ABSTRACT BOOK

BEYOND THE GENOME

28 -30 April 2024 - Cape Town - South Africa

-- BEYOND THE GENOME --

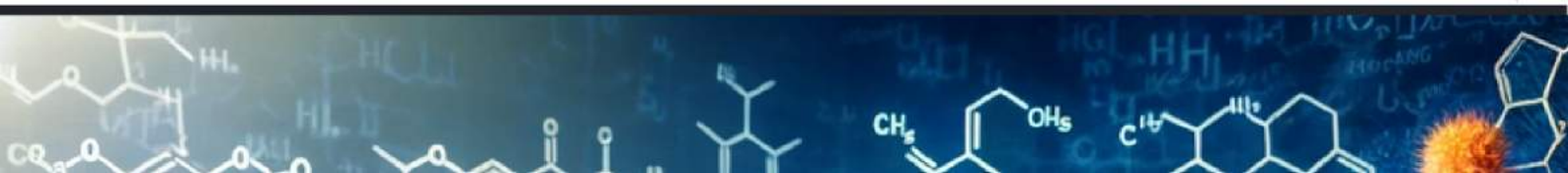
IMPC "SPRING" MEETING 2024

The first ever IMPC Spring meeting in Africa aims to convene leading international experts to deliver overview lectures that provide a global perspective on our topic: "Beyond the Genome". Advances in nucleic acid-based therapies, based on the conventional coding genome, but also on noncoding gene sequences, as well as epigenetic programming, continue to reshape healthcare worldwide, creating opportunities for us to deliver personalized medicine, innovative treatments for rare and previously incurable diseases, and the potential for more affordable therapies for all. Our meeting topics are specifically directed towards the noncoding genome and the impact of epigenetics on phenotype and disease therapy.

Genome-wide association studies (GWAS) show that the genetic changes associated with chronic illnesses like Alzheimer's, diabetes, and heart disease do not lie in the protein-coding regions, but in the noncoding DNA. Noncoding DNA contains inter alia regulatory elements, including promoters, enhancers and inhibitors or silencers of transcription and barrier insulators, some structural elements of chromosomes (including telomers and satellite DNA); repetitive sequences or transposons. Transposons reflect not only a record of crucial alterations in our DNA over millennia, but they are also mobile and move from one part of the genome to another, causing smaller or larger mutations in genes or alternatively reversing mutations.

Instructions for the formation of various kinds of non-coding RNAs, which are involved in protein assembly, blocking the process of protein production, and regulation of gene activity in response to changes in the environment are also found in non-coding DNA. Specialized RNA molecules, produced from noncoding DNA, include transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs), microRNAs (miRNAs), that block the process of protein production; and long noncoding RNAs (lncRNAs), that have diverse roles in regulating gene activity.

Non-coding RNAs are now increasingly thought to the link between the non-coding genome and various chronic illnesses. Consistent 'wrong' environmental signals can lead to RNA molecules that can cause a disease state, by altering gene activity such that it results in an inflammatory response or promotes cell death. Non-coding RNAs can enhance the activity of or switch off genes that normally prevent the formation of tumours. While the drug development industry has largely pursued proteins as drug targets, disruption of the non-coding RNAs are progressively being investigated in the field of cancer vaccines (CureVac), scar tissue formation, or fibrosis, in the heart (Haya Therapeutics). Information on noncoding gene sequences, and epigenetic programming are providing opportunities for personalized medicine as well as innovative treatments for rare and previously incurable diseases.



-- PROGRAMME --

28 April 2024 | DAY 1

07:00 - 08:15	Registration and sign Attendance Register
08:15 - 08:30	Welcome **Glaudina Loots | Director | Health & Innovation, South Africa**
Session 1	
08:30 - 09:00	Opening address and purpose of the meeting **Prof Craig Kinnear | Director | South African Medical Research Council - Genomics Platform**
09:00 - 10:00	"Loss of epigenetic information and aging and Alzheimer's Disease" **Prof Harry Steinbusch**
10:00 - 10:45	"Insights from a new generation of rodent models for understanding Down Syndrome" **Prof Yann Hérault**
10:45 - 11:15	COFFEE / TEA
Session 2	
11:15 - 12:00	"Looking to the future of genome editing for animal models" **Prof Guillaume Pavlovic**
12:00 - 12:45	"Epigenetics and drug metabolism" **Prof Rose Hayeshi**
12:45 - 14:00	LUNCH AND WALK ALONG THE BEACH
Session 3	
14:00 - 14:30	"Caecal microbiota composition in diabetic db/db mice and effects of pioglitazone and rooibos" **Dr Sylvia Riedel**
14:30 – 15:00	"The effect of long-term high-fat diet feeding on intestinal health of aged vervet monkeys" **Mr Ronaldo Mukhari**
15:00 - 15:30	"Contemporary Animal Models for Human Gene Therapy Applications " **Dr Lucy Ochola**
15:30 - 16:00	COFFEE / TEA
Session 4	
16:00 - 16:45	Remote Presentation | From Cape Town to California and back again **Dr Patrick Soon-Shiong**
18:00	COCKTAIL FUNCTION - KRYSTAL BEACH DECK
	Words of Support to the IMPC by the Deputy Vice Chancelor: R & I, NWU **Prof Jeffrey Mphahlele**

-- PROGRAMME --

29 April 2024 | DAY 2

08:00 - 08:30	Sign Attendance Register
Session 1	
08:30 - 09:15	"Expanding Horizons: Leveraging Viral Trans-Replicons for Enhanced RNA Production and Beyond-Protein Synthesis Effects" **Prof Markus Depfenhart**
09:15- 10:00	"Of maize and men: is there a place for transient gene expression in plants?" **Prof Anne Grobler**
10:00 - 10:45	Remote Presentation | "Polymeric nanocarriers in gene therapy applications" **Prof Alejandro Sosnik**
10:45 - 11:15	COFFEE / TEA
Session 2	
11:15 - 12:00	"Zinc finger(s): from a specific role to a regulatory network" **Prof Radislav Sedláček**
12:00 - 12:45	"Congenital heart defects and emphasize the usefulness of the IMPC resource for clinical research especially in the field of rare heart diseases" **Dr Nadine Spielmann**
12:45 - 14:00	LUNCH AND WALK ALONG THE BEACH
Session 3	
14:00 - 15:30	Working Groups **Breakaway Rooms**
Session 4: Panel Discussion	
15:30 – 16:30	Discussion | Feedback from Working Groups
17:45	TRANSPORT TO CONFERENCE DINNER
18:30	CONFERENCE DINNER AND INTERACTIVE DRUMMING SESSION - SPIER WINE FARM

