On behalf of the South African Medical Research Council (MRC), I welcome all of you to the MRC Awards presentation to celebrate excellence in medical research and to honour the outgoing MRC Board and welcome members of the new Board.

In revitalising the MRC, we recognised the need to strive for scientific excellence and to set benchmarks that show we are leading medical research in South Africa. One of the things we did was to establish the prestigious Flagship Projects that was applicable to South African Universities and MRC intramural research units. This evening, we are pleased to announce the names of the successful applicants and their institutions. A flagship project is an institution’s highest impact and most prestigious research project. They are “big ideas, big science for big impact”.

In keeping with its revitalised mandate to support excellence in health research, the MRC established a set of medal awards to recognize world-class science. The awards are among South Africa’s most prestigious and are dedicated to those who contribute to health research in South Africa. This evening we pay tribute to the winners for their outstanding contributions to medical research.

We also take this opportunity to thank the outgoing MRC Board and welcome the new Board members. The outgoing Board under the leadership of Prof Lizo Mazwai deserve a huge note of thanks for their fortitude as they led the organisation through the most challenging time in our existence.

In closing, I thank you all for your presence and wish each and every one of you a wonderful evening in celebrating the dawn of a new era for the MRC.
Awards

MRC SCIENTIFIC ACHIEVEMENT MERIT AWARDS
Awards

The South African Medical Research Council strongly supports excellence in health research and has established a set of awards to recognise world-class science. The Awards are among South Africa’s most prestigious and are dedicated to contributions to health research in South Africa.

There are 3 types of scientific awards: Platinum Medals for lifetime achievement, Gold Medals for senior researchers who have made seminal scientific contributions and Silver Medals for recent post-doctoral researchers who have made substantial scientific contributions. For each of these scientific awards, candidates are considered in each of two categories; 1) Scientists in MRC intramural or extramural units and 2) Scientists who are not in MRC units. In addition, there is a MRC President’s Award for contributions to health research in South Africa.

1. **MRC YOUNG SCIENTIST AWARD (Silver Medal)**
   Silver medals are awarded annually to up-and-coming scientists (at post-doctoral level) who have made important scientific contributions within 10 years of having been awarded their PhD or MBChB/dental equivalent.

   The Silver Award is a Scientific Achievement Award for a younger researcher who recently completed a doctoral/medical/dental degree.

2. **MRC SCIENTIFIC ACHIEVEMENT AWARD (Gold Medal)**
   Gold medals are awarded annually to established senior scientists who have made seminal scientific contributions that have impacted on the health of people, especially those living in developing countries.

   The Gold Award is a Scientific Excellence Award.

3. **MRC LIFETIME ACHIEVEMENT AWARD (Platinum Medal)**
   Platinum medals are awarded each year to accomplished scientists for outstanding lifetime scientific achievement in the field of health. Platinum medals are awarded to South African citizens who have made multiple seminal scientific contributions and who have also made an impact on local and/or global health and/or science policy and/or clinical practice that impact on the health of people, especially those living in developing countries. As the MRC’s highest scientific award, it recognises outstanding scientists who have had a sustained scientific impact over many years and have helped build the foundations of health research in the country for future generations.

   The Platinum Medal is a Lifetime Achievement Award.

4. **MRC PRESIDENT’S AWARD FOR EXCEPTIONAL CONTRIBUTIONS TO MEDICAL RESEARCH**
   The Award is made, at the discretion of the MRC President, in recognition of exceptional contributions to medical research and is among the highest honours bestowed by the MRC.
Dr Doherty is a Senior Specialist Scientist in the Health Systems Research Unit at the MRC. Despite being a young researcher she has a well-established research focus and identity in the field of child health and HIV. Her research has made important contributions to the evidence around operational effectiveness of PMTCT and infant feeding policies and she has been at the forefront of open debate and policy discussions in leading high impact journals. Her research has been used in the GRADE process to inform changes to WHO guidelines on HIV and infant feeding, and influenced South African National Department of Health guidelines. She is also the only scientist in the MRC Health Systems Research Unit with NRF rating.

Since completing her PhD in 2006 Dr Doherty has rapidly built up a strong publication record with over 40 peer reviewed papers. The citation record of her work illustrates the importance of her research on child health and HIV which is a priority area for research locally and internationally.

Her leadership in the field of child health is also clearly evidenced by the invitations she receives to speak at local and international conferences. She was an invited keynote speaker at a national ministerial consultation on breastfeeding in 2011, and has been the invited author for the chapter on PMTCT for the District Health Barometer publication of the Health System’s Trust annually since 2006. She is currently leading further work for UNICEF reviewing child survival intervention programmes in 6 other African countries.
Prof. Abrahams is a Senior Specialist Scientist in the Gender and Health Research Unit, which has been acknowledged as world leaders on gender-based violence and health research.

When Prof. Abrahams started gender-related research 18 years ago, gender was trivialised in the health field. However, by working with colleagues such as Prof. Rachel Jewkes, they ensured that their use of rigorous research methods and publications in leading journals, such as Science and the Lancet, and publishing in the World Health Organisation Report, contributed to the change that we see today.

In recognition of her research, she has received two honorary appointments: an Honorary Associated Professor with the University of Cape Town’s Faculty of Health Sciences in the School of Health and Rehabilitation Sciences, as well as Extraordinary Professor with the University of the Western Cape, Faculty of Community Health Sciences in the School of Public Health.

Over the past 20 years, Prof. Abrahams has made significant contributions to and provided leadership on gender-based violence research. Her PhD research measured male perpetration of violence against intimate partners. At the time, this was one of the first studies globally to focus on men. Naeemah has also made unique contributions to the research on intimate femicide in South Africa and globally, developing a method that has been hailed internationally. Naeemah’s contributions now mean that her research expertise in femicide, sexual violence and sexual assault is now recognised globally.
Prof. Meintjes is an Associate Professor in the Department of Medicine and a member of the Institute of Infectious Disease and Molecular Medicine (IDM) at UCT. He is an adult infectious diseases physician who completed his specialisation in internal medicine and infectious diseases at UCT and jointly established a busy infectious diseases referral unit at GF Jooste Hospital in Manenberg in 2004.

Prof. Meintjes is an exceptional mid-career researcher and the findings of his research have played a seminal role in defining clinical approaches and broadening understanding of a condition that has recently emerged (TB-IRIS), and improving treatment strategies for cryptococcal meningitis. His work has also informed evolving treatment guidelines for ART in South Africa and internationally.

For example, Prof. Meintjes was the lead investigator of a pioneering randomised placebo-controlled trial of prednisone for the treatment of TB-IRIS. This was the first, and to date, the only clinical trial to test a treatment strategy for IRIS. The trial findings provide the evidence-base for treating TB-IRIS globally, and have impacted national and international guidelines including the NIH-CDC-HIVMA/IDSA Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents.

In collaboration with the International Network for the Study of HIV-associated IRIS, Prof. Meintjes developed international consensus case definitions for TB-IRIS. These case definitions have played a major role in standardising research approaches to this condition, and have also assisted clinicians in the field in making diagnoses of TB-IRIS.
Prof. Chibale currently holds the DST/NRF SARChI Chair in Drug Discovery. Over the past five years, Prof. Chibale has made seminal contributions that have impacted on health, especially in developing countries. Most significantly, he led a project team that discovered the first clinical candidate, for any disease, researched on African soil by an African drug discovery centre. This team discovered a clinical candidate molecule with the potential to be used as part of a single-dose cure for malaria. The discovery of this malaria drug candidate was mentioned in the State of the Nation Address given by President Jacob Zuma earlier this year. The discovery, and Professor Chibale were featured this year in *Nature Medicine* under the headline ‘Made in Africa’, and received the 2012 Medicines for Malaria Venture Project of the Year award.

