to completely block the activity of LMO4 in the progression of the disease.

P-048: Developmental Toxicity Risk of Aspirin in Female Wistar Rats

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There seems to be a lot of new attention focused on good old fashioned aspirin, so much so that it's recently been touted as a 'wonder drug'. Evidence is rapidly growing that supports aspirin's use in lowering the rates of heart attack, stroke, colon cancer and even Alzheimer's disease. Given its widespread benefits and extremely low cost, the question is raised, "is daily aspirin therapy for everyone?" This work was carried out to generate additional information, in relation to female reproductive toxicity of Aspirin in Wistar rats during the complete female reproductive cycle at human therapeutic dose levels (250 and 500 mg/kg) on body weight basis involving the phases of gamete production, fertilization, zygote transport and implantation, embryogenesis and fetal development, parturition, lactation and post natal development. Twelve healthy female rats per group were given 0, 250 & 500 mg/kg-day of aspirin by oral gavage for 14 days before mating, and treatment continued during mating, gestation and lactation period. Additionally, clinical signs, mortality and morbidity, body weight, feed consumption, estrous cycle, fertility indices and litter indices were assessed. No significant effect was seen on implantation. Altered estrus cyclicity, increased gestation length, dystocia and increased incidences of still births were observed with effects on offspring development at 250 mg/kg. Gestation and lactation indices were significantly affected at 250 mg/kg dose. Delayed development in prenatal landmarks was noticed at 250 mg/kg. None of the pregnant females littered at 500 mg/kg. Therefore added to the confirmed results of published risk information on aspirin during pregnancy, additionally the possible impact of aspirin in estrus cyclicity was evident this study with female rats. Hence studies involving higher species are warranted before treating women population of child bearing potential with a family history of heart disease, such as coronary artery or vascular disease, or those with risk factors for heart disease such as diabetes, high blood pressure or high cholesterol.

P-049: *ZFX* gene is expressed differentially between tumoral and non-tumoral tissue specimens of gastric cancer

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Self-renewal is a hallmark characteristic of stem cells in normal and neoplastic tissues. Located on X chromosome and as a newly identified self-renewal gene, *ZFX* encodes a member of the krueppel C2H2-type zinc-finger protein family. Examining its expression in malignancies has showed that it over-expresses in prostate adenocarcinoma and B-cell lymphoma. In an attempt to establish the probable role of *ZFX* in gastric tumorigenesis, we analyzed its expression level in tumoral and non-tumoral tissues of human stomach. Relative expression of *ZFX* was determined by quantitative real-time RT-PCR in 30 tumoral and 30 morphologically juxtaposed normal gastric tissues (paired samples) that were provided from Iran Tumoral Bank. Specific primers for *ZFX* and TBP (as an internal control) were designed and used for qRT-PCR. ZFX is over-expressed in 47% of tumoral tissues, while it is under-expressed in 53% of the tissues. Statistical analyses showed that *ZFX* is differentially expressed between the different grades and types (intestinal versus diffused) of gastric tumors with the highest relative expression observed in grade III and diffused type of gastric tumors. Our results indicated that *ZFX* is differentially expressed in gastric cancer. Correlation between ZFX gene expression and tumor grades and types may suggest that it can be used as a potential candidate for developing *ZFX*-based cancer therapeutics.

P-050: A Novel Peptide Isolated From Phage Display Library Inhibits Malaria Parasite Development by Targeting Plasmodium falciparum Vacuolar-H+ ATPase

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Still approximately 500 million cases of malaria occur and it is one of the most prevalent parasitic diseases causing about one million deaths per year. Around 400 Plasmodium proteins are exported

into the host erythrocyte as a result of which Malaria infected red blood cells (IRBCs) undergo drastic membrane changes. Thus, the antigens associated with parasite as well as IRBC surface could be the targets for therapeutic/ vaccines. Recent reports in the literature have demonstrated that high-affinity peptides for protein targets could be selected from phage display peptide libraries. These peptides are capable of disrupting protein contacts by binding to a single preferred protein–protein interaction surface or "hot spot" and may provide a useful reagent to assist small-molecule drug discovery. Therefore, in view of the broad success of this approach, 7 mer cysteine constrained library was used to select the short cyclic peptide(s) that bound to the functional domain(s) of the target protein. B subunit of *P.falciparum* Vacuolar-H^+ ATPase was selected as target based on its presence on infected cell surface and function. The purified protein was used to screen its binding peptides from phage display peptide library. Few phage peptides showed good levels of binding with recombinant and native V-H^+ ATPase in both ELISA and Immunofluorescence assay. Interestingly, significant *in vitro* growth inhibition of *P.falciparum* was seen with peptide ATPase13 (77%) indicating that the peptide targeted the functional regions of the protein.

Thus, the phage display strategy helped in identifying functionally important regions on infected cell surface which can be exploited for therapeutic intervention.

P-051: Expression profile of Musashi gene family in gastric cancer

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As a multifactorial disease, gastric cancer is the fourth most common cancer worldwide. In Iran, gastric cancer is the second most common cancer in men but it is the first most lethal neoplasm overall. Being a regulator of stemness, the Musashi family comprises the MSI1 and MSI2 genes. MSI1 expression has been reported in a variety of tumoral cells. It has also been showed that MSI2 expression is highly up-regulated during human CML progression. To investigate potential involvement of Musashi genes in gastric cancer, we examined, for the first time, its expression in gastric specimens. Sixty (paired) fresh-frozen tumoral and non-tumoral gastric specimens were provided from Iran Tumoral Bank. Specific primers for MSI1, MSI2 and TBP (as an internal control) were designed and used for measuring relative expression of MSI genes by quantitative real-time RT-PCR. According to the relative expression level of the MSI genes, the samples can be categorized into 3 classes. The first class included those samples in which MSI1 and MSI2 genes over-expressed in tumoral tissues compared to their non-tumoral adjacent specimen (n=7 and n=13, respectively). In the second class, there were no significant changes in the expression level of the genes between the paired tissues (n=10 and n=1, respectively). Finally, those samples in which MSI genes under-expressed in tumoral tissues, placed in the third class (n=13 and n=16, respectively). Our results indicated that MSI genes are heterogeneously expressed in gastric cancer and have a potential to be used as a marker for classifying the tumors.

P-052: Estrogen and Progesterone Receptors in Patients with Colorectal Cancer

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The existence of estrogen (ER) and progesterone (PR) receptors in breast or endometrial carcinoma have potential diagnostic, therapeutic, and prognostic importance. However, clinical significance in colorectal cancer (CRC) is unknown. Thus, the present study sought to investigate the presences of ER/PR receptors and its clinical utility in patients with CRC. ER/PR status in normal colorectal mucosa (NM) and tumors were analyzed using radioligand–dextran-coated charcoal method. ER and PR content were observed to be similar in both NM and colorectal tumors. Further, a significant positive correlation was noted between ER and PR in both NM ($r = +0.533$, $P=0.0001$) and tumors ($r = + 0.217$, $P=0.05$). No correlation was observed with clinicopathological parameter except for menopausal status. In univariate survival analysis, ER and PR status, failed to discriminate low– and high-risk CRC patients for early recurrence or death. Conversely, patients with NMPR+ had significantly shorter OS when compared to patients with NMPR- ($c2=4.08$, $df=1$, $P=0.043$). Further, patients with synchronous PR positivity in NM and primary tumors (NMPR+TPR+) had significantly unfavorable disease outcome. The significance of PR positivity in the normal colorectal mucosa and prognosis is unclear, however, it can be postulated that histological normal mucosa may not be biologically normal. Thus, the presences of high affinity sex steroid receptors in both NM and primary colorectal tumors in the present series do indicate that "hormonal milieu" might regulate the growth of colon/rectal cancer. However, its significance is still controversial in terms of both management and prognosis.

P-053: Impact of additional chromosomal abnormalities in a large series of CML patients targeted with Imatinib Mesylate: A GCRI experience.

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Imatinib Mesylate (IM) (Glivec) induces a complete cytogenetic response in more than 80% of newly diagnosed CML patients. However, several patients do not respond completely. In most studies, IM resistance is correlated with additional cytogenetic changes. We studied the impact of additional chromosomal abnormalities (ACA) in IM treated CML patients.

The study included 393 CML patients; 361 patients were untreated and 32 patients received chemotherapy at the time of enrollment. 333 patients were treated with IM. Conventional cytogenetic studies were performed in all the patients. FISH, M-FISH and BAC-FISH were also performed.

At diagnosis, 344 patients were Ph+ve. 13 patients showed masked Ph. 4 patients had atypical CML. The cytogenetic abnormalities were categorized; (1) Classical Philadelphia (Sole) (n=311), (2) Secondary chromosomal changes (n=13), (3) Three-way translocations (n=16), (4) Complex chromosomal rearrangements (n=8), (5) Normal karyotype (n=9), (6) Ph-ve and abnormal karyotype (n=4) and (7) previously treated patient (n=32). Study revealed 23 rare and 13 novel rearrangements.

The cytogenetic response to IM in sole Ph was compared with clonal evolution from sole Ph. The overall survival (OS) was significantly (p=0.001) higher in patients with sole Ph. The cytogenetic response to IM in sole Ph with ACA was also studied. The OS was significantly lower (p=0.0001) in patients with ACA. The hematologic response to IM in sole Ph with ACA revealed that the OS was significantly higher (p=0.002) in patients with sole Ph.

The data revealed that, ACAs were associated with an adverse survival and showed heterogeneous genetic status. The combination of conventional and molecular cytogenetic analysis showed strong diagnostic, and prognostic implications in IM targeted CML patients.

P-054: Role of Conventional and Molecular Cytogenetic in ALL Patients

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In Acute Lymphoblastic Leukemia (ALL), chromosome abnormalities are of prime clinical importance. It often features recurrent, rare and novel chromosome aberrations that can be identified by conventional cytogenetics. The present study was carried out to study clinical significance of conventional and molecular cytogenetics in ALL patients.

The study included 56 ALL patients exhibiting structural chromosomal abnormalities. Of 56 patients, 22(39%) showed t(9;22) whereas, 34(61%) showed complex structural aberrations. Unstimulated bone marrow samples were cultured for GTG-banding and karyotyping as per ISCN 2005. FISH technique was performed in selected cases using commercially available Locus Specific Identifier (LSI), Whole Chromosome Paint (WCP) probes. Molecular cytogenetic using M-FISH was performed in a case of cryptic chromosomal rearrangement.

Of the patients with complex abnormal karyotypes, rare but recurrent structural anomalies were observed viz., t(6;9;22); t(2;18), ins(2;13), t(1;22); t(5;7); t(6;11); t(6;12); t(8;14); t(1;19); t(1;11); t(1;?), t(?,2), i(11q); addition in 1(p), 7(q), 13(q), and 19(p) and deletion in 2(p), 6(q), 9(q), 11(q), 13(q), 15(q), 17(q), 18(p), and19(q). Interestingly, one pediatric patient showed 46,XY,?del(1)(q),?4q,?add(6)(q),?add11q23 involving complex rearrangements in chromosome 1, 4, 6 and 11 with conventional cytogenetic approach. Further M-FISH approach revealed translocation between t(Y;3) and a four way translocation; t(1;4;6;11)(q31;q27;q22;q23). This was again confirmed with WCP and LSI FISH probes.

Present study documented usefulness of molecular cytogenetics to unravel complex karyotypes. Thus, the molecular cytogenetics was helpful to identify cryptic chromosomal rearrangements which have significant clinical usefulness.

P-055: Flowcytometric evaluation of lymphocyte subsets to assess immune status of head and neck cancer patients.

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Objective: It has been well documented that cancer including head and neck cancers, is associated with immuno-suppression. Further most of the anti cancer treatment is antiproliferative and lead to immunosuppression that may persist during the period of remission. Such down regulation of immune response could be related to higher degree of recurrence in such cases. Therefore, present study has been planned to observe immune status of head and neck cancer patients.

Material and Method: The major lymphocyte subsets total T, T-helper, T-suppressor/cytotoxic, NK and T regulatory cells were studied using respective CD antigens by flow cytometry in normal subjects and head and neck cancer patients.

Results: In comparison with controls, head and neck squamous cell carcinoma patients had low number of lymphocytes and T cells, and high number of NK T cells and regulatory T cells. The different T cell subsets were correlated with clinical (age, gender, habit of tobacco) and pathological parameters (tumor size, nodal status, disease stage, histology grade, keratin status, lymphocytic infiltration, vascular and lymphatic permeation, total WBC count). An inverse correlation of αβ T cell receptors and γδT cell receptors was observed with increasing tumor size, nodal status and disease stage. An increasing trend of T regulatory cells was noted with increasing tumor size, nodal status and disease stage. Further, correlations of T cell subsets with other clinical and pathological parameters were also evaluated.

Conclusion: In patients with head and neck squamous cell carcinoma immunosupression was noted. Increase in number of T regulatory cells protect tumor from potentially effective immune responses. So depletion of T regulatory cells are of critical importance for effective cancer therapy.

P-056: Glycolytic pathway as potential drug target in leukemia.

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The unique metabolism of tumours due to Intratumoral hypoxia leads to induction of hypoxia-inducible factor-1 (HIF-1) activity with reprogramming of cancer cell metabolism involving increased glucose transport into the cell, increased glycolysis and a concomitant decrease in mitochondrial metabolism. Fate of pyruvate, the end product of glycolysis depends on relative activities of two enzymes LDH and PDH. HIF-1 induces PDK-1 which in turn inactivate PDH and suppress kreb cycle. HIF-1 therefore acts as a metabolic switch between Glycolysis and oxidative phosphorylation. Blocking these adaptive metabolic responses may lead to accumulation of ROS and ultimately cell death. Therefore, targeting HIF-1 or metabolic enzymes encoded by HIF-1 target genes may represent a novel therapeutic approach in cancer drug discovery. These targets can be approached through exploitation of emerging in-silico, in-vitro and in-vivo models or a combination of these methods. Advances in computational biology have enabled in silico methods to expedite lead optimization and identification. Inspite of few demerits, In-silico biology paradigm provides opportunities to both synthetic chemists and biologist in expediting the discovery of new targets for cancer, and ultimately lead to compounds with predicted biological activity for these novel targets.

P-057: Histopathological comparison of Baso squamous cell carcinoma and Trichoblastoma in canine and human.

Sabale S.S., Satpute A.K., Gulawane S.U., Nehete R. S., Kadam D.P., Mahalankar S.A., Princy Thomas, Malgunde S.A., Wakhankar C., Sawale G.K., and Meshram P.V.