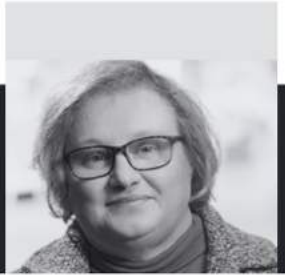
-- PROGRAMME --

30 April 2024 | DAY 3

08:00 - 08:30	Sign Attendance Register
Session 1	
08:30 - 09:15	"Remote Presentation | "Bridging Innovation: The Impact of LCSB Scientific Platforms on Biomedical Research" **Dr Jan Rozman**
09:15- 10:00	"Energy: a prime biological driver of life and death: lessons from mouse models" **Prof Francois van der Westhuizen**
10:00 - 10:45	"Paternal influence on offspring health: a touch for life" **Dr Raffaele Teperino**
10:45 - 11:15	Wrap-up **Prof Yann Herault**
11:15	COFFEE / TEA / COLLECT LUNCH BOXES
11:30	Site Visits

-- SPEAKERS --

Speakers are listed in order of the program



Glaudina Loots

Director | Dept Science & Innovation South Africa

Ms Glaudina Loots is the Director for Health Innovation at the Department of Science and Innovation in South Africa and as such is responsible for the implementation of the health components of the Bioeconomy strategy for South Africa. She concentrates on enabling research and innovation that leads to discovery and evaluation of new drug and treatment regimes, the development of new vaccines and new robust diagnostics, as well as the development of medical devices and digital health applications. Glaudina was instrumental in the creation of the Strategic Health Innovation Partnership Initiative (SHIP) at the South African Medical Research Council.
Among others, Ms Loots is a member of the Ministerial Advisory Committee on COVID-19 Vaccines, the South African National Health Research Committee, the South African National AIDS Council, and the Advisory Board of the "Towards an HIV Cure Initiative" of the International AIDS Society, as well as the steering committee of various research centres of excellence, such as SACEMA; the CAPRISA Centre of Excellence for HIV Prevention and the API Technology Innovation Cluster.

Craig Kinnear

Director | SAMRC - Genomics Platform

Prof Craig Kinnear is the director of the SAMRC Genomics Platform who obtained his PhD at Stellenbosch University in 2007. For his PhD, he focused on identifying novel genetic predisposing factors involved in the pathogenesis of obsessive-compulsive disorder and schizophrenia. Furthermore, he investigated signalling pathways involved in neuronal migration and brain development. Following his PhD, Prof Kinnear's research interest shifted towards studying the molecular mechanisms underlying the development of cardiac hypertrophy in patients with Hypertrophic Cardiomyopathy. In 2013, he joined the TB host genetics team at the Division of Molecular Biology and Human Genetics at Stellenbosch University where he is currently focusing on identifying disease-causing mutations in patients with primary immunodeficiencies who are extremely susceptible to tuberculosis. In addition to this, he is also investigating the extent to which different Mycobacteria tuberculosis strains induces autophagy in the human host.

-- SPEAKERS --

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Harry Steinbusch

Director | Maastricht University

Sir Prof. dr. Harry W.M. Steinbusch is appointed as Professor in Cellular and Translational Neuroscience at University of Maastricht at Maastricht in the Netherlands. His research interest is focused on the neurodevelopmental influences between depression and neurodegenerative diseases, i.e., Alzheimer's Disease as studied in animal models and human postmortem material. This approach will be implemented to start and prevent neurodegenerative processes. These studies use a broad range of techniques, i.e. molecular neurobiology, quantitative neuromorphology, animal behavior and epigenetics. He is currently involved as International Strategy Coordinator towards China, Japan and Korea and Coordinator of the UM-CSC Scholarship Program, covering 324 PhD students. He is Founding and Editor-in-Chief of the Journal of Chemical Neuroanatomy, current I.F. 3.1; J.C.I.: 5.2. He is appointed as Adjunctive Professor with KPMU in Kyoto, Japan; University of Colombo, Sri Lanka and DGIST, Daegu, Korea. He is Founding-Director of the European Graduate School of Neuroscience, a gathering of 8 universities in the EUregio, between the Netherlands, Germany, Belgium, France, and Luxembourg. He has thus far guided 105 Ph.D. students. He has gathered a total of 505 papers. He has been twice coordinating a Marie Curie Early-Stage Training site. His total earning power is € 46 million. He was coordinator of an Erasmus Mundus + program between 4 Euron universities and 3 universities in Japan. He is affiliated on 27 editorial board and member of 20 International review committees. His current Hirsch factor is 104, citations without self-citations: 39,701 and his M-factor is 2.3. Best Neuroscience Scientists: World place 510, the Netherlands place 10.

Yann Hérault

Chair | IMPC Steering Committee
Research Director | CNRS

Dr. Yann Hérault (Ph.D.) is a Research Director at the French National Centre for Scientific Research (CNRS). and a biologist and mouse geneticist by training. He has been leading the Mouse Clinical Institute, ("Institute Clinique de la Souris", MCI/ICS) since 2010, and a research group at the IGBMC. He worked on mouse development using genetics approach for more than 20 years. He developed a series of techniques for chromosomal engineering with the aims to study gene regulation at the genomic level in vivo. Now his research interests are focused on evaluating the consequences of gene dosage effect and copy number variation in pathological situation such as in Down Syndrome (or Trisomy 21) to further propose new therapeutic approaches.

-- SPEAKERS --

Speakers are listed in order of the program

Guillaume Pavlovic

Head of Genetic Eng | Institut Clinique de la Souris

Dr. Guillaume Pavlovic is Head of Genetic Engineering and Model Validation at PHENOMIN-Institut Clinique de la Souris (https://www.phenomin.fr), one of the largest French academic centres in phenogenomics and a founding member of the CELPHEDIA infrastructure (a national operational research infrastructure for animal research; https://celphedia.eu). His work consists of supporting the scientific community, both public and private, which has led to the development of 1,500 genetically modified rodent models. Guillaume therefore manages a range of services including genome engineering, expression analysis and microbiome metagenomics. He participates, and on several occasions coordinates for the ICS, various large national and international academic projects or collaborations with the industry.

As a technologist, he has built and applied a wide range of technologies, including recognized expertise in CRISPR/Cas9 genome editing and advanced molecular biology.

As a scientist, Guillaume has a keen interest in research reproducibility. He is actively involved in this topic as a trainer, reviewer, co-editor of journals or expert for the evaluation of infrastructure or scientific projects. In recent years, he and his team have been particularly active in publishing technical papers or reviews.

Rose Hayeshi

Director | DSI/NWU PCDDP

Prof Rose Hayeshi is the Director of the Preclinical Drug Development Platform (PCDDP), North West University. She has intensive experience in Pharmacology and holds a PhD in Biochemistry (2009) obtained from the University of Zimbabwe. Prof Hayeshi has more than ten years' experience in the field of pharmaceutical sciences gained through training and research positions held in Zimbabwe, Sweden, The Netherlands and South Africa. She spends most of her time as managing the PCDDP and as Study Director for preclinical testing in compliance with OECD Good Laboratory Practice (GLP) guidelines. Prof Hayeshi was a finalist for the 2019/2020 NSTF-South32 Awards.

