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# ScienceScope

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SOUTH AFRICA'S COUNCIL FOR SCIENTIFIC AND INDUSTRIAL RESEARCH

**Research for improved health**



**CSIR**  
*our future through science*

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This cover illustrates the hope for good health for Africa's future generations. Pictured are two children of the Lesego Early Childhood Development Centre in the Kanana township near Hammanskraal. To the left are simulated blood vessels and body tissue (© Rolffimages | Dreams-time.com); mercury (© Cerae | Dreams-time.com); and to the right, green 3D-rendered illustration of cells with nucleus (© Sebastian Kaulitzki | Dreams-time.com) and blue 3D-rendered close-up image of virus (© Sebastian Kaulitzki | Dreams-time.com)

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# Central to quality of life: **health**

THE PHRASE 'QUALITY OF LIFE' features prominently and frequently in modern-day conversations. It is used in the context of life expectancy, education, standard of living, material wealth, environmental wellbeing, philosophies about having choices, or in a political sense – where it is said to refer to the 'liveability' of a given city or nation.

The CSIR's interest in 'quality of life' is long-standing. Our mandate, as captured in the Scientific Research Council Act (1988), commits the organisation to "contribute to the improvement of the quality of life of the people of the Republic". We have defined the thematic areas in which we believe we are equipped to fulfil this mandate. These are health, the natural environment, energy, the built environment, defence and security and industry.

Health is undeniably one of the prime components of quality of life. When people are asked to name the most important problems that they face, health is often only surpassed by financial concerns. The World Health Organization, in its 2008 *World Health Report*, quoted a Kaiser/Pew poll indicating that 36% of South Africans cited health as their main concern. It featured more prominently than issues such as housing or work. The South African government recognises the challenges in the health domain and in its medium term strategic framework, commits itself to improving the health profile of all South Africans. It is within this context that the CSIR strives to impact the health of South Africans by drawing on the numerous, multidisciplinary science, engineering and technological competences it houses and nurtures.

We are encouraged by the fact that knowledge and understanding of health is growing rapidly, and that knowledge generated is shared globally and often goes hand in hand with a strong commitment to addressing global health issues.

However, progress in general health over recent decades has been disparate. Health in large parts of the world has improved, but many countries – and specifically many African countries – are losing ground. Urbanisation and a longer life expectancy in the developed world will increasingly require a focus on chronic and noncommunicable diseases such as diabetes and mental and cardiovascular diseases. In Africa, the burden of disease lies elsewhere, necessitating an inward look for technologies and solutions to fight diseases such as malaria, tuberculosis and HIV/Aids.

South Africa's health challenges require innovation and the development of a bio-economy. The CSIR believes it has a significant contribution to make in this regard. In a renewed, focused approach, it has committed itself to investing its resources in the development of affordable, novel treatments and improvement of nutrition.

In this edition of *ScienceScope* we have chosen to focus on the CSIR's impact, and intended future impact, on health. We feature some of our research approaches and progress in relation to the so-called diseases of poverty: malaria, tuberculosis and HIV/Aids, but also refer to studies that may influence decision-making and public-health policy. We outline some advances in enabling technologies for health and look at research undertaken to ensure the safety and health of some 350 000 mine workers who earn their living in conditions that require continual health and safety-related interventions.



FROM THE DESK OF THE PRESIDENT AND CEO: DR SIBUSISO SIBISI

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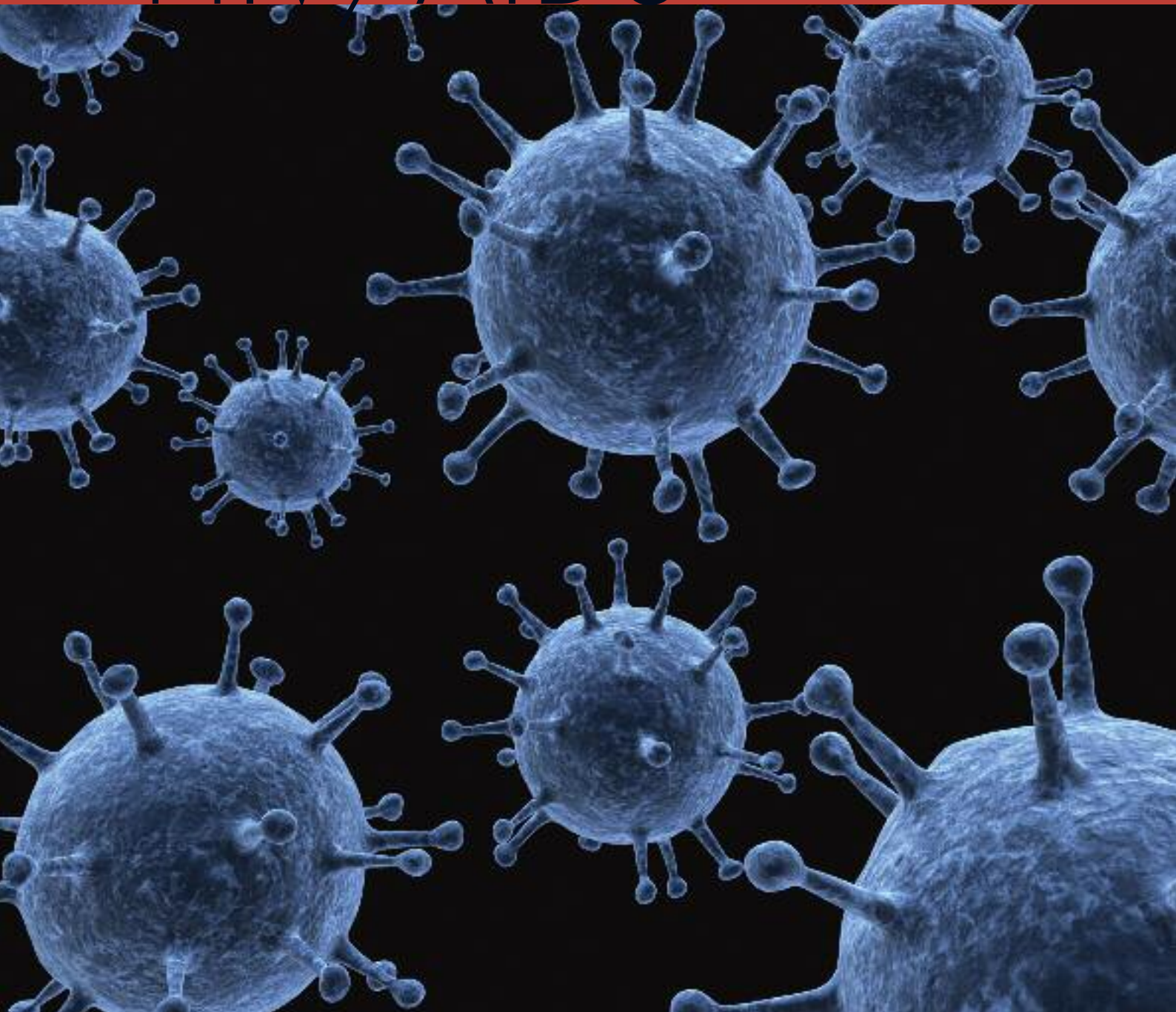
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# HIV/AIDS



# Strain of bacteria **GENETICALLY ENGINEERED** to express sought-after antiretroviral peptide for HIV/Aids treatment

**Cape Biotech backs CSIR technology to produce an affordable HIV antiretroviral peptide**

The human immunodeficiency virus (HIV) infects cells of the immune system and destroys or impairs their function. Infection results in the progressive deterioration of the immune system, breaking down the body's ability to fend off infections and diseases. Acquired immune deficiency syndrome (Aids) refers to the most advanced stages of HIV infection.

33 million people live with HIV/Aids worldwide. An estimated 2.7 million people were newly infected with the virus in 2007.

More than 5.5 million people worldwide who are in need of antiretrovirals still have no access to treatment.

An estimated 2 million people die every year from HIV/Aids.  
(Source: The World Health Organization)

IT'S ONE OF THE MOST EFFECTIVE antiretroviral treatments for HIV, but hopelessly unaffordable for most patients in sub-Saharan Africa. Now scientists at the CSIR have developed a bio-manufacturing process for Enfuvirtide that may just change all of this. And Cape Biotech, the Department of Science and Technology-funded biotechnology innovation centre, announced that it is funding proof of concept studies.



Research assistant Tovhواني Ralikhwatha inspects bacterial growth



Molecular biologists Tovhowani Ralikhwatha, Nolwandle Nxumalo, Drs Maureen Louw, Erika du Plessis and Eldie Berger. Team member Michael Crampton was on sabbatical at the Technical University of Berlin when the picture was taken.

Dr Maureen Louw, a CSIR molecular biologist with many years' experience in genetic engineering of bacteria, is heading up the project. "Instead of using a chemical process – which is how this therapeutic is currently commercially made – we have genetically modified a microorganism to harness the organism's natural ability for protein secretion and to channel it into over-expressing the peptide we need.

"Since these therapeutic peptides would be needed in large quantities, we will use fermentation processes to multiply the recombinant bacteria, and therefore increase the yield of peptides obtained. The aim is to achieve this in a more cost effective manner than the chemical process behind the commercial product on the market, which reportedly uses 106 chemical steps and 44 ingredients and is cited as the reason for the record-breaking price of the commercial product."

The CSIR has developed the technology and is now at the stage where the organisation will further refine and evaluate the cost competitiveness of the technology.

Dr Louw and the team are excited by the progress in a domain with such relevance to South Africa's people. "To put a highly

effective antiretroviral treatment within the reach of our HIV-positive population would be a career highlight for all of the scientists on the project. Every scientist wants his/her work to move from the laboratory into a real-life application. This investment by Cape Biotech brings us one step closer to this ideal," she says.

The scale of HIV in South Africa means that the country makes up a major portion of the global antiretroviral market. Estimates are that, if all those South Africans requiring antiretroviral treatment were to receive it, South Africa would represent nearly 40% of the global market. In this context, the benefit of a cheaper, locally manufactured drug speaks for itself.

Enfuvirtide is a peptide that blocks HIV infection by preventing the virus from entering the yet uninfected cells. It has become the preferred agent for heavily treatment-experienced patients who require a therapy change to improve immunologic status.

"Clinical data have confirmed Enfuvirtide's role in decreasing viral loads. But the estimated R19 300 treatment cost per patient, per month, is likely to forever prevent its pervasive use," comments CSIR research and development outcomes manager, Fanie Marais.

Cape Biotech project manager, Fred van der Post, says they are excited by the potential this project holds for the local manufacturing of antiretrovirals, and the development of an active local pharmaceutical industry. It is envisaged that successful proof of concept will lead to the technology being licensed either to an existing South African enterprise, or to a new public-private partnership.

Over the next two years, a team of CSIR molecular biologists, together with fermentation technologists from the University of Cape Town Chemical Engineering Department and the Technical University of Berlin, will be working together on increasing expression levels through genetic improvements; proof of concept studies for the production of successful products in batch fermentation; and the scale-up of the experiments to pilot-scale levels.

The CSIR's work is protected by international patents relating to the recombinant bacterial strain and a number of industrial applications associated with its use. – Alida Britz

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Nolwandle Nxumalo, a candidate researcher, determines the protein secretion of various samples in a microtitre plate in the laboratory



Bio-engineers with a common cause. Brad Cunningham, an engineering Master's student at the University of the Witwatersrand, will be working alongside CSIR senior researcher, Dr Suretha Potgieter, on the development of microfluidics chips. Potgieter has a PhD in biomedical engineering. Their joint project entails basic experimentation by the two organisations to define a firm scope and the feasibility of developing a miniature PCR and detection system to monitor an individual's HIV/AIDS viral load using microfluidics. Pictured centre is research group leader, Dr Kevin Land.

# MINIATURISATION OF TECHNOLOGIES USHERS IN AN ERA OF LAB-ON-A-CHIP DEVICES

CSIR and Wits start exploratory work on a point-of-care device to monitor the viral load of HIV/AIDS-infected individuals

RESEARCHERS AT THE CSIR and the University of Witwatersrand (Wits) are pooling their skills in a project designed to undertake the baseline work for the development of an affordable, small device to detect and monitor the viral load of HIV/AIDS-infected individuals. Microfluidics, the multidisciplinary field that deals with the behaviour, control and manipulation of sub-millilitre fluid volumes in a constrained space, lies at the heart of such a device.

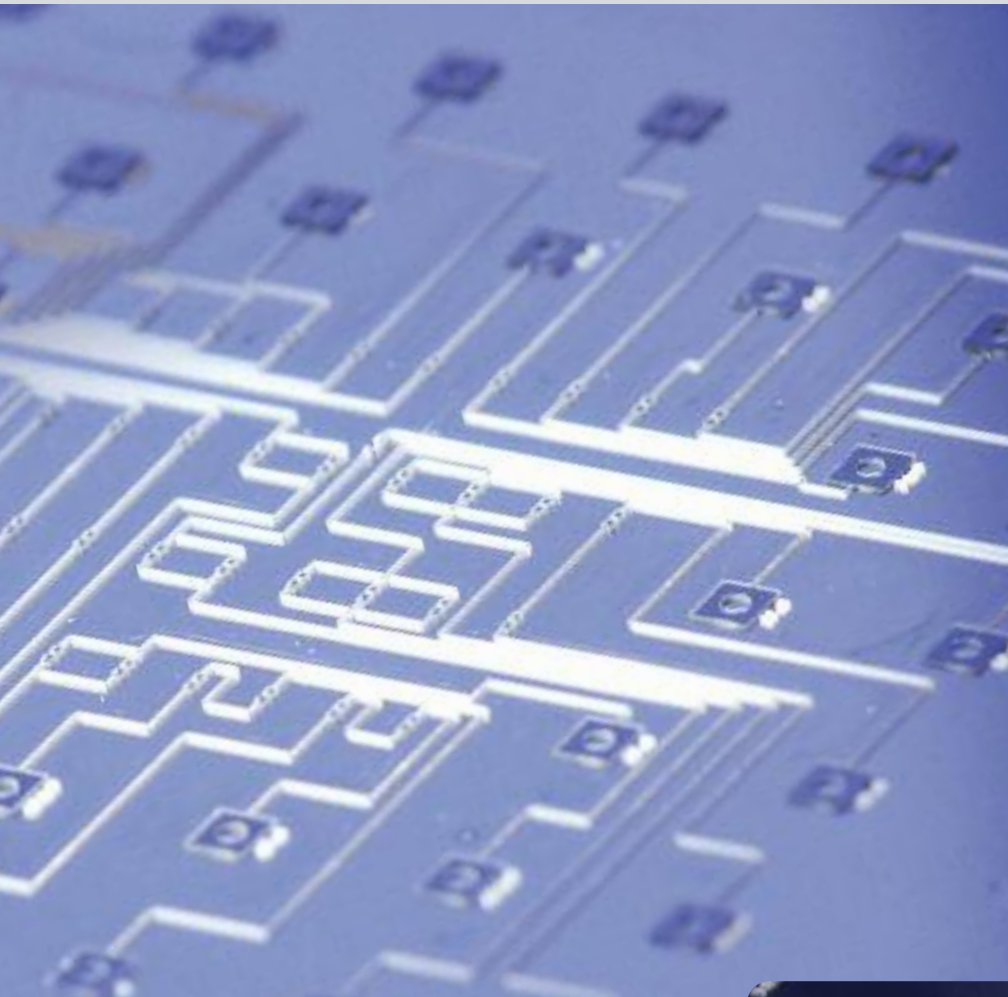
"For many years now, women have been able to buy a pregnancy test over the counter. What a difference it would make if a person

living with HIV/AIDS in a rural setting could as easily use a device to determine his or her viral load. Determining the viral load of an individual is far more complex than a pregnancy test, but microfluidics is the tool that may just change this," says CSIR senior researcher in microfluidics, Dr Suretha Potgieter.


The CSIR started its microfluidics research group in 2007 and continues to build skills in this domain. The fluid involved is typically of a sub-millilitre volume and could be ink (the first application was in inkjet printheads), blood samples or bacterial cell suspensions. The entire microfluidics system then consists of a

series of channels with pumps, valves, reservoirs and actuators to control the fluid around the circuit. This ability to miniaturise and integrate complex functions which are normally undertaken in sophisticated laboratories, holds enormous potential, and there is excitement in research circles about the potential of lab-on-chip devices for the health domain.

"In the medical fraternity the term 'point-of-care' is used to refer to the shift of medical instrumentation from laboratories to the bedside. While no point-of-care equipment to monitor the viral load present in HIV/AIDS patients currently exists, numerous research and



“THE CHALLENGES ARE FORMIDABLE, BUT THE POTENTIAL BENEFITS FAR OUTWEIGH THE CHALLENGES,” SAYS LAND.



Cunningham and Potgieter inspect a microfluidic mould which will be used to cast microfluidic devices

development bodies are focusing their efforts on achieving just this,” says Potgieter.

“Through this project, we are starting our investigation into the feasibility of making a miniaturised polymerase chain reaction (PCR) system to use as such a point-of-care device. It will amplify a DNA sample and determine the viral load in that sample. The viral load measures the severity of the viral infection by estimating the amount of virus in body fluid,” says Potgieter.