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In human medicine, Baso-squamous carcinoma of the skin is defined as a carcinoma comprised of two elements: 1) malignant basal cells with scant basophilic cytoplasm and palisading nuclei at the nest periphery, 2) aggregates of squamous cells with larger amounts of eosinophilic cytoplasm. The key to the diagnosis of baso-squamous carcinoma is the absence of a transition zone between the basal cell and the squamous cell types. Trichoblastoma is "trichogenic adnexal tumors" which show peculiar relationship between epithelial component and cellular stroma, reminiscent of mutual induction between epithelium and mesenchyme during hair development in embryogenesis. Similar histopathological alterations were observed in following study. In this study, A 13 year old male Lhasa apso with a 1 week history of unexplained pain and raised white area in mouth spreading towards mandible was referred to the Private Veterinary Clinic. Cytology of the tissue revealed round to oval hyperchromatic squamous epithelial

cells in clumps suggestive of malignancy. It was white irregular measuring about (1.5 X 1.3 X 1 cm). Histopathology revealed haphazard arrangement of hyperchromatic and anaplatic basal cells and squamous cells with inflammation and stroma. According to histopathological examination, the case was diagnosed as baso-squamous cell carcinoma. After 2 week post surgery it reoccurs with double the size and spreading toward base of 2nd molar tooth with significant weight loss and poor prognosis. In another case, a 2 years male Rottweiler dog was presented with a growth in the left ear. The growth was an exophytic mass of 5 cm in diameter extended from the epidermal-dermal interface into dermis and sub cutis. The overlying epithelium was devoid of hair and slightly ulcerated. Histopathology revealed an Island and sheets of neoplastic cells along with some amount of interstitial collagenous stroma. The neoplastic cells were basoloid with hyperchromatic, ovaloid to round nuclei and abundant granular eosinophillic cytoplasm with distinct borders. The findings were suggestive of the tumor, derived from hair germ of developing follicle known as Trichoblastoma.

P-058: Mesenchymal Stem Cells from Hematologic Malignancies

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Mesenchymal stem cells (MSC) isolated from the bone marrow (BM) have the ability to differentiate into osteocyes, adipocytes and other mesenchymal cells. MSC is also an essential component of the bone marrow microenvironment and has been reported to play an important role in regulating hematopoietic stem cells (HSC) by direct cell-cell interaction and paracrine factors. During hematological malignancies this interaction is affected resulting in bone marrow failure.

In our study, we isolated MSC from patients with various hematological malignancies involving the bone marrow. After red cell lysis, bone marrow cells from the patients were seeded on to tissue culture flasks and MSC colonies were obtained after 2-3 weeks.

Initial karyotypic analysis showed that MSC from patients had normal karyotype with 46 chromosomes. Also, patients MSC were phenotypically similar to normal MSC except decreased CD90 expression in some cases. On differentiation, the patient MSC readily differentiated into adipocytes, but displayed low differentiation into osteocytes. It is not clear at this point if the reduced osteogenic differentiation is inherent or disease induced. Interestingly, decrease in osteogenic differentiation was found to be associated with low CD90 surface expression.

From our results, we suggest that CD90 surface expression might influence the osteogenic differentiation potential of MSC. This low osteogenic differentiation will render MSC ineffective in supporting HSC function resulting in BM failure. Further investigation on the relationship between CD90 and osteogenic differentiation in MSC from hematologic malignancies might lead to discovery of new therapies for BM failure.

P-059: Hepatoprotective activity of isolated terpenoids and terpenoid fractions of Scoparia dulcis L.

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Pacific College of Pharmacy, Udaipur, Rajasthan, India

Scoparia dulcis L. is widely used in the traditional system of medicine for treating liver ailments. In the present study the terpenoids and terpenoid fractions isolated from 1:1:1 petroleum ether, diethyl ether and methanol (PDM) extract of *Scoparia dulcis* L. were tested for their *in vitro* DPPH radical scavenging activity. Selected samples from the assay were further tested for their *in vitro* hepatoprotective activity against CCl_4 induced hepatotoxicity using freshly isolated rat hepatocytes. In the *in vitro* antioxidant study, certain fractions and PDM extract showed DPPH radical scavenging activity. The phytochemical screening of all these fractions showed the presence of terpenoids. In the *in vitro* hepatoprotective study, all these fractions and the PDM extract significantly prevented the CCl_4 induced changes in the ASAT, ALAT and ALP levels ($p<0.05$). The above results were comparable with the standard drug silymarin. The results of the study indicate that the PDM extract of *Scoparia dulcis* L. possesses potential hepatoprotective activity and this may be attributed to its free radical scavenging potential, which in turn may be due to the presence of terpenoids.

P-060: Clinical Significance of Apoptosis related proteins and their gene expression in Breast Carcinoma.

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Gujarat Cancer and Research Institute, Ahmedabad-380016, India

The role of apoptosis in tumorigenesis is currently being studied extensively. Increasing evidence shows that apoptosis and also to an accumulation of mutations at the genomic level may be involved in the development and progression of cancer. The most frequently mutated gene known to date in sporadic breast cancer appears to be the tumor suppressor gene p53. So the purpose of the present study was to investigate immunohistochemical expression on paraffin embedded tumor tissue sections of apoptosis related proteins such as Bcl2, BAG-1 and p53 in breast tumors, to compare it with established clinicopathologic prognostic factors and further to investigate their clinical significance by gene expressions on fresh tissues. Monoclonal primary antibodies used were of Bcl2 (Novocastra, UK), BAG-1 (DakoCytomation, CA, USA) and p53 (Dakopatt, Denmark). Protein expression of Bcl2, BAG-1 and p53 was noted in 57%, 68% and 61% in tumors of breast carcinoma patients, respectively. The data indicated that Bcl2 negativity and BAG-1 and p53 positivity identifies aggressive phenotype of breast cancer patients. Further we investigated clinical significance of gene expression of p53 exons 5, p53 exons 7 and Bcl2 by PCR. The size of PCR product was 290bp for p53 exon 5 and 210bp for p53 exon7 and 390bp for Bcl2 primer. The gene expression for p53 exon 5, exon 7 and Bcl2 gene was noted 37%,11% and 33% respectively. p53 exons 5 and 7 expression was found to be associated with hormone dependent breast cancer. Also, down regulation of p53 protein in comparison with p53 gene expression which is associated with hormone receptors negativity.

P-061: Emerging molecular targets for novel therapeutic strategies in stroke.

Ram Raghubir

Central Drug Research Institute, Lucknow, India

The stroke is the second most common cause of death and disability. However development successful therapeutic strategies remains challenging as there is no drug available except rt-PA with narrow therapeutic window for treatment of acute stroke. There is an urgent need to develop newer therapeutic entities as world stroke campaign has indicated that one in six persons will have stroke in their life time.The most common stroke is ischemic stroke and the ischemic cascade that evolves in response to cerebral injury includes excitotoxicity, acidotoxicity, ionic imbalance, peri-infarct depolarization, oxidative and ER stress, and inflammation leading to a rapid death of neurons in the ischemic zone. Recently a great deal of knowledge has been gained about these various ischemic events and this very knowledge led to identification of suitable drugable molecular targets, which need to be incorporated in preclinical and clinical design for ameliorating ischemic pathology.

P-062: Design and synthesis of potent and orally bioavailable PAI-1 inhibitors

Vrajesh Pandya, Ganes Chakrabarti, Jigar Patel, Jignesh Joshi, Nirav Joshi, Bhavesh Parmar Hitesh Soni, Mehul Raviya, Harilal Patel, Mukul Jain

Zydus Research Centre, Ahmedabad, India

Plasminogen activator inhibitor-1 (PAI-1), a member of serpin (Serine protease inhibitor) superfamily, prevents formation of plasmin by inhibiting the activity of tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA), the key enzymes whose proteolytic action converts plasminogen to plasmin. Plasmin dissolves fibrin clots by degrading insoluble fibrin molecules to small soluble fragments. Deficiency of PAI-1 in humans results in a hyperfibrinolytic state which suggests that it has important role in fibrosis. PAI-1 has also been implicated in various patho-physiological processes, including cancer, diabetic nephropathy, obesity, metabolic syndrome and in the development of vascular diseases such as venous thrombosis and atherosclerosis. In spite of having multiple conformational forms and flexible reactive centre loop of PAI-1, several small molecules have been identified using either high throughput screening or virtual screening concepts. Therapeutic potential of PAI-1 inhibitors has been reviewed recently. Although some of these molecules have demonstrated good antithrombotic efficacy in various preclinical models but their clinical effects still remain unknown. There is still unmet need to develop potent, efficacious and orally bioavailable PAI-1 inhibitor.

Phenoxybenzoic acids derivatives were synthesized by hybridization and conformational restriction of Tiplaxtinin and piperazine derivatives. In vitro PAI-I inhibitory activity and PK profile of selected compounds in rats will be presented.

P-063: Inhibition of PKC-delta (PKCδ) isoform prevents ischemia and reperfusion induced myocardial injury.

Kamaldeep Kaur, Manjeet Singh, Nirmal Singh

Punjabi University, Patiala, India

Purpose: Myocardial ischemia and reperfusion lead to activation of two novel PKC iso-forms (PKCδ and PKCε) which are reported to play opposing roles during myocardial ischemia and reperfusion (I/R). PKCδ has been reported to mediate I/R induced myocardial injury, whereas PKCε has been reported to provide cardioprotection through preconditioning. The present study was designed to investigate the modulatory effects of Rottlerin, a PKCδ inhibitor on ischemia reperfusion induced myocardial injury.

Materials and Methods: Isolated rat hearts were exposed to 30 minutes of global ischemia followed by 120 minutes of reperfusion using Langendorff apparatus. Myocardial injury was assessed in the terms of infarct size, release of lactate dehydrogenase (LDH), creatine kinase (CK) enzymes and DNA smearing.

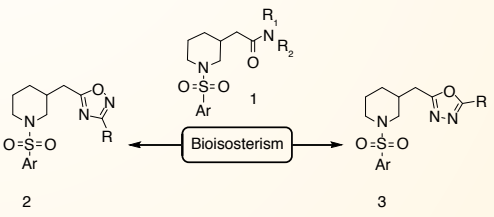
Results: Rottlerin, a selective PKCd inhibitor, did not modulate (I/R) induced myocardial injury at low dose (3 μM). However, at moderate dose (6μM) it significantly produced cardioprotective effects. On the contrary, rottlerin at high dose (12 μM) significantly enhanced I/R induced myocardial injury. However, administration of FR-167653 (1.1 μM and 2.2 μM), a selective p-38MAPK inhibitor, attenuated rottlerin (12μM) mediated enhancement in I/R induced myocardial injury in a dose dependent manner. Per se administration of FR-167653 (1.1 μM and 2.2 μM) also attenuated I/R induced myocardial injury in a dose dependent manner. Pretreatment with rottlerin (6 μM) did not enhance the cardioprotective effects of FR-167653 (2.2 μM). It may be concluded that Rottlerin mediated cardioprotective effects at moderate dose, possible due to inhibition of PKCδ; while at high dose it enhanced I/R induced myocardial injury probably by activation of p38MAPK.

P-064: 3-Substituted piperidines as 11β-HSD1 inhibitor via bioisosteric replacement of hydrazides with oxadiazoles.

Hardik A. Shah, Pinkal N. Prajapati, Jignesh P. Pethani, Krunal C. Kothari, Darshan A . Joshi, Bhushan N. Dave, Rajendra K. Kharul, Sunil Metiya, Prasenjit Mitra.

Zydus Research Centre, Ahmedabad, India

Glucorticoids play an important role in many physiological functions. 11β-Hydroxysteroid dehydrogenase type 1 11β- HSD1 is an enzyme which is involved in glucocorticoid regulation. Inhibition of 11β -HSD1 has been pursued by many pharmaceutical companies and academic laboratories as a treatment for metabolic syndrome including T2DM. Herein we disclose piperidine compounds as defined by the general formulae (2 & 3) as potent inhibitors of 11β -HSD1. From our earlier work we found that the hydrazide and amide functionality is crucial for retaining activity in inhibitor (1). To achieve desired Pharmacokinetic profile, we have bioisosterically replaced amides and hydrazides functionality with 1, 2, 4 –oxadiazole (2) and 1, 3, 4-oxadiazole (3). These desired oxadiazoles were synthesized from commercially available nipecotic acid and various sulfonyl chlorides. Further one carbon homologation was done to have precursor acid, which was converted to 1, 2, 4-oxadiazoles (1). Acid was reacted with different acidhydrazides to furnish diamide intermediate which was converted to 1, 3, 4 oxadiazoles (2). These 1, 2, 4-oxadiazole and 1, 3, 4- ox diazole derivatives were screened for their in-vitro inhibitory activity against 11β-HSD1. The most of the derivatives exhibited moderate to excellent inhibition of both human and mouse 11β-HSD1. The compounds of this invention may be therefore suitable for the prevention and treatment of disease states mediated by 11β-HSD1.



P-065: Phytopreventive antihyperlipidemic activity of *Abutilon indicum* Leaves

Neeraj Agrawal, Rohini A., Patel Pranay Ranchod Bhai

Pacific College of Pharmacy, Udaipur, Rajasthan, India

Abutilon indicum belongs to the family Malvaceae. Qualitative phytochemical analysis of *Abutilon indicum* leaves showed the presence of alkaloids, flavonoids and steroids in 50 % hydroethanolic extract prepared by hot and cold maceration process. 50 % hydroethanolic extract prepared by hot maceration

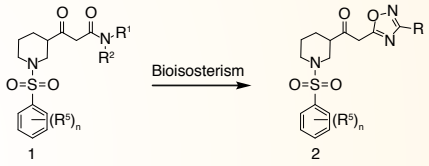
process of *Abutilon indicum* leaves was shown to have sufficient phenol content in the range of 44.71 mg/g of Gallic acid and it showed 128.83 mg/g of quercetin. *Abutilon indicum* was found to be effective in significantly reducing both triglyceride (TG) and total cholesterol (TC) levels after 12 days of pretreatment with 50 % Hydro ethanolic extract at the dose of 200 and 400 mg/kg. *Abutilon indicum* significantly reduced TG levels by 16.85 % and 20.64 % respectively and decreased TC level by 37.39 % and 43.8 % respectively. LDL levels were also found to be decreased by 31.55 % and 39.83 % respectively. VLDL levels were also significantly reduced by 16.85 and 20.63 %. No significant changes were seen in HDL cholesterol. All these decreased levels were statistically significant ($P<0.001$) and indicates anti hyperlipidemic activity of *Abutilon indicum* leaves.

P-066: β-Ketoamides, hydrazides and their bioisosters as 11βHSD1 inhibitors.