-- SPEAKERS --

Speakers are listed in order of the program

Sylvia Riedel

Specialist Scientist | SA Medical Research Council

Dr Riedel graduated from the University of Muenster, Germany, in April 2012. Her doctoral studies focused on the preventive properties of omega3 fatty acids against the induction of precancerous lesions. From 2009 to 2013 she coordinated projects on anticancer properties of rooibos and honeybush herbal teas, including effects on apoptosis and inflammation in a variety of human cell culture models as Scientist at the SAMRC. Since her transfer to the Biomedical research and Innovation Platform (BRIP) in 2014, her projects included investigation of preventive effects of plant extracts on insulin resistance in cell cultures and animal models. Dr Riedel is specialising in exploring intestinal permeability and immunological mechanisms and their role in the pathophysiology of metabolic disease for which she has received grant funding from the South African Rooibos Council (SARC), National Research Foundation (NRF) and Deutsche Gesellschaft für Internationale Zusammenarbeit (GIZ). Dr Riedel has served as peer-reviewer for 11 international journals and supervised 1 PhD student, 9 MSc students and 3 BSc Hons students. She has been affiliated with the Division of Medical Physiology at the University of Stellenbosch as extraordinary lecturer since 2016.

Lucy Ochola

Senior Scientist | Kenya Institute of Primate Research

Lucy has served at various institutes as a research fellow ICIPE, Nairobi, and Research fellow and Postdoctoral scientist, KEMRI-Wellcome Trust, Kilifi and Liverpool School of Tropical Medicine, UK. She currently hold a Senior Research position and is Head of the Department of Infectious Diseases, KIPRE. KIPRE is a preclinical biomedical research center, focuses on using Olive baboons and African green monkeys to study various diseases that afflict humans. Research in Lucy's lab focusses on infectious diseases, with an emphasis on parasitology (malaria and schistosomiasis), utilizing preclinical animal models to understand their immunology, disease manifestation and diagnosis in endemic populations. Lucy main research has focused on assessing the impact of helminth infections on candidate HIV, HPV and malaria vaccines, discovery and testing of novel malaria drugs, diagnostics and looking at genetic diversity of parasitic infections. She is currently the Secretary General for Kenya society for Immunology (KSI), council member of International Union of Immunological Societies (IUIS), Treasurer (Federation of Immunological Societies). She works to support the KSI by improving awareness of immunology through organizing workshops and providing scientists with an opportunity to network.

-- SPEAKERS --

Speakers are listed in order of the program

Patrick Soon-Shiong

Chairman & CEO | NantWorks

Dr Patrick Soon-Shiong, MD, is a surgeon, scientist, inventor, and philanthropist with over 500 issued worldwide patents and 100 scientific publications. He serves as Chairman and Chief Executive Officer of NantWorks, an ecosystem of companies with developments in a wide variety of complex industries, from medical science to biomaterials, from data transport to AI and from communications to mobility.

In 2001, Dr. Soon-Shiong founded American Pharmaceutical Partners (APP), which produced over 300 million vials of injectable products annually for cancer, infectious disease, and critical care. In 2005, the FDA approved his invention Abraxane, the nation's first protein nanoparticle chemotherapy for breast, lung, and pancreatic cancer. Abraxane has achieved over a billion dollars in annual global sales and has been placed in the medical history collections at the Smithsonian National Museum of American History.

In 2011, Dr. Soon- Shiong founded NantWorks to establish an organization addressing health care, clean energy and communication. Under this umbrella, he serves as Executive Chairman of ImmunityBio, Inc., a leading biotechnology company focusing on first in class vaccines, cytokines and natural killer and T cell therapy for cancer and infectious diseases; Chairman and CEO of NantHealth, a Nasdaq listed healthcare company converging biomolecular medicine and bioinformatics with deep learning AI to empower physicians, patients, payers, and pharma to deliver the right care at the right time; Chairman of NantG Power, a privately-held Graphene-based lithium battery company; Chairman of Calcean and NantBioPlastics accelerating the worldwide transformation to renewable biomaterials and developing industrial-scale methods of bioplastics manufacturing; and Owner and Executive Chairman of California Times, publisher of two of the state's largest newspapers, the Los Angeles Times and The San Diego Union-Tribune.

In 2021, Dr. Soon-Shiong established NantAfrica, Nant South Africa (NantSA), and Nant Botswana (NantBW) to establish a coalition of organizations for the acceleration of advance health in Africa with the goal of manufacturing a billion doses of vaccines in South Africa by 2025. In 2022, he supported the launch of the non-profit organization, Access to Advanced Health Institute, AAHI, to continue the ground breaking research of the former IDRI institute.

-- SPEAKERS --

Speakers are listed in order of the program

Markus Depfenhart

Principal Investigator | SaVaC Project NWU/
Walter Sisulu University

In 2004, Markus Depfenhart completed his medical studies and received his doctorate from the JWG University in Frankfurt am Main in 2005. He later underwent further studies in other subjects and so he now also holds a LL.M. in economic law and a PhD in business and economics. Among others he developed an algorithm for legal patent circumvention. After numerous theoretical and practical training courses, he qualified as board certified emergency physician in 2008 and worked as an emergency physician in Hamburg, but also in crisis regions such as the Balkans and Afghanistan. Since 2014, he has been a board certified specialist in plastic and aesthetic surgery. He is an expert for skin and skincare related topics and of his major focusses is now peptide and protein design. In 2018 Markus Depfenhart has been appointed as professor for aesthetic and regenerative medicine at the Venlo University/ NL. Since 2020 he is also lecturing at the FOM University of Applied Science in Hamburg/ Germany. He also works as a consultant for the industry and has a seat on the advisory board of various national and international companies. He is currently a member of the board of Lavenir Bioscience AG (Hamburg) and the Optiphi AG (Switzerland). Markus Depfenhart holds more than 30 patents and patent applications in different fields.

Anne Grobler

CEO | Pheroid Cluster Incubator

Prof Anne Grobler, the current project manager of the SaVaC project, has a PhD in Pharmaceutics (North-West University) and an MSc in Medical Biochemistry (Stellenbosch University). Her interest is the design and construction of nucleotide-based vaccines and therapeutics and bio-agricultural delivery systems. She has worked at the University of Stellenbosch and North-West University, the SAMRC, and in the private sector (head of R&D at MeyerZall Laboratories, at Austell Pharmaceuticals and now heads the Pheroid Cluster Incubator (www.pheroidcluster.com). She is a co-author of the SA Synthetic Biology Strategy, the SA Bio-Design Initiative and the Ministerial Review of STI institutions (2017). She has founded spin-off companies: The Pheroid Cluster Incubator NPC, BioPher Pty Ltd, Antech Pharmaceuticals (Pty) Ltd and Inopher (Pty) Ltd She has delivered many PhD and MSc students, both locally and internationally, authored/coauthored more than 140 ISI publications and is an inventor/author of 9 patents granted or under examination. Her awards include: NIPMO Innovators Award for most disclosures with commercial potential at the NWU (2019), BioFundi Award for Research by the Gauteng Province and Innovation Hub (2018), the NWU Innovation Evangelist Award (2017), the NSTF/BHP Billiton Award for her contribution to SETI (2014); the Swiss Bio-technology Innovation Award, Switzerland (2011); two Vice Chancellor's Honorary Award countries (2010).