Potgieter says this aim has specific relevance to the developing world. “One of the main issues in developing countries is the need to diagnose diseases as quickly, accurately and cheaply as possible – regardless of whether it is for HIV/Aids, malaria, tuberculosis, cholera, or measles.”

A device based on microfluidics will be more affordable because very small quantities of expensive chemical reagents can be used. In

addition, low production cost as a result of size would allow for disposable devices. Sampling times could also be greatly reduced.

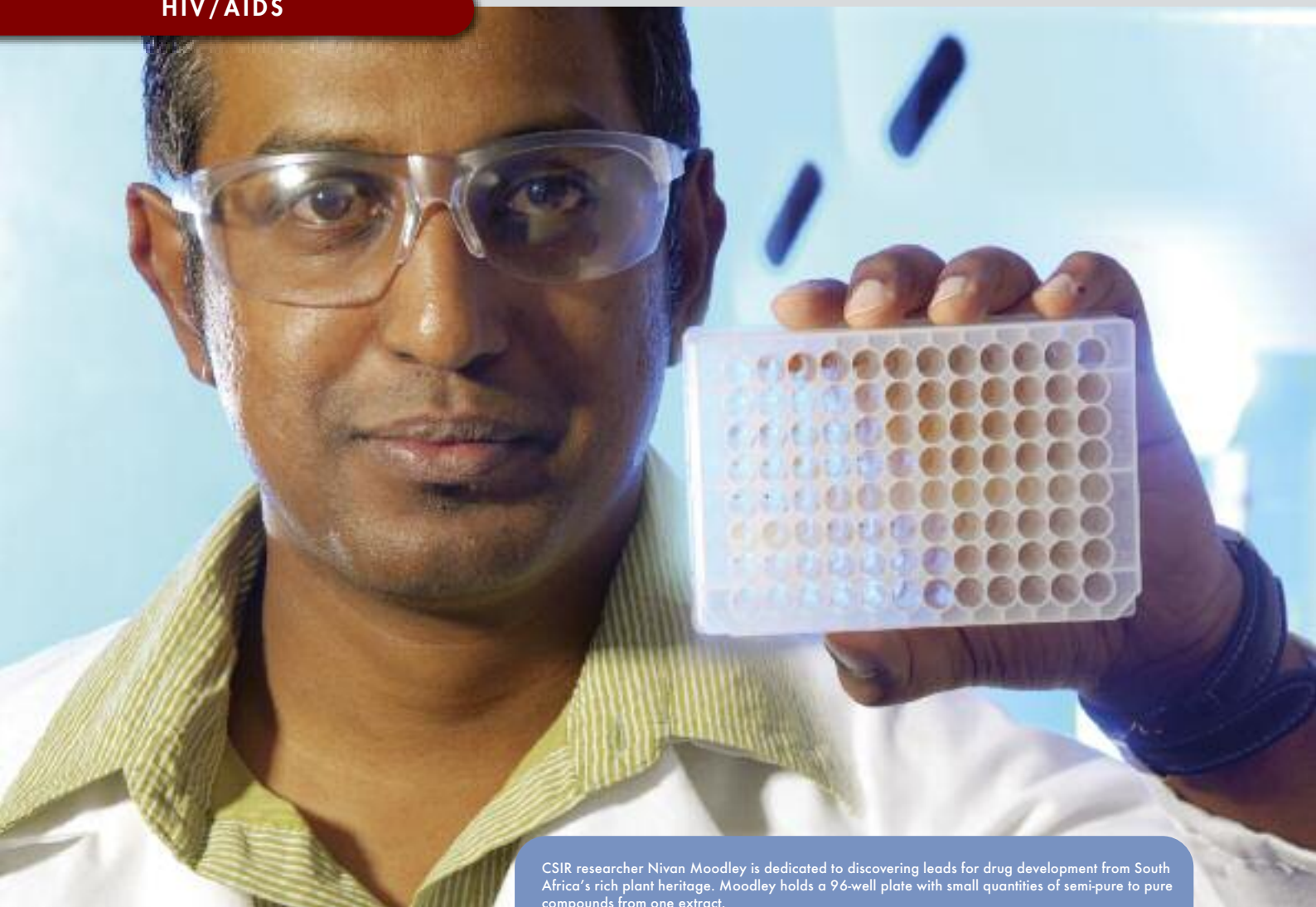
Kevin Land, CSIR principal technologist, says that while it is widely acknowledged that microfluidics holds enormous potential in the context of the developing world, there are inherent challenges to overcome. A lab-on-a-chip device would not only have to be manufactured at a low cost, it will also have to be effective despite the absence of electricity, cold storage or skilled personnel; and be able to withstand shocks and rough handling.

For the purpose of this CSIR/Wits project, the researchers strive to come closer to such a device, investigating the ability of the microfluidic system to amplify the viral-DNA load; the accuracy of viral load detection; its ability to withstand non-laboratory environments; and whether it can be fully automated. They also have to determine whether the device can be

manufactured at a low enough cost to make it widely available.

“The challenges are formidable, but the potential benefits far outweigh the challenges,” says Land. – Alida Britz

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CSIR researcher Nivan Moodley is dedicated to discovering leads for drug development from South Africa's rich plant heritage. Moodley holds a 96-well plate with small quantities of semi-pure to pure compounds from one extract.

As the third-richest centre of biodiversity in the world, South Africa has well over 20 000 indigenous plant species, providing a rich resource for drug discovery.

Together with indigenous practitioners, CSIR scientists are working to identify novel compounds for potential anti-HIV drug leads to help treat the estimated 24.5 million people in sub-Saharan Africa living with HIV/Aids.

## SOUTH AFRICAN BIODIVERSITY AS A SOURCE OF HIV/AIDS TREATMENTS

BIOPROSPECTING plays an important role in discovering leads of natural origin for drug development. Nature can provide the structural complexity and novelty required for drug discovery, which can then be synthetically modified to improve compound druggability. Although HIV is a relatively new disease, research using plant-derived substances is currently in clinical trials, proving that plants may have the potential to be one of the main sources of HIV drug treatments.

Due to the few, isolated studies undertaken to investigate the anti-HIV properties of South African medicinal plants, and the high cost and limited availability of relevant bioassays in South Africa, collaborative, consortium-based approaches are being taken by the CSIR. One example is a research programme initiated between the CSIR and the Esperanza Medicines Foundation (EMF) in Switzerland. Bioprospecting research group leader at the CSIR, Dr Vinesh Maharaj, says, "This programme screens plant extracts to identify potentially new anti-HIV drug leads, and has so far identified a number of 'hits' for further investigation.

"To date, 48 extracts from 29 plant species sourced from the CSIR's repository of 32 000 plant extracts – representing 11 000 plant species collected throughout South Africa – have been screened for their anti-HIV properties. The plant species were selected based on information on their medicinal use, which was obtained from literature sources such as books and publications. Of the 48 extracts screened, several extracts have been found to show good anti-HIV activity with limited toxicity. At this stage it is not known if a single compound is responsible for this observed biological activity or if it is a synergistic effect caused by a mixture of compounds."

Traditional healers who use medicinal plants for the treatment of HIV/Aids frequently approach the CSIR with their information, requesting that their claims for cure be scientifically validated. Following the signing of non-disclosure and benefit-sharing agreements, and in compliance with the South African Biodiversity Act and its regulations, discussions are held with the knowledge holder to obtain details on its exact use and how the material is prepared. This information is then used to reproduce the traditional preparation as well as other extracts in the laboratory.

Once prepared, the extract undergoes a series of bioassays (scientific experiments) to test for efficacy – an array of assays are used as the preparations could act as an anti-viral; treat the associated infections of HIV; or act on the immune system to help fight the

disease. Once a 'hit' is obtained from an extract, the process of isolation and identification of the active ingredient then follows. The most challenging task for the natural product scientists is to separate these highly complex extracts that contain several compounds into its individual components that are biologically active. The classical method used to identify active compounds is termed bioassay guided fraction. This method consists of a series of sequential separation steps, with samples tested for efficacy at each step – the whole process being highly iterative.

"The major shortcoming of the method is that it can take years to isolate the active compound/s and often the active ingredients are known in the public domain – this is only realised at the end of the process," says Maharaj.

The bioprospecting research group has now established an accelerated fractionation approach that is based on internationally used technology. CSIR researcher Nivan Moodley – who has just completed his post-doctoral studies at the University of Basel and a training course at the Korean Institute of Science and Technology, where he was trained in using modern technology for the rapid dereplication of complex extracts – is now leading the CSIR research using this accelerated approach. Moodley says, "Natural product extract fractionation has been a major bottleneck, limiting the pace of

drug discovery, and this accelerated approach overcomes this, speeding the process up significantly. There are many new classes of substances waiting to be discovered from South African biodiversity, and the novelty of these compounds, together with their biological properties, will ensure their demand. As a natural product chemist it is an exciting time to be working in this area."

The process involves the analysis of fractionation of crude extracts into several hundred almost semi-pure/pure compounds in one step. The fractionation process requires that fractions are collected into 96-well microtitre plates in triplicate, allowing for the simultaneous chemical analysis using mass spectrometry and biological assaying.

"The data generated are processed, leading to the identification of the active compounds in a very short period of time, typically within a few months. This early identification of the compounds allows a decision to be made on its further development based on its structure, in relation to pharmaceutical attractiveness, much earlier in the discovery stage of drug development," says Moodley.

Maharaj says the molecular complexity and diversity offered by nature surpass the mind of a synthetic chemist. "Undoubtedly, we need to exploit this natural resource, which we have in abundance and which is still largely unexplored."

CSIR researcher Jacqueline Ndllebe loads a sample into the Nuclear Magnetic Resonance instrument. The sample substance is placed in a strong magnetic field that affects the spin of the atomic nuclei of certain isotopes of common elements. A radiowave passed through the substance then reorients these nuclei. When the wave is turned off, the nuclei release a pulse of energy that provides data on the molecular structure of the substance and that can be transformed into an image by computer techniques. The NMR was acquired jointly by the CSIR and UNISA and will be invaluable, also in the training of post-graduate students.



The CSIR bioprospecting research team. They are, (front): Jeremiah Senabe, Dr Xolani Peters, Schalk van Rooyen, Nial Harding. Middle: Rudzani Nthambeleni, Andries Seolwane, Dr Dashnie Naidoo, Prenitha Sewnarian, Dr Jacqueline Ndlebe, Oscar Marumong, Dr Gerda Fouche. Back: Dr Vinesh Maharaj, Dr Nivan Moodley.



## CASE STUDY

# POTENTIAL TREATMENT FOR HIV/AIDS

THE CSIR'S COLLABORATION WITH TRADITIONAL HEALERS on the use of medicinal plants in South Africa has led to the identification of a plant traditionally used for the treatment of HIV/Aids. The plant being investigated is used by a private individual in the Eastern Cape and claimed to be beneficial in the treatment of HIV-positive patients. The plant has traditionally been used to treat other diseases and since the emergence of HIV, it has been shown to have some effect on the virus. The CSIR is working to further develop the plant extracts as potential herbal medicines for the treatment of HIV-infected patients. This includes the identification of the active ingredients responsible for the reported anti-HIV activity, which can be either further developed as a natural chemical extract or used as a biological marker in the extract.

The testing of the extract in its spray-dried form has identified a novel compound with anti-HIV activity of the same order of magnitude as the antiretroviral, AZT. Based on this data, the molecule presents an ideal lead for further development as a topical microbicide to help fight and prevent HIV infection. Funding is currently being sought to further its development.

Further development would require optimisation of the formulation, further manufacturing in compliance with good manufacturing practice preclinical safety and efficacy testing, followed by extensive clinical studies. This could take between 10 to 15 years to complete before the product would be available to the public. Processes are underway to file a provisional patent. Maharaj says, "This project demonstrates the value of bringing together indigenous knowledge and scientific innovation, and that it can lead to the discovery and development of potentially novel, high-value, high-impact products based on our unique biodiversity."

This research is currently funded through the CSIR parliamentary grant, plus additional support via several bilateral projects, including the EMF.

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Dr Moira Bode pictured with an automated parallel synthesiser

## SCIENCE AT WORK FOR CHEAPER ANTI-HIV DRUGS

ScienceScope reported in January 2009 that a new, economically competitive methodology for the preparation of an intermediate in the production of antiretrovirals AZT and stavudine has emerged from CSIR laboratories. It is hoped that this research outcome will in future help empower African governments to afford wider roll-out of ARV treatment programmes, as well as stimulating the local production of active pharmaceutical ingredients.

The investigation into mechanisms to reduce the cost of manufacturing generic antiretrovirals was first funded by the CSIR and later through the government-funded biotechnology innovation agency, Lifelab. According to project leader, Dr Moira Bode, they developed a biocatalysis reaction to produce 5-methyluridine as well as the chemistry to convert 5-methyluridine to thymidine, the intermediary needed to produce the drugs mentioned. This involved, among other things, initial screening work to identify useful enzymes, the fermentations to produce enzymes and the process development for scale-up of the biocatalytic reaction, as well as the chemistry. The entire process was scaled at the CSIR to produce thymidine at kilogram scale.

This technology has been licensed to Arvir Technologies. The CSIR has filed a patent application on the relevant technology.

**Full story ScienceScope, January 2009, page 22**

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## STRUCTURE-ACTIVITY RELATIONSHIPS: HELPING TO FIND ALTERNATIVE HIV/AIDS TREATMENTS

America's Central Intelligence Agency data (October 2007) ranked South Africa fourth (out of 179 countries) for high HIV/Aids prevalence. Perched on the summit of the table are South Africa's neighbours Swaziland, Botswana and Lesotho.

"South African scientists can contribute to finding treatments," says CSIR physicist, Dr Igle Gledhill. "Statistics and modelling are not only called upon to report the devastation of the disease, but are also used in research to find alternative drugs to treat HIV-infected individuals."

Gledhill has, over the past two years, been employing Bayesian Reasoning and genetic algorithms to evaluate the potential of compounds identified in drug development projects. "My job in these projects is to look at the research results obtained by my colleagues – who are synthetic chemists and bioscientists by training – for biological activity, and to determine which features of specific molecules will result in the highest inhibiting activity. This helps us design and optimise the best molecule," she says.

Although Dr Gledhill does most of her work in the defence arena, she has been working with biosciences researchers on these drug design projects. "The application areas may be very different; the common ground is modelling of the physical world, and applying one's mind to the problem at hand.

"HIV/Aids is difficult to treat. The virus continuously develops resistance to drugs," she says. "We have to keep on developing new drugs, and understand how the virus mutates.

"We fingerprint candidate molecular structures, and we correlate fingerprint features with activity to make predictive models based on statistical methods. Evaluating the predictive value of the model is vital. We also test other molecular properties, like the shape of a molecule, or the presence of rotatable bonds. We are progressing, and we are now more than halfway through the current project, led by my colleague, Dr Moira Bode. There is excellent potential," she says, adding that the research is intended to lead to the identification of a new class of lead compounds active against HIV.

– Mzimasi Gcukumana



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# TUBERCULOSIS





# Working towards a new, rapid and reliable APTAMER-BASED POINT-OF-CARE TB TEST

The CSIR, with financial support by BioPAD, is undertaking research directed at the development of an aptamer-based, Tuberculosis (TB) diagnostic prototype kit. BioPAD is a biotechnology regional innovation centre established by the Department of Science and Technology (DST).

TUBERCULOSIS remains a major public health problem. Approximately 1.7 billion people worldwide are infected with TB, with 8 million new cases and 3 million deaths per year. It is estimated that 35 million people will have died of TB by the year 2020. In 2004, it was estimated that more than 4% of the world's infected people living with active TB were in South Africa. During this period, South Africa accounted for about 2% of the world's new TB cases and approximately 3% of the total TB deaths. Most deaths occur mainly because the infection goes undiagnosed, or is diagnosed too late to be cured. The rapid and accurate diagnosis of patients is therefore the cornerstone of global strategies for TB control. While progress in TB diagnostics has been made in developed countries, in the rest of the world the techniques used for diagnosing TB have remained relatively unchanged for the past century.

Many of the existing tests are slow and lack sensitivity. For example: sputum smear microscopy is insensitive; the culture method is technically complex and slow; chest radiogra-

phy is non-specific, and the tuberculin skin test is imprecise and the results non-specific. The purified protein derivative (PPD) test is technically simple, relatively cheap, and reproducible if performed by skilled personnel. However, it lacks specificity in individuals vaccinated with *Mycobacterium bovis* Bacillus Calmette-Guérin (BCG) and its sensitivity in detecting active TB is limited to 75%. In addition, negative results are often associated with extensive disease.

It is also reported in individuals vaccinated with BCG or exposed to environmental mycobacterium, that PPD skin testing is found to be unreliable due to cross-reactive (false-positive) immune responses to antigens common to *Mycobacterium tuberculosis* (MTB) and non-pathogenic mycobacterium. Alternatively, T-cell assay may be used, but the requirements for *in vitro* diagnosis are more complex and include highly purified MTB-specific antigens and facilities for cell culture and cytokine assays. Hence its use as a routine diagnostic tool is limited.