Over the past 10 years, Prof. Chibale has been acknowledged for his outstanding contributions to science, technology and innovation, specifically being recognised for establishing Africa’s first integrated modern drug discovery centre – the H3-D Centre at UCT – and for establishing various modern technology platforms for the discovery of potential medicines. In this context, the pharmaceutical company Novartis has signed a collaboration agreement with UCT for H3-D to work with the Novartis Institutes for Biomedical Research. This will go a long way to bridging the gap between basic science and clinical research, with the aim of advancing innovative medicines that treat African patients.
Prof Kengne is Director: Non-Communicable Diseases Research Unit at the MRC. Prof Kengne is an established researcher on chronic diseases with a major focus on cardiovascular and metabolic diseases. His leading role on these conditions in Africa is well-recognised and his expertise at the global level is increasingly acknowledged.

Internationally, Prof Kengne has made a significant contribution to improving the understanding, quantification and reduction of cardiovascular diseases risk in people with diabetes. For example, he has contributed to the development of a new and improved model for estimating cardiovascular disease risk in contemporary populations with diabetes. This model, which was the highlight of the World Diabetes Congress in 2011, has been made available as a handheld or online calculator, and is being promoted in several countries around the world.

Over the past two years, Prof Kengne has co-led a programme of research that has provided unparalleled evidence on the increasing burden of cardiometabolic disease among mixed ancestry South Africans. The results of this work are increasing awareness on the need to improve prevention of cardiometabolic diseases in this population. Some of this work is being used as the background of the African chapter in the forthcoming edition of the World Diabetes Atlas by the International Diabetes Federation.

Prof Kengne has co-authored over 130 peer-reviewed scientific papers, several conference abstracts and book chapters. He currently chairs the taskforce on Nutrition of the Pan-African Society of Cardiology and is member of many scientific bodies and committees.
Prof. Dheda is a professor of respiratory medicine, and Head of Division of Pulmonology, Department of Medicine at UCT and at Groote Schuur Hospital. During his research career, Prof. Dheda has made substantial contributions to the management and control of drug-resistant TB in South Africa. He has been internationally recognised for this by being awarded the 2010 International Union Against Tuberculosis and Lung Disease Scientific Award.

XDR-TB threatens to destabilise TB control in South Africa and several other regions of the world. However, there is hardly any data on which to base policy recommendations. The work that Prof. Dheda has published in the Lancet, together which other research results have shaped clinical definitions for treatment failure in XDR-TB, provided specific guidelines on how XDR-TB patients should be managed, and provided valuable data that informs and guides management decisions by the national TB programmes from resource-limited settings.

His work that demonstrated an increased risk for health-care workers developing drug-resistant TB makes it imperative that governments now take immediate measures to provide the resources required to enable all hospitals and clinics to implement the recommended WHO infection control procedures, which will go a long way to protect health-care workers and their patients from acquiring MDR/XDR-TG. Prof. Dheda’s report also heightens the urgency for all health facilities and laboratories to be equipped with the newer diagnostic testing platforms, so that all patients and health-care workers can be rapidly identified and appropriately isolated to minimise the risk of transmission within hospitals and the community.

This week he led a team, which published their findings in The Lancet showing that placing new rapid TB diagnostic technology (Gene Xpert) in a clinic was feasible when testing is performed by a nurse and this approach led to rapid diagnosis of drug-resistant TB and more patients being placed on treatment. The findings suggest that a health care worker-led diagnostic strategy could be useful to fight the disease in TB hotspots in the country.
PROFESSOR SHABIR MADHI (MRC)

Prof. Madhi is Director: National Institute for Communicable Diseases, Director: MRC’s Respiratory and Meningeal Pathogens Research Unit, Professor of Vaccinology: Wits, and holds a DST/NRF Chair: Vaccine Preventable Diseases. Prof. Madhi is an internationally recognised clinical-scientist in his field of vaccinology and respiratory and meningeal pathogens.

Prof. Madhi’s involvement in pneumococcal conjugate vaccines and on rotavirus vaccine studies has contributed to the WHO advocating the importance of these vaccines in improving child health and recommending their routine use in developing countries, including in settings with a high prevalence of HIV infection. This research also contributed to advocacy that led the South African government to be the first in Africa to introduce these vaccines into the public immunisation programme since 2009, an initiative which is expected to save the lives of approximately 6000-7000 South African children annually, particularly in communities with limited access to curative health-care facilities.

His work has been particularly relevant to sub-Saharan African countries with their high burden of HIV-infection, where he has established himself as a leader in research on the effect of childhood HIV on the epidemiology of pneumonia and the safety, immunogenicity and efficacy of vaccines for this vulnerable population. Prof. Madhi has made and continues to make a huge contribution to improving child health not only in South Africa but throughout Africa and in developing countries.

Prof. Madhi’s international standing is such that he was listed among the ‘100 World Class South Africans’ in the City Press in April of this year, a list that has included luminaries such as past presidents Nelson Mandela and Thabo Mbeki.
Emeritus Professor Bateman is Director: UCT Lung Institute, and honorary consultant at the Division of Pulmonology at UCT. He has an outstanding record as a clinician scientist in South Africa in the field of pulmonology and related topics. He is highly regarded internationally and is in great demand as a speaker, collaborator and consultant in working groups. Prof. Bateman is an international leader in research areas of asthma, chronic obstructive pulmonary disease in developing countries, and in research and implementing methods for improving primary health care for chronic and infectious diseases in resource-poor settings.

Prof. Bateman showed his remarkable leadership qualities in raising funds for and building the UCT Lung Institute on the Faculty of Health Sciences Campus, and has run it for the last 13 years funded entirely from research. Even more remarkable has been its growth and research output under his directorship and research leadership. The motivation behind his development of the Lung Institute was to engage in population-wide interventions to improve respiratory care in South Africa. Over the past 13 years, what began as an intervention for assisting frontline clinicians in the integrated care of chronic respiratory diseases has developed into Primary Care 101. Developed over the past three years, this has now been accepted by the Minister of Health as the centre piece of his rejuvenation project for primary care clinics and is being rolled out country-wide.

Prof. Bateman’s full research record confirms Professor Bateman’s status as a clinician-researcher whose lifetime contribution to medical research both nationally and globally has been remarkable in its breadth and depth.
Prof Paul van Helden obtained his doctorate in Biochemistry in 1978 and has been at Stellenbosch University since 1979 where he is presently professor and head of the division of Molecular Biology and Human Genetics and also Director of the MRC Centre for Molecular and Cellular Biology, as well as Director of the DST/NRF Centre of Excellence for Biomedical TB Research.

He has been awarded the Vice-Chancellors’ award for Excellence in Research (Univ. Stellenbosch 2000); the Gold Medal Award, South African Society for Biochemistry and Molecular Biology 2001; the MRC Silver Medal for Research in 2004; the NSTF Award for Outstanding Contribution to Science and Technology in the RSA over 5 years in 2005; and the Gold Medal of ASSAF in 2009.

He has published over 300 research publications and has extensive global networks. He was recently listed as having the 4th highest impact in TB research publishing by ThomsonReuters.

