The burden of disease in Africa remains one of the continent’s biggest obstacles to progress. Researchers across UCT have stepped up the battle against the main health challenges facing the continent and are paving the way for significant breakthroughs – with vaccines, cures and workable treatments no longer a distant dream, but an imminent reality.
PAVING THE WAY FOR A HEALTHIER CONTINENT

In its 2014 bulletin on world health statistics, the World Health Organisation (WHO) reports that the average life expectancy in sub-Saharan Africa for men and women is still below 55, despite global trends towards living longer. The risk of a child dying before its fifth birthday is eight times higher in the WHO Africa Region than in the WHO European Region.

The statistics point relentlessly to the fact that Africa’s development remains severely hampered by disease. Sub-Saharan Africa is the region worst affected by HIV/AIDS. South Africa has the highest prevalence of the disease in the world. About 5.6 million people are currently living with HIV in South Africa.

The country also has one of the most serious tuberculosis (TB) epidemics in the world, coupled with a rising number of TB cases as a result of HIV and TB co-infection. TB is now the leading cause of death in South Africa and, according to some estimates, about 80% of the population has latent TB. Other serious infectious diseases include malaria, which kills two children every minute in Africa.

Non-communicable diseases (NCDs) are also on the rise. Heart disease, stroke, diabetes and some cancers currently account for 30% of deaths in South Africa. About 6.3 million South Africans have high blood pressure and three million have type 2 diabetes. In addition, wider access to antiretroviral therapy has transformed HIV/AIDS into a chronic disease, meaning people are living long enough to be at risk from NCDs.

AT THE VANGUARD

Keenly aware of these statistics, the Faculty of Health Sciences is at the vanguard of the fight to contain the impact of disease on the continent. One of the largest and most prolific health faculties in Africa, it celebrated its 100th anniversary in 2012 and is moving into the next 100 years with some of the world’s top research groupings poised to make a tangible difference to the health of millions of Africans.

It is also one of the most well-resourced faculties in the developing world, attracting significant investment in its research. A highlight in 2013 was the fact that UCT drew more funding for direct grants from the prestigious National Institutes of Health (NIH) in the USA than any other non-American university in that year (see p144).

The NIH is the largest source of medical funding in the world. When asked at a recent international press conference why so many principal Investigators in the projects it was funding were from South Africa, the answer, they said, was scientific quality.

The faculty is “the crown jewel of medical schools in South Africa”, says its dean, Professor Wim de Villiers, who is proud of its place among the top medical schools in the world.

INTERDISCIPLINARY STRENGTH

One of the strengths of the faculty is the ability of its researchers to work together across various platforms in multidisciplinary collaborations to achieve extraordinary results, says Professor Bongani Mayosi. He is head of the Department of Medicine, the largest department in the faculty, which plays a leading role in medical education and research, as well as providing clinical services to the communities of the Western Cape.

“There are many examples of leading research in which we have made major discoveries that have deepened our understanding of biology based on the definition of new mechanisms of disease. We are also making an impact on the practice of medicine through the discovery of new diseases, and new ways of diagnosis and treatment of old diseases,” says Professor Mayosi.

The Institute of Infectious Disease and Molecular Medicine (IDM) exemplifies the interdisciplinary nature of the work in the faculty. “We have a critical mass at UCT: a large number of people working at the intersection of the basic, clinical and public health sciences. We are developing a culture of working together instead of in silos,” says Professor Valerie Miznah, who heads up the institute.

AFRICAN INNOVATION IN AFRICAN HEALTH CARE

A unique collaboration between the UCT Faculty of Health Sciences and the UCT Graduate School of Business (GSB) was launched in 2013 to pioneer inclusive and innovative solutions to healthcare challenges in Africa.

Jointly based in the Bertha Centre for Social Innovation and Entrepreneurship at the GSB and in the Department of Medicine and Groote Schuur Hospital, the Inclusive Health Innovation Initiative (IHII) is a response to the complexity of the challenges facing health care.

“Now, more than ever, innovation is required to develop solutions that can improve the delivery of health care in Africa in an inclusive, effective and affordable manner,” says Dr François Bonnici, director of the Bertha Centre. “These solutions must transcend current challenges in the system to improve health outcomes for patients, but also to change the routines, responsibility and values of our health workers responsible for delivering the care.”