Despite the huge need for new, improved, affordable and readily accessible point-of-care TB diagnostics, there is generally a lack of interest. Moreover, the high-technology, rapid tests available in developed countries – where less than 5% of global TB cases are found – are too complex and costly for the resource-poor settings where TB is most prevalent.

Although an estimated US\$1 billion is spent annually around the world on TB diagnostics, World Health Organization statistics of 2006 also indicate that only one-third of this is spent in low or middle-income countries where 73% of TB diagnostic testing takes place. A rapid, more sensitive and specific diagnostic test needs to be developed as a matter of urgency to enable early and accurate diagnosis to help control the spread of the disease, especially in developing countries. For these reasons, the CSIR is currently exploiting the high affinity, sensitivity and specificity of synthetic nucleic acid ligands – called aptamers – to develop a simple, inexpensive, rapid and accurate point-of-care TB diagnostic prototype kit.

## TUBERCULOSIS

Aptamer technology is a relatively new technology that emerged in the 1990s with a wide range of potential applications, including drug discovery, therapeutics and diagnostics. Aptamers are selected according to their ability to bind to a target molecule, which varies depending on the application. Also known as chemical antibodies, aptamers are emerging as a class of molecules that rivals conventional antibodies in both therapeutic and diagnostic applications. Like antibodies, aptamers recognise a target with high affinity and specificity, but can also discriminate between very subtle structural differences. The main competitive advantage of aptamers over conventional approaches includes their high specificity, high sensitivity, relatively low pro-

duction costs, convenience and simplicity, which allows for rapid point-of-care diagnosis.

Following the establishment of the CSIR aptamer technology group in 2006 under the leadership of Dr Makobetsa Khati, and the subsequent launch of a TB project in 2007, significant progress has been made in identifying aptamers that can be used in the diagnosis of TB. The group's first phase of research has focused on selecting suitable aptamers that bind to relevant TB antigens. These target proteins are secreted by the TB bacteria in infected patients, so their presence indicates active TB infection. Dr Khati explains that "aptamers could potentially fill the current gap in the availability of optimum TB diagnostic kits by providing enhanced molecular recognition of biomarkers of active TB infection." He adds, "the envisaged aptamer-based point-of-

care TB diagnostic kit will be relevant for resource-poor settings because it embraces important considerations such as sensitivity, specificity, affordability by those at risk of infection, ease of performance and reliability."

The next stage of research in developing this technology platform, funded by BioPAD for three years, will enable further characterisation of the aptamers identified, leading to the development of a novel, aptamer-based, TB diagnostic prototype kit. Once the prototype kit has been validated, optimised and benchmarked, it is set to be packaged and commercialised through a spin-off company. Other anticipated outputs of this research will include publication of results and extensive development of human capacity in this emerging field, favourably positioning South Africa as one of the world leaders in aptamer technology.

The initial phase of funding was supported jointly by the CSIR and DST, including additional multi-million rand funding from the DST for the establishment of a world-class P3 containment facility, required for work with clinical isolates of TB. The containment level 3-facility will be commissioned by the end of the year.

This research group is the only one of its kind focusing on aptamer technology in Africa and one of the few in the world. If successful, this TB diagnostic kit could significantly impact the lives of South Africans and contribute to the development of the South African biotechnology sector.

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The aptamer technology research team. In front is Dr Makobetsa Khati (group leader), flanked by intern Charlotte Maserumule. At the back are senior researchers Lionel Gresh and Jabulani Nhlapo.

# A novel way to deliver drugs found through **NANOTECHNOLOGY**

Nanotechnology is at the root of a drug-delivery mechanism that could see tuberculosis (TB) patients treated successfully within six to 12 weeks rather than six to nine months.



CSIR PRINCIPAL RESEARCHER Dr Hulda Swai explained in the March 2009 edition of *ScienceScope* that current TB therapeutics often fail because of patient non-compliance to the requirement of taking up to four anti-TB drugs several times a week for up to nine months. Swai and her team are developing a slow-release mechanism within the body so that not all the medicine is delivered at once.

Instead, the medicine is released over a number of days and only taken up by the body and delivered to the respiratory system gradually, making the medicine very effective. In tests conducted by the CSIR, the bio-availability of the CSIR-formulated drugs was up to six days as opposed to the 10 hours of the conventional method. Swai believes that the technology can be applied in future for delivering a number of drugs for a number of other illnesses and the team is now initiating research into the encapsulation of anti-malaria drugs with various research teams in East Africa.

In October the CSIR team working on this novel treatment walked away with the laurels at the SA Bio Plan Competition, organised by the Innovation Fund (IF) in collaboration with the biotechnology regional innovation centres and in partnership with Emory University of Atlanta, Georgia USA. The competition encourages the development of biotechnology businesses in South Africa. Hulda Swai, Lonji Kalombo, Boitumelo Semete, Tebogo Macheche and Phumza Langa received cash prizes and the project stands to gain an investment of R15 million from the IF to advance the technology to the point of commercialisation.

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# MALARIA



## CSIR research responses to the burden of malaria



Malaria is caused by a parasite called *Plasmodium* which is transmitted via the bites of infected mosquitoes. The most common type of parasite affecting humans is *Plasmodium falciparum* – this parasite multiplies in the liver, and then infects red blood cells.

If not treated, malaria can quickly become life-threatening by disrupting the blood supply to vital organs.

According to the World Health Organization, there were 247 million cases of malaria in 2006, causing nearly one million deaths, mostly among African children.

Malaria takes an economic toll – cutting economic growth rates by as much as 1.3% in countries with high disease rates. Over the long term, these aggregated annual losses have resulted in substantial differences in GDP between countries with and without malaria (particularly in Africa).

## EFFORTS TO STAY ONE STEP AHEAD OF THE MALARIA PARASITE

THE REMARKABLE ABILITY of all life forms to continuously adapt has ensured the survival of many species over many centuries. However, for those battling malaria, this ability is a stark reminder of the present-day dilemma of drug resistance, the ability of a parasite to survive despite the presence of a drug – essentially outsmarting mankind through continuous adaptation.

Drug resistance has become the number one concern in the battle against malaria: resistance to a first-line malaria drug like chloroquine emerged as far back as the 1960s, with follow-up drugs soon following this route. The fear is that resistance to current front-runner antimalarials, and eventually even to the combinations of these drugs, could see the world run out of treatment options. Some sources claim that malaria is re-emerging in areas where it had previously been eliminated.

The CSIR draws on an arsenal of knowledge in a variety of fields for its research in the quest to find effective new malaria treatments. This knowledge originates from the domains of natural product chemistry, synthetic chemistry, pharmacology, computational chemistry and aptamer technology.

# THE SYNTHETIC CHEMISTRY APPROACH NOVEL, COST-EFFECTIVE ANTIMALARIAL CHEMOTHERAPEUTICS

## Beating the malaria parasite at its game

In their quest to find new chemical entities for malaria drug development, Amanda Rousseau, CSIR principal researcher, and her fellow chemists David Gravestock, Arina Lourens and Simon Moleele, are concentrating on antifolates, a class of drugs that targets folate metabolism in *Plasmodium falciparum*, the parasite that causes malaria.

Their discovery of a series of compounds that has shown remarkably potent activity against a resistant strain of *Plasmodium falciparum* could potentially lead to a drug candidate. Their discovery has generated interest from investors and a full proposal for an interested party is under development.

Explaining the mode of action of antifolates in general, Rousseau says that folic acid derivatives are essential components in a number of key cellular processes in living organisms, for example DNA synthesis. Humans get their supply of folic acid from their diet, as the human body can't make it, although the body does have the ability to recycle the ingested

supply. The parasite on the other hand, has the ability to both synthesise and recycle folic acid derivatives. "Antifolates are drugs that inhibit the ability of the parasite to make and recycle folic acid," she says.

"Drugs targeting only the *de novo* synthetic pathway in the parasite – responsible for the synthesis of folate derivatives – are generally not all that effective when administered on their own and combination therapies are often used. The particular class of compounds we have designed targets the salvage pathway in the parasite, which is responsible for recycling folate derivatives."

She adds that when designing a drug that targets this pathway, the subtle differences in enzyme structure between the parasite and man must be taken into consideration, to ensure that man's ability to recycle folic acid is not inhibited.

Rousseau says the team chose to work on antifolates because this class of drugs is

cheap to produce – an important consideration in the African context. To boot, the target – the enzyme dihydrofolate reductase-thymidylate synthase (DHFR-TS) – is well known, and the mechanisms of drug resistance are very well understood.

While the essence of the innovation will be kept confidential until patents have been granted, Rousseau reveals that the innovation centres on the ability of their series of compounds to be sufficiently flexible to inhibit both drug-sensitive and drug-resistant forms of the parasite.

But Rousseau points out that finding a new active compound is only the beginning. "Finding an active compound does not equal finding a new drug. The compound also has to exhibit suitable bioavailability and toxicity profiles. Our hit compound meets the requirements of a 'validated hit' as defined by the Medicines for Malaria Venture – but we are a long way from having a drug available on the market."



Malaria fighters, from left Drs Simon Moleele, Arina Lourens, David Gravestock and Amanda Rousseau

“Over the next three years, we hope to optimise the pharmacokinetic properties of our lead compound, and this will require a multi-disciplinary team of chemists, pharmacologists, analysts and formulation specialists. We have a number of collaborators who will assist in this development process. In the first instance, a collection of analogues will be prepared, which will be evaluated in an extensive series of *in vitro* tests – tests that take place in an artificial environment outside a living organism – in an attempt to anticipate the behaviour of the compound in a biological system (i.e. its pharmacokinetic properties). Thereafter the research can progress to testing in small animals, such as mice, followed by larger animals. Only once safety is established in these models do you have a drug candidate, and Phase I clinical trials can be considered for human subjects.”

“To date, the South African research system has not developed a new molecular entity with biological efficacy to the point where it is a genuine clinical candidate, ready for further

safety and efficacy evaluation in humans. We think that our compound has the potential to be developed to the candidate stage in the next phase of our research and this would represent a significant achievement.

“Taking this project forward is challenging, but we have been excited and encouraged by our preliminary work. During *in vitro* tests, one of our compounds was found to be approximately 15 000 times more active than the existing antifolate, cycloguanil, with the majority of compounds showing potent activity against a drug-resistant strain of *Plasmodium falciparum*. Equally important is the lack of acute cellular toxicity.

“Although we are very far from having a new, affordable drug on the market, the development of a clinical candidate will greatly contribute to the fight against a disease that predominantly affects the African continent. It would also go a long way in stimulating a local pharmaceutical industry,” Rousseau concludes. – *Alida Britz*



CSIR principal researcher, Dr Amanda Rousseau

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## MALARIA



Synthetic chemists Dr Edwin Mmutlane, Lungi Sitole and Dr Chris van der Westhuyzen

## PICKING UP WHERE PHARMACEUTICAL GIANTS HAVE LEFT OFF: Developing an artemisinin alternative

IN ANOTHER RESEARCH PROJECT, Dr Chris Parkinson and his team of synthetic chemists are pursuing a similar objective: a new malaria drug; fewer side effects; affordable; with reduced reliance on a single source. They have set their minds on developing an artemisinin-based derivative. This class of drugs, called peroxides, is the only class of drugs to which *Plasmodium falciparum* has not yet shown signs of resistance. Recent Cambodian studies, however, have shown a slowing down in the rate at which the artemisinins act – suggesting that true resistance may emerge in the near future.

Worldwide, derivatives of this drug are used in combination with other drugs to abate the problem of resistance. Artemisinin-derived molecules are extremely potent antimalarials. It is extracted from a single species of a traditional Chinese medicinal plant – *Artemisia annua* – that grows in China and Southeast Asia and which is the prime source of artemisinin worldwide. However, the potential risk in availability, coupled with the fear for resistance development, is the drive for research on artemisinin derivatives and simplified peroxidic drugs. Furthermore, researchers hope that they will be able to remedy some of the undesirable properties of the drug.

One of the outstanding features of artemisinin is that it acts a lot faster than other drug classes. A new derivative should mirror or outperform this rapid action property as well



Dr Chris Parkinson

as the way it accumulates in the parasite. Ideally, the potential drug should degrade slower in the body and be amenable to single or two-dose therapy.

“In earlier CSIR-funded work, we have made good progress. Simplified, we tinkered with the skeleton – or structure – of artemisinin, to interfere with the parasite’s ability to respond to ‘invaders’, blocking its stress response and making it incapable of generating dihydroartemisinin (the metabolite responsible for many of the side effects). We developed synthetic protocols of the generation of a series of compounds and our *in vitro* tests showed activities more than ten times that of the parent in some cases, without apparent cytotoxicity. We have also made good progress in determining the onset of drug-induced stress,” says CSIR chief researcher, Dr Chris Parkinson.

Parkinson says the next step is to develop the drug lead further by investigating potency, bioavailability, toxicity and stability. Only then will the lead progress to small animal studies and regulatory pre-clinical evaluations. A portion of this is funded by the South African Malaria Initiative, a partnership established to facilitate the integration of malaria research and related capacity development in South Africa and the rest of Africa. He says international pharmaceutical companies are increasingly focusing their efforts on treatment for chronic diseases and diseases associated with aging. “The African continent will have to stand up for itself to address the neglected diseases that are ravaging the continent.”  
– Alida Britz

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# SELECTING FROM NATURE'S PHARMACY: BOTANICAL RESEARCH LEADS SHOW PROMISE IN THE FIGHT AGAINST MALARIA

IN THIS APPROACH to find a new malaria treatment, natural product chemists rely on their library of extracts of indigenous South African plants. They screen these extracts for activity against the malaria parasite. "In what is called a whole-cell assay, a red blood cell is infected with the malaria parasite, to see whether any extracts inhibit the growth of the parasite. An extract can be quite a complex mixture of compounds and the extracts are therefore fractionated – separated into components – to try and find the specific active compound in its purest form. It is not always simple, because it could also be a combination that acts against the malaria parasite," says research group leader, Dr Vinesh Maharaj.

As part of a multi-disciplinary consortium initiative, funded by the Department of Science and Technology, CSIR researchers have screened 134 plant taxa for *in vitro* antimalarial activity against a chloroquine-sensitive strain of *Plasmodium falciparum*. Forty-nine percent of these showed antiplasmodial activity with an IC<sub>50</sub> (concentration that inhibits parasite growth by 50%) of less than 10 µg/ml, while 17% were deemed highly active (IC<sub>50</sub> ≤ 5 µg/ml). Two of the compounds isolated are undergoing further development as potential antimalarials through funding by the Innovation Fund and the European Union's Antimalarial Programme. The compounds showed significant antiplasmodial activity in *in vitro* assays against both the chloroquine-sensitive and resistant strains of *Plasmodium falciparum*. They are currently being synthetically modified to improve on their antiplasmodial activity, selectivity (cytotoxicity vs. bioactivity) and bioavailability (rate of absorption). Only once this can be successfully achieved, can these leads progress to small animal studies and pre-clinical evaluations.

"These are not the first examples of nature providing template compounds for antimalarial drug discovery – both the quinoline and endoperoxide-based antimalarials originated from plants. It is by no means an easy task; it will be a remarkable achievement if the CSIR can come up with a new class of antimalarials originating from South African biodiversity," says Maharaj.



Dr Vinesh Maharaj and senior researcher Dr Xolani Peters study the results of an analysis to determine the compounds of a plant extract

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## MALARIA

They grow the malaria parasite in blood samples, often donated by themselves, in tissue culture flasks and then subject them to drugs and drug compounds, all the while studying every single move of every single cell. Pictured in front are PhD student Claire Rossouw and intern Sindisive Buthelezi. At the back are Patricia Mathabe, researcher; Dr Tharina van Brummelen, researcher; Dr Dalu Mancama, research group leader; Dr Tsepo Tsekoa, senior researcher and Dr John Becker, senior researcher. Dr Stoyan Stoychev (not pictured) makes up the eighth member of the team.



# A tool to assist in malaria drug discovery: A BIOMARKER THAT WILL TELL THE FULL STORY EARLY ON

UNDERSTANDING PRECISELY what happens at the molecular level when a malaria drug enters the system of a parasite – figuring out the mode of action – is key when trying to improve existing drugs to which resistance has developed, or to develop effective, new drugs. This is exactly the mission of a group of scientists in the CSIR's systems biology group.

The group has been studying the pathway of known antimalarials – analysing the data they have generated to understand the series of chemical reactions within the cells of drug-treated parasites, to learn as much as possible about the drug's mode of action. They are able to do this using the so-called 'omics technologies': genomics, transcriptomics and proteomics. These global approaches make it possible to (instead of studying one gene or protein at a time) understand the dynamic aspects in living organisms, for example, how proteins interact with one another. And it can be done in a high-throughput manner.

Dr John Becker, senior scientist and molecular biologist, says massive data sets are gene-

rated in the process of finding the target pathway of a drug. As part of their earlier work, they have a database of gene and protein expression profiles of the *Plasmodium falciparum* parasite that has been treated with malaria drugs such as artemisinin, cyclohexylamine, and others. This is being expanded, and additional profiles are being obtained for parasites treated with important drug classes not yet previously profiled," he says.