Prof van Helden describes his efforts as attempting to develop a continuum of activities to span the divide between basic research and clinical practice. Molecular TB research at CMCB and Stellenbosch University was initiated by Prof van Helden in 1989, with one PhD student. His main research interest is tuberculosis ranging from diagnostics, through immunology and genetics, to clinical trials and veterinary TB. This interest has grown and is now a major focus area of the division and faculty and sole focus of the CMCB.

Apart from generating a large sample bank which some have described as an “international heritage site”, he has achieved many firsts, such as the description of reinfection and mixed infection as a real and considerable phenomenon in TB.

His work showed that one can use modern molecular biology in a developing country to good effect, particularly for diagnosis of drug resistant TB, and his team paved the way for the introduction of such technologies, now being used in state diagnostic labs.

He also led the team to develop useable technologies for speciation of the M. tuberculosis complex and other members of the genus Mycobacterium, which were used in a huge prevalence survey in the RSA and Zambia recently.

His work has placed Stellenbosch University at position 20 in the top 20 research institutions globally in TB research. He has been ranked 4th globally in terms of total impact for TB research.

Prof van Helden has built up a world-class research centre focussing on tuberculosis. This has been achieved by allowing each member of the team guidance but freedom to achieve in their own niche. Many of the people in the CMCB are now globally renowned in their own right. Over the last few years he has moved his name from last authorship to allow for building the CV’s of group leaders who then become the senior author. This is essential to build capacity and allow succession. There is no doubt that Paul van Helden has put South African research on the TB world map.
Award
FOR EXCEPTIONAL CONTRIBUTIONS TO MEDICAL RESEARCH

PROFESSOR MALEGAPURU WILLIAM MAKGOBA

Prof Makgoba has made an outstanding and lasting contribution to South African medical science, holding up and enhancing the reputation of science in this country and in the international community, and encouraging and supporting young scientists. He continues this service now as Vice-President for Planning and Review of the Paris-based International Council for Science.

Prof Makgoba’s contributions to medical science are vast and numerous. He served as President of the MRC during the difficult years of AIDS denialism in South Africa. Under Prof Makgoba’s guidance, the MRC became a considerable larger and more efficient institution, ensuring the relevance for South Africa of many of the research programmes supported and fostered by the MRC. He has insisted on the highest ethical standards in the conduct of medical research and has had a major influence in the transformation of the South African science landscape. The South African AIDS Vaccine Initiative was an original and model example for public-private partnerships to conduct important basic and applied research.

Prof Makgoba has at times stood for scientific integrity against considerable interference when, for example, he stood up against the pressures applied to him for calling an end to the unscientific and damaging ideas about the non-infectious causes of HIV/AIDS. Had he not done so, South Africa would have been ridiculed by the international scientific community. It is his clarity and forthrightness in dealing with these and other issues that have done much to guard the reputation of South African science and medicine.
Flagship Awards
Cardio-metabolic diseases are increasingly common worldwide, and disproportionately affect people in developing countries. Furthermore, within developing countries such as South Africa, the cardio-metabolic traits are increasingly common among disadvantaged or previously disadvantaged populations who were thought to be at lower risk of such conditions. For instance, recent data have shown that the prevalence of diabetes (28.2%) in the mixed ancestry (coloured) population has more than doubled just within a decade. Moreover, about 2/3rd of those with the disease (18.1%) are not aware of their condition, and are therefore not receiving interventions with proven benefits on the adverse health consequences of diabetes. Similar trends are also reported in Black South Africans. The increasing diabetes figures around the world have been largely attributed to the environmental changes that promote the adoption of unhealthy behaviours and development of obesity which in turn is implicated in insulin resistance, inflammation, and subsequent progression to diabetes mellitus and cardiovascular diseases. However, available data suggest that the distribution of traditional diabetes risk factors such as obesity is not appreciably different between mixed-ancestry South Africans with diabetes or at high future risk of diabetes, as compare with those without the disease, or who do not progress to the disease stage in the future. This failure of traditional factors to fully explain or to explain most of the risk of diabetes among mixed-ancestry South-Africans indicate the need for more research efforts into identifying the context specific diabetes risk factors and the pathophysiological pathways linking them to diabetes occurrence. These efforts are needed to assist the formulation and implementation of effective detection, prevention and control strategies for diabetes in this population. Emerging data from around the world support the pivotal role of chronic inflammation in the occurrence of diabetes mellitus and related complications. However; determinants and key players involved in diabetes related inflammations vary across populations and are yet to be investigated among South Africans. Therefore, the overarching objective of this flagship project is to investigate the connections of low-grade inflammation with diabetes risk and subclinical cardiovascular disease among coloured South Africa. This will be achieved by conducting a population-based survey targeting the recruitment and examination of about 5000 adult mixed-ancestry South Africans across selected townships in the metropolitan city of Cape Town. A combination of whole study participants and nested case-control approaches will be used to carefully examine each of the research objectives, and provisions made for long-term follow-up using approaches previously piloted by our group. It is expected that this study will help uncover diabetes in about 900 people based on a prevalence of undiagnosed diabetes of 18%, who will then enter the healthcare system for follow-up and mitigation of risk of complication. The contribution of low-grade inflammation to diabetes risk in this population will be established and the genetic-environmental, genetic-epigenetic enablers characterized. The results from this study may also be applicable to other emerging ethnic groups who are in a state of economic transition.
The isolation of the crystalline ‘active principle’ 青蒿素 or artemisinin from the traditional medicinal herb 青蒿 (Artemisia annua), and its conversion into derivatives by Chinese scientists represent one of the great events in medicine in the late 20th Century. Artemisinins are highly active against all blood stages of the malaria parasite, including those of the most dangerous, Plasmodium falciparum (Pf). They are now used worldwide for treatment of malaria in combination therapies (ACTs) with longer half-life antimalarial drugs such as mefloquine. Artemisinins are also active against Mycobacterium tuberculosis (Mtb), the pathogen of tuberculosis, and the ubiquitous parasite Toxoplasma gondii (Tpg) that causes toxoplasmosis, an opportunistic co-infection of HIV-compromised individuals.

Our group has been engaged for some time in the preparation of rationally-designed new artemisinin derivatives: one such, artemisone, was threefold more efficacious than a current artemisinin in curing non-severe malaria patients in Thailand. It was also active against Tpg and yet another derivative possessed useful activity against Mtb in vitro. The cytotoxicity of artemisinins is due to their rapid oxidation of reduced flavin cofactors of flavoenzymes otherwise required for critical intracellular functions: the oxidation results in immediate abrogation of enzyme activity with the consequence of rapid buildup of cytotoxic reactive oxygen species (ROS). This oxidant action is amplified by a redox drug. This drug through cycling through a reduced form that is re-oxidized by oxygen to generate the original drug and ROS thereby maintains activity over a relatively protracted period. This is illustrated by methylene blue (MB); this affects the same flavoenzymes and directly contributes to ROS generation through intracellular oxidation of its reduced form leucomethylene blue by oxygen. The closely-related redox drug clofazimine (CFZ) inhibits an essential respiratory flavoenzyme of Mtb, and thereby is active against multidrug resistant Mtb. Just as for MB, redox cycling mediates formation of ROS. The focus is on malaria, TB and related diseases that involves collaborating groups at centres in South Africa and internationally. Thus, redox drugs will be rationally combined with oxidant drugs comprising newer artemisinins, and a third drug. Undesirable properties of MB and CFZ will be bred out by synthesis of derivatives and/or analogues and other redox drugs. These chemical activities will be coupled with development of clinically-approved formulations that enhance efficacies and ameliorate toxicities. The artemisinins and redox compounds including formulations will be screened against Pf, and relevant Pf flavoenzymes to ensure ‘proof of principle’. Screening against Mtb will entail enzyme assays, in vitro assays, and macrophage and others involving quiescent Mtb. Known or new lead compounds/combinations will be screened against MDR and XDR Mtb. In vivo screening of lead compounds/formulations will use established animal models for malaria, TB and TXP. For new drugs, preclinical toxicology and Phase I/II trials will eventuate under follow up programmes. The work will greatly enhance capabilities for the conduct of drug research and development in South Africa, and a successful outcome will confer treatment benefits on a world-wide basis.
Professor Heinrich Hoppe, Rhodes University