Kicking off its activities, the IHII hosted a summit in Cape Town in January 2014, the first of its kind in Africa, that gave international and local innovators, experts and influencers the opportunity to discuss and debate what healthcare innovation means in and for an African context. The summit was one of the first official events on the World Design Capital 2014 calendar, and was organised around the theme of “designing solutions, addressing needs”.

The IHII also hosted the country’s first health hackathon a week before the summit. Based on a proven international innovation model, this event exposed participants to the role technology can play in transforming healthcare delivery in an African context, and challenged participants to create and build innovative mobile health applications that addressed real and pressing health challenges.
The IDM celebrates its 10th year in 2014 and has become a hub for interdisciplinary collaboration. Almost a fifth of the university’s research income is raised by members of the IDM, who are drawn from several departments in the Faculty of Health Sciences and the Faculty of Science.

WORKING AT THE CUTTING EDGE
When talking about the burden of disease, Professor Mizrahi says, “It’s not a pretty picture. The urgency of the medical need makes it essential to research new interventions and to learn as much as we can in the process.”

The IDM has become known as a leader in the areas of HIV/AIDS, TB, TB-HIV, human papilloma virus and parasitic disease research, with more than 20 research groupings, many of which have built a world-class reputation for their work in novel and innovative strategies to address disease in Africa.

One such group, the H3-D Drug Discovery and Development Centre, is led by Professor Kelly Chibale from the Department of Chemistry in the Faculty of Science, is Africa’s first integrated modern drug discovery and development centre whose objective is to deliver drug candidates for clinical development. In 2013, the centre completed a study that is set to find a novel, pre-clinical drug candidate for malaria. The same year, H3-D also received a major boost from Celgene Global Health (CgH), a division of Celgene Corporation, a global biopharmaceutical company, to help identify novel drugs for the treatment of TB. Under the collaborative agreement, Celgene will provide H3-D with compounds that target TB, and H3-D scientists will optimise these compounds to deliver pre-clinical candidates suitable for testing in humans.

H3-D will also benefit from a new R370 million biotechnology partnership between UCT and the South African Medical Research Council (MRC) with funding and support from the Bill and Melinda Gates Foundation, the Department of Science and Technology and the Department of Health. The partnership’s purpose is to develop new medicines, vaccines and other biotechnologies to combat Africa’s big killers: HIV/AIDS, TB and malaria.

TB: A PERFECT STORM
Of the three, the disease that is the closest to home is TB. “There is more TB in Cape Town than in Canada, the US, France and Germany put together. And it’s getting consistently worse,” Emeritus Professor Robin Wood from the Department of Medicine said earlier in 2014, after he was awarded an A2 rating by the National Research Foundation, pegging him as a world leader in his field of HIV/AIDS and TB.

RISING STAR

Associate Professor Graeme Meintjes.

Since 2005, Associate Professor Meintjes has also collaborated with researchers from St George’s Hospital, London, on trials aimed at improving initial treatment of cryptococcal meningitis.

As a result of this research, he was asked to be a member of the WHO’s Guidelines Development Group for guidelines on the diagnosis, prevention and management of cryptococcal infection in adults and children, thereby impacting policy and clinical practice in Africa.

This was the first clinical trial of IRIS treatment and the evidence has been incorporated into national and international guidelines. His work has defined the diagnostic approach to TB-IRIS, highlighting the importance of excluding drug-resistant TB. Professor Meintjes says there is definitely a need for TB-preventive therapy that, when added to ART, reduces the risk of TB by 37%, as reported in The Lancet recently by a team led by Dr Molobogang Rangaka of the Clinical Infectious Diseases Research Initiative.
While a vaccine is often seen as a silver bullet, more research is needed in these areas. Currently, drug-discovery research, UNC researchers are set to receive funding from the MRC and NIH for TB-vaccine and drug-development research. With new vaccines, they provided critical information for shaping the global agenda for TB-vaccine research. Although the results disappointed in terms of efficacy, it is common knowledge that a vaccine can protect against TB or infection in infants and contribute immensely to the reduction of TB incidence by 37%.