"So, for the data sets generated, we have elucidated how most of the parasite's genes and a subset of the proteins respond to the drug treatments performed," he says.

But working with large data sets has its challenges. "If you don't know what you're looking for, it's like looking for the proverbial needle in a haystack," says his fellow researcher and pharmacist, Dr Tharina van Brummelen.

She explains: "When you don't know where the answer lies, you have no choice but to look at all the possibilities. And the possibilities are vast. For starters, there are 5 000 to

6 000 predicted genes in the malaria parasite genome, which are represented by about 8 000 oligonucleotides on the microarray chip. Then you have to take into consideration that the parasite has a 48-hour life-cycle, so you have 8 000 values for every time-point sampled. In a set of 60 arrays, you generate 60 data files, each with approximately 8 000 value points. And then take into consideration that we are not only interested in gene expression, but also in proteins and metabolites."

Sound mathematical and statistical skills are needed to make sense of this data. Hypotheses are formulated from the mathematical results and confirmed with additional techniques.

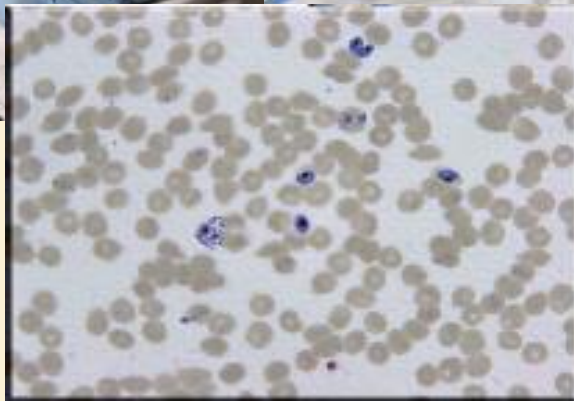
"Tedious and complicated as it may be," says Becker, "analysing these big data sets has proven to be a valuable exercise and has led us to our current research angle. It became evident to us that some genes seem to play a more critical role than others after drug treatment. In other words, when the parasite is under stress (brought about by drug administration), certain genes appear to be affected



Dr John Becker



Dr Tharina van Brummelen



*Plasmodium falciparum* parasites (mixed stages) in human erythrocytes

## THE COMPLEXITY OF STUDYING THE MALARIA PARASITE

Dr Tharina van Brummelen says the sequence of the malaria parasite genome was published in 2002. "The functionality of about 60% of the parasite's genes is still unknown – although the sequences are known, we do not know what most of the genes do. In mammalian cells, there are established techniques, but in working with the malaria parasite, you constantly have to optimise methods to do things," she says.

"The parasite's genetic code is very rich in "A" and "T" combinations, in other words, of the four nucleic acid bases that make up DNA, the malaria parasite has more than 80% Adenine/Thymine pairs – far more than in human beings, for example, and which makes it difficult to work with when using standard techniques. To boot, you are working with a parasite within a blood cell, which adds another level of complexity."

in a manner that suggests they play a critical role in the parasite's survival."

"We believe that these secondary effects – stress indicators – could be vital in the development of biomarkers. A biomarker is basically a substance that indicates biological status and can thus be used to assess health (in this instance the health of the parasite) or make a diagnosis of disease," he explains.

"Currently, when you test how effective a malaria drug is, a parasite count (or assay indicating the size of the parasite population) is done after 48 hours of drug treatment. (Typically the parasite multiplies by five in one cycle.) What these tests don't tell you, is which stage of the 48-hour life-cycle of blood stage parasites is sensitive to the drug. This is important information, because if the potential new drug is only active at a specific stage, its efficacy may be compromised, depending on when (at what stage of the parasites' development) the patient took the drug.

"Finding the answers through light microscopy is also problematic, because detecting subtle

morphological changes of such a small organism during the various development changes are prone to margins of error.

"But a biomarker would be very useful. It is our aim to develop a biomarker that can be used in early drug discovery. It should be useful to determine how effective a drug is; to determine its rate of activity; and at which stage the drug acts. This would greatly help all those researchers involved in early drug discovery," says Becker.

Research group leader Dalu Mancama is optimistic about the group's chances of success. "We are in year one of a two-year project. The team is working on three promising leads, including one which represents the most potent antimalarial described to date. Understanding the molecular effects of these compounds is key to identifying new targets within vulnerable systems in the parasite, that most likely have not been investigated or validated elsewhere.

These can subsequently be exploited towards developing new, more effective compounds

that expand the current range of drug classes available to combat the disease. The vast amount of information generated by this work makes it possible to, at the same time, mine this data to identify new biomarkers indicative of drug mode of action, and to validate recently discovered biomarkers developed for determining antimalarial drug efficacy.

Ultimately it is hoped that this new knowledge will contribute to expediting the drug discovery and development process," he says.  
– Alida Britz

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# DDT The devil you do,

Research by the CSIR and the University of Pretoria has shown that people living in areas sprayed with DDT are at risk of developing illnesses such as cancer when they consume the chicken, fish and vegetables produced in that area.

WHILE AN ESTIMATED 880 000 people – most of them young children – die each year of malaria in the developing world, we may underestimate the potential effects of continued DDT use on future generations.

In South Africa, as in several other developing countries, the use of the powerful insecticide DDT is allowed for malaria control in high-risk areas such as KwaZulu-Natal and Limpopo. However, DDT is also one of the 'dirty dozen' synthetically-produced chemicals banned by the rest of the world, as well as an endocrine disrupting chemical – meaning it can mimic or antagonise the function of hormones – giving rise to babies being born with severe genital ambiguity, or decreased semen quality in young men.

In a study funded by the Water Research Commission, researchers found disturbingly high levels of DDT and one of its byproducts, DDE, in the water, sediment, soil, vegetables, chicken and fish meat of the Vhembe District Municipality in Limpopo, on the border with Zimbabwe and Mozambique. According to the Limpopo Malaria Control Programme, this area has been sprayed with DDT annually since 1966.

Based on the results of their study, CSIR researcher Bettina Genthe, together with Drs Riana Bornman and Irene Barnhorn from the University of Pretoria, found that people living in areas sprayed with DDT, such as the Vhembe district, are at risk of developing especially cancer when they consume the chicken, fish and vegetables produced in that area.



Bettina Genthe



# the devil you don't

"Endocrine-disrupting effects were also observed and can be anticipated in the exposed population with effects observed in both the human and animal population and at the cellular level," they write in their report *DDT for malaria control: Effects in indicators and health risk*.

"In general, assuming exposure as described in the main body of the report, the health risk assessment indicates that the potential for serious health effects exists if people are exposed to affected water and selected food from the test areas, as well as part of the control areas. These possible health effects include neurological, reproductive and developmental effects. In addition, DDT is known to mimic oestrogen, while DDE is anti-androgenic. People will be exposed to a risk of developing cancer as well as toxic effects if they make use of untreated dam water. Ingestion of affected chicken or fish results in the highest risk of developing cancer and toxic effects."

According to Genthe, the World Health Organization is reconsidering its recommendation for allowing DDT in certain cases after the publication of the Pine River Statement on the human health consequences of DDT use in May this year. In 2008 a group of international researchers reviewed 494 studies that investigated the human health consequences of DDT and DDE exposure. They came to the conclusion that DDT may pose a risk to human health, and recommend further research to focus on human exposure and health effects in communities where DDT is currently being sprayed for malaria control, as well as more research into the development of safe and effective alternatives to DDT.

## DDT AS AN ENDOCRINE-DISRUPTING CHEMICAL

According to Genthe, DDT is not toxic to humans in the sense that you can die if you swallow it, for example. However, it is highly dangerous for the foetus of pregnant woman during certain critical stages of its development.

For example, all humans have 22 pairs of chromosomes and two sex chromosomes – the XX for females and XY for males. However,

the medical world has only recently discovered that just a very small portion of the Y-chromosome is actually responsible for the male gender. There is thus an entire continuum of possibilities (in terms of chromosomes, that is), before a female XX becomes an XY male.

"The Y chromosome might be small, but it contains a very important gene that determines the sex of a baby. We all begin life as a female in the womb. As we develop in the uterus, if the foetus is a male, the gene will cause a cascade of hormones to be switched on, which signals the female sex glands to develop into testes. It is still entirely possible, though, to have males with XX chromosomes. How? The gene responsible for switching on the male sex glands is moved to the X chromosome. It is also possible to have females that are XY with the male sex gene absent from the Y chromosome," Genthe explains.

In addition to chromosomal abnormalities, this process can also be affected by endocrine disruptors that inhibit the switching on of the male sex gene or mimic the female sex hormones. Endocrine disruptors such as DDT disrupt this process, so that you can have a person with female external genitals, but male chromosomes (Androgen insensitivity syndrome), and vice versa.

## HISTORY OF DDT USE

The most powerful synthetic insecticide then known was discovered in 1939 by the Swiss chemist Dr Paul Muller. He found DDT to be fatal on contact in extremely minute quantities to an incredibly wide range of insects, with no obvious toxic effect on humans. In the middle of the Second World War doctors opted for this synthetic, mass-produced and cheap wonder-insecticide to tackle malaria, epidemic typhus (carried by body lice), and dysentery and typhoid fever (both carried by houseflies) to protect their soldiers all over the world.

After the war DDT was made available for public use and took the world by storm. According to the *American Heritage Magazine* it was estimated that "by 1950 DDT had saved five million lives over the world through destruction of malarial mosquitoes". In 1948 its inventor was awarded the Nobel Prize for Medicine.

At the same time, however, the American writer and biologist, Rachel Carson, caused a revolution with her book *Silent Spring*, in which she described a world destroyed by the genetic evolution caused by a manmade pesticide as powerful as DDT. In other words, because DDT is so persistent (it can take 6 to 10 years to degrade), it accumulates in the fatty tissue of organisms, eventually finding its way to man at the top of the food chain, in a process called bio-magnification. While DDT does not kill directly, it inhibits reproduction because of its endocrine disrupting characteristics. In her book, Carson created an apocalyptic view of the world in her final chapter where eventually neither humans nor nature are capable of reproduction. By 1963 the US recommended the reduction of the use of DDT.

In 2001, more than 100 countries signed the Stockholm Convention on Persistent Organic Pollutants (POPs), committing to eliminate the use of the twelve POPs of greatest concern to the health of the global community. By 2008, 160 countries had ratified the Stockholm Convention, including South Africa, making it one of the most successful international environmental agreements. – Wiida Basson

## THE PINE RIVER STATEMENT: HUMAN HEALTH CONSEQUENCES OF DDT USE

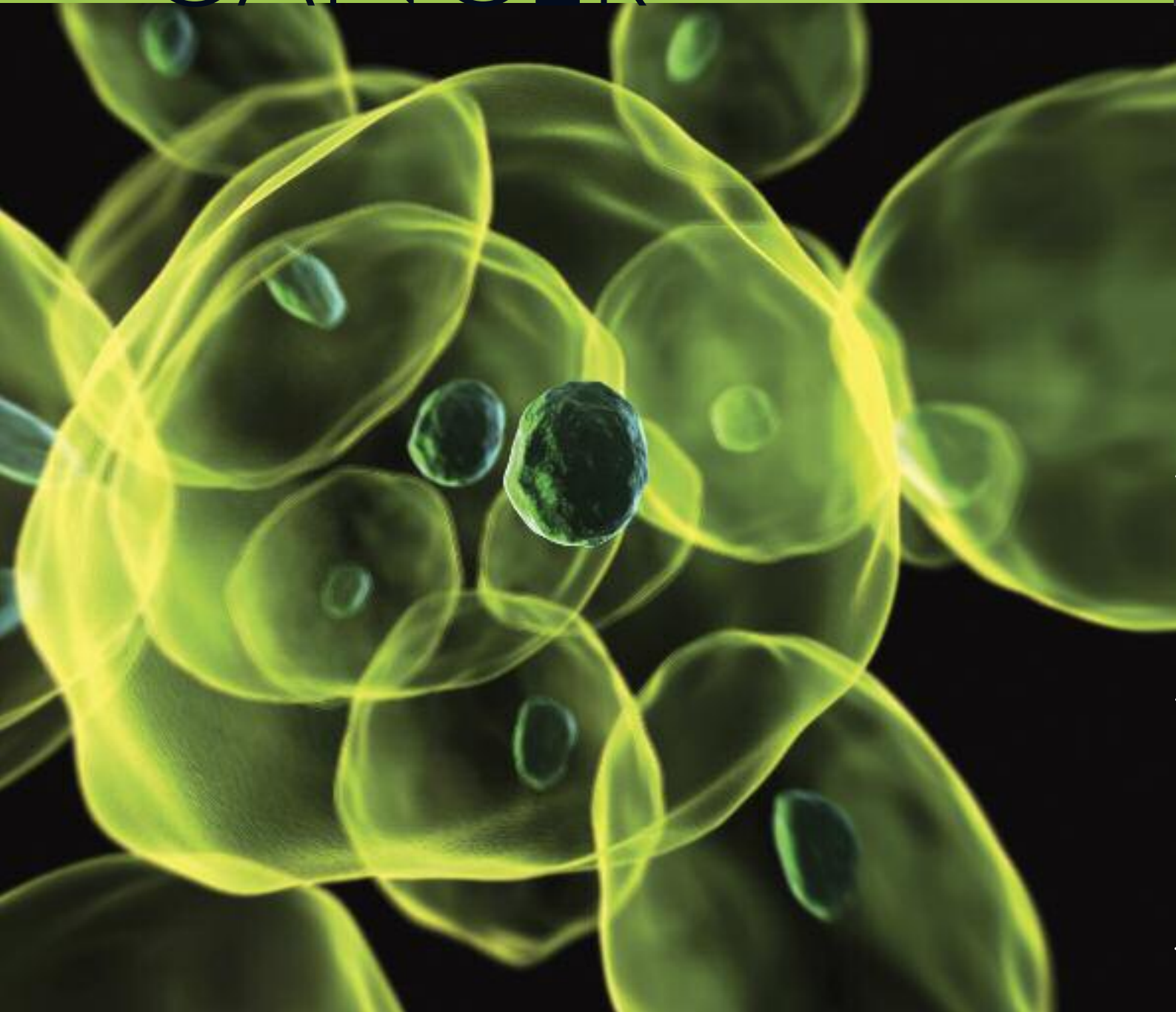
"Current evidence on DDT exposure to human populations and on its potential health effects supports the Stockholm Convention on Persistent Organic Pollutants which emphasises that DDT should be used with caution, only when needed, and when no other effective, safe and affordable alternatives are locally available. Under the Convention, each country currently using DDT is required to provide an implementation and management plan to limit the use of DDT to disease vector control, and to reduce reliance on DDT."

"We are concerned about the health of children and adults given the persistence of DDT and its active metabolites in the environment and in the body, and we are particularly concerned about the potential effects of continued DDT use on future generations."

Source: Eskenazi, Brenda et al. 2009. The Pine River Statement: Human Health Consequences of DDT Use. Environmental Health Perspectives. Available at <http://dx.doi.org>

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# CANCER





Aletta Karsten

# LASER STUDIES ON SAFE DESTRUCTION OF CANCEROUS CELLS

According to the latest statistics of the Cancer Association of South Africa, the lifetime risk of a South African male to get cancer is one in six, and for females, it is one in eight.

Cancer arises from a change in one single cell. The change may be started by external agents and inherited genetic factors.

The World Health Organization projects that deaths from cancer worldwide will continue rising, with an estimated 12 million deaths in 2030.

According to ehealth MD web site, ultraviolet (UV) radiation from the sun is the main cause of skin cancer. UV rays damage DNA, the genetic material that makes up genes.

SOUTH AFRICA'S SUNNY SKIES is both a boon and a curse – while one group of scientists is working on energy solutions from South Africa's abundant sunshine, another is striving to find solutions for skin cancer, often caused by overexposure to sun.

Researchers at the CSIR are working with South African universities on an alternative method of treating cancer. Photodynamic therapy (PDT) is a treatment where a photosensitiser (PS) or drug is applied (either topically in the form of a cream or intravenously) to the tumour and after a period, the tumour is irradiated with a light source – normally a laser of a specific wavelength – that is absorbed by the photosensitiser.

The reaction between the activated PS and oxygen in the cells yields oxidation radicals (primarily singlet oxygen). These radicals attack critical sites in the cells, causing cumulative oxidative damage. When the accumulated damage exceeds a threshold, cell death occurs.

"Basically, our research focuses on light interaction with biological materials," says senior biophotonics researcher Aletta Karsten, adding that PDT has been approved in the US and in European countries and that there are more than 25 approved treatment modalities – but not yet in South Africa. Work in the CSIR labs focuses on PDT treatment of skin cancer and evaluating the drugs developed in South Africa. The chemistry department at Rhodes University, under the leadership of Professor Tebello Nyuokong, is developing the drugs currently under investigation.

She points out that, to deliver the correct amount of laser power to the tumour, it is important to understand the interaction of laser light with the tissue. "When treating patients, it is imperative to deposit the minimum laser light required throughout the

treatment area, without causing damage to the healthy tissue by depositing too much energy or heat," she explains.