The Centre for Chemico- and Biomedicinal Research (CCBR) represents a major strategic initiative at Rhodes University, involving more than 20 academic researchers from the departments of Chemistry, Biochemistry and Microbiology and the Pharmacy faculty. The overall purpose of the CCBR is to articulate individual medicinal research activities at Rhodes into an integrated platform for the discovery of drug lead compounds from synthetic and natural sources. In spite of encouraging progress across several fronts, meaningful realisation of the Centre’s potential has encountered three obstacles that are common in academic drug discovery programmes throughout South Africa:

i) Reliable access to bioassays for the evaluation of the biological activity of compounds produced by CCBR and allied scientists. This has proved the most persistent bottleneck in individual medicinal chemistry projects.

ii) The identification of novel drug targets through molecular cell biology research that can feed into the programme. Current projects have to rely on well-established targets that are also pursued by other groups worldwide.

iii) Synchronisation of the activities of individual participants in multi-disciplinary projects. Fluctuation in funding and resources in individual research groups often disrupt their ability to fluently complement each other in pursuit of common project goals.

The Flagship project will address these obstacles by integrating bioassay capacity, existing medicinal chemistry programmes and target discovery through basic cell biology research. In particular, it aims to establish a dedicated bioassay facility capable of rapidly and rigorously assessing the therapeutic potential of compounds produced by CCBR and associated programmes in the Eastern Cape region. In addition, it will explore critical aspects of the molecular cell biology of cancer cells (particularly cancer stem cells) and malaria parasites to identify and validate novel drug targets for these diseases. This would not only provide a seminal contribution to fundamental knowledge of these diseases, but the opportunity to initiate uniquely South African target-based drug discovery projects. Finally, the project will supplement existing multi-disciplinary CCBR projects aimed at the discovery of lead compounds for malaria, HIV/AIDS and cancer from synthetic chemicals and natural product sources, in order to ensure that all contributing groups are sufficiently resourced to interdigitate seamlessly. The Flagship project is further strengthened by dovetailing with the objectives of the recently awarded SARChI chair in Marine Natural Products at Rhodes University. The chair programme builds on the strong tradition of marine and aquatic research at Rhodes and aims to explore the rich biodiversity of South African marine invertebrates and the microbial flora that inhabit them (particularly in the Algoa Bay region) for novel molecules with pharmaceutical potential.
Flagship Project

HIGH ENERGY X-RAY BEAM ADVANCED RADIATION DOSIMETRY AND VERIFICATION (HARD)

Dr Frederik du Plessis, University of the Free State

In this project we strive as a Medical Physics Department to play a leading role in central South Africa, to develop: research capacity building, solving of current radiation treatment planning issues, and development of leaders in research and critical thinking.

In terms of current scientific challenges we will address the following: Improved radiation beam modelling for linear accelerators using Monte Carlo particle transport techniques. Implementation of radiation source models for improved cancer radiation treatment planning accuracy, and address Electronic Portal Imaging Device based beam quality assurance (QA).

QA challenges in Intensity Modulated Radiation Therapy and Intensity Modulated Arc Therapy are also addressed with much work to be done in these areas of medical physics. During the process it is envisioned that at least 18 Post graduate scholars will obtain Masters and Ph.D. degrees obtained through research in current Medical Physics problems. This will be accomplished with state-of-the art equipment.
Flagship Project

COMPREHENSIVE BACTERIAL ANALYTICAL TOOLKIT FOR TUBERCULOSIS RESEARCH (COMBAt-Tb)

Professor Alan Christoffels, University of the Western Cape

Functional genomics is a branch of genomics that determines the biological functions of genes using large volumes of data obtained through high-throughput techniques categorized under the umbrella of transcriptomics, proteomics and genomics. Collectively the analyses underpinned by these ‘omics approaches converge on a systems biology rationale to understand the functions of an organism or in the case of a disease, the mechanisms underlying a disease within an organism. The successful exploitation of this diverse biological data relies on the interactions of researchers in mathematical, computational, statistical and biomedical sciences.

The use of ‘omics technologies is increasing in South Africa. Yet, the South African competitive edge can only be realized with the development of computational algorithms to rapidly synthesize this rich genetic resource and be accessible as a user-friendly interface for a biomedical researcher. There remains a need to train biologists with similar skills to meet the demands of a post-genomic era in South Africa and on the African continent in a resource-limited setting. Our ability to rapidly analyze the unique datasets in South Africa will shape our technology innovation strategy. The dilemma of a lack of human capital resources to carry out large-scale computational biomedical analyses underlies the dichotomy of making Africa’s unique genetic resources available to the international community and at the same time have the opportunity to answer specific research questions governing our local context.

The proposal sets out to address two needs that face researchers around the world but specifically impacts research development on the African continent, namely; (i) access to computational tools for rapid deployment in a resource-limiting laboratory; and (ii) access to an integrated environment that will allow researchers to interrogate their in-house data as well as interpret their data in the context of data available in public repositories. These two needs might appear to be disconnected but in reality feed off each other. For example, data repositories or archives provide a space for researchers to store their data in a predefined format. Yet other resources attempt to connect these independent resources in an apparent integrated platform to glean insights from overlapping data. At the same time the upstream steps or protocols that generate all the data that feed these repositories, are not developed in a way that provides a communication layer to the data repositories. Conversely, the data repositories do not necessarily model their storage design based on the range of data types that are being generated using high-throughput technologies. Underlying our integrated knowledge system is a strategy to validate preliminary computational functional predictions of nucleotide variation on the metabolism of TB drugs and the identification of TB biomarkers informed by high throughput sequencing technologies that measure host response to mycobacterial infection.

A multidisciplinary team representing researchers from the Universities of Benin, Cape Town, KwaZulu Natal, Stellenbosch and Western Cape were assembled to deliver on a much-needed platform to support South African and African researchers.
Tuberculous (TB) pericarditis is a severe form of infection with Mycobacterium tuberculosis, causing death or cardiac disability in nearly half of those affected despite antituberculosis chemotherapy. In areas where TB is endemic such as ours, patients with a large pericardial effusion are usually treated empirically with anti-TB medication because the aetiology is tuberculous in 70% of HIV negative, and over 90% of HIV positive patients. This approach, however, is associated with a high case fatality rate of 26% at 6 month. It has been found that unstimulated interferon-γ (uIFNγ) offers superior accuracy for the diagnosis of microbiologically confirmed TB pericarditis compared to new GenXpert MTB/RIF and established diagnostic tools e.g. adenosine deaminase. Furthermore, complete evacuation of pericardial fluid may improve outcome by reducing the likelihood of cardiac tamponade, pericardial constriction and death.