Another noteworthy project, spearheaded by Dr Malebogeng Rangaka, working with Professor Gary Maartens of the Division of Clinical Pharmacology and Professor Robert Wilkinson, director of CIDRI, showed a role for isoniazid preventive therapy (INH) in combating a disease. A study led by Professor Keertan Dheda, who heads the Lung Infection and Immunity Unit in the Department of Medicine at UCT and Groote Schuur Hospital, found that an innovative TB diagnostic tool developed in the US – the GeneXpert – can be placed in community clinics and operated by trained nurses to deliver quicker TB test results, resulting in a more rapid diagnosis and better prognosis for patients. This paves the way for using new tests in TB hot-spots such as prisons, mines and high-burden clinics where drug-resistant TB is common.

A trial of isoniazid preventive therapy (IPT) plus antiretroviral therapy (ART) to prevent TB has shown safety and efficacy in patients with HIV, according to a UCT research team, whose findings were published in *The Lancet* in 2014. TB is the biggest cause of morbidity and mortality in people infected with HIV in Africa. Both IPT and ART protect against TB in HIV-infected people, but it was not known if the two would give additional protection or could be safely combined.

The research team was headed up by Dr Malebogeng Rangaka and included clinic staff working for Médecins Sans Frontières (MSF) and the Western Cape Provincial Government, with supervision from Professor Gary Maartens and Professor Robert Wilkinson from the Department of Medicine. They conducted a trial of IPT in patients on ART to prevent TB at Khayelitsha Site B Clinic in Cape Town. The addition of IPT was found to be safe and to reduce TB incidence by 37%.

Discussing the purpose of the study, Professor Maartens explains that it is well established that the risk of TB can also be reduced by IPT in HIV-infected people not on ART. However, ART also reduces the risk of TB. It was previously unknown whether isoniazid would give additional benefit and whether it was safe in patients on ART.

“These findings will change clinical practice and contribute immensely to the reduction of the scourge of TB. It is one of the highlights of research in the faculty in recent times,” says Professor Bongani Mayosi, head of medicine.

The study was funded by the Department of Health, MSF, the Wellcome Trust and the European and Developing Countries Clinical Trials Partnership, while MSF were key partners in conducting the study.
A critical barrier in the development of an HIV vaccine is the identification of mechanisms to generate antibodies through vaccination that can neutralise an array of HIV variants. Professor Williamson was involved in the discovery of how changes in the position of sugar moieties (a portion or part of a molecule) on the surface of the virus can result in the development of these types of antibodies, providing a potential approach that can be recapitulated through vaccination.

Her group also identified superinfection with a second HIV strain in a woman in KwaZulu-Natal who responded to her HIV infection by making antibodies that researchers were able to identify and clone. The antibodies, called broadly neutralising antibodies, are particularly potent because they can kill multiple strains of HIV. The cloned antibodies were then used in a series of experiments in the laboratory to understand the development pathway followed by the woman’s immune system to make these potent HIV-neutralising antibodies. This work is crucial as it points to the discovery of mechanisms to elicit broadly neutralising antibodies through vaccination.

**NEW IDEAS IN THE FIELD OF HEART DISEASE**

While TB and HIV tend to dominate the conversation around disease in Africa, UCT researchers are also engaged in leading research into NCDs. WHO statistics show that coronary ischaemic heart disease is one of the top three causes of premature death in the world today. According to the Heart and Stroke Foundation (South Africa), 33 people die of a heart attack each day in South Africa. UCT researchers from different disciplines such as surgery, engineering, biomaterials and cell biology are working on finding solutions to address the many issues surrounding this killer.

A recent boost to this research has been the installation of National Research Foundation-funded state-of-the-art intra-operative medical imaging equipment (a Philips Pulsera C-Arm x-ray and angiography system and a General Electrics Vivid I portable cardiovascular ultrasound system) in the Cardiovascular Research Unit, which is enabling the study of therapies for heart attacks and subsequent heart failure. The development of an affordable prosthetic heart valve for easy implantation outside big medical centres that could benefit millions of South Africans and Africans is a heart transplant, but Dr Davies’ work has shown that hydrogel injections can improve the heart’s function after an infarction (tissue death) and prevent the heart’s enlargement, the precursor of heart failure. This work has also shown that treating a patient several days after the infarct may be more beneficial than immediate biomaterial injection.

**BEHIND THE SCENES**

Much of the work against these diseases, both infectious and chronic, takes place in quiet laboratories and university offices away from the frontlines of medical care, where fundamental research is helping to uncover new knowledge about how disease works.