Computer modelling is used to determine the laser power at different depths in the skin and tumour. It is hoped that this will aid health practitioners to determine the best combination of the laser power on the tissue surface and the optimal treatment time.

Human skin is considered to be a highly scattering medium for light and the melanin in the skin acts as an absorber of light. The scattering and absorption effect in the skin attenuates the amount of laser light that reaches a certain depth in the skin.

The optical parameters (absorption, scattering, anisotropy and refractive index) at the treatment wavelength – as well as the thickness of the skin layers, especially the epidermal layer that contains the absorbing melanin or melanosomes – are important when the amount of laser light, or dose, is calculated. To do this, it is important to understand the effect of the different optical properties in skin and their influence on the absorption of the light.

"We treat the cancer cells *in vitro* in the laboratory with a drug and shine a laser on it. It is also important to test the drugs on healthy cells to ensure that one does not kill too many healthy cells during the treatment," says Karsten.

The CSIR is at present investigating how much of the drug and how much laser light is needed to kill a specific form of skin cancer. The organisation has been working on this research for about two years. "We are testing three different drugs on three different cancers and we are getting good results," Karsten says. – Mzimasi Gcukumana

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# DIARRHOEA





## CSIR researchers appeal for monitoring of diarrhoea in adults

Diarrhoea mostly results from contaminated food and water sources.

The most severe threat posed by diarrhoea is dehydration.

Diarrhoea is a symptom of infections caused by various bacterial, viral and parasitic organisms. It mostly spreads through faeces-contaminated water. Infection is more common when there is a shortage of clean water for drinking, cooking and cleaning.

Worldwide, around 1 billion people lack access to improved water and 2.5 billion have no access to basic sanitation.

Source: The World Health Organization

## Diarrhoea now the **THIRD-BIGGEST KILLER** in South Africa

INCREASING NUMBERS OF CHILDREN, the elderly and even adults, are dying from diarrhoea in South Africa, making it the third-leading cause of death in the country.

A recent CSIR study has reported a steady increase in diarrhoeal death statistics in South Africa over the last 12 years – with a significant increase in diarrhoea-related deaths for adults aged between 45 and 64.

Diarrhoea as underlying natural cause of death for all ages has increased from being the 10th leading cause in 1998 to become the third-leading underlying natural cause of death for two consecutive years in 2004 and 2005.

While the highest death rates were recorded for the vulnerable age groups (children under five and the elderly), the researchers were surprised to note an increase in adult deaths due to diarrhoea for each province. The trend was particularly visible for the age groups 45 to 55 and 55 to 64.

## DIARRHOEA

According to CSIR researchers Maronel Steyn and Bettina Genthe, diarrhoea statistics are an important indicator of the health of a community. "Diarrhoea incidence for children under the age of five is noted at hospitals and clinics and is available on a national database. However, currently almost no attention is given to adult diarrhoea," they argue in a paper presented at the International Water Association's Health-Related Water Microbiology Conference this year.

Despite major efforts and impressive improvements in recent years, 2.11 million South Africans still lack access to any water infrastructure, with more than 6 million not enjoying access to private water supplies. According to the Department of Water and Environmental Affairs more than 12 million South Africans still lack access to any form of sanitation.

The researchers used data from the Department of Health's National Information System (1997-2003) and National Population Survey results from Statistics South Africa (2005) to assess the current trends in diarrhoeal death and disease in the country. When this data were compared with the factors contributing to diarrhoeal disease it indicated an interesting correlation between the number of people with HIV/AIDS and people not having access to private water supply.

According to Steyn and Genthe, people who have to collect water from outside the family unit, from a communal tap for example, are more at risk of contamination than if they had access to private water within the family unit (even though that water could also be contaminated). Therefore access to private water within the family unit is critically important.

"Access to piped water does not indicate any health benefits. If people have to collect water from a communal tap there is a chance of contamination from outside the family unit, whereas if water is contaminated in your own yard it will come from within the family unit and not cause additional adverse health effects. In other words, all germs are not created equal," explains Genthe.



Maronel Steyn

### ALL GERMS ARE NOT CREATED EQUAL

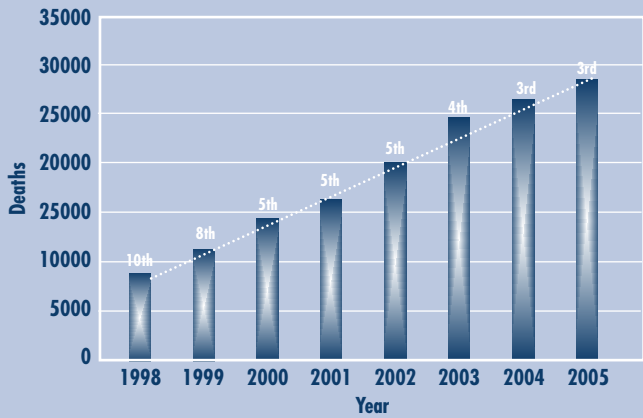
According to an earlier international study in the journal *Water Resources Research*, family members are likely to develop some level of immunity to those germs commonly encountered in their own household environment. In addition, even if one or two individuals in the household are HIV-positive or in any other way immuno-compromised, they are more likely to be adversely affected by germs transmitted by other individuals than by the contaminated water within that household. People are put at risk the moment new germs are introduced to a household either via an outside water source, or via person-to-person contact or food contamination. Therefore the hypothesis that "all germs are not created equal".

Van Derslice, J., and J. Briscoe (1993), All Coliforms Are Not Created Equal: A Comparison of the Effects of Water Source and in-House Water Contamination on Infantile Diarrheal Disease, *Water Resour. Res.*, 29(7), 1983-1995.



Bettina Genthe

### DIARRHOEAL DEATH RATES FOR ALL AGES IN SOUTH AFRICA



Diarrhoeal death rates for percentage of households with access to private water supply according to province



KwaZulu-Natal, Limpopo and the Eastern Cape have the lowest percentage of access to private water supplies in the country – this puts them most at risk for microbiological contamination of treated water supplies and associated diarrhoeal disease burden.

- No access to private water supply (eg uses communal taps, rivers, springs)
- Access to private water supply (eg water in yard or house)

Merely providing people with access to good-quality water isn't enough. People with compromised immune systems can easily get infections and develop diarrhoea. It is important that these people should be provided with private access to good water supplies, either in their yards or in their homes."

According to Steyn and Genthe a change in policy – for example reporting on diarrhoea for all age groups – could assist in determining the extent of diarrhoea in the total population to allow for proper planning to prevent unnecessary deaths from diarrhoea. –Wiida Basson

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# SILICOSIS AND NOISE-INDUCED HEARING LOSS

## SCIENCE AT WORK TO ENSURE **THE HEALTH OF SA'S MINERS**

The CSIR recently reorganised its mining research and launched the Centre for Mining Innovation, based in Johannesburg. The centre intends to meet current and projected future needs of the mining industry by focusing on research into real-time risk management, novel mining methods and human factors.

In terms of human factors, both the physiological and psychological impact of environmental, organisational and job factors associated with mining on mine workers are being researched. CSIR principal researcher Schu Schutte and leader of the human factors research group says there are enormous requirements for research to identify measures to reduce and prevent workplace risks, such as the eradication of noise-induced hearing loss and silicosis, a lung disease caused by inhaling particles of silica, for example. (See adjacent articles on research in this regard.)

But, increasingly, says Schutte, there is awareness amongst mining researchers that psychological factors,

When going to work could mean gradually becoming hard of hearing

## TOWARDS **ERADICATING HEARING LOSS** IN THE MINING SECTOR

such as work stress, are impacting on people-orientated work systems and that this may be contributing to accidents and injuries. Over the next year, a research team, in collaboration with developers of a psychological fitness index, will investigate biological indicators of stress in a mining environment in an attempt to quantify the prevalence and impact of workspace stress. Increases in cortisol levels, glucose levels, heart rate and core body temperature are some of the biological indicators of psychological and physiological strain and are aspects that will come under investigation. After an exploratory study which will basically be aimed at understanding the reality of work in mines, a larger sample in the mining industry will participate in the research project. Results of the research will be communicated upon its completion by the last quarter of 2010.

Also read about CSIR guidelines drawn up to prevent fatigue in the work environment, *ScienceScope* January 2009, p54.

Far below the earth's surface, inaudible to most South Africans, high-power drills and mining equipment are noisily generating revenue. This noise can be deafening to the operators.

Approximately 350 000 South African miners earn their living in arguably the noisiest of all industries – one which, without the implementation of hearing conservation programmes, goes hand-in-hand with the loss of hearing and associated reduction in quality of life. CSIR researcher and audiologist, Anita Edwards, outlines the issue: "Our laws accept 85 decibels as the acceptably safe noise level for exposure during an eight-hour work day without ear protection. A drill used in a mine can generate noise levels of over 110 decibels. By comparison, a jet engine on the runway typically generates a noise of about

120 decibels." Edwards says that before 1996, hearing conservation programmes were not enforced in South African mines and in an informal context, hearing loss was, shockingly, a measure of how experienced a worker was in the industry. "Deafness in an older man with years of experience earned him respect," says Edwards.

Much progress has been made since. South Africa's Mine Health and Safety Council (MHSC), with its mandate to improve occupational health and safety in mines, has set the industry a target of reducing all noise sources underground to below 105 decibels by 2013. They also believe that there should no longer be cases of hearing loss of more than 10% as a result of exposure to noise in the mining sector.



The mining sector is striving to eliminate cases of hearing loss of more than 10% as a result of exposure to noise. Engineering advances to equipment such as this, used by an underground worker at Tau Tona mine, and high-quality hearing protection will contribute to this aim. (Image courtesy AngloGold Ashanti)

## SILICOSIS & NOISE-INDUCED HEARING LOSS



Protective gear is provided to help protect miners, such as this worker at the Tau Lekoa Mine. (Image courtesy AngloGold Ashanti)



Edwards believes this is within reach: engineering advances should be applied to reduce the noise generated by equipment; miners should be equipped with the highest quality hearing-protection devices; and training on the issue must be pervasive. Edward argues that loss of hearing is preventable. "No mine worker should find himself relegated to a lower-earning job because his hearing has been affected."

But there are factors at play which complicate the prevention of hearing loss. "Wearing protective devices means that you block out speech sounds as well, so to hear your colleague, you have to remove the protection. The heat, coupled with physical activity, makes wearing hearing protection devices uncomfortable for some. And increasingly, it is becoming evident that the synergistic combination of environmental health stressors and lifestyle stressors adversely impacts hearing," she says.

### CSIR RESEARCH ON ALTERNATIVE TESTING METHODS FOR HEARING LOSS

Edwards and her colleagues have undertaken various research projects in the area of hear-

ing loss of mine workers. In a pilot study undertaken in a platinum mine last year, Edwards and her fellow researchers investigated an alternative testing mechanism for determining loss of hearing during annual medical check-ups by correlating the results of behavioural audiograms (the current standard) with distortion-product otoacoustic emissions. The researchers found that it is feasible to use otoacoustic emission testing during annual medical surveillance but that obstacles, such as skills levels for testing and interpretation, must be addressed.

Edwards compares otoacoustic emissions to an X-ray on which you can see the physical mark on a lung and predict what problems will be experienced with the patient's breathing. In the same way, this technology indicates the health of the outer hair cells of the cochlea.

"Audiograms are subjective. A cultural difference between the tester and the individual being tested can impact on the result. The test can also be manipulated by an individual who exaggerates a hearing loss for purposes of financial compensation. Otoacoustic emission testing allows for diagnosis of hearing damage and could even play a preventative role through early indication of hearing loss." Some of the results in the pilot study included the fact that 73% of those with normal hearing

already had cochlear damage, despite the lack of evidence on the screening audiogram. Similarly, in a group with mild hearing loss, 42% of subjects showed more cochlear damage than would be expected based on the audiogram. It is hoped that the results will direct the way in which noise-induced hearing loss is managed in the future.

### CSIR RESEARCH INTO THE USE OF TRAINING MATERIAL FOR THE PREVENTION OF NOISE-INDUCED HEARING LOSS

Knowledge and awareness of noise-induced hearing will remain key in its prevention, says Edwards. The CSIR was contracted by the MHSC to evaluate and improve existing training material on noise-induced hearing loss. A survey was conducted to assess accessibility of the material; its motivational value, relevance, enabling value and technical quality. The results were used to upgrade and modernise the existing training video and booklets. Training materials are now available in more African languages. Once completed, the training material was evaluated and proved more effective than previous material.

She has tested more than 10 000 ears in her working career and remains passionate about hearing conservation. Anita Edwards is an occupational audiologist, in the final throes of her PhD studies, who wants to continue research that will help prevent hearing loss amongst ordinary citizens.

The CSIR has also recently evaluated all locally available hearing-protection devices, specifically in relation to frequency-specific noise exposure. A compendium was compiled that allows occupational health practitioners to choose the most effective hearing-protective device.

## CSIR RESEARCH ON 85 DECIBELS AS THE OCCUPATIONAL EXPOSURE LIMIT

Speaking at a conference hosted by the Southern African Institute of Mining and Metallurgy in the last quarter of 2009, Edwards said recent evidence pointed to a synergistic effect of chemicals; exercise or workload; and heat, on the inner ear. "The fact is that miners are not exposed only to noise in isolation. The concern is that the 85 decibel exposure limit may not be enough to prevent hearing loss in miners in light of the combined effect of these environmental stressors," says Edwards. A pilot study was undertaken in the CSIR's climatic chamber, using otoacoustic emissions as a measure of stress to the cochlea, during controlled exposure of a healthy group to noise, heat and exercise.

"When we combined physical exercise with noise, the measurements pointed to a synergistic impact. Noise combined with heat, had more of an impact than noise alone. When all three stressors were combined, levels deteriorated at five of the frequencies tested," said Edwards.

Edwards hopes to expand this research to bigger sample sizes, saying that the study was a first step in beginning to quantify the individual and combined effects of health stressors. – Alida Britz

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## MINING AND HEALTH

Mining remains one of the most hazardous occupations in the world, both in terms of short-term injuries and in terms of long-term impacts such as respiratory conditions and noise-induced hearing loss.

Compensation claims related to noise-induced hearing loss cost the SA mining industry over R890 million from 1998 to 2008.



Cecilia Pretorius, analytical chemist by training, and a team of occupational hygienists at the CSIR Centre for Mining Innovation, are committed to understanding how the different compounds in dust in the mining sector affects human health.

# SILICOSIS: DUST DEVIL

Research in support of the eradication of silicosis

Silicosis, a deadly lung disease, is one of the oldest occupational diseases in the world. It is caused by inhalation of respirable dust (particles less than ten micron) containing free crystalline silica, which is a basic component of many minerals and rocks. South African miners, particularly gold miners, face this lurking danger during underground operations. Gold ore typically contains a lot of quartz, which is the most common form of crystalline silica.

## EFFORT TO REDUCE SILICOSIS

The World Health Organization is driving efforts worldwide to eliminate the disease. South Africa, through the Department of Minerals and Energy, has set a target of eradicating the disease in mines by 2013 – no previously unexposed miners should acquire this disease thereafter. The country's Mine Health and Safety Council (MHSC) has been funding projects in dust measurements since its formation in 1994. In 2006, the council awarded a five-year research project to the CSIR to measure and analyse the occurrence of silica dust as well as how it was reported; to identify sources of dust and recommend how to control it and to monitor the results of environmental control engineering measures. Currently in year four, CSIR researchers are measuring the silica levels following implementation of control measures. Sampling at coal mines after implementation of control measures has been completed, while post-sampling in gold mines is set to start shortly.

## CONTROL AT SOURCE

Researcher at the CSIR Centre for Mining Innovation and analytical chemist by training, Cecilia Pretorius, says the occupational hygiene approach is always to control at source. "It is not as simple as issuing miners with dust-masks or respirators. The conditions in mines are harsh. Convincing someone to wear a filter when he is hot; needs to communicate with his colleague; is breathing heavily as a result of physical work; and needs good vision from all angles, is problematic and as a sole preventative measure, will not halt silicosis. The dust has to be controlled at source," she says. This principle is at the root of existing environmental control practices, which, for example, include specified re-entry periods after rock blasting; enclosure of transfer points to reduce dust from tipping; and the use of auxiliary ventilation air to reduce dust by dilution and displacement.



## CSIR RESEARCH OUTCOMES TO DATE

During the first phase of the research, dust sources in gold and coal mines were identified and sampled to ascertain their contribution to the overall respirable dust load in the underground working environment. Commenting on some of the research outcomes in the chosen gold mine, Schu Schutte, CSIR principal researcher, says that development drilling, rock hoisting and wire mesh drilling were the three activities that contributed most to the overall respirable dust load. The main contributors to the overall respirable silica dust load were rock hoisting, shaft ore passes, conveyor belts and transfer points. The dust sources in a selected coal mine were also assessed and the results showed that continuous miner cutting and the transfer points contributed the most to the overall respirable dust load. Future aims of the study include assessing the dust sources in a longwall coal mine, after which dust control technologies will be implemented in all three these commodities. Measurements will then follow the implementation in a post-evaluation study to determine the effectiveness of these controls in lowering the respirable dust and silica dust liberated into the air by the underground mining activities, hence lowering the exposure to these dusts.