We hypothesise that patients with suspected TB pericarditis randomised to complete percutaneous pericardiocentesis and a positive uIFNγ test for TB will have at least a 15% reduction in major clinical outcomes compared to standard treatment.

The primary objective of the IMPI-2 Trial is to determine the effectiveness of complete percutaneous pericardiocentesis plus uIFNγ testing compared to standard empiric therapy without pericardiocentesis in reducing the composite outcome of death, constriction or pericardial drainage for cardiac tamponade in patients with TB pericardial effusion.

Secondary objectives of the study: (i) to assess the safety of percutaneous pericardiocentesis, (ii) to assess and monitor the management of patients with an alternative diagnosis of pericarditis through the prospective IMPI Africa registry, (iii) to assess the accuracy of uIFNγ, GeneXpert and LAM for TB diagnosis using both a microbiological and a clinical reference standard, and (iv) assess the desirability, feasibility and acceptability of real-time monitoring of adherence to TB medication among study participants.

This is a prospective multicenter randomized trial involving 1630 participants with TB pericarditis; 850 patients will be allocated to invasive diagnostic group and 850 to the conservative group. They will be recruited over 30 months from 27 hospitals in South Africa, and follow the last patient enrolled for 6 months. Patients will be seen at prescribed intervals and followed up for three years. The IMPI Project Coordinating Office at the University of Cape Town will coordinate the study in association with the proposed TB Pericarditis Clinical Research Unit in WSU.

This study will address a very serious complication of tuberculosis, occurring in the young, and will create the capacity and network to address similar important health problems in resource poor settings.
Flagship Project

UNDERSTANDING THE SHARED ROOTS OF NEUROPSYCHIATRIC DISORDERS AND MODIFIABLE RISK FACTORS FOR CARDIOVASCULAR DISEASE (SHARED ROOTS)

Professor Soraya Seedat, Stellenbosch University

SHARED ROOTS is an interdisciplinary flagship project that will investigate the molecular and brain circuitry aetiology of two major categories of chronic non-communicable disease, namely neuropsychiatric disorders (NPDs) and cardiovascular disease (CVD). It will be led by the SU research group IMAGINE (IMaging And Genetics In NEuroscience).

The proposed research design contains integrated and complementary elements from various disciplines: clinical psychiatry, clinical neurology, genomics, bioinformatics, neuroradiology, cardiovascular medicine and physiological sciences. NPDs have multifactorial and polygenic aetiologies and a variable course. These disorders are underpinned by complex and dynamic gene-environment interactions that intervene across the lifespan. Clinical diagnosis on the basis of current clinical criteria remains largely unsatisfactory as firstly, these disorders are characterised by marked phenotypic heterogeneity and secondly, diagnosis is often complicated by the co-existence of other medical illness, such as CVD. Yet despite the huge impact of CVD and metabolic disruptions in patients with NPDs, delineation of the molecular pathobiology linking NPDs with CVD remains rudimentary. A better understanding of how ‘nature’ and ‘nurture’ factors influence the convergence of these conditions will improve knowledge of possible preventative measures and could ultimately contribute to the development of more effective, targeted interventions.

The overarching aim of SHARED ROOTS is interrogation of genomic, neural, cellular and environmental signatures that are common to NPDs and CVD risk, as defined by the MetS, and that contribute to co-morbidity, symptom severity, and treatment outcomes. We propose to use a ‘whole systems’ biology approach to biological, environmental and behavioural signatures of disease comorbidity in NPDs, in order to direct future prevention and treatment. We will achieve this by combining genomic, transcriptomic, epigenetics, and complementary phenotypic and multimodal neuroimaging data, to disentangle mechanistic pathways that lead to the development of comorbidity of these disorders. NPDs that will form the focus of investigation include posttraumatic stress disorder (PTSD), schizophrenia, and Parkinson’s Disease (PD). These disorders have been selected on the basis of their relevance to the South African context, as well as existing expertise in these areas. They will be examined in the presence of multiple interrelated risk factors for CVD and diabetes, namely metabolic syndrome (MetS). Integrated data from this project will contribute to new knowledge of the functional pathogenic factors that lead to the development of dysregulated pathways in these NPDs with and without comorbid MetS, with the potential to improve health outcomes. Identification of modifiable mechanisms is arguably a necessary first step toward intensifying interventions for dual screening and management of this double burden of disease. In addition, this project will: (i) yield a complete and unique catalogue of coding sequence variation and associated frequency information from South African exomes and transcriptomes, (ii) contribute to the co-capacitation of bench- and clinician- neuroscientists, and (iii) lead to the establishment of a reference hub for neurogenomics and neuroimaging research on the African continent.
Flagship Project

TUBERCULOSIS TRANSMISSION: HOST, BACTERIUM AND ENVIRONMENT

Professor Robin Wood, University of Cape Town

We have identified tuberculosis (TB) transmission as an important but under-studied area of research. We have assembled a multidisciplinary team to systematically address bacterial, host and environmental factors contributing to TB transmission in a high-burdened target community. This well-characterised community will provide TB cases and a relevant study environment in which to investigate TB transmission. Existing community information includes: TB and HIV prevalence and incidence; age-relevant social-mixing patterns; a 10-year TB specimen repository allowing identification of successfully transmitting TB strains. The team’s collaboration, together with an appropriate research site, will enable a broad-based scientific investigation of the bacterial, host and environmental contributions to TB transmission.

Hypotheses to be tested:
1. that phenotypic and genotypic characteristics of potentially transmitted organisms may differ from those organisms isolated by conventional sputum based techniques
2. that host immune (inflammatory) signatures may differ between high and low transmitters
3. that transmission is determined by the quantity of air exchanged from infective to susceptible individuals and the prevalence of potentially infective particles in that air.

The 3-year project will be based on an adaptive design. In year-1, social and environmental networks of adult TB cases will be mapped within the community and fresh bacteriologic and immunologic samples will be collected to characterise correlates of infectivity (conventional sputum-based identification of “super-spreaders”). In parallel to sputum sampling, exhaled air sampling through cough and tidal breathing assays will be used to develop non-culture-based bacteriologic methods including whole genome sequencing and phenotypic mass spectrometry to identify mycobacterial proteins and lipids of airborne *M. tuberculosis*. In year-2, the air sampling and non-culture-based assays will be used to quantify numbers of potentially infectious expired particles and the immunological characteristics of identified “super spreaders”. It will also be decided when our tools are able to rapidly identify “super-spreaders” to allow more intensive monitoring of fewer participants with well-defined clinical characteristics. Genotypic sequence comparisons will be made between sputum, airborne and stored *M. tuberculosis* organisms from the community TB repository. Potential infectiousness of airborne organisms will be further determined by an *in vitro* macrophage assay. Social and environmental studies will expand to include randomly selected age-stratified community cohorts. In year-3, intensive monitoring of TB cases during early TB therapy will help identify the magnitude and time course of host and bacterial responses to treatment. The air-sampling assay will be used to explore organism adaption to particle size and environmental stress. It is projected that by year-3, the defined networks of TB cases and the susceptible population will allow spatial analysis to enable a focus change from high-risk individuals to high-risk environments contributing to transmission. The transmission-risk mathematical modeling will be used to identify those parameters such as per-person ventilation levels to identify future environmental interventions.
Flagship Project