Professor Mizrahi says that a “blue skies” element is absolutely critical in the battle against the burden of disease. “By understanding disease mechanisms at a fundamental level, we can contribute significantly to the development of new tools to control these diseases, be they diagnostics, vaccines or drugs. For me, there is nothing more rewarding than making a fundamental discovery that has an impact on how we think about disease pathogenesis,” she says.

By understanding how infection works, a fuller picture of the disease is obtained, providing important answers for those working on protection against diseases like TB, agrees Professor Frank Brombacher, who holds the DST/NRF SARChI Chair in the Immunology of Infectious Diseases in Africa. “Some of our findings will feed into translational research to develop efficient drugs and vaccines. Fundamental research is a requisite for translational research. When someone develops a new vaccine, very often it depends on the fundamental research.

“The nature of clinical human research is restricted in its experimental approaches. In contrast, experimental infection studies in mice and particularly in transgenic mice, developed by us and others, allow us to uncover the role of a candidate gene in a particular disease, like TB from the molecule to the whole organism,” says Professor Brombacher. He is engaged in ground-breaking work on immunological mechanisms in experimental murine models for human diseases like TB, African trypanosomiasis, leishmaniasis and helminthic infections, including bilharzia, four of the top 10 diseases declared by WHO as threats to combat and all leading to chronic disease.

**THE URGENCY OF THE MEDICAL NEED MAKES IT ESSENTIAL TO RESEARCH NEW INTERVENTIONS AND TO LEARN AS MUCH AS WE CAN IN THE PROCESS.**

Professor Brombacher has published more than 170 original papers and during 2013 made several important discoveries, for instance on leishmaniasis, where he demonstrated that IL-4-instructed dendritic cells are important for host resistance in cutaneous leishmaniasis. This is the most common form of leishmaniasis, a skin infection caused by a single-celled parasite that is transmitted by sandfly bites, which has notable implications for efficient vaccination.

In terms of helminth infection (caused by a worm-like parasite), Professor Brombacher and Dr William Horsnell of the Division of Immunology studied B-cell function in protective TH2 immunity against N brasiliensis infection. The findings of the study showed that rational vaccination strategies against nematode parasites such as hookworms need to be developed with an understanding of primary and secondary immune responses, in order for mechanisms other than antibodies to be optimally protective.
Professor Brombacher and his team also showed that statins can increase protection against TB and listeriosis – important footwork for vaccine research.

TRANSLATING RESEARCH INTO ACTION

Research excellence is not only about finding vaccines and testing drugs. It is also about developing programmes and solutions for community clinics and the national and provincial health departments regarding the diagnosis and treatment of health problems. UCT researchers are playing a pioneering role in translating research into policy and action.

The UCT-based Chronic Diseases Initiative in Africa (CDIA) has established itself as the group to consult in South Africa on NCDs. It played a significant role in advising the national Department of Health when South Africa became one of the first countries in the world in 2013 to regulate salt content in foods. South Africa has one of the highest levels of hidden salt in food in the world, which contributes to hypertension and obesity, and which in turn is a driver for heart disease, stroke and some cancers.

The CDIA’s work is also serving as an incubator to develop and test innovations in NCD care with the potential to be rolled out across Africa. Research highlights in 2013 include the publication of the highly innovative Primary Care 101 guidelines on the management of NCDs. The initiative was also involved with group diabetes education programmes, as well as the development of mobile technology to deliver SMS support to patients with hypertension to promote adherence to treatment. This work is being evaluated in a clinical trial in collaboration with researchers from Oxford University.

FORWARD TO THE FUTURE

The many different kinds of research activity, interdisciplinary and international collaborations, as well as provincial and national success stories, illustrate why UCT is currently standing out as a place where major funders are coming to invest in long-term programmes. The university is also attracting top people in the field are developed. The impact of this “seeding” effect is profound,” says Professor Mizrahi.

UCT’s role in the fight against disease is results-driven and on the cusp of making major discoveries, leading to potentially breakthrough treatments and paving the way towards a healthier continent. Professor Mayosi says, “We are facing formidable health challenges in Africa, but I’m optimistic about UCT’s role and the researchers’ ability to address these challenges. It turns out we are up to the task. In South Africa, at UCT, we have the intellectual power to deal with these problems, and we have the resources as well.”