-- SPEAKERS --

Speakers are listed in order of the program

Alejandro Sosnik

Research Prof | Technion, Dept Material Science & Engineering

Prof. Alejandro Sosnik, a pharmacy graduate from the University of Buenos Aires, pursued extensive professional and academic paths. After early roles in public hospitals, he ventured into organic chemistry research before migrating to Israel for further studies. There, he earned M.Sc. and Ph.D. degrees in applied chemistry. His postdoctoral tenure in Canada focused on hybrid matrices for tissue engineering. Returning to Argentina, he became an Assistant Professor and established a research group in pharmaceutical technology, delving into drug crystallization, nanotechnology, and drug delivery. He founded the RIMADEL network and advised pharmaceutical companies. In 2014, he joined Technion-Israel Institute of Technology, leading research in pharmaceutical nanomaterials. His work spans various disciplines, from drug self-assembly to pediatric cancer therapy. Prof. Sosnik has earned numerous grants and accolades, authored over 190 publications, and contributed significantly to patents and patent applications in biomedical innovation.

Radislav Sedláček

Director | Czech Centre for Phenogenomics

Radislav Sedláček (RS), the director of the Czech Centre for Phenogenomics (https://www.phenogenomics.cz/) hosted by the Institute of Molecular Genetics, focuses on functional analysis of gene functions, chairing in 2021-2022 the steering committee of IMPC, a worldwide consortium aiming to produce a genome-wide catalogue of gene function data that enable therapeutic discovery and genomic medicine. RS is (2020-2021) a past chair and now a member of the Strategic Working Group for Health and Food (HF TWG). Besides these strategic functions serving the scientific community, RS's research is devoted to utilization of genome editing technologies and in-deep phenotyping analysis of animal models to uncover novel genetic mechanisms of human diseases. RS also devotes his research towards experimental precise and gene therapies as well as preclinical development.

-- SPEAKERS --

Speakers are listed in order of the program

Nadine Spielmann

Scientific head | Helmholtz Munich

Head of the Cardiovascular Research
Institute of Experimental Genetics, Helmholtz Munich
https://www.helmholtz-munich.de/en/ieg
nadine.spielmann@helmholtz-munich.de

·Studied at University of Basel (CH) und Humboldt University of Berlin; PhD in sports medicine; postdoc at Pennington Biomedical Centre, Marie and Pierre Curie University Paris and UCLA in Los Angeles.

·Since Oct 2017 Head of the Cardiovascular Research, German Mouse Clinic, Institute of Experimental Genetics, Helmholtz Munich, Germany.

·Leader of the Cardiovascular Working Group at the International Mouse Phenotyping Consortium (IMPC).

·Additionally funded by a grant of the German Heart Alliance.

·Focus of research: Congenital heart defects and rare cardiovascular diseases using mouse models for translational and preclinical (treatment) studies.

Jan Rozman

Scientific Co-ordinator | LCSB

My scientific expertise is focused on investigating the physiological, genetic, and molecular mechanisms underlying metabolic disorders such as obesity and T2DM, using animal models. Some of my notable research includes exploring the role of adipose tissue in metabolic dysfunction and identifying novel molecular targets for treating insulin resistance I have also had the opportunity to contribute to large-scale biology projects like the International Mouse Phenotyping Consortium, which aims to systematically analyze the function of every gene in the mouse genome. Through these collaborations, I have gained valuable experience in managing research infrastructure and working with interdisciplinary teams.

My ultimate vision is to improve human health by better understanding the underlying mechanisms of metabolic disorders and developing new therapeutic strategies. To achieve this, I plan to continue collaborating with scientists from diverse fields and applying cutting-edge technologies to advance our understanding of these complex diseases.

-- SPEAKERS --

Speakers are listed in order of the program

Francois vd Westhuizen

Deputy Dean | NWU / Natural Sciences, Research & Innovation

Francois started his academic career in 1993 as junior lecturer and is currently Professor of Biochemistry and the Deputy Dean (Research and Innovation) at the Faculty of Natural and Agricultural Sciences at the North-West University (NWU). His teaching expertise has been enzymology, molecular biology and bioenergetics. After receiving his PhD in 1998, his research focus narrowed to mitochondrial disease. Since 2002 he helped establish the Mitochondria Research Group at the NWU, which focusses on mitochondrial- and other neuromuscular diseases in SA, as well as research on bioenergetics and mtDNA and their role in health and disease.

Raffaele Teperino

Head Env. Epigenetics | Helmholtz Diabetes Centre

I am a physiologist and pharmacologist by training and obtained a PhD in Molecular Pathology at the University of Naples with a thesis on genetic and epigenetic alterations in type 2 diabetes (Teperino et al. Journal of Biol. Chem. 2008 and Diabetologia 2010). After completing my PhD, I joined the group of Prof. J. Auwerx at the Ecole Polytechnique Federale de Lausanne (EPFL) for a first postdoc. There I worked on the cross-talk between cellular metabolism and epigenetics (Teperino et al. Cell Metab. 2010). Afterwards, I took a second postdoc in Freiburg (DE) at the MPI for Immunobiology and Epigenetics in the group of Dr. A. Pospisilik to shed light on the role of developmental regulators (including epigenetic modifiers) in adult metabolic physiology (Teperino et al. Cell 2012, Dalgaard et al. Cell 2016, Posavec Marjanovic et al. Nat. Struct. And Mol. Biol. 2018, Lu et al. Cell Metab. 2018). Since 2015 I have joined the Institute of Experimental Genetics at the Helmholtz Zentrum München (HMGU), where I am heading an independent research group on Environmental Epigenetics. The overarching goal of my group is to study the interface between genetics, lifestyle, epigenetics and systems physiology with a special focus on parental effects, epigenetic inheritance and early programming of late onset diseases, such diabetes, obesity and neurodegeneration (Gerlini et al. Mol. Metab. 2018, Darr et al. Cell Rep. 2020, Lassi et al. Sci. Adv. 2021). Since 2021, I chair the Molecular Phenotyping Working Group of the International Mouse Phenotyping Consortium.

The role of loss of epigenetic information and aging in Alzheimer's Disease

Harry W.M. Steinbusch
Maastricht University, the Netherlands

The loss of epigenetic information is increasingly recognized as a significant factor in the aging process and the development of neurodegenerative diseases such as Alzheimer's Disease (AD). Epigenetics refers to changes in gene expression that do not involve alterations in the DNA sequence itself.

1. Aging and Epigenetic Changes: As individuals age, there is a tendency for the epigenetic landscape to become altered. This can include changes in DNA methylation patterns, histone modifications, and alterations in the activity of non-coding RNAs. These changes can affect gene expression patterns, leading to a decline in cellular function and an increased susceptibility to age-related diseases.