Jignesh P. Pethani, Pinkal N. Prajapati, Amol A. Thorave, Hardik A. Shah, Krunal C. Kothari, Darshan A. Joshi, Rajendra K. Kharul*, Sunil Metiya, Prasenjit Mitra, Mukul R. Jain

Zydus Research Centre, Ahmedabad, India

Glucorticoids play an important role in many physiological functions. 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) is an enzyme which is involved in glucocorticoid regulation, and inhibition of 11b -HSD1 has been pursued by many pharmaceutical companies and academic laboratories as a treatment for metabolic syndrome including T2DM. Herein we disclose β-Ketoamides, hydrazides and their bioisosters of substituted piperidine compounds as defined by the general formulae (1 & 2) as potent inhibitor of 11β-HSD1. These piperidine derivatives were synthesized from commercially available nipecotic acid and various sulfonyl chlorides. Further acid was converted to its acid chloride and reacted with mixture of tert-butyl acetate and LiHMDS to yield the corresponding β -keto ester. β-keto ester was reacted with different amines in presence of catalytic DMAP in toluene at 100 °C to furnish different β-keto amide derivatives. These piperidine derivatives were screened for their in-vitro inhibitory activity against 11β-HSD1. To increase the potency further and increase mouse selectivity, amide group was replaced with its bioisoster 1, 2, 4-oxadiazoles (2). The most of the derivatives showed moderate to excellent inhibition of both human and mouse 11β-HSD1. The compounds of this invention may be therefore suitable for the prevention and treatment of disease states mediated by 11β-HSD1.



P-067: Antihyperlipidemic activity of *Cassia auriculata* Linn. Leaves

Patel Vrajesh T., Warjurkar Rohan N., Patil Savita D., Patel Milap R.

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Introduction: Atherosclerosis is the leading cause of CVD-related mortality, accounting for nearly three-fourths of all deaths from heart disease. LDL plays a major role in the initiation and promotion of atherosclerosis.

Cassia auriculata Linn. (Caesalpiniaceae) is branched shrub that grows in the Ceylon, Central Provinces and Western coast of India. The plant species has been of interest to researchers because of its chemical constituents viz flavonoid and sterols, secondary plant metabolites which are commonly used as antioxidants.

Material & Methods: The antihyperlipidemic activity of ethyl acetate fraction of leaf of *Cassia auriculata* was investigated for the first time.

Chemical constituents of ethyl acetate fraction obtained from *Cassia auriculata* leaves were analyzed by high performance liquid chromatography (HPLC) and the effects of flavonoid and sterols were investigated using several models viz L-N$^{\omega}$ nitroarginine, high fat diet, and antiplatelet aggregation activities.

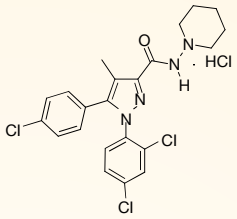
Result: Results demonstrated that the ethyl acetate fraction of *Cassia auriculata* leaves strongly inhibited platelet aggregation, decreased elevated level of serum lipid profile significantly in L-N$^{\omega}$ nitroarginine and high fat diet induced hyperlipidemia model.

P-068: Novel Substituted 1, 5-diphenyl-4,5-dihydro-1H-pyrazole-3-yl methyl amide derivatives a potent CB1 Receptor Antagonists: Synthesis and Biological Evaluation

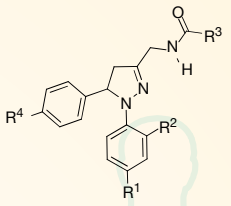
Sandeep Shedage[1], Shivaji Gugale[1], Rina Soni[1£], Jayendra Patel[1] Rahul Salunke[1], Sidhartha Kar[1], Pravin Kadam[1], Saurin Raval[1], Purvi Vyas[3], Priyanka Priyadarsiny[3] Amit Joharapurkar[2], Samadhan Kshirsagar[2], Harilal Patel[4], Mukul Jain[2], Pankaj Patel[1] and Brijesh Kumar Srivastava[1]

1 Dept of Medicinal Chemistry; 2 Dept of Pharmacology; 3 Dept of Cell Biology; 4 Dept of DMPK, Zydus Research Centre, Ahmedabad, India. ¤Present address- Dept of Chemistry, University of Warwick, UK.

CB1 receptor antagonists are known for the treatment of obesity and associated metabolic disorders. However, this class of compounds was being subjected to rigorous scrutiny owing to the discontinuation of Rimonabant (Fig.1) from the market. Herein, we report the optimization efforts on a series of potent Substituted 1, 5-diphenyl-4, 5-dihydro-1H-pyrazole-3-yl methyl amide derivatives (Fig. 2, 2-14). The lead compound has been identified with more distribution in periphery and no symptoms of nausea in rodents, thus compound may be free from side effects such as anxiety and depression.



1
Rimonabant
Figure 1.



2-14
Figure 2.

P-069: Comparative evaluation of dietary anti-oxidants in Triton WR-1339 induced acute hyperlipidemia in rats

Sameer S. Patel, Somsuvra B. Ghatak, Shital J. Panchal

Department of Pharmacology, Institute of Pharmacy, Nirma University, Ahmedabad-382 481, Gujarat, India

Higher cardiovascular complications are seen in hyperlipidemic conditions, wherein, imbalanced diet and stressful lifestyle are considered as prime etiological factors. In hyperlipidemia, oxidative stress is key player for developing atherosclerosis via oxidation of various lipoproteins like LDL, VLDL. On the other hand, dietary anti-oxidants like vitamin-E, ferulic acid esters and Co-Enzyme Q-10 have been reported for their potential anti-oxidant activity along with some beneficial effects in hyperlipidemia via reducing plasma lipids. Hence, the present study was designed with an objective to comparatively evaluate the potential effects of dietary anti-oxidants like vitamin-E and ferulic acid esters (FAE).

Wistar Rats (either sex) were divided in five groups: Normal vehicle control, Induced control, FAE-50mg/kg, FAE-100mg/kg, Vit-E-100mg/kg, Atorvastatin (10mg/kg). The treatment with FAE, vitamin-E and a reference standard Atorvastatin was given for 21 days. On the 21st day of the treatment acute hyperlipidemia was induced using WR-1339 (300mg/kg ip). Serum lipid level like triglycerides (TGs), total cholesterol (TC), low density lipoprotein (LDL) and high density lipoproeitn (HDL) were measured.

In the groups FAE-100mg/kg and Vit-E-100mg/kg there was a significant decrease in TGs, TC and LDL levels and increase in HDL level as compared to induced control group. The decrease in TGs, TC and LDL, and the increase in HDL level by FAE (100mg/kg) treatment was significantly high as compared to Vit-E (100mg/kg). There was no significant effect of FAE treatment at the dose of 50mg/kg.

P-070: Neuroprotective effect of Peroxisome Proliferator-Activated Receptor gamma agonist and Statin on cerebral ischemia and reperfusion-induced cerebral injury in Sprague Dawley rats.

Chitrang Trivedi, Suresh Giri, Ganesh Ghangale, Lalabhai Patel and Mukul R. Jain

Zydus Research Centre, Ahmedabad, India

Stroke is characterized by sudden onset of nonprogressive, focal brain dysfunction as result of an ischemic infarction or hemorrhage. Most of the drugs for stroke show good neuroprotective efficacy in preclinical models, however, the same is not translated to human clinical conditions. The reasons for this discrepancy could be the difference in study design in preclinical models & actual therapeutic time window available in humans. Peroxisome Proliferator-Activated Receptor gamma (PPARγ) agonists and statins exhibit potent anti-inflammatory and antioxidant actions.

The present study was aimed to evaluate the effect of prophylactic and curative treatment of pioglitazone and rosuvastatin in Middle Cerebral Artery Occlusion (MCAO) induced stroke in rats. For prophylactic treatment, pioglitazone (30mg/kg, po) or rosuvastatin (20 mg/kg, po) was administered for 14 days before MCAO in rats. For assessment of therapeutic time window, rats were pre-treated (24 hr or 1 min. before MCAO) with pioglitazone and rosuvastatin (10 mg/kg, ip) as well as 2, 4 and 6 hour after the MCAO and the effect was compared with a group that was given 14-day pre-treatment plus a dose given 2hr after the MCAO.Repeated administration of pioglitazone and rosuvastatin for 14 days before MCAO shows

excellent neuroprotection by reducing the infarct size by 40% and 63.9 % respectively along with 43% and 55.6% improvement in neurological deficit. Acute administration of these agents given immediately before and up to 2 hrs of MCAO also showed significant neuroprotective effect. However, acute administration of drugs beyond 2 hr after cerebral injury shows no neuroprotection. Results of the study indicate that pioglitazone and rosuvastatin may not be effective in providing neuroprotection if administered after 2 hr of cerebral ischemic stroke in rats.

P-071: Effect of Perindropril, an Angiotensin-Converting Enzyme Inhibitor on Ischemic Stroke in Middle Cerebral Artery Occulsion Model in Rats.

Ankit Sheth, Shraddha Bhadada, Shital Panchal

Institute of Pharmacy, Nirma University, Ahmedabad, India

Stroke is third leading cause of death worldwide. Recent trials suggest that ramipril, an angiotensin-converting enzyme inhibitor (ACEI) is effective in prevention of the ischemic stroke. The study is aimed to evaluate the effect of an ACEI, perindopril, in the middle cerebral artery occlusion model of ischemic stroke in rats and to find out the possible mechanism lying beneath the effect.

Ischemic stroke in rats was induced by middle cerebral artery occlusion using 3-0 intraluminant filament coated with poly-l-lysine. Wistar rats (either sex) were divided into the groups: Normal control, diseased control, continuous treatment for four weeks with perindopril (Per (2w/2w)), pre treatment for two weeks with perindopril (Per (2w/-)), post treatment for two weeks with perindopril (Per (-/2w)), and continueous treatment with standard aspirin (Asp(2w/2w)). Perindopril (0.5 mg/kg/day) and aspirin (30 mg/kg/day) were administered orally. Various parameters like infarct volume, neurological score, brain weight , nitric oxide, lipid peroxidation, catalase & reduced glutathione level were assesed.

The animals of the group Per (2w/2w) and Per (2w/-) showed significant reduction of brain damage as compared to animals of diseased control group. In both the groups, there was significant reduction in infarct volume, nitric oxide level, lipid peroxidation and restoration of antioxidant enzymes in both groups, as well as normalization of neurological behaviour.

The possible mechanism for the effect of perindopril could be attributed to the inhibition of activity of angiotensin II such as vasoconstriction, formation of reactive oxygen species and iNOS expression.

P-072: High fat diet increases sensitivity to efficacy and toxicity of rosuvastatin in hamsters.

Lalabhai Patel, Suresh Giri, Chitrang Trivedi, Rakesh Kothiya and Mukul R. Jain

Zydus Research Centre, Ahmedabad, India

Statins (Hydroxymethylglutaryl-coenzyme A reductase inhibitors) are the most effective drugs for management of dyslipidemia. The preclinical and clinical safety studies for these drugs have been carried out on normal subjects whereas the efficacy parameters are evaluated in dyslipidemic conditions. In order to assess the safety concerns of statins in dyslipidemic patients, present study was carried out in normal and high-fat, high-cholesterol diet-fed conditions, which simulate dyslipidemia in human patients.

Hamsters were given HF-HC (high fat- high cholesterol) diet containing 35% Fat & 0.5 % Cholesterol. HF-FC-fed hamsters were administered with rosuvastatin at the dose rate of 0.1, 0.3, 0.5, 1 and 1.5 mg/kg and normal chow diet fed hamsters were administered with rosuvastatin at doses of 1, 10, 25, 50 and 100 mg/kg for 14 days orally. Comparative pharmacokinetic studies were also done on both diet groups that indicated 2 fold higher peak plasma levels (Cmax) and 1.5 fold higher AUC(0-t) in HF-HC diet fed hamsters.. Rosuvastatin showed significant LDL-cholesterol lowering effect at 50 and 100 mg/kg doses in normal diet fed hamsters, but in HF-HC diet-fed hamsters significant LDL-lowering effect was observed at 0.3, 0.5, 1.0 and 1.5 mg/kg doses. Toxicity biomarkers like ALT, AST, ALP, CK were significantly elevated at 50 and 100 mg/kg dose in normal diet fed hamsters along with histopathology of liver and heart tissue. Whereas in HF-HC diet fed hamsters similar changes were observed at relatively lower doses of 0.3, 0.5, 1.0 and 1.5 mg/kg. Gene expression studies revealed that high fat diet feeding decrease mRNA levels of MTTP, SREBP and LDL-R genes.

Our study has revealed that high fat high cholesterol diet feeding makes hamsters 100-150 times sensitive to rosuvastatin induce efficacy and toxicity. This raises potential concerns for safety of statins in dyslipidemic patients

P-073: Design and Synthesis of a Newer α-acyl β-phenylpropanoic acid as PPAR Dual Agonist.

Manish Sharma, Rambabu Gupta, Ritesh Mathure, Kamlesh Thakur, Ruchi Malik.

Centre for QSAR and Molecular Modeling, Department of Medicinal and Pharmaceutical Chemistry,TIFAC-CORE, B.R. Nahata College of Pharmacy (SIRO), Mandsaur, 458001, MP, India.

A comparative QSAR study through Hansch analysis on PPARγ agonists was carried out on following three series:

1) 2-Alkoxydihydrocinnamates.

$-\log EC_{50}=2.053(\pm0.899)R_1Vw-1.921(\pm0.625)R_2Vw+6.476(\pm0.375)$

$n=12, r=0.95, s=0.18, F=41.37, R^2=0.90, R^2_{adj}=0.88$, RMSE=0.38, $Q^2=0.81$

2) Azaindole-α-alkyloxyphenylpropionic acids.

$-\log EC_{50}= -0.96(\pm0.472)RVw+0.847(\pm0.344)I_1+0.495(\pm0.249)I_2+6.476$

$n=18, r=0.94, s=0.19, F=32.58, R^2=0.88, R^2_{adj}=0.85$, RMSE=0.20, $Q^2=0.78$

3) Oxime ethers of α-acyl-β-phenylpropanoic acids.

$-\log EC_{50}=11.344(6.549)MR-0.415(0.255)MR^2-68.072(42.133)$

$n=15, r=0.90, s=0.26, F=24.84, R^2=0.82, R^2_{adj}=0.80$, RMSE=0.41, $Q^2=0.73$

On the basis of internally and laterally validated QSAR models, scaled optimum molar refractivity (MR) value of 14.3 for molecules was required for maximum agonistic activity. Using this clue some oxime ethers of α-acyl-β-phenylpropanoic acids were proposed which were within the probability density derived applicability domain. The structural effects of ligand binding were examined on the basis of hydrogen bond interactions and binding energies in the final complexes obtained from molecular docking simulations. Compound 7p was found to possess optimum calculated activity, passed Lipinski's "rule of five" for oral absorption and lacked toxicity (mutagenicity,carcinoge nicity,teratogenicity and embryotoxicity predicted by *PASS*). The derivative was synthesized and characterized by their physicochemical data and spectral analysis(F.T.I.R,^{1}HN.M.R.,Elemental analysis and Mass spectroscopy). Test compound (100mg/kg and 150mg/kg) exhibited a dose dependent significant anti-hyperglycemic activity. The anti-hyperglycemic effect of test compound was found to be less effective than the reference standard.