A MULTI-DISCIPLINARY APPROACH TO UNDERSTAND THE CAUSES AND CONSEQUENCES OF HIV TRANSMISSION AND DRUG RESISTANCE IN HYPER-EPIDEMIC SETTING IN RURAL SOUTH AFRICA (UKSNHIVEPI)

Professor Tulio de Oliveira, University of KwaZulu Natal

Three decades after the first reported cases of AIDS, for the first time there is scientific consensus that the tools now exist to control and reverse the HIV epidemic. Indeed mathematical models suggest that the epidemic could halt by 2050 if high-levels of ART coverage are achieved (in combination with other effective interventions such as medical male circumcision). Key to devising the most efficient and cost-effective combination of interventions will be a clear understanding of patterns of HIV transmission in a typical rural African hyper-endemic setting. Recent methodological innovations in viral gene sequencing technology combined with a reduction in cost provide an unparalleled opportunity to understand patterns of HIV transmission and drug resistance and to establish the most effective HIV prevention and treatment approaches in a typical rural sub-Saharan South African setting. The overall aim of the research is to quantify HIV transmission and drug resistance patterns and to identify the most effective combination of HIV prevention and treatment approaches in a hyper-endemic rural South African setting. Our specific objectives are to:

1. Use molecular epidemiological approaches to develop a clear understanding of HIV transmission dynamics in a typical rural African population and to characterize the individuals and sub-populations responsible for a disproportionately large number of transmission events.
2. Identify clinical, demographic, genetic and social factors associated with failure of antiretroviral treatment and development of drug resistance in a rural primary health care-based public HIV treatment and care programme.
3. Optimise scientific collaboration between phylogeneticists, geneticists, geographers, public health professionals, health economists, computer scientists, social scientists, modelers and epidemiologists from the Africa Centre and University of KwaZulu-Natal (UKZN) to develop new approaches to address the overarching aim and objectives 1 and 2.
4. To rapidly translate scientific findings into policy by ensuring close collaboration with the National Department of Health and international health policies agencies

The proposal brings together a diverse set of experts to identify the most effective combination of HIV prevention interventions through a thorough exploration of the social, epidemiological and molecular characteristics of HIV transmission networks and the quantification of emergence of drug resistance. For this purpose, we will organize workshops that present our data and work with the UKZN collaborators in order to derive appropriate hypothesis and methodologies that can be applied to our datasets. Our aim is to identify the causes and consequences of HIV transmission and drug resistance, which in many cases can be due to social-economic reasons, which a biomedical analysis cannot detect. Identification of the most effective HIV prevention and treatment approaches based on clear understanding of the patterns and determinants of HIV transmission and drug resistance acquisition in a typical rural sub-Saharan South African setting. Furthermore, as a matter of urgency given decreasing support for global HIV programmes, we will combine these results with cost data to directly inform the most cost-effective combination of interventions (measured in terms of cost per HIV infection averted).
Drug-resistant TB is a burgeoning epidemic in South Africa with trebling of rates over the last decade. It is of considerable concern because mortality is high and the increasing cost to manage this disease (now 45% of the national TB budget) is unsustainable. The highest mortality and per capita costs are attributable to XDR-TB, which is virtually untreatable with the conventional empiric regimens used in South Africa (capreomycin and PAS-based regimen). New multi-drug regimens are urgently needed.

Our aims is to use a gene-targeted diagnostic approach (mutational analysis) combined with newer drugs to evaluate the impact of a new treatment regimen by randomising patients with newly diagnosed XDR-TB to a linezolid and TMC207-based regimen compared to the conventional capreomycin and PAS-based regimen. The second study aim is to evaluate the impact of ART on TMC-207 (bedaquiline concentrations) in HIV-infected patients in the intervention arm. The third aim is to evaluate the impact of the new treatment regimens on patient infectiousness compared to the conventional regimen using cough aerosol sampling (CASS) and GPS/CO2-detection technology.

A prospective randomised control trial will be conducted at 5 recruitment sites in South Africa (Cape Town, Upington, Port Elizabeth, Durban, Johannesburg/Pretoria). 134 patients with newly diagnosed XDR-TB will be randomised to the conventional capreomycin PAS-based empiric regimen compared to a regimen using a mutational analysis approach to rapidly select other drugs to which the patient is susceptible and containing linezolid and bedaquiline. This regimen will, unless capreomycin sensitivity is demonstrated, not contain capreomycin and thus will make the regimen injectable free. Both HIV-infected and uninfected patients will be enrolled. Outcomes that will be controlled for include HIV status, CD4 count, history of previous MDR-TB, body mass index, number of drugs used in the regimen and disease extent on chest x-ray. The primary outcome will be mortality at 12 and 24 months and secondary outcomes will include time specific culture conversion rates, adverse events, 24-month cure/completion, adherence to therapy in those receiving and not receiving injectables, and the interaction between bedaquiline and ART. A novel cough aerosol sampling technology will be used serially during treatment to evaluate the impact of the treatment regimen on patient infectiousness. This will help us to design interventions that will impact the transmission of XDR-TB.

We hope to prove that our new regime of treatment will significantly reduce mortality compared to a conventional capreomycin and PAS-based empiric regimen. With this regimen adherence will be better; adverse event rates will be lower; and dosage adjustment in HIV-infected persons will be required. We also expect the improved regimen to significantly reduce the infectiousness of patients with XDR-TB. This information will be critical to policymakers when calculating the cost effectiveness of this new regimen.
With an almost unparalleled richness in biodiversity and natural resources, and perhaps the greatest degree of human diversity on the planet, South Africa has the potential to become a major global economy and also to contribute significantly to the wellbeing of others in many parts of the world. Yet according to the World Economic Forum’s 2012-2013 Global Competitiveness Index (GCI), South Africa is ranked 52nd out of 144 countries. One of the major reasons is a life expectancy at birth of 52.1 years, which places South Africa at position 133 (out of 144). This low life expectancy is the consequence of a high burden of disease, which includes communicable (infectious) diseases, non-communicable diseases (including diseases of lifestyle and cancer), high maternal and infant mortality rates, and the consequences of injury and violence. Novel approaches are urgently needed to deal with this quadruple burden of disease.

One of the most exciting and rapidly growing areas of medical research involves the use of stem cells for the treatment of patients with a variety of diseases and for tissue repair. In the context of the SA Universities Flagship Projects, our focus is on stem cells and the potential impact their clinical translation will have on the quality of health of many South Africans. This proposal is centered on a bedside-to-bench approach, in which research capacity (current and future) in the stem cell field will be used to address major contributors to the burden of disease.

The scientific aims include (a) the development of a gene-therapy for HIV; (b) exploration of a potential new reservoir for TB; (c) the development of techniques for the expansion of hematopoietic stem cells; (d) identification of novel quality control parameters for bone marrow transplantation; (e) understanding the molecular mechanisms underlying the therapeutic effect of mesenchymal stem cells; and (f) the use of mesenchymal stem cells for therapeutic purposes. In addition to the scientific and medical impact, the project will address stem cell and related human tissue legislation in South Africa, and also the role of bioentrepreneurship in bringing stem cell products and services to the market. We are confident that the outcomes of this approach will lead to new discoveries and applications that will contribute to the alleviation of the burden of disease in South Africa.