2. Epigenetic Dysregulation in Alzheimer's Disease: Epigenetic dysregulation has been implicated in the pathogenesis of Alzheimer's Disease. Studies have shown alterations in DNA methylation patterns and histone modifications in the brains of individuals with AD compared to healthy controls.

3. Role of Environmental Factors: Environmental factors such as stress, diet, and exposure to toxins can influence epigenetic modifications and contribute to both aging and the development of AD.

4. Therapeutic Implications: Understanding the role of epigenetic changes in aging and AD opens up new avenues for therapeutic intervention. Epigenetic-modifying drugs, such as histone deacetylase (HDAC) inhibitors and DNA methyltransferase inhibitors, are being investigated as potential treatments for AD and other neurodegenerative diseases. These drugs have the potential to reverse aberrant epigenetic changes and restore normal gene expression patterns, thereby mitigating disease progression.

5. Challenges and Future Directions: Despite the promise of epigenetic-based therapies, there are still many challenges to overcome. These include the need for better understanding of the specific epigenetic changes associated with aging and AD, as well as the development of targeted and safe epigenetic-modifying drugs.

In conclusion, the loss of epigenetic information is emerging as a key factor in both aging and the development of Alzheimer's Disease. Further research into the role of epigenetics in these processes may lead to new insights and therapeutic strategies for combating age-related neurodegeneration.

Looking to the future of genome editing for animal models

Guillaume Pavlovic
Head of Unit, Genetic Engineering and Model Validation Department
Institut Clinique de la Souris- PHENOMIN- IGBMC

The last two decades have seen impressive advances in functional genomics, but we are still far from understanding the complexity of gene function: despite incredible progress, challenges remain in capturing genetic diversity and fully understanding gene complexity.
The technologies available today, especially genome editing, allow us to make an incredible range of genetic modifications. In this talk, we will provide examples of complex mutations like complete gene humanization models or specific cell/time reversion of disease. Genetic mutations are also now achievable in a large panel of animal models, allowing the selection of more translatable models for human health.
Other challenges lie ahead: next-generation models must encompass all genetic elements and allelic variants, leveraging advanced genome editing and polygenic approaches. In addition, phenotyping paradigms and computational tools are essential for interpreting complex data sets. As we delve deeper into genomics, the complexity of gene function becomes increasingly apparent, underscoring the need for continued innovation in animal models to realize the promise of personalized medicine.
Finally, reproducibility in animal research can be hampered by inconsistent reporting of animal genetics. The future of animal models also lies in better validation and reporting of genetic background and genetic alterations.

Epigenetics and drug metabolism

Rose K Hayeshi
North-West University, Potchefstroom, South Africa

The meeting theme, "Beyond the Genome," underscores the crucial role that factors beyond DNA sequence play in health and disease. Pharmacoepigenetics, the field studying how epigenetic modifications influence drug response, is a powerful lens through which to explore this concept. This presentation will delve into the interplay between epigenetics and drug metabolism, highlighting its significance for personalized medicine and therapeutic development.

Epigenetic Regulators and Drug Metabolism Enzymes: Epigenetic modifications, such as DNA methylation, histone acetylation, and microRNAs, influence the expression and activity of drug metabolizing enzymes. These enzymes play a critical role in determining a drug's efficacy and potential for toxicity. By understanding how epigenetic marks regulate these enzymes through the lens of pharmacoepigenetics, we can gain insights into individual variations in drug response.

Epigenetic Impacts on Drug Transporters: Drug transporters are another key player in drug metabolism, facilitating the movement of drugs into and out of cells. The presentation will discuss how epigenetic alterations can affect the expression and function of these transporters, impacting drug distribution and elimination within the body.

Pharmacoepigenetics in Personalized Medicine: By incorporating individual epigenetic profiles into the equation, we can move towards personalized medicine strategies for drug therapy. Tailoring drug selection and dosage based on a patient's unique epigenetic makeup, as informed by pharmacoepigenetics, holds promise for improving treatment efficacy and reducing adverse effects.

In conclusion, pharmacoepigenetics offers a new frontier in understanding drug metabolism. By unraveling the intricate dance between epigenetic marks and the enzymes and transporters involved in drug metabolism, we can pave the way for more effective and individualized therapeutic approaches. This presentation will highlight the current state of knowledge in this area and its far-reaching implications for the future of pharmacology.

Caecal microbiota composition in diabetic db/db mice and effects of pioglitazone and rooibos

Sylvia Riedel
Sylvia S Riedel1,2, Nireshni N Chellan1,2, Johan J Louw1,3, Christo JF Muller1,2,3

1Biomedical Research and Innovation Platform, South African Medical Research Council, Tygerberg, South Africa. 2Centre for Cardiometabolic Research in Africa, Division of Medical Physiology, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, South Africa. 3Department of Biochemistry and Microbiology, University of Zululand, KwaDlangezwa, South Africa

Breakdown of the intestinal barrier can lead to leaky gut and systemic lipopolysaccharide-induced endotoxemia, which has been implicated in the development of type 2 diabetes (T2D). Gut microbiota regulate intestinal barrier function and inflammatory responses, which can be mediated and mitigated by immunoglobulin A (IgA).

We aimed to investigate (i) composition and diversity of caecal microbiota in leptin receptor deficient diabetic (db/db) mice compared to non-diabetic (db/+) mice and (ii) the effect of a green rooibos extract (Afriplex GRTTM) with anti-diabetic potential, thereon. Four groups (n=8/group) of db/+ and db/db mice received: (i) control, (ii) low dose GRT (74 mg/kg/day), (iii) high dose GRT (740 mg/kg/day) and (iv) pioglitazone (PIO, 15 mg/kg/day) for 16 weeks thereafter an oral glucose tolerance test was completed. IgA expression was assessed using immunohistochemistry. Microbial DNA was extracted from caecum content and seven hypervariable regions in the 16S ribosomal RNA gene were sequenced using the Ion Torrent S5™ platform at Central Analytical Facilities, Stellenbosch University.

PIO improved oral glucose tolerance ($p=0.004$), and marginally increased IgA positive areas in the small intestine ($p=0.069$), while GRT displayed no affect. The Chao1 index (α-diversity) increased in db/db mice compared to db/+ ($p<0.001$) and decreased with GRT treatment ($p<0.05$). Db/db mice displayed increased abundance of various species, e.g. Corynebacterium, Eubacterium and Staphylococcus spp. and decreased abundance of Ruminococcus gnavus, Desulfovibrio C21_c20 and Roseburia intestinalis. PIO treatment increased abundance of Bacteroides acidifaciens compared to LD and HD ($p=0.0502$). The Firmicutes to Bacteroidetes ratio remained unchanged.

Caecal microbiota diversity and composition was modulated in db/db mice. As PIO increased glucose tolerance and improved IgA expression, investigating interactions between IgA and microbiota could offer new insights into the relationship between gut microbiota and glucose homeostasis.