P-074: Role of Rosiglitazone (PPARγ agonist) and its combination with amiloride (ENaC inhibitor) in aortic constriction induced congestive heart failure model in rat

Suresh Giri, Kavan Desai, Lalabhai Patel, Chitrang Trivedi, Rakesh Kothiya and Mukul R. Jain

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Diabetes is primarily responsible for morbidity & mortality associated with cardiovascular diseases. PPAR γ agonists are very effective in treatment of diabetes, but the main side effect associated with these drugs hypervolaemia due to fluid retention which in turn may aggravate the cardiac hypertrophy and possible risk of congestive heart failure (CHF). Although, some of the PPAR γ agonists have shown adverse cardiac effects in clinic, but there are also reports that PPAR- γ agonists may have beneficial effects through mechanisms involving attenuation of ET-1-induced vasoconstriction, inhibition of the NF-κβ and increased nitric oxide etc. that may lead to lowering of blood pressure and reduction in cardiac afterload. Although, the precise involvement of PPAR γ in congestive heart failure remain controversial, it is believed that the fluid retention caused by PPAR γ agonists may be caused by sodium retention by their action on epithelial Na channel (ENaC) situated in the collecting duct. The present studies were carried out to find out if reduction in preload with the help of ENaC inhibitor would be beneficial in combination with PPAR γ agonists.

The Sprague Dawley rats were subjected for aortic constriction surgery and after 2 weeks they were given treatment with rosiglitazone (40 mg/kg) alone or a combination of rosiglitazone (40 mg/kg) with ENaC inhibitor, amiloride (2 mg/kg). The results show that two week-repeated dose treatment with rosiglitazone (40 mg/kg) caused increase in plasma volume indicating increase in preload but the combination with amiloride reversed the effect of rosiglitazone on plasma volume and animals showed improvement in BNP, left ventricular hypertrophy and blood pressure indicating an overall improvement in the congestive heart failure condition.

P-075: Effects of *Asparagus racemosus* (Willd.) extract in haemostasis and on arterio-venous shunt thrombosis.

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Objective: The present study was carried out to evaluate the *in-vivo* effect of *Asparagus racemosus* (Willd) for its antithrombotic potential in rat arterio-venous (AV) shunt thrombosis and in mice tail transection bleeding time assay models.

Methods: Sprague Dawley rats and albino mice of either sex were administered with root extract of *Asparagus racemosus* (100 and 200 mg/kg) one hour prior to the experiments and antithrombotic activity were assessed respectively by weighing thread weight after stabilizing shunt for 10 minutes and by measuring bleeding time after tail transection.

Results: Pretreatment with *A. racemosus* in a dose of 100 and 200 mg/kg p.o. in rats, resulted in a dose-dependant reduction in thrombus formation by 18 and 54% respectively, comparable to that of aspirin and clopidogrel. Further, a significant dose dependent prolongation in bleeding time comparable to positive controls was also observed in mice.

Conclusion: *Asparagus racemosus* (AR) produces dose-dependent antithrombotic activity following the oral administration in arterio-venous shunt thrombosis and in bleeding time assay models.

P-076: Cardiac MHC Gene Modification in Defending Heart Function By 3,5,3'triiodo –L-Thyronine in Hypothyroid Rats

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Various regulatory and structural proteins in myocardium found to be responsive to thyroid hormone. However, use of thyroid hormone is limited by cardiac effects. This study was undertaken to explore the cardioprotective action along with general toxicological impact induced by the 3, 5, 3'-triiodothyronine (T_3) in a surgically developed hypothyroid female Wistar rats by administration of T_3 at the dose of 2, 10, 20 & 40 µg/kg orally for 7 days. Increased alertness and locomotor activity was observed from 10µg/kg. Normalization of heart rate and body temperature was noticed at 10 and 20µg/kg dose of T_3 treated hypothyroid rats when compared with normal rats. Low density lipoprotein, triglyceride, total protein and creatinine levels were altered in T_3 treated rats marked at 40µg/kg. Dose dependent higher heart weight was observed, with significant from 20µg/kg in comparisons with hypothyroid rat, however rat treated with 2 and 10µg/kg shown normal weight and is comparable with euthyroid rats. Myosin heavy chain alpha and beta gene expression ratio tend toward normalization at 10 and 20µg/kg and was comparable with normal rats. Histopathological examination of heart revealed mononuclear cells infiltration with of fibroblast proliferation at 10 and 20µg/kg.

Based on the finding of restoration of cardiac function in terms of heart rate, heart weight, body temperature, myosin gene expression alpha and beta ratio and proliferation of fibroblast in heart tissue indicate T_3 may be explored further in treatment of hypothyroidism by precise dose selection for cardiac protective function.

P-077: Effect of a Deacyl gymnemic acid enriched extract on glucose homeostasis and metabolic parameters in a rat model of metabolic syndrome

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Background and objective: Metabolic syndrome (MS) comprises several cardiometabolic risk factors, which include obesity, hypertension, hyperglycemia, hypertriglyceridemia and decreased HDL cholesterol . Leaf extract of *Gymnema sylvestre* has been shown to possess glucose lowering activity in animal models. The present study was carried out to assess the efficacy of DAGA enriched extract, active constituent of *Gymnema sylvestre,* in a rat model of metabolic syndrome.

Methods: Six groups of Wistar rats were fed with high fructose diet (HFD) for a period of 20 days to induce metabolic syndrome. High fructose diet was continued and different doses of *DAGA enriched extract* (50, 100 and

200mgkg^{-1}) were administered orally and pioglitazone 2.7mgkg^{-1} was used as a positive control for next 20 days (day 40). Systolic blood pressure (SBP) was measured using tail cuff method. Oral glucose tolerance test (OGTT) was done at baseline and at day 20 and 40. Blood samples were collected from the rat tail vein for glucose, insulin and lipid profile on these respective days. Homeostasis Model Assessment - insulin resistance (HOMA-IR) and HOMA -β were assessed.

Results: Administration of HFD for twenty days resulted in weight gain(> 10%) , increase in systolic blood pressure, fasting plasma glucose (FPG) and triglycerides fulfilling the criteria of metabolic syndrome. Administration of DAGA enriched extract (200 mgkg^{-1}) for next 20 days significantly reduced the SBP, FPG, HOMA-IR and modest improvement in lipid profile without decrease in body weight. Similar alterations were seen in pioglitazone group.

Interpretation & conclusions: DAGA enriched extract possesses significant glucose lowering activity and improves insulin resistance in a rat model of metabolic syndrome induced by high fructose diet.

P-078: Myosin Heavy Chain Gene Expression In Euthyroid Wistar Rats

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Thyroid hormones specifically T_3, improves lipid and energy homeostasis along with significant effects on cardiac contractility through thyroid hormone receptor (TR) agonism. Such effects are amplified under hypothyroid animal models and have been routinely studied. To investigate similar effects in euthyroid rats, the present study was carried out using commercially available 3, 5, 3'-triiodothyronine (T_3) at the dose of 0.065, 0.26 and 0.39 mg/kg/day for 7 consecutive days. Clinical signs observed were hyperthermia, hyperesthesia, lethargy and increased salivation from 0.26mg/kg dose. Blood examination revealed marginally lower platelet count along with significant alterations in the levels of thyroxine, lipid profile, total protein, urea, creatinine, alkaline phosphatase, calcium and phosphorus. Histopathological changes were observed in heart, liver, kidney, thymus and thyroid tissues. Heart revealed multifocal myocardial degeneration with incidences of inflammatory cell infiltration from 0.26mg/kg dose. Quantitative estimation by the ratio of myosin heavy chain (MHC α and β gene) transcripts shown marked up-regulation in the cardiac tissues from the lowest dose of T_3. Therefore, studying molecular expression of myosin genes along with histopathological evaluation of heart tissue with clinical pathology may be of added advantage in identifying cardiovascular toxicity of thyromimetic drugs.

P-079: Synthesis and biological evaluation of novel heterocyclic analogs of biaryl urea as DGAT1 inhibitors.

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The worldwide incidence of obesity, a common metabolic disorder, has drastically increased in the past few decades. Obesity is a risk factor for hypertension, diabetes, and cardiovascular disease. The present therapeutic options for the treatment of obesity target a reduction of energy intake either by inhibiting appetite or by reducing lipid absorption from the small intestine. However there is a huge scope for improved therapies, that are either more efficacious or give rise to fewer side effects or both. This has led to the exploration of newer mechanistic targets, including those that seek to inhibit triacylglyceride synthesis and storage in adipose tissue. The diacylglycerol acyltransferase enzyme DGAT-1 presents itself as a potential target as this enzyme is dedicated to the final committed step in triglyceride synthesis. We have synthesized and evaluated novel heterocyclic analogs of biaryl ureas as DGAT1 inhibitors. Compounds within this series exhibited potent DGAT1 inhibition when evaluated using an *in vitro* assay that measures the formation of radioactive triglyceride. Selected compounds were also subjected to an oral fat tolerance test in mice where the percent triglyceride reduction versus a vehicle control was evaluated. The synthesis and biological data will be presented.

P-080: Combination of MTP inhibitor with triiodothyronine improves insulin sensitivity and symptoms of metabolic syndrome in Zucker fatty rats.

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Dyslipidemia is the disorder of lipoprotein metabolism associated with obesity and diabetes. Microsomal Triglyceride Transfer Protein (MTP), the enzyme involved in the secretion and assembly of ApoB containing lipoprotein from liver and intestine, is overexpressed in dyslipidemic conditions. MTP inhibitors have hypolipidemic activity, but the potential for hepatic steatosis limits their therapeutic use. Thyroid hormones are known to reduce body weight and cholesterol. We have investigated effects of combination of MTP inhibitor with triiodothyronine on metabolic syndrome in Zucker fatty rats. Male Zucker fa/fa rats of 8-12 weeks age were treated with BMS201038 (0.3mg/kg), T_3 (13µg/kg) and combination of BMS201038 and T_3 for 2 weeks. Daily administration of BMS201038, T_3 or combination of BMS201038 and T3 administration over 14 days significantly lowered the body weight as compared to vehicle-treated controls. The effect of the combination was more pronounced than any single treatment. T_3 showed increase whereas BMS201038 resulted in prominent decrease in the feed intake; but neither effect was seen in combination treatment. Glucose tolerance was significantly improved by combined drug treatment, whereas T_3 treatment alone had minimal effect on glucose homeostasis. These changes were accompanied by a significant improvement of insulin sensitivity and improvement in lipid profile in all treatment groups. Increase in the hepatic triglyceride content seen with BMS201038 treatment was not observed with the combination treatment. These data indicate that increased thyroid effect and blockade of MTP action using T_3 and BMS201038, respectively, provides an effective means of countering obesity and related abnormalities in a genetic model of obesity and dyslipidemia. Either of the agents lacks acute effect on glucose homeostasis, but a synergistic effect was observed in glucose tolerance, lipid profile, and body weight and insulin sensitivity upon repeated dose treatments

P-081: Diabetic retinopathy: An Indian perspective

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Diabetic retinopathy (DR) can be defined as damage to microvascular system in the retina due to prolonged hyperglycaemia. The prevalence of DR in the Chennai Urban Rural Epidemiology (CURES) Eye Study in south India was 17.6 per cent, significantly lower than age-matched western counterparts. However, due to the large number of diabetic subjects, DR is likely to pose a public health burden in India. CURES Eye study showed that the major systemic risk factors for onset and progression of DR are duration of diabetes, degree of glycaemic control and hyperlipidaemia. Hypertension did not play a major role in this cross-sectional analysis. The role of oxidative stress, atherosclerotic end points and genetic factors in susceptibility to DR has been studied. It was found that DR was associated with increased intima-media thickness and arterial stiffness in type 2 Indian diabetic subjects suggesting that common pathogenic mechanisms might predispose to diabetic microangiopathy. Curcumin, an active ingredient of turmeric, has been shown to inhibit proliferation of retinal endothelial cells in vivo. Visual disability from DR is largely preventable if managed with timely intervention by laser. It has been clearly demonstrted that in type 2 south Indian diabetic patients with proliferative DR who underwent Pan retinal photocoagulation, 73 per cent eyes with good visual acuity (6/9) at baseline maintained the same vision at 1 yr follow up. There is evidence that DR begins to develop years before the clinical diagnosis of type 2 diabetes. Our earlier study demonstrated that DR is present in 7 per cent of newly diagnosed subjects, hence routine retinal screening for DR even at the time of diagnosis of type 2 diabetes may help in optimized laser therapy. Annual retinal examination and early detection of DR can considerably reduce the risk of visual loss in diabetic individuals.

P-082: Solifenacin ameliorates obesity and improves glucose tolerance by enhancing energy expenditure and reducing adiposity

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Enhanced adiposity and increased insulin resistance leading to obesity and obesity-associated type 2 diabetes have contributed most to the healthcare burden in the current century. Central and peripheral cholinergic pathways play important role in regulating appetite and fat storage. The muscarinic receptor actions are implicated in regulation of glucose and energy homeostasis. Members of the muscarinic acetylcholine receptor family (M1-M5) have key roles in the regulation of many fundamental physiological functions. We have evaluated effect of M3 antagonist, solifenacin on reduction on adiposity, energy expenditure and glucose regulation in diet induced obese (DIO) C57 mice and db/db mice. Solifenacin, a M3 receptor antagonist was intraperitoneally administered to DIO mice at 1 and 3 mg/kg once a day for fourteen days, while it was administered centrally (icv) to DIO mice at 0.03 mg/5µL per

animal for seven days. In DIO mice, Solifenacin showed significant decrease in food intake, reduced body weight and peripheral fat deposits, and significantly lowered serum insulin and leptin at 3 mg/kg dose. Energy expenditure was significantly enhanced, with marked reduction in adiposity in DIO mice treated with central administration of solifenacin. The glucose regulation and insulin sensitivity was also ameliorated by the treatment of solifenacin both peripherally as well as centrally. The increase in energy expenditure represents a major factor contributing to the reduced body weight and adiposity, whereas enhanced insulin sensitivity could be attributed to reduction in calorie intake and the observed increase in energy expenditure, which are predicted to represent major factors responsible for the improvements in glucose homeostasis.