## THE SCIENCE OF MEASURING DUST

During dust-measurement studies, sampling is done by attaching an air filter – placed in a cassette and connected to a sampling pump – to the lapel of a miner's clothing in his 'breathing zone'. The volume of air inhaled is calculated and a time-weighted average determined for an eight-hour shift. The milligram per cubic metre of silica exposure is thus determined. The sampling process is overseen by CSIR occupational hygienists and then analysed by laboratory analysts. "There are many variables in measuring and analysing exposure to silica. This is one of the reasons that the measuring of dust exposure has almost become a science in itself," says Pretorius.

She says the CSIR uses numerous laboratory-based techniques for exact measurements of exposure to dust. She is quick to point out that workers also suffer from other respiratory diseases as a result of exposure to dust, and therefore not only silica particles are of significance when analysing dust samples.

The scarring of the lungs by silica dust particles causes stiffening of the lung, which obstructs breathing.

Once exposed to silica, the disease will progress, even when exposure stops – it is irreversible.

The damage-causing particles are invisible to the human eye, and can remain air-borne for extended periods of time.

Silicosis is a slowly progressive disease – it can remain symptom-free for up to two decades after exposure has stopped.

Silicosis results in conditions such as fibrosis and emphysema, and according to international research claims, is associated with lung cancer.

"Firstly, we do gravimetric weighing to determine the quantity of respirable dust to which a mine worker has been exposed during his/her shift. Occupational exposure limits for dust are set for mines and depend on the commodity that is being mined. We also use a highly specialised process called X-ray powder diffraction to determine the concentration of crystalline silica in the respirable dust sample.

"Particle-size analysis is the next technology we employ, and for this we use laser light scattering to determine the sizes of the particles to which a mine worker was exposed. Larger particles are typically prevented from reaching the lung's gas exchange region (alveoli), while smaller particles are generally considered the most dangerous. Our recent acquisition of an infrared microscope further enables us to differentiate between different chemical compounds on a filter (direct-on-filter), so that the concentration of silica can be pinpointed," Pretorius explains.

"Scientific advances have made it possible for us to measure and identify dust particles, but for testing to be truly pervasive, we have to ensure that tests can be done quickly and cost effectively. In support of the mining industry's efforts to reduce not only injuries and accidents, but also harm to workers, the CSIR intends to continue with its efforts to optimise

analytical methods to measure dust," says Pretorius.

Experts in the analysis of silica from around the world gathered at the CSIR in October this year when the CSIR hosted an ISO workgroup on silica, which forms part of a sub-committee on air quality. The workgroup has already developed a guidance method for the measurement of respirable crystalline silica, ISO 24095. The workgroup is embarking on a project to develop a new international method for the direct-on-filter analysis of silica using X-ray powder diffraction.

Also read about the measurement of diesel exhaust emissions in mines in *ScienceScope*, January 2009. Exposure to diesel particulate matter has been linked to various health problems. The CSIR made numerous recommendations, some of which have been implemented in a select group of mines, despite the fact that no legislation is currently in place to guide local mines on safe levels of diesel exhaust permitted underground. – Alida Britz

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# MALNUTRITION



# Nutritionally enhanced SORGHUM for improved African health

Novel technology developed by CSIR researchers and Pioneer Hi-Bred Inc offers an enhanced transformation process for use in genetic engineering of crops.

Nutrition disorders can be caused by an insufficient intake of food or of certain nutrients or by an inability of the body to absorb and use nutrients.

Vitamin A deficiency is a micronutrient deficiency and the leading cause of preventable blindness in children. It increases the risk of disease and death from severe infections.

Source: The World Health Organization

AS PART OF AN AFRICAN-LED consortium, the CSIR is progressing significantly on the African Biofortified Sorghum (ABS) project, and in early 2009 filed two patents in collaboration with Pioneer Hi-Bred Inc. The aim of the ABS project is to develop a more nutritious and digestible sorghum, containing increased levels of essential amino acids (especially lysine), pro-vitamin A and vitamin E and bio-available iron and zinc. Luke Mehlo, CSIR researcher, says, "Sorghum is uniquely adapted to the climatic conditions of the African continent and copes well with marginal agronomic conditions including tired, nutrient deficient soils and droughts - so much so that even when under extreme water stress, it produces some yield because it continues to photosynthesise and stays green."

However, although highly adapted to African conditions, sorghum is deficient in essential amino acids and vitamins. The little protein and micronutrients it does contain are 'locked up', making this goodness even more unavailable when cooked. Despite being relatively low in nutritional value, sorghum is grown and eaten extensively in Africa, and already feeds millions on the continent. Although it has been improved to some degree by traditional breeding, sorghum research has lagged behind major crops such as rice and wheat, which are eaten throughout the world. Mehlo explains that sorghum is "ripe for further improvement, especially for a continent that is plagued by malnutrition, which remains a leading, direct cause of the rise in many non-communicable diseases, especially in Africa."

Scientific evidence shows that deficiencies in essential micronutrients - such as iron, zinc, vitamin A and others - can cause impaired immune systems, blindness, low birth weight, impaired neuropsychological development and growth stunting.

Within the ABS project, CSIR researchers are improving sorghum's nutritional value using genetic modification (GM) techniques, which



From embryo to transgenic sorghum: high-throughput transformation system for sorghum established at the CSIR

## MALNUTRITION



From the lab to the greenhouse: A tissue culture room is a transition phase for nutritionally fortified sorghum. Pictured in the tissue culture room is Nompumelelo Mkhonza who was selected to represent SA at an international biosafety assessment course.

are considered more precise, predictable and quicker than traditional plant breeding. Selected genes from other edible plant species, such as maize, are being introduced into the sorghum genome. For some traits (desirable characteristics), sorghum genes are improved and reinserted, and for others, genes within sorghum are being 'switched off' as they hamper the accumulation of nutrients (e.g. breaking down accumulated pro-vitamin A).

A bacteria called *Agrobacterium tumefaciens* is being used to insert the genes. In nature, *Agrobacterium* transfers a segment of its DNA, called T-DNA, into plants, 'tricking' the plant into expressing this gene and producing nutrients for the *Agrobacterium* to survive. This system is being exploited by researchers, by modifying the T-DNA section of the *Agrobacterium* and using it as a 'transporter'. The T-DNA is replaced with the desired trait genes of interest and the *Agrobacterium* transfers these to the plant cell, 'thinking' it is transferring its own genes to produce nutrients.

These genes are then integrated into the plant's genome. Ultimately, all of these desired traits will be combined into one 'stacked' sorghum variety.

Since sorghum is indigenous to Africa and wild relatives are found throughout the continent, precautions are being taken to ensure these populations are protected. Antibiotic resistance markers are not used in this project. This is in line with international trends to phase out this type of marker. New technologies such as positive selection are being investigated, which make use of existing abilities and traits of the plant. In the ABS project, a safe positive selection system based on the gene *phosphomannose isomerase* (*pmi*) is used. This system allows transgenic cells to utilise mannose instead of sucrose in the tissue culture.

The two patents being filed under the ABS project relate to different aspects of the transformation process. One improves gene transfer efficiency by activating genetic sequences in the *Agrobacterium* that are responsible for transferring the T-DNA. This improves the uptake of the genes being transferred by *Agrobacterium* – a system that allows uptake of mostly one copy of the transferred gene, which is preferential to multiple copies. The other patent involves a method to convert normal cells into a form of progenitor cell line – which is undifferentiated and developmentally

flexible - and easily become a number of different types of cells as directed by hormones. Together, these novel technologies impact various stages of the transformation process, by targeting the plant cells to receive the DNA and to grow well in tissue culture, and by providing flexibility, enabling the transformed cells to organise into tissues, organs and whole plants. Once approved, this technology will be a world first. These patents are being filed to protect the technology being developed to enable it to be made available to the poor in line with the policy of the project funders (global access strategy).

"The ABS project partners have worked hard to reach this point, with the initial permit for contained greenhouse trials of GM sorghum being refused in February 2007," says Mehlo. "Following an appeal, and constructive engagement by the CSIR and the GMO Executive Council – the decision-making body for GMO permits in South Africa – the permit was eventually granted in September 2008." This was conditional upon the completion of the newly constructed level 3 containment greenhouse facility at CSIR, needed to prevent the GM sorghum from 'escaping' into local wild populations. The outcome of this engage-

ment and the granting of the permit reflect an important aspect of the ABS project – that of strict compliance with national and international GMO regulations and upholding the safety of environmental, human and animal health over research.

The first phase of the ABS project began in 2005 and is due to be completed in 2012. Led by Africa Harvest Biotech Foundation International, the consortium involves nine other members contributing different aspects to this project. The ABS project is funded by the Bill and Melinda Gates Foundation as a Grand Challenge in Global Health initiative. Funding is currently being sought for a second phase of the project until 2017.

## COLLABORATION AND CAPACITY BUILDING

Collaboration is key to the success of this project and has enabled extensive human capacity to be developed to date. CSIR researchers Luke Mehlo and Andile Grootboom both spent extensive periods at the Pioneer laboratories in the US to become familiar with the cutting-edge molecular biology and plant modification techniques. According to Mehlo, this “enabled the project to be kick-started” and has resulted in the novel techniques developed to date. Complementary funding from the Biosafety Research Network enabled CSIR MTech student, Nompumelelo Mkhonza, who was selected to represent South Africa, to attend an eight-week course on biosafety assessment at the University of Nebraska in the US.

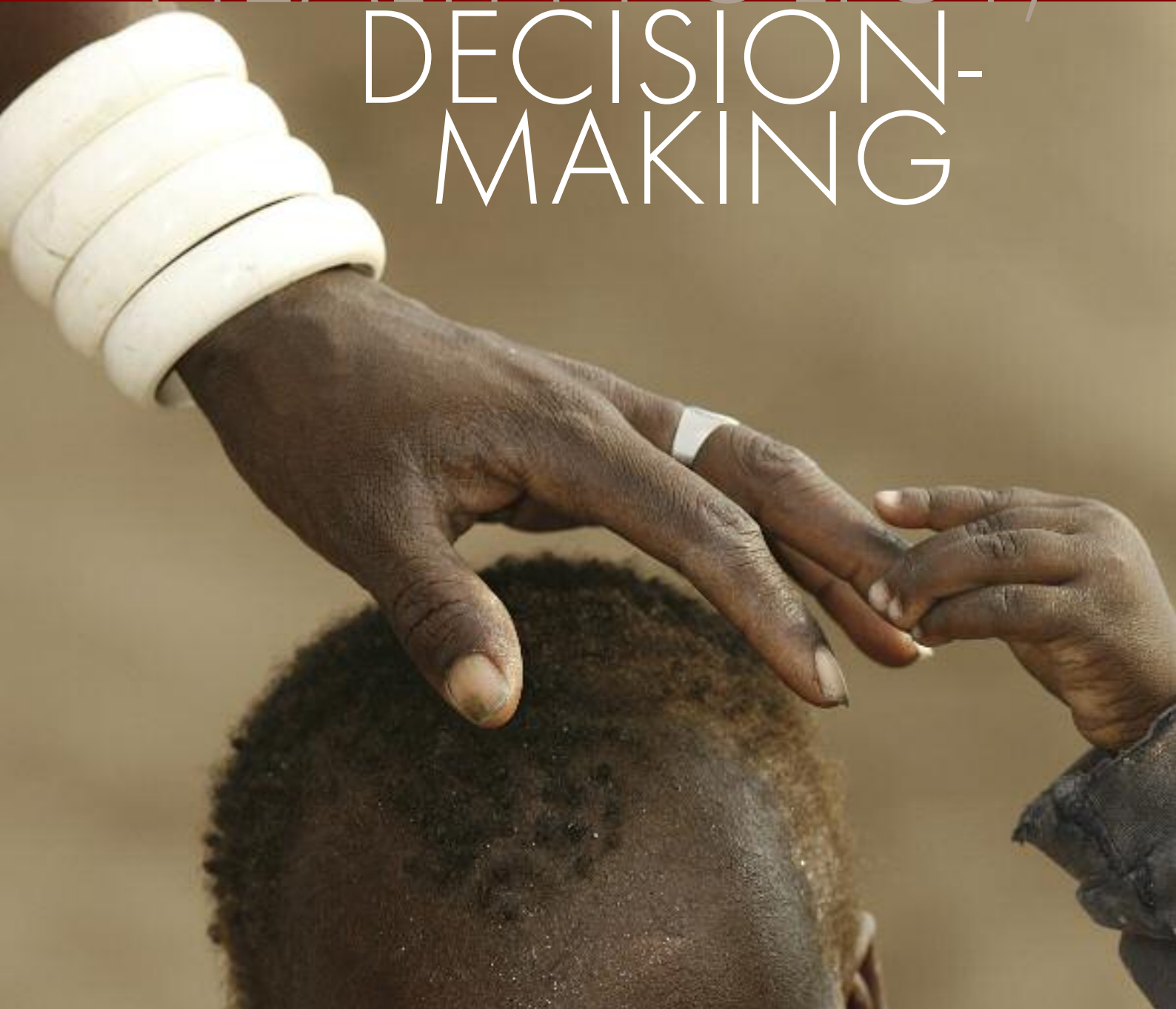
Mkhonza has since completed her MTech (*cum laude*), which was financed by the CSIR and the ABS project. MSc student, Zodwa Mbambo, is on a four-month visit to the Brazilian Agricultural Research Corporation (Embrapa) focusing on related research within the ABS project, including similar work on soybean. It is anticipated that throughout the lifespan of the project, a large number of young postgraduate students will benefit from training in some form, either at the CSIR or one of the other two South African partners (the University of Pretoria and the Agricultural Research Council) – helping to increase capacity in the science sector, something that is desperately needed.

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CSIR researchers are improving sorghum's nutritional value to help combat vitamin A and micronutrient deficiency

# PUBLIC HEALTH POLICY, DECISION- MAKING



# Weight and growth from birth linked to adult health

The links between childhood development – specifically size at birth and weight gain in the first four years – and adult diabetes are being investigated and analysed by a team of medical researchers and CSIR statistician, Dr Zaid Kimmie.

Dr Zaid Kimmie, CSIR statistician, who is involved in a research project on the links between childhood development and adult diabetes

“THE BIRTH TO 20 cohort study is the only one of its kind in Africa, and one of only five long-term cohort studies in the developing world,” says Kimmie. A cohort study entails observing a group of subjects over an extended period of time and is used to investigate a suspected association between cause and effect in people living in their natural environment. The study group is observed over a long period of time to determine the incidence of diseases being studied – in this case mainly diabetes, high blood pressure and growth-related diseases.

The aim of the research is to feed the results into public health policy, as diabetes is increasing significantly and the long-term treatment of this condition will place an added strain on the South African health system. The research findings will be publically available to people who need to tap into and scrutinise the results.

“The main geographical focus area of our study is people from Soweto and Johannesburg,” notes Kimmie. The University of the Witwatersrand is driving the medical aspects of the study, which started in 1990 with some 3 300 babies who were enrolled in the programme, with their parents’ informed consent. A cohort study has to be approved by an appropriate institutional ethics committee.

“Through natural attrition, including people moving away from the study area, we now have 2 800 people enrolled. There is limited statistical capacity in our country to analyse these sorts of data, particularly when we are interested in understanding the causal relation-

ships over time; I became involved with the analysis and statistics in 2008,” explains Kimmie, who holds a Master’s in public health and a doctorate in mathematics.

The advantage of cohort study data is the longitudinal observation of individuals through time, and the collection of data at regular intervals. “Our data include factors that could lead to poor health, taking into consideration social circumstances, environmental factors and genetic make-up. The pay-off for participants is that they get a full medical examination twice a year,” he says.

Data are obtained on height, weight, blood pressure, bone density, hearing, sight and dental condition. Participants are also asked questions relating to lifestyle, schooling, dietary habits, family circumstances and sexual activity, where appropriate. Data are adjusted taking into account a number of factors, including age, gender, socio-economic status at birth, maternal education, adult height and adult waist circumference.

The South African study is sponsored partially by the Medical Research Council, the Human Sciences Research Council and some international partners.

To observe health patterns over extended periods in the context of developing countries, this cohort study slots in with similar studies conducted in Brazil, Guatemala, India and the Philippines. It thus forms part of a consortium on health-orientated research in transitional societies. Data are pooled from all five participating countries.



“One of the initial conclusions of our studies is that low birth weight is a risk factor for adult diabetes, while conditional weight (i.e. the change in weight growth relative to expected weight) at age two and four years is not directly related. Understanding the components of early weight gain is important in the formulation of effective public health policy and life-course interventions,” comments Kimmie. – Hilda van Rooyen

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# CSIR RESEARCH TO IMPACT POLICY ON SA'S PUBLIC HEALTH FACILITIES

Infrastructure is a key and chronically under-recognised resource for public health service delivery. Infrastructure that is both fit-for-purpose and fit-for-service, and located in the right places, provides an enabling environment for the provision of healthcare services.