The effect of long-term high-fat diet feeding on intestinal health of aged vervet monkeys

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The consumption of high-fat diets (HFDs) dysregulates intestinal barrier components which may lead to subclinical systemic and tissue inflammation implicated in type 2 diabetes (T2D) development. This study investigated intestinal barrier function and inflammation in intestinal tissues of vervet monkeys (Chlorocebus aethiops) maintained on a maize-based control diet (MD) (n=3) and an HFD (n=6), respectively for 15 years. Serum was used to assess levels of high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C). Immunohistochemistry (IHC) was used to enumerate immune cell populations by assessing the expression of immunoglobulin-A-positive (IgA+) cells in intestinal tissues. Western blot analysis was used to assess the expression levels of markers that are involved in the synthesis of pro-inflammatory mediators, extracellular signal-regulated kinase 1/2 (ERK1/2) in the ileum and colon. HDL-C ($p=0.048$) and LDL-C ($p=0.017$) levels were significantly increased in HFD-fed vervet monkeys. HFD significantly increased ($p=0.046$) the population of IgA+ cells in the duodenum when compared to MD-fed vervet monkeys, but not the jejunum, ileum and colon. Western blot analysis revealed that, while not significant ($p=0.134$), a trend towards increased phosphorylation of ERK1/2 was detected in the colon of the HFD group when compared to the MD group. In this study HFD-fed vervet monkeys developed hypercholesterolemia, which increases the risk of cardiovascular disease. In addition, the increased population of IgA+ cells in the duodenum of HFD-fed vervet monkeys indicates potential irregularities in mucosal immunity regulation.

Contemporary Animal model for Human Gene Therapy applications

Lucy Ochola
Kenya Institute of Primate Research, Nairobi, Kenya

The Kenya Institute of Primate Research (KIPRE) was established 56 years ago as an institute to initially study monkey behavior and human evolution. Since then, it has evolved into a preclinical biomedical facility, utilizing laboratory animal models to address human health in the area of emerging and infectious diseases, reproductive health, non-communicable diseases. Non-human primates (NHP) comprising of Papio anubis and African Green monkey are widely used as models for preclinical studies at KIPRE.

We highlight research involving the two NHP animal models: vervets as natural hosts of simian immunodeficiency virus (SIV) and their value in evaluating leishmaniasis, trypanosomiais diseases and dengue virus vaccine research. While, Olive baboons have had wider applications from understanding the pathogenesis of P. knowlesi malaria and schistosomiasis models to analyzing co-infections and evaluating vaccine outcomes, to evaluation of behavioural genetics and immunity.

NHPs are our closest relatives according to phylogenetics, anatomy, physiology, behavior and genetics and by characterizing them and tapping into their genomes sequences we can explore novel gene therapies. Expanding genomic information on NHPs in KIPRE provides an opportunity to further expand and improve these models for human disease.

Expanding Horizons: Leveraging Viral Trans- Replicons for Enhanced RNA Production and Beyond-Protein Synthesis Effects

Markus Depfenhart

In the rapidly advancing field of biotechnology, the development of innovative delivery systems is crucial. Our latest breakthrough involves a DNA-launched trans-replikon system, which functions as a self-amplifying RNA platform. This cutting-edge technology not only boosts RNA production significantly but also supports the expression of both coding and non-coding RNA, thus expanding the potential applications far beyond traditional protein synthesis.

This presentation will explore the mechanics and advantages of our DNA-launched, self-amplifying viral trans-replikon system. The robust nature of this system makes it an ideal candidate for a variety of therapeutic applications, including gene therapy, cancer immunotherapies, and treatments for autoimmune diseases. Specific case studies will be presented to demonstrate the system's capability to produce large volumes of functional RNA, fostering diverse immunological and therapeutic effects.

While adaptable for mRNA-based applications, our system shows distinct advantages when implemented through DNA, particularly due to the enhanced stability and extended expression profiles that DNA vectors offer. These features make it particularly effective not only in vaccine development but also in pioneering treatments for cancer and autoimmune disorders.

By showcasing the broad utility and transformative potential of our system, this presentation will underscore how advanced RNA production technologies are setting new benchmarks in genetic engineering and immunotherapy. Attendees will gain insight into a future where the boundaries of medical treatment are continually expanded, leveraging our platform's ability to manipulate a wide array of RNA molecules for therapeutic gain.

Of maize and men: is there a place for transient gene expression in plants?

Anne Grobler
Pheroid Cluster Incubator, South Africa

While no DNA sequence alteration underlies the epigenome, changes in the plant epigenome results in heritable changes in gene expression: epigenetic modifications, leading to epialleles, can be passed on from generation to generation, so resulting in a heritable 'memory' for environmental cues and adaptations by the plant. This phenomenon, known as transgenerational, regulate the activation or silencing of genes in response to environmental signals. For example, more than 99% of the methylome in maize and Arabidopsis is preserved between accessions. Such changes have been used in epibreeding programmes for crop improvement.

Epigenetic modifications can be caused by stress, such as drought or cold, to activate protective genes and enhance their survival chances, to regulate flowering time, fruit ripening. These responses are in turn regulated by DNA/RNA methylation, posttranslational histone modifications and non-coding RNAs.

Transient gene expression in plants on the other hand is not heritable and provides a valuable tool for functional genomics research, protein expression studies, pathway analysis, trait testing, and biotechnological applications. Three transient expression systems are typically used in plants:Agroinfiltration, viral vectors or DNA administered by mechanical means.

It may be beneficial to be able to express genetic material using a system that is nonviral and non-bacterial. In this presentation, the use of a DNA vector system that supports systemic transient expression to the extent that it can result in a change in traits will be discussed. Using this DNA-launched RNA expression system, the expression and distribution of a green fluorescent protein were monitored in the leaves of plants.There is no interferon-γ response in plants, hence the duration of expression was found to be longer, the yield of proteins higher and the distribution better.

-- ABSTRACTS --

Bridging Innovation: The Impact of LCSB Scientific Platforms on Biomedical Research

Jan Rozman
Luxembourg Centre for Systems Biomedicine

The LCSB Scientific Platforms serve as biomedical research infrastructure at the University of Luxembourg, offering comprehensive solutions to researchers worldwide. These platforms, comprising genomics, imaging, metabolomics & lipidomics, in vivo disease modeling, cell-based methodologies, drug screening, and bioinformatics, facilitate innovation and knowledge exchange across academia and industry. Staffed by seasoned experts, these facilities not only provide cutting-edge services but also offer guidance on experimental design, data analysis, and training to empower researchers in utilizing advanced technologies. By bridging the gap between basic research and drug development, these platforms play a pivotal role in advancing biomedical science and fostering translational research efforts.