P-083: Antidyslipidemic activity of Modified Furano-flavonoids

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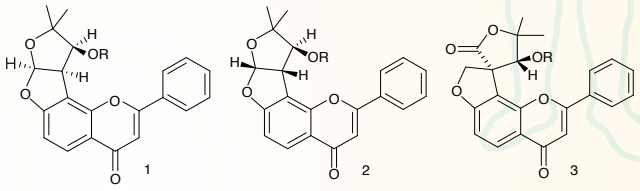
The herb, *Indigofera tinctoria* Linn., commonly known as 'neel', belonging to the family of Papilionaceae is widely used in the Indian system of medicine for epilepsy, nervous disorder, bronchitis and liver ailments, as ointment for sores, old ulcers and hemorrhoids and acts as an insecticida and hepatoprotective. Literature survey of *I. tinctoria* has revealed the presence of very few chemical constituents such as Apigenin, Kaempferol, Luteolin, Quicertin, Deguelin, Dehydrodegulin, Rotenol, Rotenone, Tephrosin, Sumatrol, Indigo, and Galactomannan.

Towards pharmacological studies, the alcoholic extract as well as the chloroform fraction of *I. tinctoria* leaves was evaluated and revealed noticeable antidyslipidemic activity in Hamster model. Repeated column chromatography of active chloroform fraction afforded three active furano-flavonoids 1, 2 and 3.



The activity results of the pure compounds 1-3 prompted us to perform the chemical transformation to enhance their activity. We therefore attempted to incorporate lipid lowering pharmacophores such as fibric acid, nicotinic acid and fatty acid derivatives in our molecules and the activity results of derivatives of 1-3 will be presented.

P-084: Peripheral administration of GLP-1 agonist restores sensitivity to centrally administered leptin in diet induced obese mice.

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Body weight is regulated by complex neurohormonal interactions within several endocrine signals. Leptin and GLP-1 plays pivotal role in regulating energy homeostasis and body weight regulation in rodents and humans. Diet induced obese (DIO) mice exhibit leptin resistance with high circulating leptin level. The mechanistic basis for leptin resistance is poorly understood, although rodent data implicates saturation of leptin transport across blood brain barrier, leptin receptor down-regulation, and reduced hypothalamic post receptor signaling. The prolonged exposure to high fat diet profoundly abolishes the central leptin sensitivity causing hyperphagia and obesity. These animals also develop hyperglycemia and insulin resistance. We have investigated the effects of peripheral administration of GLP-1 agonist in combination with central or peripheral leptin treatment in DIO mice on obesity. Two weeks of GLP-1 agonist treatment caused reduction in body weight and feed intake, which was not augmented by peripheral administration of leptin in DIO mice. Whereas the central (icv) administration of leptin in combination with peripheral administration of GLP-1 agonist significantly reduced feed intake and body weight, leptin alone had moderate effect on weight and hyperphagia indicating the vital role of GLP-1 mediated actions. The synergistic effects of central administration of leptin with peripheral treatment of GLP-1 agonist could be attributed to GLP-1 mediated restoration of leptin receptor sensitivity in brain, and leptin mediated restoration of insulin sensitivity in peripheral organs

P-085: A Cynomolgus Macaque Model of Obesity and Metabolic Syndrome by Dietary Manipulation

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With the recently escalating global obesity and metabolic syndrome (MS) epidemic in the human population, the establishment of animal models has been the focus of preclinical research to study the phenomena that underlie these conditions and facilitate the investigations of potential and novel therapeutic modalities. The obese nonhuman primate, particularly the cynomolgus macaque, has been considered as a reliable model of human obesity and metabolic diseases due to its genetic and pathophysiologic similarities to humans. In this study, adult cynomolgus macaques were fed with a specially formulated high fat diet (HFD; 35% energy from fat) for over a three-month period to induce and characterize an obesity/MS model. The incremental changes in body weights and BMI, lipid, and intravenous glucose tolerance tests glucose and insulin measurements in response to dietary manipulation over time were presented. Longitudinal whole body scans were taken by dual energy x-ray absorptiometry (DXA), and the body compartment composition for fat mass, lean body mass, and bone mineral density and content were analyzed. The responses of these adult monkeys were compared to an older cohort of MS-predisposed, pre-diabetic/diabetic cynomolgus macaques that were fed with a similar HFD. HFD consumption was associated with enhanced weight gain and BMI, and marked increases in the lipid profile of cynomolgus macaques similar to the characteristics of metabolic syndrome and its associated co-morbidities in humans. The results of this study provide evidence that the diet-induced obesity/MS cynomolgus monkey model offers a reliable animal model of human obesity and metabolic diseases.

P-086: Triiodothyronine (T3) treatment improves glucose homeostasis and renal dysfunction in multiple low dose streptozotocin induced diabetes in C57 mice.

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Thyroid hormones regulate serum lipids and energy expenditure through two thyroid receptors (α and β) with multiple splice isoforms and tissue distribution profiles. Though they do not regulate the glucose homeostasis directly, thyroid hormones affect the cell apoptosis, proliferation and neogenesis in a receptor-dependent mechanism, in key organs like liver, pancreas as well as in renal proximal tubular epithelial cells. Renal failure is a common and serious complication of longstanding diabetes mellitus. It has been reported that progression of renal failure in type 1 diabetes patients can be prevented by triiodothyronine treatment. We have investigated the effect of triiodothyronine (T3) on the development of hyperglycemia and insulitis, and renal dysfunction induced by multiple low doses of streptozotocin (MLDS) in C57 mice. MLDS-induced diabetes results in a loss of body weight, hyperglycemia and hypoinsulinemia. Triiodothyronine (T3, 100µg/kg, PO) treatment significantly reversed the hyperglycemia and hypoinsulinemia, though it did not improve body weight change. MLDS-induced diabetes also produced a significant bradycardia, hyperlipidemia and decreases in the levels of triiodothyronine and thyroxine. T3 treatment succesfully reversed these alterations. Significantly, triiodothyronine treatment has reduced the increase in urine volume and albuminuria in MLDS-induced diabetes in C57 mice. It was also associated with significant improvement in glucose tolerance, and %HbA1c levels in these animals. Thus, the results indicate that triiodothyronine treatment can improve the symptoms of diabetes and renal dysfunction induced by multiple low dose streptozotocin in C57 mice.

P-087: Epigenetically regulated AT1 and AT2 receptors explain link between insulin resistance and abdominal aortic aneurysms

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Several studies pointed out the negative link between diabetes and abdominal aortic aneurysms (AAA) but the mechanism remains largely unknown. Hence the present study was conceived to delineate the association between insulin resistance (IR), prediabetic condition and AAA. Insulin resistance was rendered in SD rats by high fat diet

feeding for four weeks. Functional (ex-vivo) studies have shown increased and unaltered Ang II mediated vascular responses in thoracic and abdominal aorta of HFD rats respectively. Interestingly AT2 receptor mediated relaxation was increased in abdominal aorta of HFD rats but not in thoracic aorta. Western blot and RT-PCR analysis revealed increased protein and mRNA expression of AT2R in abdominal aorta of HFD rats. Dramatically AT1R mRNA and protein expression was unchanged in abdominal aorta. Chromatin immunoprecipitation assay shown increased Ser-10 H3 phosphorylation on AT2R gene promoter region while no effect on AT1R gene promoter region in abdominal segment was observed. To best of our knowledge this is the first report that shows the epigenetic regulation of AT2 receptors expression and hence functional responses in abdominal aorta of insulin resistant rats. Thus, understanding of these mechanisms (AT2R upregulation) may provide treatment regimen to abdominal aortic aneurysms and reveals negative link between IR and AAA.

P-088: Trifluoro propan-2-one oxime, A Novel Bioisostere of Trifluoroamino propanol used to design CETP inhibitors

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

Tertiary trifluoro-3-amino-2-propanol class of compounds has been identified as potent CETP inhibitor and SC-795 is a lead compound from this series. Various SAR studies are reported in the literature on this class of compounds especially on benylic group and on phenyl group. However, no studies have been disclosed discussing the SAR on trifluoro aminopropanol group of SC-795 class of compounds. Our efforts towards design, synthesis and SAR study on trifluoro aminopropanol group of SC-795 class of compounds leads to equipotent trifluoro propan-2-one oxime group. Synthetic methodology, *in vitro* potency and pharmacokinetics of some of the compounds will be presentated.

P-089: High glucose enhances cellular responsiveness to thrombin via protease-activated receptor-4 in human vascular smooth muscle cells.

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Diabetes is associated with vascular remodeling and enhanced thrombin generation. Thrombin, a serine protease, promotes vascular smooth muscle cell (VSMC) mitogenesis and migration via protease-activated receptors (PAR)-1, PAR-3 and PAR-4. Here we investigated the effect of high glucose on thrombin receptor expression and function in human VSMC.

Human VSMC were incubated under normal (5.5 mmol/L) or high (25 mmol/L) glucose conditions. High glucose induced a rapid and sustained increase in PAR-4 mRNA (3.5±0.6 fold at 1.5h, and to 2.7±0.4 fold at 96h; n=7, $p<0.05$) as determined by real-time PCR, while expression of PAR-1 and PAR-3 were unaffected. PAR-4 protein and cell-surface expression were also increased by 2 fold. Accordingly, high glucose pretreatment (48h) enhanced thrombin (3U/mL) induced intracellular calcium mobilization (4.2±0.18 fold of basal), SMC migration (5.5±1.2 fold) and TNFα transcription (2.6±0.40 fold; all n=3-6; $p<0.05$). PAR-4 siRNA abolished the enhancement of thrombin stimulated VSMC migration and TNFα transcription in cells exposed to high glucose.

Exposure to high glucose increased PAR-4 luciferase activity by 6-fold (n=5; $p<0.05$). Accordingly, high glucose regulation of PAR-4 was prevented by knockdown of protein kinase C-δ or NFκB. High glucose increased the nuclear transition and binding of NFκB to the PAR-4 promoter in ChIP assay.

Immunohistochemistry and in-situ hybridization of human diabetic vessels showed upregulation of PAR-4 in diabetes.

In conclusion, these data show enhanced vascular responses to thrombin by high glucose through selective upregulation of PAR-4 via PKCδ/NFκB signaling. The study suggests that PAR-4 may play an important role in diabetes associated vascular pathologies.

P-090: Modulation of pancreatic glucokinase action affects GLP-1 mediated insulin secretion in mice.

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Glucose-stimulated insulin secretion (GSIS) by pancreatic beta cells requires the generation of ATP from the metabolism of glucose. Glucokinase is the glucose sensor enzyme in pancreas and it catalyzes initial step of glucose metabolism by converting glucose into glucose-6-phosphate. Glucokinase plays a key role in glucose homeostasis, regulating insulin secretion in response to glucose availability in the beta cells. Alloxan, streptozotocin and glucosamine are the known inhibitors of the pancreatic glucokinase enzyme. Exendin-4, through its action on GLP-1 receptors modulates glucose-stimulated insulin secretion. To investigate the role of glucokinase in this effect of Exendin-4, GSIS was evaluated in pancreatic islets with and without alloxan, streptozotocin and glucosamine. Pancreatic islets were isolated by collagenase digestion method from C57 mice. These islets were incubated with different concentrations of Exendin-4 at 16.7 mM of glucose. Exendin-4 induced GSIS was then evaluated after preincubation of alloxan, streptozotocin and glucosamine. Exendin-4 incubation in isolated islets resulted in increased GSIS as compared to control. Conversely, preincubation with alloxan, streptozotocin and glucosamine in isolated islets compromised both, Exendin-4 induced and physiological GSIS. To investigate the role of the GK in GSIS, a murine model of beta cell deficiency was created using streptozotocin injections. Pancreatic insulin content was decreased, and blood glucose levels increased in this model. The streptozotocin treatment reduced pancreatic glucokinase activity, which was partially restored by Exendin-4 treatment. Exendin-4 treatment also reversed the impairment in the glucose tolerance test and *in vivo* insulin secretion. These data indicate that inhibition of pancreatic glucokinase affects Exendin-4 mediated GSIS.

P-091: Rosiglitazone mediated neuroprotection in MCAO model is not mediated by Glutamate Transporter-1

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Glutamate transport represents an important mechanism for maintaining low levels of this neurotransmitter in the extracellular milieu to promote synaptic signalling and to restrict potential neurotoxicity resulting from the excitotoxic action of glutamate released during ischemia/reperfusion injury. Recently it was reported that GLT-1 is a novel target for PPARγ agonist, which shows neuroprotection following OGD in neuronal-astrocytic co cultures, hence, the present study was undertaken to investigate the role of rosiglitazone in neuroprotection mediated by GLT-1 following focal cerebral ischemia/reperfusion (I/R) injury in rat. We found that rosiglitazone (2mg/kg i.p.) pre or post treatment significantly improved behavioral outcome and decreased infarct volume and cerebral oedema. However no significant changes were observed in GLT-1 mRNA and protein expression in rosiglitazone treated rats following 1/24 h of I/R injury. Further rosiglitazone neither increased ^{3}H-glutamate uptake in glial enriched preparations nor did it cause any change in glutamine synthetase activity. But there was a significant ($P<0.05$) down regulation in TNFα and IL1β gene expression. The later effects were more pronounced in post treatment group. Further post-treatment with rosiglitazone also significantly abolished the increase in PGE2 level in the brain.

Therefore, the present findings suggest that neuroprotective effect of rosiglitazone does not seem to be mediated by modulation of GLT-1 protein expression or activity in focal cerebral ischemia model. But the results do provide growing evidence that neuroprotective effect may be mediated by its anti inflammatory action.

P-092: SIRT1 activator SRT1720 decreases feed intake and body weight due to gastric distension.

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Resveratrol, a naturally occurring phytoalexin, plays a role in prevention of diabetes and diabetic complications, as an activator of SIRT1. SIRT1 is an NAD1-dependent deacetylase, which is a principal modulator of pathways downstream of calorie restriction that produces beneficial effects on glucose homeostasis and insulin sensitivity. However, the exact mechanism of glucose regulation mediated by SIRT1 activators is yet unknown. We have investigated the activity of Resveratrol and selective and potent SIRT1 activator (SRT1720) in db/db mice model of type 2 diabetes. Resveratrol (500mg/kg, po) once daily treatment for seven days has reduced the body weight and feed intake, higher doses upto 2g/kg had no further improvement. SRT1720 (100mg/kg, po) treatment was significantly more effective in reducing the feed intake and body weight in db/db mice. The effect of intraperitoneal administration of SRT1720 was also similar. This treatment also resulted in significant improvement in glucose tolerance and insulin sensitivity. The pair fed group also showed similar reductions in body weight, feed intake, and glucose homeostasis. When SRT1720 was tested at 50mg/kg and 200mg/kg doses, a dose-dependent effect was observed, however, significant mortality were seen at 200mg/kg dose level. The postmortem analysis indicated gastric distension as the apparent cause of mortality. Acute administration of 50 to 500mg/kg dose of SRT1720 by both intraperitoneal and oral routes to db/db and lean C57 mice showed a dose-dependent and significant decrease in gastric motility. However, such acute treatment did not show any changes in glucose tolerance or insulin release in both the species. Our results indicate that selective and potent SIRT1 activator SRT1720 resulted in significant gastric distension, leading to reduction in feed intake and body weight. Absence of such effects in Resveratrol-treated animals might be due to its lower efficacy and/or poor bioavailability.