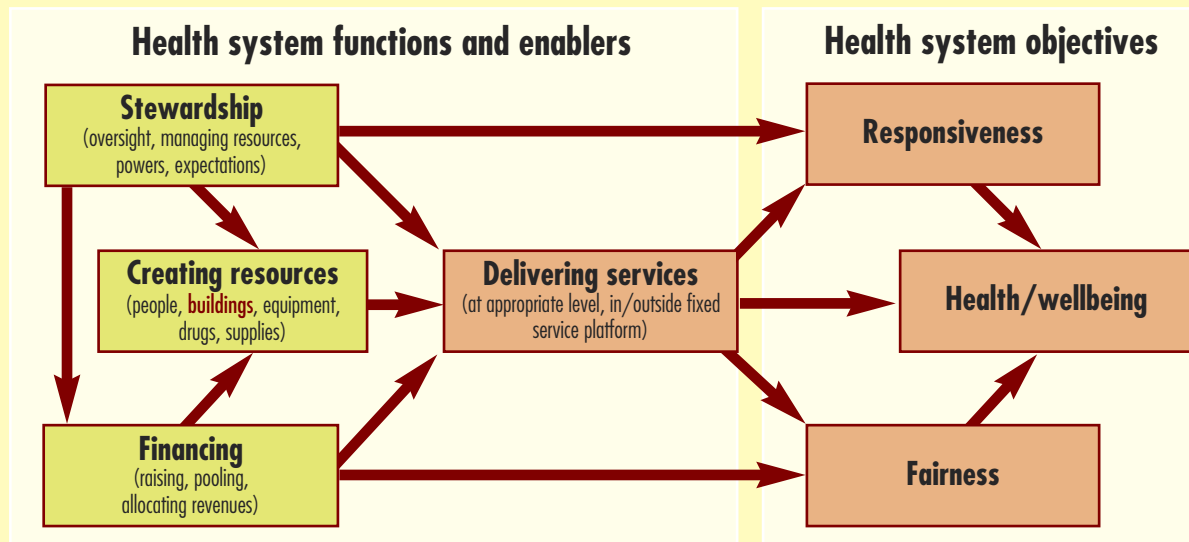
Geoff Abbott and Peta de Jager who looked at key issues relating to the provision and maintenance of health infrastructure





# Healthcare facilities in South Africa

## Health system performance framework



Source: INFRASTRUCTURE BAROMETER 2008, Development Bank of Southern Africa

CSIR EXPERTS conducted research on the current health infrastructure, its condition and suitability for services to be provided. The results will inform debates on infrastructure within the health sector. Geoff Abbott and Peta de Jager were invited to partner with the Development Bank of Southern Africa (DBSA) in co-authoring a chapter on health for the bank's biennial *Infrastructure Barometer* publication.

The report, subtitled '*Economic and Social Infrastructure in South Africa: Scenarios for the Future*', is a dipstick measure of the state of infrastructure across various sectors. Health was included for the first time in the 2008 Barometer.

The state of the nation's health has a clear and direct impact on the economic growth and development of the country. Investment in health services is key to securing the nation's health and health infrastructure, which is an important enabler for successful healthcare delivery.

"In addition to dealing with the legacy of an existing, outdated health estate, health facility planners have to address infrastructure implications of the new burdens of HIV/Aids and drug-resistant tuberculosis," note Abbott and De Jager. "As a developing country, we have a high incidence of infectious diseases, a growing burden of lifestyle diseases associated with a society in transition, and a high incidence of trauma."

The health estate in South Africa is a complex mixture consisting of over 4 000 facilities with a replacement value of more than R180 billion. "It is not sufficient just to increase budgets and spending on health; to optimise

our healthcare infrastructure we need to address a number of interrelated areas. We need to understand the relationships between access to services, investment, affordability, systems and healthcare outcomes. Research programmes can provide the evidence-base necessary to inform both long-term strategic planning as well as short-term delivery in health," say Abbott and De Jager.

They focused on a range of areas impacting on successful stewardship of the health estate, including:

- An analysis of the extent of existing infrastructure
- Capital and maintenance budgets and expenditure
- Public and private sector health services and resource distribution
- Human capacity and skills in the health sector
- The construction sector
- Health policy and the regulatory environment
- Procurement processes
- An overview of some current national initiatives to respond to health infrastructure planning, delivery and maintenance challenges
- Health and infrastructure management information systems.

The health chapter identifies key issues relating to the provision of infrastructure and provides a basis for informing future planning and research agendas. While the study on health noted the shortfall in budget to meet current and future infrastructure needs, the importance of a multi-factorial approach was emphasised.

"We are delighted to have been involved in this key study initiated by the DBSA. Our

chapter on health provides input towards informing debates in the health sector," note Abbott and De Jager.

The CSIR researchers' health report clearly shows that there is a risk posed to the sustainability and affordability of the current health service model through potential over-investment in capital expenditure and under-recognition of maintenance needs. All capital outlay in the health sector must be supported by sufficient provision for operational and maintenance spending over the full projected life cycle of the estate.

"While the promise of a biennial health sector review process will allow for tracking performance and impact over time and is a welcome start, it needs to be expanded," comment Abbott and De Jager. "To really support planning for infrastructure investment, more detailed research and sustained oversight of health infrastructure and its affordability are required," they note.

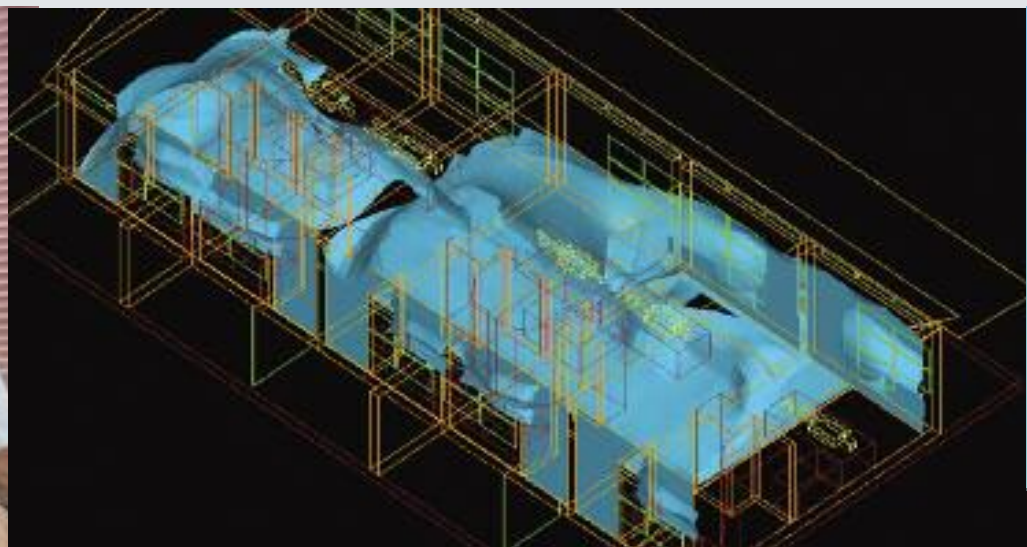
The overall objective of the *Infrastructure Barometer* is to measure the effect of the provision of infrastructure on the South African economy. The information for all sectors was used to construct imaginary future scenarios for infrastructure investment. This approach was used to bring complex findings into a form that brings home the plight of the general public with particular attention to those who rely most on public health services, namely the vulnerable and the poor. – Hilda van Rooyen

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# Ensuring patient safety through facility design and management

The CSIR's Dr Sidney Parsons, who leads research to improve patient safety within healthcare facilities

BY DR SIDNEY PARSONS



THE LATEST ESTIMATES by the World Health Organization (WHO) show an on-going and uncontrolled tuberculosis (TB) epidemic in South Africa. The number of TB cases diagnosed has increased each year, with nearly 1% of the population developing TB in 2006.

In addition, extensive drug-resistant TB (XDR-TB) has emerged on top of the rise in multi-drug resistant TB (MDR-TB). Infrastructure constraints such as existing buildings remain an obstacle as the spatial planning in many buildings impedes the implementation of airborne infection control. In South Africa, hardly any facilities exist that are able to isolate suspected or confirmed TB patients.

The CSIR's health technology group is involved in a number of research initiatives to improve patient safety within healthcare facilities. One of the main purposes is to contribute to strengthening the South African Department of Health (DoH), provincial governments and

partners in the US President's Emergency Plan for AIDS Relief (PEPFAR) in the area of patient safety, including airborne-related infection control.

PEPFAR funds and provides technical expertise through US government organisations such as the Centers for Disease Control and Prevention. Several hundred organisations in South Africa are PEPFAR partners, actively involved in the prevention, treatment and care of people infected with and affected by HIV/Aids, and one of the largest drivers of the epidemic, TB. The CSIR became a PEPFAR partner in 2008 due to its expertise in infection control of airborne micro-organisms such as *M. tuberculosis*, particularly in health facilities.

In providing support to the DoH and provincial governments, CSIR researchers give input into TB and HIV policies and guidelines and assist in developing enabling systems and processes for the management of treatment facilities.

They are also developing training material, guidelines and tools to minimise the impact of the TB epidemic in South Africa. The team, headed by Dr Sidney Parsons, includes Geoff Abbott, Dr Dirk Conradie, Peta de Jager, Sheldon Bole, Faatiema Salie and Lerato Motsatsi.

The CSIR's health technology expertise finds application in a number of projects aimed at improved patient safety.

## IN SUPPORT OF THE DOH

As a PEPFAR partner, the CSIR is mandated to provide the DoH with technical support for a variety of programmes. These include developing enabling systems and processes; implementation support; capacity development and institutional support.

The CSIR has developed a series of planning, design, operation and management guidelines

for drug-resistant TB facilities. These guidelines for health facilities are used throughout Africa and also in certain countries in Europe. Researchers have had close collaboration with the WHO and the International Union of Architects in this regard. As part of this project, CSIR researchers have developed toolkits for risk, functional and condition-based assessments, as well as a database and GIS planning toolkit.

Implementation support is provided by the CSIR for the national roll-out of the South African National Treasury and Global Fund investment programmes for drug-susceptible and resistant TB.

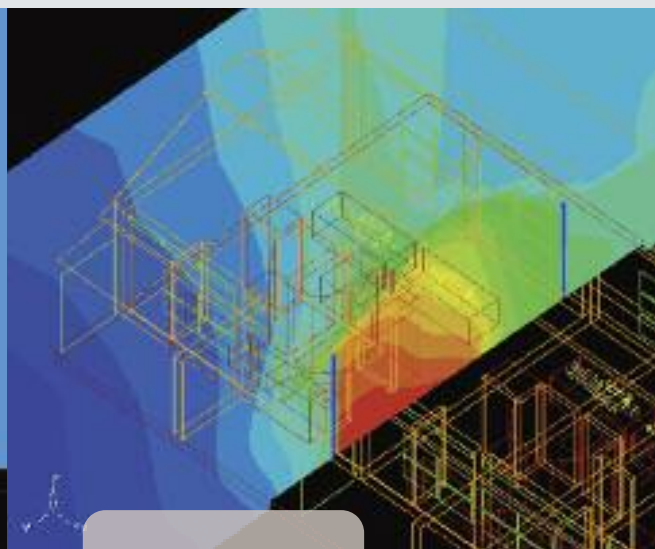
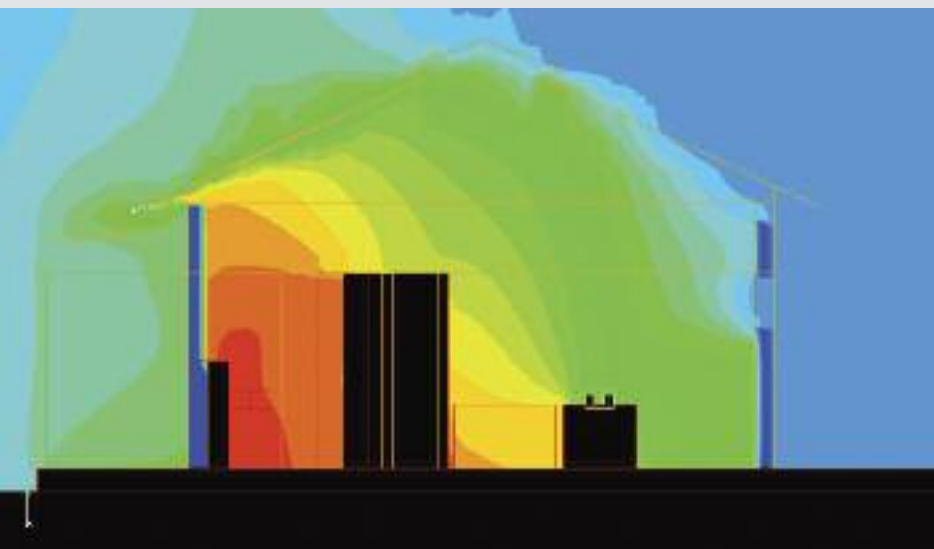
## ONGOING RESEARCH

Drug-resistant TB infrastructure is being developed in South Africa as part of a DoH/Global Fund programme. The International Global Fund provides grants to strengthen national and provincial capacity in South Africa for the prevention, care and treatment of HIV/Aids and TB. The lack of appropriate infrastructure is a key constraint in the effective treatment and rehabilitation of patients, thus 332 beds are being added at nine facilities in seven provinces.

The CSIR has been tasked to provide support for the roll-out of US\$12,3 million sourced

from the Global Fund for new patient accommodation at existing drug-resistant TB hospitals. The designs have been based on research undertaken by the CSIR to understand the complexity of accommodating M(X)DR-TB patients referred for treatment in health facilities.

- Basic simulations that use a 'broad spectrum' product to provide performance assessments such as solar projections, shadows, reflections and shading, space planning assessments, lighting and thermal analyses



Diagrams illustrating the 'age' of air in a specific area, ranging from red (the oldest air) to blue (the freshest). This is one of the direct indications of the effectiveness of the natural ventilation present.

In the past three years, the CSIR has given technical support to the TB directorate of the DoH and has played a pivotal role in ensuring infection control remains a priority.

To assist with capacity development, CSIR researchers have developed training material and provided infection control training. Thus provincial healthcare staff are assisted to manage and implement infection control interventions. This was started in the Camdeboo sub-district of the Eastern Cape, where more than 30 healthcare facilities were assessed for risk, after which training was provided on addressing such risk items.

To ensure good practice regarding patient safety, CSIR researchers also contribute to the development of a drug susceptible and resistant TB infrastructure database. This includes a database of non-governmental organisations involved with TB infrastructure-related activities.

CSIR researchers, in collaboration with a team from the Medical Research Council and international experts, have provided technical engineering input for the development and use of the South African airborne infection research laboratory. Expertise was pooled to investigate various interventions for minimising the risk of drug-resistant TB infection. Various environmental control measures will be investigated.

A building performance laboratory has also been developed at the CSIR to evaluate the distribution of aerobiological agents (such as *M. tuberculosis* bacteria bearing droplet nuclei) within healthcare facilities. In this re-

search, CSIR research focuses on predictive simulations technology to enable architects and engineers to review and fine-tune environmental and functional performance during the design phase of buildings. Two levels of simulation are being developed for modelling air movement and micro-organism dispersion within healthcare buildings:

- Advanced simulations that use computational fluid dynamic software to provide dynamic airflow modelling.

The Bill of Rights contained in South Africa's Constitution states that everyone has the right to an environment that is not harmful to their health or wellbeing. Healthcare facilities are, after all, essentially only shelters where healthcare functions can be performed. Research on improving health infrastructure for patient safety and healthcare capacity development is therefore crucial in the fight against diseases like TB.

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Wilna Bean and Nadia Viljoen, the CSIR team who works on an expansion strategy and transportation models for the South African Breastmilk Reserve network

## Research to assist in getting breast milk to micro-premature babies

A CSIR PROJECT is supporting the expansion of the South African Breastmilk Reserve (SABR) network by research aimed at facilitating the successful transportation of breast milk from donors to participating hospitals.

A premature baby who is younger than 14 days and weighs less than 1,8 kg is highly susceptible to a number of possibly fatal infections. One such condition is necrotising enterocolitis (NEC), where portions of the bowel undergo tissue death, known as necrosis.

Initial symptoms of NEC include feeding intolerance, increased gastric residuals, abdominal distension and bloody stools. Symptoms may progress rapidly, requiring intensive medical support.

Feeding a baby formula milk increases the risk of NEC 10-fold compared to infants who are fed breast milk only. Healthy donor breast milk strengthens the immune system of the baby, effectively helping the infant survive the first two weeks of life.

The SABR, a public benefit organisation, facilitates the collection, pasteurisation and distribution of healthy donor breast milk to micro-premature babies. During 2008, some 350 donors sustained the wellbeing of about 1 000 infants in perinatal care. The SABR needs to expand its networks and services geographically as these are currently not available in all provinces.

CSIR industrial engineer Nadia Viljoen explains how the CSIR's expertise comes to play in this initiative. "The main stumbling block with the SABR's expansion strategy is the transportation of breast milk from donors to participating hospitals, and at the appropriate temperature. In the first phase of our research, which has just been completed, we used business process engineering and supply chain design to develop a successful expansion strategy into all the provinces. We also made recommendations around four alternative transportation models."