The project will be led by Prof. Michael Pepper who has been productive in the field of molecular cell biology both in South Africa and abroad. In addition to a young dynamic team at the University of Pretoria, the project will involve groups led by accomplished scientists from other parts of South Africa (Professors Sue Kidson and Nick Novitzky, University of Cape Town; Professors Ames Dhai, Patrick Arbuthnot and Marco Weinberg, University of the Witwatersrand; Prof. Melodie Slabbert, University of South Africa; Dr. Earl Rose, Rhodes University) and abroad (Prof. Roberto Speck, University of Zurich; Prof. Karl-Heinz Krause, University of Geneva; Prof. Vincent Praloran, University of Bordeaux).

This is an ambitious but forward-looking project involving accomplished scientists from diverse disciplines, which aims to contribute to the alleviation of the heavy burden of disease in South Africa through the translation of high quality, high impact research findings into practice and policy.
HIV/AIDS continues to be South Africa’s major health challenge and many consider a vaccine to be the only real solution. Neutralizing antibodies mediate protective immunity for most viral vaccines and studies in animals have provided compelling evidence that the same will be true for HIV. Results from a recent clinical trial have provided hope that a vaccine against HIV is possible. Protection in this trial correlated with the elicitation of antibodies that targeted the HIV envelope glycoprotein but these antibodies lacked detectable neutralizing activity. Uncovering the functional activities of these vaccine-elicited antibodies and determining if they are the precursors to broadly neutralizing antibodies that evolve in some HIV infected individuals is now an intensive area of research.

In this proposal we aim to isolate vaccine-elicited antibodies from participants in HIV vaccine trials and trace their ontogenic pathway, through deep sequencing of immunoglobulin genes. This will provide a unique insight into how antibodies develop in vaccinees compared to those in infected individuals, in which we have considerable experience. We will apply a rational structure-based approach to genetically engineer improved neutralizing capacity of vaccine-elicited mAbs by transferring the features of broadly neutralizing antibodies that recognize the same epitopes or share the same germline genes. If vaccine-elicited antibodies can be “helped” to acquire neutralization breadth, this would suggest that these antibodies inherently have this potential but are still at an early stage in the developmental pathway.

How non-neutralizing antibodies mediate protection against HIV infection is currently unknown. This raises questions about the utility of in vitro methods to assess the functional activity of antibodies. As part of this proposal we aim to directly test the protective capacity of vaccine-elicited (as well as those that are genetically enhanced) mAbs using a humanized mouse model. Antibodies will be cloned into adeno-associated virus (AAV) vectors and expressed in RAG-hum mice that will be challenged with infectious HIV. This vector-based immunoprophylaxis (VIP) approach will allow us to define the genetic and functional properties of in vivo protective antibodies. Combined with the evolutionary studies these data will define the pathway for vaccine-induced antibodies to acquire neutralization breadth.
Little prior research has examined whether alcohol reduction interventions improve antiretroviral therapy (ART) adherence and HIV treatment outcomes. The broad goal of the study is to assess the efficacy of an intervention for hazardous/harmful drinking among people living with HIV and AIDS (PLWHA) who are on ART. The primary research hypothesis is that the alcohol-focused intervention will bring about a significant reduction in average volume of alcohol consumed, which will lead to significant improvements in ART adherence and HIV treatment outcomes among PLWHA. Specific aims include: (1) adapting a blended Motivational Interviewing (MI) and Problem Solving Therapy (PST) intervention to address harmful/hazardous alcohol use in HIV populations in Tshwane, South Africa; (2) evaluating the efficacy of the alcohol-reduction intervention for (a) reducing alcohol consumption; (b) improving ART adherence, (c) increasing ART continuation, and (d) improving ART treatment response; and (3) assessing intervention participants’ subjective assessments of the alcohol-reduction intervention.

A repeated measures randomized controlled trial will evaluate the intervention among ART patients in four public sector hospital-based HIV clinics in Tshwane; 151 eligible patients will be recruited from each, and randomly assigned to alcohol (75), nutrition (38), and control (38) conditions. Follow-up assessments will be conducted at 3, 6 and 12 months post-intervention. We will recruit patients who are (1) HIV-positive; (2) on ART for at least 3 months; (3) not currently receiving treatment for TB; (4) 18 years of age or older; (5) classified as “harmful/hazardous drinker” (6) resident in the Tshwane Municipality; (7) having no substantial cognitive impairment; (8) not currently enrolled in another trial; and (9) not having extremely poor general health/functional status. To ascertain participants’ subjective assessments of the acceptability and perceived effectiveness of the interventions, interviews will be conducted with 10% of the participants from each site immediately after intervention delivery.

Patients in the intervention condition will receive four sessions of the MI-PST intervention to reduce harmful/hazardous alcohol use. Patients in the equal-attention nutrition intervention condition will receive MI-PST to improve nutrition and adoption of a healthy lifestyle. Patients in the control condition will receive treatment as usual (TAU). Participants will complete an interviewer-administered questionnaire at baseline and 3, 6 and 12 months post-randomisation. It will comprise measures of socio-demographic factors; alcohol consumption; ART adherence; psycho-social and structural factors associated with ART adherence; and physical and mental health. In addition, we will collect biological specimens to test for recent alcohol consumption, and assess CD4 T-cell counts and HIV RNA viral loads. The primary outcome will be reductions in the volume of alcohol consumed. The secondary outcomes will include (a) reductions in AUDIT scores (harmful/hazardous use of alcohol); (b) reductions in Ethyl Glucuronide and Phosphatidylethanol scores (biological markers indicative of drinking); (c) increases in adherence rates; (d) reductions in viral loads; and (e) increases in CD4 T-cell counts. Repeated analysis of variance, analysis of covariance, and multiple linear and logistic regression analyses will be conducted to assess the impact of the alcohol-focused intervention.
A Comparative Risk Assessment (CRA) is important as it quantifies, using a standardized approach, the relative burden of disease attributable to modifiable risk factors. The initial National Burden of Disease (NBD) Study for South Africa for the year 2000 was accompanied by a CRA providing information on the contribution of 17 selected risk factors in terms of numbers of deaths and disability adjusted life years (DALYs)—the latter combing both the fatal and non-fatal outcomes of disease.

The MRC Burden of Disease Research Unit has analysed national mortality data from 1997-2010. Concurrently, the 2010 Global Burden of Disease (GBD) study undertook an extensive synthesis of global epidemiological data and has developed a suit of complex models to estimate trends in DALYs for 291 conditions and the contribution of 67 risk factors for each country. Collaboration with the GBD 2.0 initiative aims to update the global estimates as well as an opportunity to harness the extensive synthesis of global epidemiological data.

This CRA project will aim to estimate the contribution of 20 selected modifiable risk factors on the burden of disease in South Africa (see Table), and assess the avertable burden of climate change. The first step will be to estimate the cause-specific non-fatal burden for 2010 in terms of years lived with disability (YLDs) from available data, models and GBD 2.0, and—combined with premature mortality estimates—to provide disability-adjusted life years (DALYs). The list will be finalized after consultation with stake holders and subject experts. South African data on the exposures to risk factors and hazard size will be sourced and assessed for bias. Reviewed data will be submitted to the GBD 2.0 initiative. Country-level risk factor models will be developed for comparison and calibration of the global study, making use of the latest version of DISMOD (disease modeling software).

This flagship project will provide updated information about the priority diseases, and risk factors for these diseases, that need to be addressed to improve the health of the nation. Together with cost-effectiveness information, this provides an evidence base for prioritizing interventions to promote health or prevent disease in a population. The information provided by this project can be expected to influence decision- and policy making across many government departments, with a particular utility in the health sector.