P-093: Synthesis and Antifungal Activity of Novel Substituted 5-Membered Heterocycles

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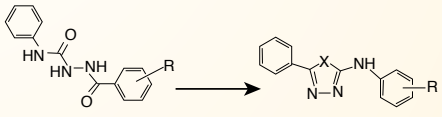
Antifungal agents mainly act by disruption of osmotic integrity of the fungal membrane or by inhibiting an early step of ergosterol biosynthesis. The range of antifungal drugs for treatment of mycoses is continuously improving particularly with new generation of triazoles, Polyenes, allylamines, echinocandins etc. Extensive literature review suggests that compounds bearing 5 membered heterocyclic ring system containing more than 1 nitrogen demonstrate a wide range of activity such as anti inflammatory, anti fungal, antiviral and analgesic activity. Various azoles show broad spectrum fungicidal activity, predictive pharmacokinetics with least drug-drug interactions, high safety, efficacy, and suitable routes of administration. Various azole derivatives were synthesized and evaluated for antifungal activity. The key intermediates, substituted thiosemicarbazides were synthesized by reaction of substituted phenyl isothiocyanates and phenyl acetic acid hydrazide. The lead compounds 1,2,4-triazole , 1,3,4-oxadiazole, and 1,3,4- thiadiazole were synthesized by treatment of synthesized intermediates with sodium hydroxide, concentrated sulfuric acid and potassium iodide in alkali respectively. The identity of all the derivatives was established by ^{1}H NMR, IR, and mass spectroscopic techniques. All the derivatives were evaluated for the antifungal activity using agar well diffusion technique against fungal strains *C.albicans*, *A.niger* and *F.oxysporum*. Fluconazole (20 mg) was used as standard drug. Some compounds showed comparable antifungal activity amongst which [5-benzyl-4-phenyl]-3-mercapto-4H-1, 2, 4-triazole showed good antifungal activity against all the fungal strains used in study.



R=H,3-Cl, 4-F, 2-F
X=N,S,O

Nevertheless selecting promising targets from cell signaling pathways is extremely challenging but combination of new scientific knowledge is likely to lead in the development of novel drugs for effective treatment and management of ischemic stroke in human.

P-094: Correlation between inflammatory and adipogenic biomarkers in white adipose tissue (WAT) of young and adult db/db mice

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Metabolic diseases are often accompanied by altered adipogenesis in white adipiose tissues (WAT). The relationship between adipogenesis and inflammatory adipokines along with their exact role in metabolic diseases are poorly understood. There are lots of *in vitro* reports stating that elevated cytokine levels in the adipocytes lead to alteration in the expression of target genes involved in adipogenesis.

The aim of the present study was to evaluate the correlation between inflammatory and adipogenic biomarkers in WAT. The evaluation was done using two different age groups of genetically obese diabetic db/db mice and lean C57BL/6 mice where mRNA expression of cytokines and biomarkers of adipogenesis were monitored in WAT. We observed that, in early obesity (4 weeks), there was significant decrease in the expression of markers of adipogenesis including PPAR gamma, C/EBP alpha, aP2 and LPL; however, there was no change in the classical inflammatory markers such as TNF alpha, IL-6 and COX-2 compared to C57BL/6 mice. Interestingly, we found that in 12 weeks old db/db mice, which exhibited suppression of adipogenic markers similar to the 4 weeks old animals, there was significant up-regulation of all the inflammatory markers. In conclusion, our results have revealed an age-dependent correlation between inflammation and adipogenesis in WAT which can only be seen at an advanced stage of obesity.

P-095: Antidermatophytic activities of some Medicinal Plants used by the tribal people of N. E Region of India: In-vitro and In-vivo evaluation.

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Dermatophytic fungi are one of the main agents of skin diseases of man and animal and remain a threat to public health in the tropical countries like India, more particularly in the North Eastern Region due to the extreme humid environment. Although a large number of synthetic allopathic drugs are present to treat dermatophytosis, the increasing incidences of fungal resistance towards these synthetic drugs combined with their associated side effects and limited efficacy has forced scientists to search for new antimicrobial substances from natural sources. People now are opting more for Natural origin drugs. Based on the ethnobotanical knowledge and local use of some plants against common skin diseases, an attempt has been made to assess the antidermatophytic properties of the organic and aqueous extracts of four plants- *Trachyspermum ammi, Cinnamomum porrectum, Piper betle Linn., Allamanda cathertica Linn.* and their (w/w) combination against five species of dermatophytes *viz. Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Trichophyton tonsurans*, *Microsporum gypseum* and *Microsporum fulvum*. The inhibition zone diameter for different extracts were determined by Agar cup diffusion technique. *In-vitro and in-vivo* results (Individual as well as the mixed formulation) are very encouraging. MIC values (ranging between 0.312-1.25 µg/ml) are close to standard drug following the standard protocol.

P-096: Dual PPAR agonist represses expression of P2X7 in Rodent Uterine Tissues

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Dual PPAR agonist imparts variable degree of pharmacological effect and toxicity on animal models depending on the proportion of PPAR-alpha and -gamma agonism it possesses. Most of the PPAR agonists produce exaggerated effect in the hepatic tissues of the rodent models. However, the effects observed in urinary tract and other non-hepatic tissues are variable and require alternate strategy to draw any inference. In the current study two standard PPAR agonists were selected to study the drug-induced organ-specific changes in female Wistar rats. Animals were subjected to an acute 14-days repeated dose treatment regimen. Two molecular markers per organ were analyzed for their expression level and were compared with the level observed in control animals. In case of the urinary bladder, CyclinD1 and Uroplakin3a were used as the specific markers, whereas, incase of uterus CyclinD1 and P2X7 were used as specific markers to profile the PPAR activators. Analysis of CyclinD1 showed a dose dependent increased expression in uterus of animals treated with almost all PPAR activators tested in the study. However, the change in the expression of CyclinD1 observed in urinary bladder was not that drastic as compared to the level of expression detected in the uterine tissue of the same animal. In uterine tissues, expression of P2X7 was drastically reduced in muraglitazar treated animals, but the effect was insignificant in rosiglitazone treated animals. Negative regulation of P2x7 has been associated with cervical tumors and has been predicted as a potential cancer marker in

human. In conclusion, analysis of changes in specific molecular cancer markers observed in the short term rodent models can be an ideal tool to derive important information about potential outcome of longterm carcinogenesis studies in conjunction with other microscopical indications observed in rodents.

P-097: Telemedicine as a boon for rapid growth of medical tourism in India

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Medical Tourism is a process where people travel across borders for treatments including medical, surgical dental or cosmetic needs, due to higher treatment costs in their countries, delays in the getting the treatment and sometimes even legal reasons. The concept of medical tourism is based on combining prompt medical treatment with travel and tourism at a fraction of cost incurred in the patient's own country.

As per today's trend, countries like India, Singapore, Thailand, Jordan, Malaysia, Philippines, Brazil, Turkey, Costa Rica etc are very well liked amongst the medical tourism fraternity. Above all, India has drawn a great deal of attention of numerous medical tourists by offering economical, speedy and world class health care facilities with superior technology and competent healthcare personnel. Introduction of Ayurveda and Yoga to foreign nationals while promoting exotic tourist places has made India the most sought-after location.

However, interaction between healthcare provider and receiver is the subject of prime concern in the medical tourism industry of India. Telemedicine plays a pivotal role by bridging the communication gap between care receiver and provider. In today's era, telemedicine has revolutionized the medical tourism industry in India by making physical distances irrelevant and by abolishing the absolute necessity of long distance traveling.

It may reasonably be assumed that telemedicine is an integral component of medical tourism industry. In view of the fact that the medical tourist is always a distant individual, the physical gap cannot be easily bridged without effective use of telemedicine.

P-098: Development of Proline based DPPIV Inhibitors for the treatment of Type II Diabetes

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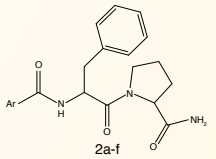
The incidence of type II diabetes mellitus (T2DM) is increasing worldwide due to changing lifestyle and prevalence of obesity and associated metabolic syndrome. Currently available antidiabetic drugs are not adequate for the safe and effective treatment of T2DM. In this regards, development of new class of selective DPP-IV inhibitors were found to be attractive and promising approach. The major advantage of developing selective DPP-IV inhibitor could be low risk of hypoglycemia and no weight gain. The two compounds (Vildagliptin, Sitagliptin) from this class are already in the market for T2DM treatment. In the present communication, we have developed novel proline based DPP-IV inhibitors. Synthesis of titled compounds (2a-f) was carried out by using Solid Phase Peptide Synthesis (SPPS) approach. The in vitro DPP IV inhibitory activity and selectivity of test compounds were evaluated by fluorescence-based enzyme activity assay and compounds 2d & 2f showed good in vitro DPPIV inhibitory activity and selectivity over DPP8, DPP9 & QPP. Further both these test compounds were subjected for in vivo antidiabetic study in C57 mice and compound 2f exhibited remarkable antidiabetic activity.



2a-f

2a: Ar-4-Hydroxyphenyl;/2b: Ar-3,5 dihydroxyphenyl; 2c: Ar-2, 4 dichlorophenyl;/2d: Ar-2-methoxyphenyl; 2e: Ar-2-acetoxyphenyl;/2f: Ar-2-nitrophenyl;

P-099: Development and characterization of Methotrxate solid dispersions prepared by hot melt extrusion technology.

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Formulation of active pharmaceutical ingredients (API) in high-energy amorphous forms is a strategy to enhance solubility, dissolution rate and, consequently, oral bioavailability of poorly water soluble drugs. Amorphous APIs are, however, susceptible to recrystallization and, therefore, there is a need to physically stabilize them as solid dispersions in polymeric carriers. HME is an approach utilized in the delivery of poorly water-soluble, class II and class IV compounds due to the increased dissolution

achievable, and hence improved absorption and therapeutic efficacy. Methotrexate (MTX) is a class IV drug with low solubility and bioavailabilty, widely used in the treatment cancer. The objective of this study was to improve the dissolution properties of MTX by preparing extrudates utilizing HME technology. Melt extrusion of the drug and soluplus mixture was arried out using a small scale Thermo Scientific Haake Mini Lab twin screw extruder (BASF, India Ltd) at 20%, 30% and 40% drug loads and temperatures of 150-170 °C. The extrudates were milled and screened prior to mixing with microcrystalline cellulose (Avicel PH102) and poloxamer 407 in the external phase. The mixture was filled in size 2 hard gelatin capsules at an appropriate weight so that each capsule contained 10 mg of drug substance. All extrudates showed higher dissolution than the control formulation made of crystalline drug, 30% drug load showing a 5-fold greater solubility. DSC, XRD, NMR and FTIR studies of melt extrudate samples confirmed that no crystallinity existed in any of the samples.

P-100: Datamonitor India Limited

Jill Morjaria

Datamonitor, Hyderabad, India

The Datamonitor Group is a world-leading provider of premium global business information, delivering independent data, analysis and opinion across the Automotive, Consumer Packaged Goods, Energy & Sustainability, Financial Services, Logistics & Express, Pharmaceutical & Healthcare, Retail, Sourcing, Technology and Telecoms industries. Combining our industry knowledge and experience, we assist over 6000 of the world's leading companies in making better strategic and operational decisions.

The key areas of our research are Therapeutic Analysis, Company Analysis and Strategic Analysis mainly across 12 key geographies globally.

Therapeutic Analysis research covers:

- Disease analysis including cardiovascular diseases, central nervous system, immune diseases, urology and gender-specific health
- Commercial analysis including infectious disease, oncology, respiratory, and diabetes and metabolic disorders

Company Analysis research focus areas include product and financial forecasts, performance metrics and strategic insight within a company's portfolio. It covers big Pharma, mid Pharma, Japanese Pharma, biotech, generics, specialty Pharma, medical devices and benchmarking.

Strategic Analysis portfolio provides analysis of external challenges and emerging opportunities impacting the pharmaceutical industry. The two focus areas are: M&A activity, R&D licensing, sales and marketing, outsourcing, lifecycle management.

P-101: Correlation between Streptococcus pneumoniae biofilm formation and surface properties

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Pneumococcal disease is a leading cause of serious illness in children and adults throughout the world. The disease is caused by pneumococcus, which can attack different parts of the body. The pneumococcal infections results in pneumonia, bacteremia, meningitis, otitis media (middle ear infection) and sinusitis etc. many of the common pneumococcal diseases are caused by biofilm mode of growth of invading pathogen. Pneumococcal biofilms remain a problem from decades due to increased drug resistence expression of pathogenic gene and poor understanding of bioflm mode of growth.

In the present study, Streptococcus pneumoniae biofilm formation was studied on polyvinylchloride (PVC) and polystyrene (PS) surfaces. Confocal lasrer scanning microscopy studies were carried out after staining with FITC-ConA and PI. Further, data was supported by biofilm quantification by crystal violet quantification method, Atomic Force Microscopy (AFM) for surface roughness, and Goniometric analysis for surface hyrophobicity. Data showed that PVC with roughness 134nm and contact angle 97^0 supported 60% more colonization than polystyrene with roughness 24nm and contact angle 91^0. XZ directional analysis of biofilms showed 42µm and 17µm biofilms in case of PVC and PS respectively. It was concluded that Pneumococcal biofilm depends on surface properties hence its colonization can be controlled by alteration in these properties.

P-102: Structural Role of Individual Helices in Glucokinase: A Molecular Dynamics Study

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Glucokinase (GK) plays a key role in the control of blood glucose homeostasis. Glucokinase is a monomeric enzyme that displays a low affinity for glucose & a sigmodial saturation curve for its substrate, two properties that are important for its playing the role of glucose sensor in pancreas & liver. The crystal structure of glucokinase exits in active and inactive forms which demonstrate that global conformational changes. It is reported that mutations caused severe and possibly fatal hypoglycemia, whereas other mutations are associated with mild hypoglycemia and are in some cases asymptomatic. Here we describe the structural role of the α5 and α13 helice of human pancreatic glucokinase enzyme using molecular dynamics simulations. In order to understand the structural importance α5 helix that connects the activator and substrate, molecular dynamics simulation of 5 ns were carried out. Detailed analysis of helice and individual amino acids of helix gave insights into enzyme regulation mechanism.

P-103: Evaluation of locomotor and anxiolytic activity of steroidal saponin rich fraction of *Lepidium sativum* seeds (linn) (ahliva). (fam.cruciferae) in rodents

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Introduction: Study of drugs,Interact with neurons in brain to affect mood, sensation, behaviour. Animal tests of anxiety are based on behaviors that depend on body activity & locomotion. Trying to interpret behavioral tests & separate emotional from non-emotional components was a major concern of behavioral scientists in the pre-molecular era.