-- ABSTRACTS --

Energy is a prime biological driver of life and death: lessons from mouse models

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The production and regulation of cellular energy is fundamental to health, disease, and aging. Organisms have evolved sophisticated and highly active mechanisms to harness energy from the environment, in eukaryotes predominantly through the mitochondrial oxidative phosphorylation system (OXPHOS) – fuelling cellular activities, supporting growth, reproduction, and maintenance of homeostasis. Since unravelling the OXPHOS system in 1961, the unique features of mitochondrial genetics and function, and the interplay with glycolysis and other metabolic reactions as key players in bioenergetics, have been revealed. The involvement of bioenergetics in the most common inherited metabolic, but also several non-communicable, and infectious diseases, has been established. In fact, mitochondrial bioenergetics have been implicated, either in a primary or secondary way, in four of the ten most common causes of death in humans, fuelling generalizing hypotheses such as the "mitochondrial bioenergetic aetiology of disease" hypothesis.

More than 50 mouse models of deficiencies of the OXPHOS system to study primary mitochondrial disease (MD) - a highly heterogeneous inherited disease affecting ~1 in 5,000 newborns – have been developed to study human disease phenotypes, gene function, pathophysiology, and treatment strategies. Although these models present with the hallmark MD syndromes and phenotypes in humans, affecting various tissues requiring energy, they also lead to a diversity of phenotypes associated with immunological, metabolic, degenerative diseases, cancer, and aging - illustrating the range of consequences of progressive bioenergetic decline. To better understand the factors affecting this significant variation, we present metabolomics and enzymology data from urine and various tissues from an nDNA mouse model (Ndufs4 knockout), as well as urine from an mtDNA disease model (Mitomice), illustrating the metabolic variation and tissue dependence of this debilitating disease.

Paternal influence on offspring health: a touch for life

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Paternal intergenerational effects are highly conserved. In mammals, the sperm epigenome, as well as the composition of the seminal fluid are sensitive to the environment and influence offspring health. The best known of these mechanisms are DNA methylation and small non-coding RNAs in spermatozoa and the balance between inflammatory and tolerogenic cytokines in the seminal fluid. Small non-coding RNAs are mostly acquired by maturing spermatozoa during the epididymal transit from extracellular vesicle of epididymal epithelial origin.

We use two paternal paradigms of pre-conceptional challenge in wild-type C57BL6 mice: high-fat diet feeding for 2 weeks and circadian disruption for 4 weeks before conception. The duration of the environmental challenges has been chosen to meet timing of sperm maturation in the mouse (high-fat diet) or to be the minimum sufficient to induce circadian disruption without overt side effects. Exposed males and their offspring have undergone deep metabolic and molecular phenotyping.

Paternal circadian disruption leads to gender-specific hyperphagia, hyperglycemia, hypercorticosteronemia and partial circadian disruption in unexposed male offspring. Mechanistically, mouse seminal fluid contains corticosterone, whose appearance dynamic follows the organismal circadian rhythm and is blunted upon circadian disruption. Offspring phenotypes are sensitive to the levels of corticosterone in the seminal fluid and consequential to impaired placental function and fetal growth restriction.

Paternal exposure to acute high-fat diet, instead, leads to a male-specific and 30% penetrant glucose intolerance phenotype. Mechanistically, this is linked to a burst of mitochondrial DNA transcription in spermatozoa. Mitochondrial-encoded small non-coding RNAs accumulate in spermatozoa, are inherited at fertilization, and reprogram early embryo transcription towards premature activation of oxidative metabolism. Importantly, phenotypes and mechanisms are conserved in highly characterized human cohorts.

These studies strengthen the importance of paternal health at conception for pregnancy and offspring health and identify germ-cell and non-germ cell factors as potential mechanistic mediators.

Hypermethylation of the BRCA1 promoter in Black African women with early-onset breast cancer

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Introduction:
Breast cancer (BC) remains the most frequently diagnosed female malignancy worldwide. Over the years, the BC burden has shifted to low- and middle-income countries and Africa currently has the highest age-standardized BC mortality rate in the world. Ethnic variations in BC mortality exist, with African women presenting with more aggressive BC and a higher mortality rate compared to Caucasians. Most BC cases develop due to a complex interplay between genetic, lifestyle and environmental factors and it is plausible that epigenetic mechanisms are involved. While the development of next generation sequencing (NGS) has led to rapid advances in understanding epigenetic mechanisms underlying BC etiology, women of African ancestry remain underrepresented in the literature. To address this knowledge gap, the present study aimed to investigate DNA methylation signatures associated with BC in Black African women.

Materials and Methods:
Black African BC patients were recruited from the Inkosi Albert Luthuli Central Hospital in KwaZulu Natal, South Africa. DNA methylation differences between breast tumours and healthy adjacent tissue were analysed using NGS and pyrosequencing. The association between DNA methylation changes and patient clinicopathological characteristics were determined using orthogonal partial least-squares discriminant analysis and Spearman/Pearson's correlation coefficients.

Results:
Hypermethylation of six CpG sites within the BRCA1 promoter was observed in tumour versus normal adjacent tissues. DNA methylation differences were most significant in young, premenopausal ($p=0.0134$), obese ($p=0.0087$) women with luminal B ($p=0.0096$), grade II ($p=0.0453$) tumours. Importantly, BRCA1 hypermethylation was independent of the presence of BRCA1 mutations.

Conclusion:
The findings from this study may aid in elucidating key epigenetic alterations underpinning breast cancer in an African population and aid in appropriate interventions and more equitable clinical outcomes to reduce the surging impact of this disease.

Looper, a closed loop feature detection platform for automated neonate cardio-respiratory analysis

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Introduction:
Sudden Infant Death Syndrome (SIDS) is thought to partly result from unseen brain abnormalities affecting cardiorespiratory function, but for which no clear genetic or environmental mechanisms are known. Mouse genetic and exposure models present an opportunity to uncover molecular and environmental mechanisms. However, measuring cardio-respiratory function in neonate mice is expensive, difficult, and inefficient. One major challenge is the time needed to carry out such measurements. The neonate autoresuscitation assay, consisting of repeated anoxic exposures followed by recovery, requires the full attention of an observer for the multi-hour duration of a single subject assay, limiting throughput. To address this, we developed a closed-loop feature detection platform for automated neonate cardio-respiratory measurements.

Materials and Methods:
Our platform (Looper) consists of:
1) a pneumotachograph face-mask for precise respiratory measurements.
2) a micro-controller automated bell-housing gas switching system for rapid induction of respiratory challenges.
3) a micro-computer-based data-acquisition system with closed-loop real-time feature detection and outputs for controlling gas exposure (Physiology Command Center).
4) a data analysis suite that assists with recordkeeping and provides a facile method to extract key outcome measures (Breathe Easy).

Results:
Gas challenges are administered via the rotating bell housing system. A python program detects waveform features in real-time, such as apnea and bradycardia. Upon apnea detection, the system switches to a rescue gas. Resumption of normal breathing and heart rate can also be detected and incorporated into criteria for automated initiation of the next anoxic exposure trial. Data is stored for later offline automated analysis using the data analysis suite.

Conclusion:
The system offers a relatively inexpensive approach for automated high throughput neonate cardio-respiratory assessment. The improvements permitting increased throughput and reduced variation in experimental parameters make the system suitable for screening of genetic and exposure risks as well as potential therapeutics for SIDS..