PUTTING CHILDREN AT THE TOP OF THE HEALTH AGENDA

Child health is a major challenge for South Africa and for the continent, where there is high childhood mortality and preventable morbidity. There is an epidemic of infectious diseases such as pneumonia, diarrhoea and TB. Research in child health has been particularly under-resourced, given the large burden of disease and the high proportion of children in the South African population.

In October 2013, the Research Centre for Adolescent and Child Health (REACH) was opened at the Red Cross War Memorial Children’s Hospital. This state-of-the-art expanded clinical research centre is devoted to child health and is headed by Professor Heather Zar, head of the Department of Paediatrics and Child Health in the Faculty of Health Sciences.

REACH is the first of its kind in Africa and also serves as a hub supporting other clinical research sites in the community and at other healthcare facilities, and contributing to the development of capacity in child health and in clinical research.

The centre has about 40 full-time members of staff funded through grant support, and has several local, national and international collaborations. It is undertaking research with an important impact on child health globally.

Studies currently under way address key health priorities such as childhood TB, pneumonia, whooping cough, HIV and adolescence, and diarrhoea. A unique birth cohort study, the Drakenstein Child Lung Health study, is currently under way in Paarl and is supported by this core centre.

This study, a first for Africa, investigates the determinants of child health from the antenatal period through birth and early childhood and includes a focus on maternal and paternal health.
UCT attracts lion’s share of NIH direct grants

UCT’s reputation for research excellence was endorsed with news in 2013 that the university attracted more funding for direct grants from the National Institutes of Health (NIH) than any other university in the world outside the USA. The NIH, the USA’s medical research agency, is the largest source of medical funding in the world.

These research grants, which amount to more than US$9 million, make it possible for UCT’s researchers to tackle some of Africa’s most intractable health problems, such as HIV, TB and malnutrition. Most of the projects are large in scale and many involve collaboration with partner universities elsewhere in Africa. The funding may come from the USA, but one of its most significant impacts is building capacity in Africa to address its own health problems.

Unraveling the mysteries of sickle cell anaemia

Associate Professor Ambroise Wonkam, senior specialist in the Division of Human Genetics in the Faculty of Health Sciences, runs one such project focusing on sickle cell anaemia. “Seventy percent of those with the disease were born in Africa, yet 70% of what we know about it was discovered outside Africa,” says Associate Professor Wonkam. “We in Africa have to solve these problems ourselves: it is our duty.”

The immediate goal of Associate Professor Wonkam’s project is to find out why some patients get sicker than others, despite having the same gene malformation. He and his colleagues are looking for variations in other parts of the genome: this will help determine which patients have the disease from birth, enabling early interventions, and may lead to developing a drug to treat it.

Schizophrenia in the Xhosa population

Professor Dan Stein, head of the Department of Psychiatry and Mental Health, is leading a project on the genetics of schizophrenia in the Xhosa population of South Africa. Professor Stein says, “This project will be the first to use modern genomic sequencing approaches to study schizophrenia in a population of Sub-Saharan African lineage. If successful, our approach will identify genes important for the disorder in populations worldwide … and help develop more effective treatment and prevention strategies.”

HIV: eliminating mother-to-child transmission

Dr Mary-Ann Davies, senior researcher at the Centre for Infectious Disease Epidemiology and Research (CIDER), is looking at closing the gaps in prevention of mother-to-child transmission of HIV coverage, early infant diagnosis and treatment. “Virtual elimination of transmission of HIV from mothers to their babies is within reach in South Africa. Despite high levels of HIV among pregnant mothers, transmission to their babies has been reduced to less than 2%,” says Dr Davies. If there were no interventions, the figure would be closer to 30%, so the programme has been hugely successful. “Yet, elimination remains elusive, with up to 1 000 infants still acquiring HIV in the Western Cape each year.”

High-calibre research

It is the calibre of the scientists leading these projects at UCT that is part of the secret to South Africa’s outstanding success in attracting grants from the NIH. The NIH have said that scientific quality is one of the main reasons why so many of its funded projects are located in South Africa.

“They fund based on excellence,” says Associate Professor Nicola Mulder, head of the Computational Biology Group that receives NIH funding for bioinformatics. “It is an equal, peer-reviewed process, in which reviewers score the proposals based on scientific excellence.”