Material & Methods: In Laboratory modified Open field having 34 cm × 22 cm ×14.5 cm & alternate blocks painted white and black. Also sound proof room with video recording systems ANY- MAZE software for behavioral analysis was used.

1. Habituation session (Day-one): Habituation for open filed apparatus for 3 min.
2. Test session (Day-Two): Before 1hr prior to test, animal treated orally in the doses 50,100,200 mg/kg of SFLS & Diazepam (2mg/kg) (ip) & Caffeine (8mg/kg) (ip). Placed in open field at the center. Observed for 5 min for following parameters.

Apparatus Measurements:

Measurements for CENTER, CORNER, SIDE Zones:

No.of entries to the zone, Time in the zone (s), Avg. duration of visit to the zone (s), Time orientated towards centre of zone when inside zone (s), Time freezing in the zone(s).

Result: At a dose of 100 & 200mg/kg mice shows increase in time spent, mobility, distance travelled in centre zone after 60, 90 &120 min time with ($p < 0.05$).With Comparison of CAFFEINE, SFLS shows increase in no. of entries in side zone at dose of 100 & 200mg/kg after 60 & 90 min. of dosage.

Conclusion: It makes clear by going through the procedure that SFLS having anxiolytic activity & increase in locomotion.

P-104: Role of peripheral mechanisms in acute orexigenic effect of triiodothyronine

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Hyperthyroidism is known to increase food intake, to compensate the negative energy balance. Central administration of T3 into the third ventricle of the hypothalamus, or increased hypothalamic deiodinase (D2) activity contributes to acute orexigenic effect in rodents. However, the mechanism involved in acute effects of triiodothyronine (T3) administration on appetite are currently unknown. Ghrelin is a peripheral orexigenic hormone primarily released from stomach. Ghrelin increases food intake, adiposity and weight gain. Ghrelin secretion is regulated by metabolic state, as well as by hormones leptin, insulin and GLP-1. We have investigated whether T3 influences appetite by modulating circulating ghrelin in Zucker fatty rats, a model of hyperphagia and obesity. Oral administration of T3 (10-100 µg/kg) increased food intake in overnight fasted as well as in meal restricted rats over four hours, with concomitant increase in serum T3 levels. T3 treatment was associated with increase in serum ghrelin. An additive effect on appetite was observed when T3 (oral) was administered with central (icv) as well as peripheral administration of a ghrelin mimetic, MK-0677. In vagotomized rats, T3 did not show increase in appetite, despite increase in serum T3 levels. The serum ghrelin levels were unchanged in these animals after T3 treatment. However, T3 showed increase in serum triglyceride levels indicating

its peripheral lipolytic effect, in vagotomized as well as sham treated animals, whereas the serum glucose was increased only in sham treated animals. The results indicate that the acute orexigenic effect of T3 is associated with increased ghrelin secretion and activity. This effect seems to be mediated via vagus nerves.

P-105: Evaluation of Anti Convulsant activity of Steroidal saponin rich fraction of roots of Eranthemum roseum in a mouse models.

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Introduction: The *Eranthemum roseum(*Vahl) R.Br. a shrub from Acanthaceae family is popularly used in folk medicine for treating variety of disorders like Vertigo, Leucorrhoea, Ulcer etc.The steroidal saponin rich fraction of *Eranthemum roseum* (SFER) was administered orally and it was tested for PTZ-Strychnine induced convulsions in mice.

Material & Methods: 6 mice were taken in 6 group of each.1St three groups received fraction from plant as 30, 60, 120 mg/kg (p.o.). Fourth group was served as positive control and fifth group was toxicant PTZ/Strychnine control with doses mention below. Sixth group served as a vehicle (1ml/kg). After 30min pre-treated fraction i.p. or after 1hr pre-treated with fraction (p.o.) all the mice received Pentylenetetrazole (60mg/kg) (i.p.)/ Strychnine (2.5mg/kg) (i.p.). Falling and jerking was considered as a beginning of convulsions. The mice that did not show convulsion within 30 min was considered as protected. Time required for induction of convulsion, duration of convulsion and number of animals protected was observed.

Result: After induction of convulsion by PTZ, induction time was prolonged by the SFER and STD Diazepam. The significant increase in induction time was observed for SFER 60 mg/kg ($P<0.05$) and SFER 120mg/kg ($P<0.01$) when compared with the PTZ control. For Strychnine induced convulsion the SFER 120 mg/kg observed significant ($P<0.05$) increased in induction time and diazepam was observed to be more potent in the study for prolongation of induction time.

Conclusion: It makes clear by going through a procedure that SFER exhibit remarkable anti-convulsant (PTZ induced) action. Result suggest that the leaf flavonoids and sterols have excellent antihyperlipidemic activities and thus have great potential as a source for natural health products.

P-106: Carbon monoxide releasing molecule-2 (CORM-2) prevents apoptosis of cardioblastic H9c2 cells in doxorubicin-induced cardiotoxicity

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It has been known since decades that carbon monoxide (CO) exerts its toxic effects when inhaled in high doses or for long time by mammalians. In the last few years' research on beneficial role of CO in the regulation of various physiological processes has been emerged. We examined whether and how pretreatment with fast CO-releaser, CORM-2, prevents apoptosis of cardioblastic H9c2 cells against doxorubicin-induced cardiotoxicity. Exposure of cardiomyogenic cells to doxorubicin (2.5 μM, 48 hr) induced apoptotic nuclear fragmentation and increases the activity of caspase-3. CORM-2 (50 μM, 1 hr) pretreatment attenuated these apoptotic changes and reduces caspase-3 activity. These results suggest that doxorubicin induces apoptosis and CORM-2 prevents apoptotic changes which may be mediated via caspase-3 pathway.

P-107: Protective effect of Asparagus racemosus (Willd.) against experimentally induced reflux esophagitis in rats.

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Asparagus racemosus an ayurvedic rasayana, finds mention in ancient Indian texts for treatment of gastric ulcers. The present study first time evaluates the therapeutic potential of *Asparagus racemosus* (AR*)* against experimentally induced reflux esophagitis (RE) in rats. RE is a chronic gastrointestinal disorder caused by a mechanically defective lower esophageal sphincter or increased exposure and/or sensitivity of the esophageal mucosa to excess reflux of gastric contents. RE was developed by ligating limiting ridge and pylorus portion. *A.racemosus* pretreatment (100

and 200 mg/kg, p.o.) significantly reduced the haemorrhagic lesions and volume of gastric secretion ($P < 0.01$), while total acidity is reduced at the dose of 200 mg/kg ($P < 0.01$) and free acidity ($P < 0.01$) at both the doses. *A.racemosus* significantely reduced volume of gastric secretion ($P < 0.05$), total acidity ($P < 0.01$) and free acidity ($P < 0.01$). A significant decrease in lipid peroxidation ($P < 0.05$) and glutathione ($P < 0.05$) level was observed at the dose of 200 mg/kg. The effect was comparable to omeprazole, a standard proton pump inhibitor. *A. racemosus* demonstrates its protective effect against reflux esophagitis possibly due to its antisecretory, antioxidant and cytoprotective activity.

P-108 : Effects of acute high dose of erythropoietin on ex vivo platelet aggregation using healthy rats

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Erythropoietin (EPO) is the primary stimulator of erythropoiesis and recombinant human EPO (rHuEPO) is widely used in the treatment of anemia in cancer, stroke and chronic kidney disease patients. In cancer and stroke patients high dose treatment of EPO seems to improve the condition of patients but may be associated with increased thrombotic risk. The rapid rise in haemoglobin and platelet count was cited as reasons for this effect but the mechanism is still unclear. We investigated the acute effect of high dose treatment with rHuEPO on platelet aggregation in healthy rats. Animals received three daily doses of rHuEPO (25 and 50 µg/kg, s.c.) were studied as compared to vehicle control group. EPO treated animals showed significant increase in platelet aggregatory response to various aggregating agents such as ADP, thrombin, arachidonic acid and collagen. These findings suggest that platelets become more reactive after EPO administration and this may be one of the probable reasons for higher risk of thrombotic events.

P-109: Obstacles and opportunities in translational research

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New developments in science are rapidly influencing and shaping basic and clinical research and medicine. This has led to the emergence of multiple opportunities and challenges on many levels in the bio-medical and other associated fields. To face these opportunities and challenges, new concepts and strategies are needed. These can be provided by translational research/medicine as an integrative concept based on a multidirectional understanding of research and medicine embedded in a socio-economical environment. Although the implementation of translational research/medicine faces many obstacles, some of its goals have already been part of new programs in local institutions and in medical or scientific societies. These implementations are important in creating a unified national and international system of translational research/medicine. The rapid evolutions in science have generated a tremendous spectrum of new technologies and tools in both basic and clinical research/medicine. This includes the constant improvement of old and the discovery of new diagnostics and therapies, which increasingly contain and integrate elements from different fields, such as biomedical and other sciences, modern and traditional medicine and various technology branches. In addition, the applications of these developments in clinical settings have created a "feed-back-loop" providing crucial information about their feasibility and success in improving human health. This network of scientific and clinical research/medicine has become one of the factors in shaping modern societies not only by being a major economical factor details, but also by challenging basic values and traditional thinking. To face the emerging challenges of creating a balanced and effective healthcare system, new concepts are needed for providing a framework of integrative strategies and solutions that efficiently combine basic and clinical research/medicine

P-110: Mapping the Bottlenecks in Translational Medicine-The Indian Perspective

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The traditional boundary between basic research and the patient oriented clinical research are in convergence to make a single, continuous, bi-directional spectrum which is termed now "Translational Research or Translational Medicine". The process is best described as a "Translational continuum" which advances the discoveries from "Bench to Bedside".

Although the goals are essentially no different from the two conventional entities like the academic laboratory and the hospital base, conducting their relevant researches, Translational Research emphasizes strategies to expedite the successful implementation of Translation going beyond coordinating the research and dealing with public health, health policies and pharmacoeconomics – management.

This manuscript reviews and synthesizes the literature to provide an overview of the current translational research model prevailing in India with reference to, the more or less consolidated processes of the pioneering countries like US and Europe.

Mapping of the bottlenecks by identifying and critically describing the activities like implementation, adoption research within the Translational continuum of the process in the Indian context, is the objective of this research.

A modification of the existing model is proposed to create a framework which defines the translational process at par to the previously mentioned and consolidated ones.

The core of the modification is to progress through reorganization of research teams in the academic culture which is of utmost urgency, as the translational orientation is seriously lacking in that island.

We examine the individual interactions and dynamics involved through a case study "Leveraging the Antibiotic Minocycline's other face as an Anti-inflammatory" and the Translational flow that results.

The manuscript concludes, pointing to the relatively stronger role of Industry oriented translational process in place and the weaker role of academic laboratories in India.

P-111: Design and evaluation of triazine derivatives as dihydroflate reductase (DHFR) inhibitors in Mycobacterium tuberculosis

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An increase in the incidence of MDR/XDR tuberculosis has compelled researchers to look for new targets for anti-tubercular drug research. DHFR (enzyme encoded by *dfrA* gene) is a well-known target of tetrahydrofolate synthesis pathway; however this has not been explored for tuberculosis. Several triazine derivatives were designed as DHFR inhibitors using molecular modelling techniques including docking using GLIDE module of Schrödinger LLC, NY and physico-chemical property validation using QikProp of Schrödinger LLC, NY. The synthesized compounds were tested by various in vitro techniques for anti-tubercular activity. The minimum inhibitory concentration (MIC) of all synthesized compounds was determined against *Mycobacterium tuberculosis* $H_{37}Rv$ using Resazurin Microtitre Assay (REMA) plate method, a well-known whole cell assay method. The synthesized compounds exhibited MIC in the range of 1.5-88µM. Also, cytotoxicity studies were carried out on mammalian VERO cell line (C1008) by MTT assay and the CC_{50} values were found to be non-toxic in this assay. To evaluate the mechanism of action of these compounds, radial enzyme assay was undertaken to determine the zone of inhibition against an engineered strain of *Saccharomyces cerevisiae* containing *dfrA* gene from *Mycobacterium tuberculosis*. IC_{50} values were determined for some compounds by spectrophotometric method using DHFR enzyme isolated from above mentioned engineered strain. The results indicate the potential of these compounds as leads for anti-tubercular activity.

P-112: New method for Six membered to Five membered ring contraction in Taxanes using BF_3.Et2O

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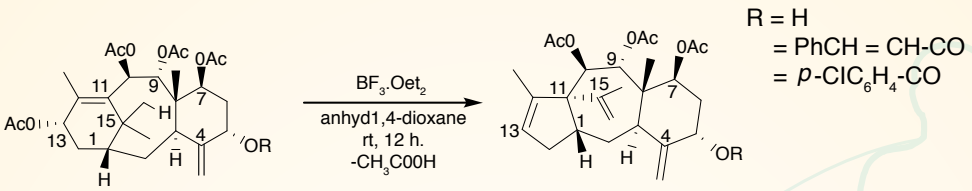
In continuation of our drug discovery program on anticancer agents we isolated 2-deacetoxytaxinine J (2-DAT-J) in reasonably good yield (0.1%) from the Indian T. baccata (sp. wallichiana). 2-DAT-J was also reported from several other Taxus species. 2-DAT-J exhibits no cytotoxicity and tubulin affinity and is considered a powerful inhibitor of P-gp) activity, acting as an efficient reversing agent in MDR cancer cells. Botta and co-workers synthesized a small library of analogues of 2-DAT-J to develop a potential MDR-reversing agent.

Recently we also reported the in vitro anticancer activity of 2-DAT-J and its new derivatives and the in vivo anticancer activity of 2-DAT-J in animal models. During this chemical transformation process we attempted to remove the C-13 acetyl group from 2-DAT-J using $BF_3.OEt_2$, which surprisingly resulted in the regioselective removal of the acetoxy

group followed by an unprecedented rearrangement to provide 1(15→11) abeotaxane (Scheme 1) by six membered ring to five membered ring contraction in reasonably good yield (70%). Extensive 2D NMR studies were carried out to elucidate the structure of 1(15→11) abeotaxane. We employed the same method for other taxanes to support the generality of the methodology.



P-113: Flurbiprofen Neuroprotective Effect In Focal Cerebral Ischemia

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There is a dramatic increase in intracellular calcium acting through various pathways, which is responsible for neuronal death in cerebral stroke. Earlier this calcium overload was considered to be mainly glutamate dependent but the failure of glutamate antagonists in clinical trials suggested the existence of glutamate independent mechanisms contributing to neuronal injury. Recently Acid Sensing Ion Channels (ASIC's), which are activated following acidosis in ischemic brain, were found to promote glutamate independent neuronal Ca^{2+} overload and subsequent injury in stroke. Interestingly, the ASIC1a was found to be inhibited by flurbiprofen, which prompted us to investigate the neuroprotective profile of flurbiprofen in cerebral ischemia/reperfusion injury.