## Risk Factors to be investigated in the 2nd Comparative Risk Assessment

<table>
<thead>
<tr>
<th>Childhood and maternal under nutrition</th>
<th>Sexual and reproductive health</th>
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<tr>
<td>1. Underweight</td>
<td>12. Unsafe sex</td>
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<td>2. Iron deficiency</td>
<td>13. Tobacco smoke</td>
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<tr>
<td>Other nutrition-related, physical inactivity and physiological risk factors</td>
<td>15. Illicit drugs (cannabis, opioids and amphetamines and injecting drugs)</td>
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<td>4. High blood pressure</td>
<td>Environmental risks</td>
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<td>5. High cholesterol</td>
<td>16. Unsafe water, sanitation &amp; hygiene</td>
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<td>6. High BMI (over-weight &amp; obesity)</td>
<td>17. Indoor smoke from solid fuels</td>
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<tr>
<td>7. Low fruit and vegetable intake</td>
<td>18. Lead exposure</td>
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<tr>
<td>8. Low whole grain</td>
<td>19. Urban air pollution</td>
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<tr>
<td>9. High sodium</td>
<td>Sexual abuse and violence</td>
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<tr>
<td>11. Physical inactivity</td>
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TB diagnosis and treatment problems include the lack of point of care diagnostics and the extended treatment period. We wish to establish a number of projects which will help to establish a long term research site in a socially depressed area (Delft, part of greater Cape Town). In brief, these projects include on or near on-site diagnostics, recruitment of patients for candidate antibiotic clinical trials, bacteriology, biobanking to support other projects and to initiate a long term multidisciplinary team relationship by bringing health systems research into our work for the first time. Our external (non-MRC unit) partner has already established a physical facility on site next to the municipal clinic, which is approximately equivalent to 5 shipping containers in extent. It is this facility that we wish to commission and utilize for our work. Currently, diagnostics are done off site at a central laboratory (NHLS). Research in a similar but less deprived area has shown that this results in an immediate loss to follow up of at least 20% of cases. We wish to establish diagnostics on site in order to assess whether we can improve that loss to follow up. We wish to utilize this site to evaluate existing (e.g., GeneXpert) and new diagnostics which we are currently developing with partners. The diagnostics will include rapid testing for antibiotic sensitivity. This rapid on-site diagnostics will also allow us to more easily recruit subjects for clinical trials. We wish to introduce a new class of antibiotics into the TB field by combining several compounds to optimize antituberculosis effect of the class. Specifically, β-lactam antibiotics have been previously proposed as antituberculosis agents. Recently, intravenously applied meropenem/clavulanic acid (CA) has been anecdotally reported to improve the outcome of patients with highly resistant tuberculosis. Moreover, faropenem, an orally bioavailable compound with favorable properties has become available. Most recent in-vitro research had shown that the antituberculosis activity of meropenem/CA and faropenem/CA can be further increased by the addition of ampicillin, another beta-lactam antibiotic. All those compounds are registered with regulatory authorities for clinical use and have proven to be safe drugs in the clinic but their antituberculosis activity has not been investigated in humans yet. Although this is our initial trial plan, there are many others in our pipeline, many of which are aimed at evaluating new dosages, new compounds and others targeted at shortening therapy time. Such a site can also be used to acquire critical samples for biomarker work, which is not part of this proposal but which we are doing separately. In addition, this platform will provide a steady flow of bacterial samples for our basic and applied research. Finally, the patient cohort will also provide samples for immunology, urine, serology and genetics studies. Host genetic and immunology studies are likely to lead to new disease insights and although extensive work has identified a host genetic component in TB, major breakthroughs in identifying the causative genes or immune phenotypes are lacking.
Rape is highly prevalent in South Africa and providing evidence-based services to rape survivors to prevent or mitigate health consequence is of great importance. Yet despite the magnitude of the problem the long term impact of adult rape on the mental and physical health of survivors, including HIV acquisition and care, has not been described either in South Africa or elsewhere. There has been no longitudinal research and so the full range of health consequences, proportion and risk factors for developing these, and the extent to which they require treatment from the health services remain substantially unknown.

At the end of this study we will have evidence of the short and medium term (2 year) impact of rape on HIV incidence, sexual and reproductive health, psychological health and risk factors for non-communicable diseases. We will have described risk factors, key pathways and will have identified areas for priority interventions. We will have expanded understanding of the impact and barriers posed by rape to linkage to and retention in care for HIV+ women and made recommendations for intervention to address these.

This cohort study will women aged 18-40 from post-rape care services and from family planning clinics. Data will be collected three monthly and we will test for HIV, STIs, pregnancy, and in HIV+ women, viral load and CD4. We will assess mental health status using DSM-IV diagnostic instruments (the Mini), substance abuse using the DUDIT and AUDIT and assess sexual practices, including sexual risk taking. We will assess non-communicable disease risk factors. We will assess the circumstances of the rape, coping and experience of stigma post-rape, exposure to intimate partner violence and other trauma and health care seeking practices among HIV+ women.
SAGE is a collaborative project of the South African Cochrane Centre and Health Systems Research Unit at the South African Medical Research Council (MRC) and the Faculty of Medicine and Health Sciences, Stellenbosch University. It aims to provide an innovative leadership plan for disseminating and implementing South African context informed clinical practice guidelines efficiently and effectively to improve practices and outcomes within the context of primary health care (PHC). The research process is cumulative and each goal builds on the next.

The first goal will use qualitative and social network analysis to describe the role players, processes and setting for guideline use for PHC conditions in South Africa. In particular, gaining an understanding of the politics, drivers and contexts of guideline development and use will inform the approach to improve the quality and impact of South Africa-relevant guideline activities.

The second goal will evaluate the availability, accessibility and quality of international PHC-related guidelines, and those currently in use in South Africa. The evaluation of strengths and weaknesses of these guidelines will assist to identify gaps in methodological quality of guideline construction and reporting, and areas where impact on PHC service quality could be improved.

The third goal will evaluate the needs of guideline users working at all levels of the South African PHC system to understand context-specific facilitators and barriers to guideline use. We will embark on broad public engagement, to ensure buy-in across sectors, disciplines and agendas and we will explore current best evidence on implementation strategies and link this with locally-acceptable effective strategies that support South African evidence implementation, and guideline use.

These three goals will form the foundation for the development of a stakeholder-driven guideline manual including templates for de novo guideline development, guideline adaptation and contextualisation, with a focus on implementation of context-specific recommendations using comprehensive dissemination strategies. This aims to be an easily navigable ‘how to do it’ manual.

We will seek broad endorsement of the manual and its purpose by relevant end-user groups and broad South African agreement to adopt the manual to inform future South Africa-driven and focused guideline initiatives. It will include effective implementation strategies embedded in the manual to address a range of common barriers with effective incentives and relevant audit measures and processes, to assist with assessing behavior change, best practice processes and health outcomes.

The fifth goal for this project will be to develop, implement and evaluate best-practice learning modules regarding clinical practice guidelines. The participatory course, grounded in adult learning theory, will be based on the guideline manual and will enable appropriate and wide dissemination to relevant stakeholders. It is intended to be an accredited e-learning ‘clinical guidelines’ module available for developers and implementers of guidelines, users of guidelines, decision makers and researchers in South Africa and the region.