A high fat high sugar diet induces Insulin-like Growth Factor 2 hypermethylation in male Wistar rats

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Introduction:

The prevalence of obesity and insulin resistance (IR) has increased at an exponential rate worldwide. Although several mechanisms such as dysregulation of the epigenome have been implicated, the disease pathophysiology remains to be fully elucidated. The primary objective of this study was to elucidate DNA methylation profiles and gene regulatory networks that are altered in the skeletal muscle (SM) during the development of obesity and IR in male Wistar rats.

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Materials and Methods:

Male Wistar rats (n=20) were fed either a high fat, high sugar (HFHS) or a standard diet (STD) for 12 weeks. SM was harvested for histology, gene expression measured using RT2 Profiler™ PCR arrays and Taqman® assays and global and gene-specific DNA methylation were quantified using pyrosequencing.

Results:

Rats in the HFHS group gained more weight (567.5 ± 8.8 vs 474.0 ± 10.5 g, $p < 0.0001$) and had increased insulin concentrations (6.1 ± 0.9 vs 3.8± 0.6 ng/ml, $p < 0.05$) compared to the STD-fed rats, while no histological differences were noted. Increased expression of Insulin-like growth factor 2 (Igf2) was associated with HFHS diet exposure. Whilst no global DNA methylation changes were observed, we identified hypermethylation of an intronic CpG site within Igf2 ($p < 0.01$). In silico analysis identified binding sites for transcription factors CCCTC-binding factor (CTCF), Myogenin and myoblast determination protein 1 (MYOD) within close proximity to the hypermethylated CpG.

Conclusion:

This study provides information about dysregulated DNA methylation and gene expression signatures during the progression of obesity and IR in SM.

A high fat, high sugar diet induces hepatic Pgc1a hypermethylation in male Wistar rats

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Introduction:
High fat, high sugar (HFHS) diet feeding has been shown to induce adiposity, hyperinsulinaemia, hyperleptinaemia, hypertriglyceridaemia and increase liver mass in male Wistar rats. These changes may cause or arise from changes in DNA methylation of hepatic glucose and lipid-associated genes. In the present study, we investigate the mechanisms underlying the increased liver mass by assessing hepatic lipid accumulation and the expression and methylation status of key metabolic genes using histology, quantitative real-time PCR and pyrosequencing, respectively.

Results:
The HFHS diet induced hepatic steatosis, increased hepatic triglycerides (1.8-fold, $p<0.001$), and increased the expression of sterol regulatory element-binding transcription factor 1 (Srebf1) (2.0-fold, $p<0.001$) and peroxisome proliferator-activated receptor gamma (Pparg) (1.7-fold, $p=0.017$) in the liver. The expression of peroxisome proliferator-activated receptor gamma coactivator 1 alpha (Pgc1a) was decreased (2.6-fold, $p<0.010$), which was accompanied by hypermethylation ($p=0.018$) of a conserved CpG site in the promoter of Pgc1a in HFHS fed rats compared to controls. In silico analysis identified putative binding sites for CCAAT/enhancer-binding protein beta (C/EBPß) and hepatocyte nuclear factor 1 (HNF1) within proximity to the hypermethylated CpG.

Conclusion:
Hypermethylation of this conserved CpG site in the promoter of Pgc1a may be a possible mechanism underlying the development of hepatic steatosis in response to a HFHS diet.

Epigenetic profiling in South African women with Gestational Diabetes Mellitus

Epigenetic profiling in South African women with Gestational Diabetes Mellitus

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Methods:

In this cross-sectional study, 181 women with (n=63) and without (n=118) GDM were recruited at Steve Biko Academic Hospital at <28 weeks of gestation. Gene-specific DNA methylation was quantified from peripheral blood using pyrosequencing assays. Three CpG sites corresponding to genes, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PPARGC1A), protein tyrosine phosphatase receptor type N2 (PTPRN2) and Insulin gene enhancer protein (ISL1), were selected based on significance from previous genome-wide data and relevance to GDM pathophysiology. In silico analysis was performed using ALIBABA 2.1 and ALGGEN-PROMO to identify potential transcription factors that bind within the region spanning the CpG site.

Results:

Differentially methylated CpG sites of interest were validated in intron 1 of PTPRN2, intron 1 of PPARGC1A and exon 1 of ISL1. DNA methylation levels were significantly increased for ISL1 gene, important for the regulation of insulin gene transcription, at two CpG sites CpG5 (-9271) and CpG7 (-9277) in women with GDM ompared to women without GDM. Transcription factors, E2F transcription factor 1 (E2F-1), Wilms tumor 1 (WT1) and GC factor (GCF), known to play a role in cell signalling, development and metabolism, binds to specific GC-rich sequences between the methylated CpG sites of ISL1.

Conclusion:

This study showed gene-specific DNA methylation differences in women with GDM, which validated our previous genome-wide findings. Further analysis in an in vitro model of GDM will be conducted to determine the biological significance of ISL1 differential methylation in GDM pathophysiology.

Epigenetic profiling in South African women with Gestational Diabetes Mellitus

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Conclusion:

This study showed gene-specific DNA methylation differences in women with GDM, which validated our previous genome-wide findings. Further analysis in an in vitro model of GDM will be conducted to determine the biological significance of ISL1 differential methylation in GDM pathophysiology.

Diet-Induced Cardiovascular Disease: Insights from Whole Genome Bisulfite Sequencing in Wistar Rats

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Several mechanisms have been implicated in the pathogenesis of diabetic-induced cardiovascular disease (CVD), and recently, increasing evidence suggests that dysregulation of the epigenome may play an important role. More specifically, DNA methylation, an epigenetic modification responsible for gene transcription regulation, has been extensively investigated and implicated in the development of chronic diseases such as obesity, type 2 diabetes (T2D) and CVD. This study therefore firstly explored the gene expression networks activated during diet-induced CVD and the ability of a green rooibos extract, Afriplex GRTä, to alter this consequence. Secondly, the study aimed to evaluate aberrant DNA methylation associated with diet-induced CVD to further elucidate pathophysiology. RNA sequencing conducted on the hearts of Wistar rats exposed to a high fat, high sugar (HFHS) diet revealed a downregulation of genes involved in antioxidant activity and inflammatory response, along with an increase in the expression of hypertrophic genes. Supplementation with Afriplex GRT™ yielded no high confidence results for the amelioration of the transcriptomic signatures resulting from HFHS diet feeding. To profile DNA methylation throughout disease progression, cardiac tissues of male Wistar rats fed a HFHS diet were subjected to whole genome bisulfide sequencing. Data revealed aberrant DNA methylation of genes linked to phagosome, platelet activation, toll-like receptor signaling and diabetic cardiomyopathy. Collectively these results demonstrate the ability of the HFHS diet to act as a pathological stimulus capable of inducing altered gene expression and DNA methylation associated with increased risk of CVD development.