Focal cerebral ischemia was induced in male S.D. rats (250 ± 20g) by occlusion of middle cerebral artery (MCAO). Flurbiprofen was administered at various doses prior and post induction of ischemia to assess its therapeutic window. Neurological deficit and brain infarct volume were measured to assess the neuroprotection. Spectrin break down products (SBDP's) were also measured to analyze calcium mediated calpain activity. Further, the effect of acidic pH, in absence and presence of flurbiprofen, on $[Ca^{2+}]i$ in rat brain synaptoneurosomes were analyzed.

Flurbiprofen pre & post treatment in MCAO rats, resulted in significant improvement in neurological deficit and infarct volume. Further, ischemia caused significant increase in brain SBDP's level which were significantly ameliorated with flurbiprofen treatment. Moreover, flurbiprofen ameliorated the acidic pH mediated rise in $[Ca^{2+}]i$ into rat brain synaptoneurosomes. These results indicate that flurbiprofen may benefit stroke therapy through ASIC1a inhibition apart from its anti-inflammatory potential.

P-114: K9 mono methylation: gene inactivation marks both at promoter and transcribed regions of genes

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Among the different mechanisms that could lead to induction of life style disorder, type2 diabetes, the role of post translational histone modifications in dysregulating the expression of genes, has emerged as a potential important contributor in the last decade. Once regarded as stable or irreversible, current evidence suggests that histone lysine methylation is a more dynamic process. Due to controversial reports on the function of histone H3 Lysine 9 monomethylation (H3K9me) in gene activation or inactivation, we carried out the present study to delineate the functional relationship of this histone modification with regulation of gene expression and also its association with histone H3 acetylation (H3ac) and H3 lysine 4 monomethylation (H3K4me). We performed the CLUSTER analysis on ChIP-chip data and demonstrate that H3K9me levels are inversely correlated with mRNA expression levels and H3 acetylation/H3K4me levels under diabetic condition across the transcribed regions of the genes. Further ChIP-chip data shows downregulation of histone acetylase Myst4 and histone H3K4 methylase Jmjd2 and upregulation of histone deacetylase Set and histone H3K4 demethylase Aof1. ChIP-RT-PCR analysis shows direct regulation of these genes by H3K9me and H3K9me levels was inversely proportional to their mRNA levels. To best of our knowledge this is the first report that shows the direct regulation of histone de/acetylases and de/methylases by H3K9me at transcribed regions of genes thus placing this epigenetic modification as potential candidate to provide treatment regimen against diabetes.

P-115: Effects of acute versus chronic treatment of ketamine in mice: Behavioral and neurochemical abnormalities.

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A major factor limiting research on schizophrenia research has been the lack of a suitable animal model simulating human psychosis. The present study has been designed to evaluate the effect of both acute and chronic administration of ketamine, an NMDA receptor antagonist, in various behavioural and neurochemical parameters. Acute treatment of ketamine (100mg/kg, ip) induced hyperlocomotory response and reduced the transfer latency time in passive avoidance test but was ineffective in the forced swim test (negative symptoms). However, chronic administration of ketamine (100mg/kg, ip) for 10 days not only produced significant 'hyperactivity' response with increased stereotypy counts but also enhanced the immobility period in animals during the forced swim test and reduced the latency period in the passive avoidance test. Acute treatment with ketamine was found to increase monoamine oxidase A (MAO-A) enzyme activity in cortex and striatal regions and MAO-B activity in striatal regions of mice brain. However, chronic treatment of ketmaine shows depletion of both MAO-A and MAO-B activity in striatal regions. Similarly, ketamine administration showed differential and region specific effects in neurotransmission of Acetylcholine (ACh), Dopamine (DA), Serotonin (5-HT) and Noradrenaline (NA). The above results suggest that chronic ketamine treatment induces behavioural and neurochemical abnormalities similar to schizophrenia in mice which can be used to screen novel antipsychotic drugs. This model can be used for further investigation of molecular and neuronal basis of schizophrenia pathophysiology.

P-116:A novel one-pot synthesis of 2-benzoylpyrroles from benzaldehydes

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Pyrrole is the core unit of many therapeutically active molecules such as tolmetin, atorvastatin, chlorfenapyr, premazepam, pyrvinium, roseophilin, zomepirac and natural products such as bilins, bilanes, phycobilin, porphyrin and chlorophyll. The reactions of pyrrole are dominated by electrophilic substitution because of the lone pair of electrons on the nitrogen and consequent stability of the σ-complexes. Such reactions necessitate that a delicate balance be achieved between the exploitation of nucleophilicity for the required electrophilic substitution, and the containment of nucleophilicity either through electronic or steric means to inhibit over-substitution and/or unwanted transformations. The reactions of pyrrole at position-2 often requires the use of protecting groups at N1 which needs the additional steps of protection and deprotection. We herein report a novel one-pot reaction for benzoylation of pyrrole which have been previously synthesized using Friedel–Crafts acylation or Vilsmeier–Haack reaction. The key step in the reaction is generation of di(1H-pyrrol-1-yl)zirconium(IV) chloride complex which reacts with benzaldehydes and methyl benzoates to give 2-benzoylpyrroles as the major product. This improves upon previous syntheses of 2-benzoylpyrroles, which had taken place in three to four steps affording products with low yields[1].

1. Sharma, R.; Chouhan, M.; Nair, V.A. Tetrahedron Lett. 2010, 51, 2039-2043.

P-117: *In vivo* Acute and Sub-acute oral Bisphenol A toxicity in albino rats

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The present investigation was undertaken to study the effect of acute and sub-acute bisphenol A (BPA) toxicity in albino rats. The approximate lethal dose of BPA was determined as 3375 mg/kg body weight. A total number of ninety rats were divided at random into five equal groups for sub-acute toxicity, having 18 rats each (9 males + 9 females). BPA was administered @ 50, 200 and 600 mg/kg body weight in group III, IV and V respectively for 28 days. Group I served as normal control while group II served as vehicle control (propylene glycol). Feed intake and body weight gain were significantly ($P < 0.05$) reduced in the rats of group III, IV and V in dose dependant manner. Haematological parameters were affected in rats of all the treated groups at 50, 200 and 600 mg/kg body weight. The biochemical examinations revealed significant ($P < 0.01$) increase in mean values of AST, ALT, ALP and creatinine and significant ($P < 0.01$) decrease in the values of plasma total protein, globulin and glucose with the increase in dose of BPA in all the treated groups. The values of BUN significantly ($P \leq 0.01$) increased in the rats of group IV and V and values of uric acid were increased significantly ($P < 0.01$) in the rats of group V. Significant (P

≤ 0.01) decrease in antibody titre to SRBCs in group V and significant (P < 0.01) depression of CMI in all the BPA treated rats were observed. Administration of BPA caused a reduction in the epididymal sperm count and sperm motility and increase in dead sperm count and head and tail abnormality in a dose-dependent manner. The study suggested that sub-acute exposure of BPA has significant adverse effect on various organs in rats.

P-118: Blood brain barrrier penetration: an *in vitro* brain artificial membrane permeability (BAMPA) model for high throughput screening (HTS) of CNS drugs

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Blood-brain barrier (BBB) is one of the key issues in the pharmaceutical industry since the central nervous system (CNS) drugs need to penetrate the barrier, while the peripherally acting drugs should be impaired in the passage. Most of the CNS drugs enter the brain by transcellular passive diffusion mechanism due to the presence of zonula occludens and limited transport pathways. Recent reports conclude that 80–95% of the commercial drugs are absorbed primarily by passive diffusion.

Both *in-silico* and experimental methods are available today for prediction and screening of properties related to oral drug absorption. Although most of the experimental cell-based techniques, like MDCKII-MDRI monolayer model give reliable results their complexity and time consuming nature limits them to be used in a true high-throughput format. Cell culture systems; on the other hand have the advantage of incorporating both passive and active transporters. However, their application as a high throughput screening tool is limited by the elaborate membrane preparation and the cost of resources. The BAMPA assay has the advantages of predicting passive blood-brain barrier penetration with high success, low cost, and reproducibility.

Herein, we have developed an *in vitro* BBB model in order to maximize high throughput nature by reducing the incubation time. Moreover, we have compared the permeability of 16 structurally diverse, commercially available drugs assessed in two different PAMPA models: (1) a PAMPA-PBL (Porcine brain lipid) (2) a PAMPA-Phosphatidylcholine lipid. Both the models successfully identify CNS+ (High brain penetration) and CNS (Low brain penetration) drugs. Our models using PAMPA-PBL and PAMPA-Phosphatidylcholine has been able to reproduce all the known compounds as per the literature classification. A comparison of the permeability by plotting P_{app} values from both tests allows forecasting capacity of the assays. The correlation of the P_{app} value of the both assays with the literature reports showed good correlation of r^2 of 0.9487 and 0.930. Additionally, an *in-silico* analysis was also performed to predict logBB, Caco-2 permeability, and MDCK permeability parameters for all the compounds in the test set. Both models showed very good correlation with *in-silico* logBB value.

P-119: Micellar spectral and biochemical investigations on complexes of Gd (III) and Ho(III) with amides.

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Organized molecular assemblies called micelles/reverse micelles are formed if the critical micelle concentration (cmc) is exceeded for an amphiphilic molecule also known as surfactant, which consist of a hydrophobic chain joined to a hydrophilic head group. The hydrophobic part is generally a long chain hydrocarbon, typically 8-18 atoms. Micelles enhance the solubility of organic compounds in water by providing local nonpolar environments. The absorption spectra of lanthanide ions have been a subject of several investigations because of their possible use as laser materials, diagnostic tools and sensors. Study of absorption spectra in visible and near infrared regions yields useful information regarding energy and intensity parameters, and nature and probabilities of transitions. The present investigation deals with determination of spectral, energy & intensity parameters of amide complexes with Gd(III) and Ho (III) in different medium. It has been found that micellar medium has not only increased the solubility and stability of the complexes but a marked increase in absorption intensity also observed.
Various energy and intensity parameters such as Racah (E^K), Slater-Condon (F_K), Lande' (ζ_{4f}), Oscillator strength (P) and Judd-Ofelt parameter (T_l) etc. have been computed using partial and multiple regression methods. Also the nephelauxetic ratio (β) and Bonding parameter ($b^{1/2}$) have been evaluated. Results were compared for micellar medium and normal medium. The order of Slater-Condon parameter is found to be $F_2 > F_4 > F_6$. The observed values of F_6/F_2 are less than F_4/F_2. Antibacterial studies have been

studied on staphylococcus in alcoholic medium and also in micellar medium. The effect of structure and position of secondary group on antibacterial activity have also been investigated and in general it has been found that ortho effect reduces the antibacterial activity but in case of amino derivatives results were reverse in order. Further effect of concentration on antibacterial activity have also been investigated in general increase in concentration antibacterial activity was found to increase for complexes.

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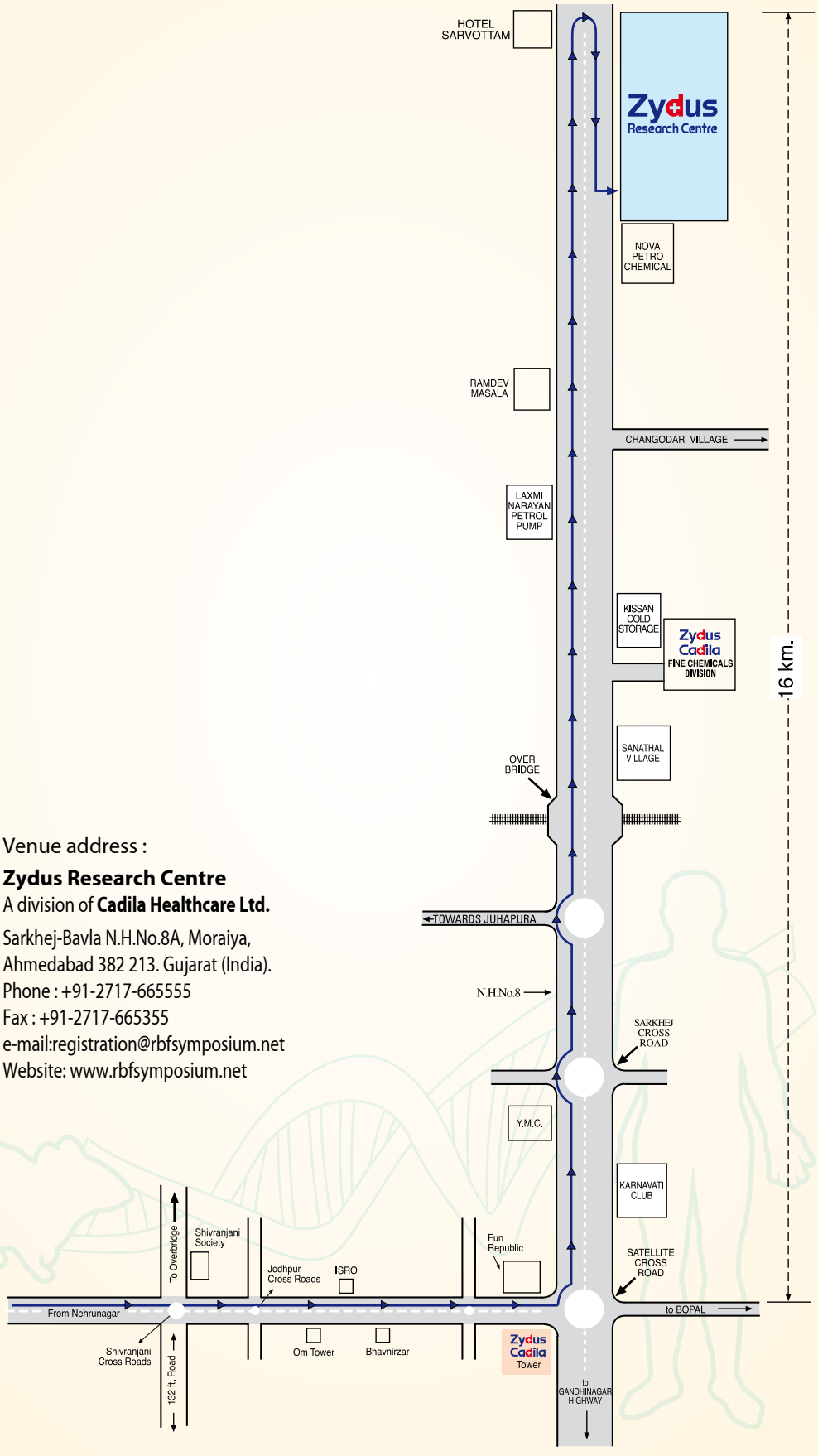

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