The alternatives proposed by the CSIR include using and paying independent couriers; establishing an in-house logistics capability at the SABR to service all nine provinces; encouraging network players to take up transportation responsibilities and using the services of medical staff such as doctors, sisters, pathologists and lactation consultants, who travel between hospitals in the course of their work day.

"During the next phase of our research, we'll develop each alternative solution in detail and perform economic and strategic analyses to determine which alternative would be the best and most sustainable. We will establish a baseline of the current costs first for comparison purposes. Knowledge of logistics, economical models and quantitative methods will be applied," she notes.

This CSIR research is one of five sub-projects included in the Department of Science and Technology's humanitarian logistics and humanitarian operations research project. The primary objective of the overarching project is capacity development in the fields of logistics and supply chain research, operations research, data administration and information management, and decision analysis.  
- Hilda van Rooyen

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# TOWARDS IMPROVED QUALITY HEALTHCARE IN HOSPITALS

THE ACTIONS AND BEHAVIOUR of healthcare workers in hospitals impact directly on the quality of healthcare that patients receive in such facilities. Be it medical doctors, nurses or support staff, their working conditions in the hospital and their perceptions of the care they provide are linked to the quality and safety of patient care.

Dr Sonali Das, who specialises in both applied and theoretical statistics at the CSIR, has been involved with longitudinal analysis of huge amounts of data collected as part of a large-scale study conducted in North America. To improve the healthcare received by patients as part of the US government's Veterans Health Administration (VHA), the VHA has initiated substantial efforts over the past decade. It is the largest health support system in North America.

"The aim of the surveys includes to determine healthcare workers' perceptions of customer satisfaction and their relationship to the organisation, as well as to identify intervention strategies designed to improve working conditions and quality of care. These surveys have been conducted to capture primary features of the work conditions and workplace traits relating to certain outcomes regarding patient care. An objective understanding of the employees' working conditions is needed to devise intervention strategies to improve patient care," Das explains.

Interventions centre initially on the relations between employee satisfaction and retention, perception of patient satisfaction and quality of care provided, and the workplace traits of leadership, resources and support for healthcare workers. "My involvement in the VHA project started when I was still at the University of Connecticut and continued when I joined the CSIR in 2007. I used structural equations modelling (SEM) in the analysis of

the data as it is a powerful multivariate regression technique to handle scenarios where the predictor and outcome variables can be either latent or observed. We have also developed more sophisticated models to include demographic information into the SEM models and used Bayesian methods for model parameter estimations. Our methods have been accepted in peer-reviewed journals, including the prestigious *Bayesian Analysis* journal.

"As many of the questions posed in the surveys are of a sensitive nature, a confidentiality agreement was reached between management and labour not to identify individual respondents. To participate in the research analysis, I had to pass an ethics examination because of the human issues associated with the project. This is compulsory in all cases where one has to do statistical analyses with human data," says Das.

Asked whether similar surveys could be conducted and analysed in South Africa, or even Africa, Das explains that such large-scale surveys and the analysis of data can be expensive even though conducting such surveys can be achieved effectively online. However, SEM techniques can also be applied to small surveys. It is very important for decision-makers in hospitals to understand the dynamics of facilities in terms of the quality of service being provided to patients beyond the clinical part of the service.

Any researcher working with variables that are latent can use the SEM technique to answer other research questions. "We have used SEM in collaboration with environmental research colleagues to determine risk factors associated with environmental health outcomes of respiratory and waterborne diseases. In future, we hope to explore the application of SEM, among other techniques, in another health-related project to be led by a national

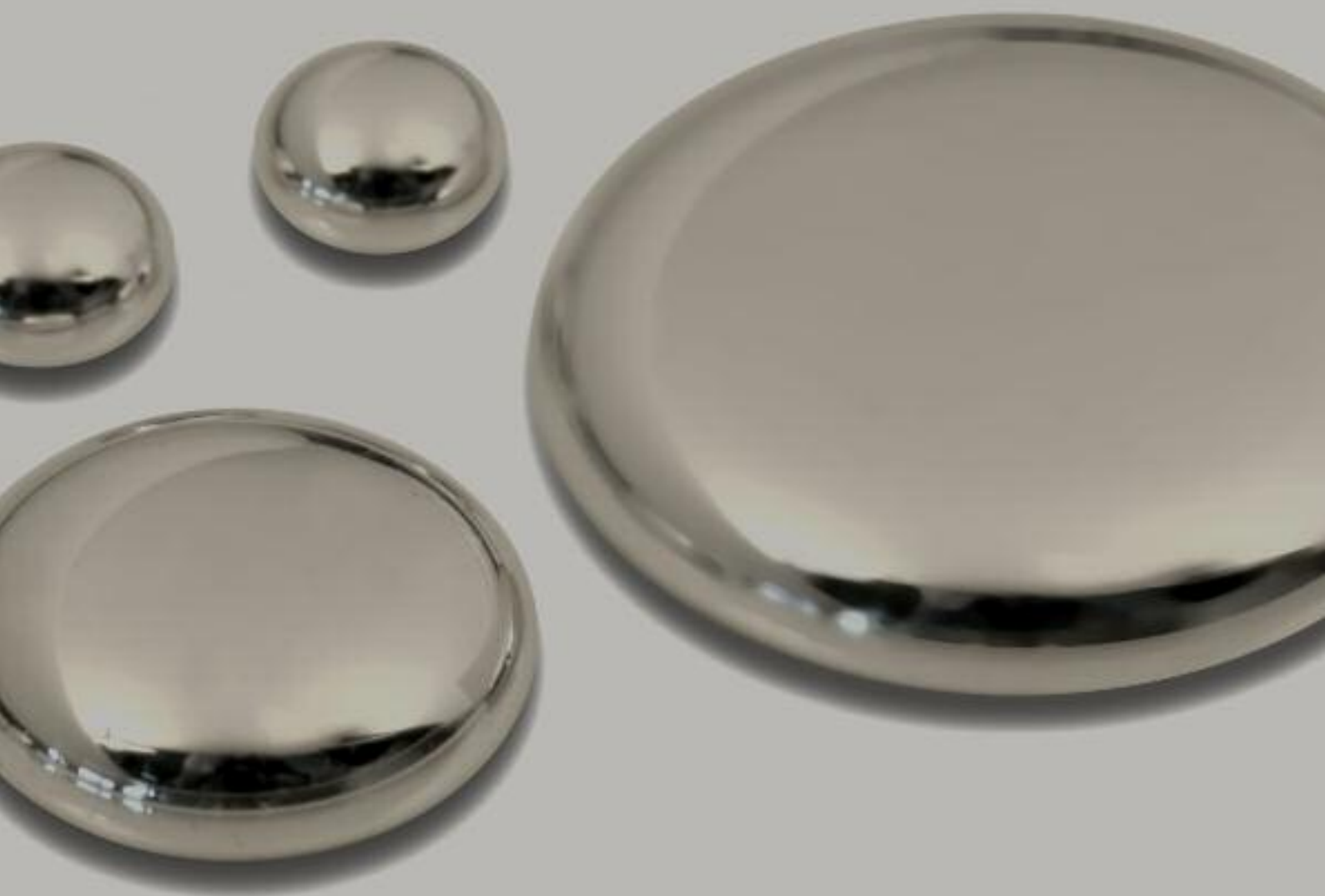


Dr Sonali Das, who specialises in both applied and theoretical statistics at the CSIR

centre of excellence established by the Department of Science and Technology and the National Research Foundation. The proposed research will involve epidemiological modelling and analysis of data collected in the HIV/Aids context," she concludes. – Hilda van Rooyen

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# CHEMICAL SAFETY





## WHAT IS MERCURY?

Mercury occurs naturally in the environment and can also be released into the air through industrial pollution. Mercury falls from the air and accumulates in streams and oceans where it turns into a more harmful version called methylmercury. Fish absorb the methylmercury and it builds up in their tissue. Bigger fish feed on smaller fish, resulting in the levels of mercury accumulating mainly in the fatty tissue of those higher up in the food chain.

Source: <http://www.fda.gov/Food/FoodSafety/Product-SpecificInformation/Seafood/FoodbornePathogens-Contaminants/Methylmercury/ucm115662.htm>

MERCURY POISONING COULD RESULT FROM DAILY INTAKE OF SOME LOCAL FISH, CSIR STUDY FINDS

## Appeals for ongoing fish sampling and data collection

SUBSISTENCE FISHERMEN along the South African coastline should be warned to limit their intake of locally caught fish due to the potential of mercury poisoning. Mercury monitoring in coastal waters should also be continued and extended to include a comprehensive list of marine fish species.

A recent CSIR study found that mercury concentrations in Red Roman, Red Panga and Silver Fish caught along the South African coast line exceeded the World Health Organization's guideline value of 0.2  $\mu\text{g/g}$  for sensitive subpopulation groups.

Concentrations ranged from 0.014  $\mu\text{g/g}$  for Mullet to 0.486  $\mu\text{g/g}$  for Red Roman and showed great variability across loca-

tions and fish species. The highest mercury concentrations recorded during the study occurred in False Bay, followed by the West Coast, Durban, Kalk Bay and Yzerfontein.

The study was initiated by the former South African Mercury Assessment Programme (SAMA) and focused on assessing the potential health risk from consuming locally caught fish off the South African coastline. This initiative was broadened in 2008 to include a focus on a broader scope of heavy metals within a CSIR trace metals research programme.

As part of an international collaboration agreement, researchers from the University of Connecticut in the US visited South African shores to train CSIR researchers to conduct the mercury sampling. As part of



Mamopeli Matookane

this initiative, CSIR researcher Chavon Williams visited the US for six weeks where she received training in the analysis of fish samples for mercury contamination, using the Direct Mercury Analyser and Cold Vapour Atomic Fluorescence Spectrometer. Today she is skilled in doing the same analysis in the CSIR's own state-of-the-art mercury testing lab in Stellenbosch.

According to CSIR researcher Mamopeli Matookane, the preliminary results suggest that subsistence fishermen and especially sensitive subpopulation groups such as pregnant women and children are potentially at risk from consuming local fish.

"In the short term these risks should be communicated to these communities. In the long term, ongoing fish sampling and additional data collection should take place," she argues in a paper presented at the annual conference of the International Society for Exposure Science held in the US this year.

Matookane also suggests further research to include biomonitoring in the target population in order to improve exposure and risk estimates. Currently South Africa has no fish consumption guidelines based on health risk, particularly for population groups with high consumption rates such as subsistence fisher-

men. The results from this study highlight the importance of addressing this critical knowledge gap in order to safeguard the health of consumers. – Wiida Basson

### HOW SAFE IS OUR FISH?

While mercury-contaminated fish is not a uniquely South African problem, we lack specific guidelines or information about the levels of mercury contamination in the country. In the United States, the Environmental Protection Agency and the US Food and Drug Administration warn people that nearly all fish and shellfish contain traces of methylmercury – therefore one should control one's intake and vulnerable groups like young children and pregnant women should be very careful. The best advice would be for consumers to be aware of these risks and to obtain information from advisory groups if they have questions. However, consumers should know that eating fish containing chemical pollutants may cause birth defects, liver damage, cancer and other serious health problems.

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# Small-scale gold miners vulnerable to dangers of mercury poisoning

ABOUT 20 000 SMALL-SCALE GOLD MINERS in South Africa could be unwittingly exposing themselves and the surrounding environment to mercury poisoning due to their operations.

According to a CSIR study in a rural community close to a river and gold-mining operations in Mpumalanga, nearly half of the people tested had urine and blood mercury levels that may cause symptoms such as fever, insomnia, mood swings and tremors.

Small-scale gold miners, mostly illegal, are at risk of inhaling mercury vapours when the gold/mercury amalgam is heated, often in open containers, when they attempt to extract the gold.

According to CSIR senior researcher Riëtha Oosthuizen, the inhalation of mercury vapours is a significant threat to human health: "Although the miners handle mercury directly, it can also affect the environment. Exposure of people living in close proximity to mine sites is primarily via mercury vapours from amalgam-burning or gold-melting, or via consumption of contaminated water or fish." However, samples of the water and edible fish from the specific river showed normal levels.

"If exposure is via inhalation of mercury vapour, about 80% of the mercury may enter the bloodstream and is distributed to other organs, including the brain, where it affects the central nervous system. These effects may be irreversible. Metallic mercury may also cross the placenta of pregnant women," she explains.

The study was complicated by the fact that most of these mining operations are taking place illegally, without mining permits or the permission of the owners. In addition the miners are mostly illiterate and therefore generally unaware of the danger associated with the use of mercury in the amalgamation process.

After completion of the survey those individuals with elevated mercury levels in their urine and blood were referred to a local occupational outpatient clinic specialising in mercury poisoning. - Wiida Basson

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# PRIMARY HEALTHCARE



# Using ICT to support rural clinics in MANAGING CHRONIC LIFESTYLE DISEASES

According to the World Health Organization, a renewed focus on primary healthcare is required. "In far too many cases, people who are well-off and generally healthier have the best access to the best care, while the poor are left to fend for themselves," the organisation said in a statement at the launch of the World Health Report 2008 titled *Primary Health Care (Now More Than Ever)*

"Primary health care brings balance back to health care, and puts families and communities at the hub of the health system. With an emphasis on local ownership, it honours the resilience and ingenuity of the human spirit and makes space for solutions created by communities, owned by them, and sustained by them," the release states.

A project by the SAP Meraka Unit for Technology Development (UTD) is developing rural clinic-based, patient-oriented, user-friendly software solutions to manage chronic lifestyle diseases, with the aim of improving the quality and efficacy of primary healthcare systems in emerging economies.

According to Professor Jan Eloff, SAP Meraka UTD research director, the unit's research agenda has three main focus areas: the development of new, innovative business solutions for very small enterprises, specifically in emerging economies; the application of ICT to support emerging economies in areas such as health and the sustainability of small enterprises; and customer-centric design which focuses on adapting software to be more useful and user-friendly for users in emerging economies.

Titled Project PatHS (derived from 'patient health system'), the initiative is aimed at building the capacity of rural health service staff to work with computer-based solutions for health, and to develop a technological solution (prototype) that improves the communication between the health service and the patients they serve.

A basic electronic patient record system from a local software company has been further enhanced and implemented at three primary healthcare clinics. Understanding user characteristics and solving practical implementation, maintenance and support issues are critically important if ICT solutions are to succeed in ultimately improving patients' health in these remote rural areas.

In addition to SAP Meraka UTD, collaborators on the PatHS project include the School of Public Health at the University of the Wit-

watersrand and iNathi Technology Holdings, with support from the Mpumalanga Department of Health and Social Services, the national Department of Science and Technology, German development agency DEG and Sagem Sécurité, a leader in digital fingerprint biometrics.

"Primary healthcare in developing countries presents specific challenges," explains Dr Danie Smit, SAP principal researcher and PatHS project leader. "Rural health services are under-resourced and have to cope with high demand, in the face of challenges such as lack of infrastructure, remote locations and high staff turnover.

Patients usually have to rely on a handful of nurses providing the most basic medical treatment, with only the most severe cases, for example, suspected HIV/Aids, hypertension or tuberculosis, being referred to doctors based at district hospitals."

To investigate how computer-assisted methods could improve efficiency and the quality of services, SAP Meraka UTD and its partners implemented a basic electronic health system at three pilot clinics in the Mpumalanga province, close to the Kruger National Park.

Preparation for the project started almost three years ago, with several meetings and workshops discussing initial ideas and establishing relationships between various potential partners and stakeholders. "It became clear very early on that the wide-ranging priorities and expectations of stakeholders would need to be managed carefully to ensure the success of the project," says Smit.

The project team followed the Living Lab approach, which prescribes direct end-user involvement throughout the software development lifecycle, from the creative stages in a project up



Team members Elmarie Venter, Dr Danie Smit, Prof Jan Eloff and Moses Dlamini

## WHO/WHAT IS THE SAP MERAKA UTD?

Founded in 2007, the SAP Meraka UTD is a public-private partnership between the CSIR's Meraka Institute and SAP Research in Pretoria.

It is widely viewed as one of the first truly collaborative, multi-disciplinary technology research centres in South Africa. As a public-private partnership, it enjoys the support of the South African government, through the Department of Science and Technology, as well as global business software giant, SAP AG.



Nursing sisters during training in the use of the patient health system. Photo courtesy Danie Smit

to final delivery. This approach also seeks to involve all other stakeholders, such as non-governmental organisations, small and medium enterprises, volunteers, private sector organisations, academia and government.

The first step to implementing new healthcare systems at the three pilot clinics was to provide the local healthcare workers with basic computer literacy training. "Most of the healthcare workers we trained were clearly passionate about their profession and very excited about getting in touch with computers for the first time," Smit says.

To improve the practical use of the clinics' technologies, patients' demographic details are captured through local client-server architectures at each clinic. In this context, patients' fingerprints, for example, are stored for identification and verification during subsequent visits.

"We are planning to start working on synchronising clinic databases over pre-existing low-bandwidth General Packet Radio Service data connections on the Global System for Mobile communication mobile phone networks in future," Smit explains. "This is seen to be a more feasible connectivity model for large remote areas in Africa already serviced by mobile phone operators. Software systems should be able to function on pre-existing connectivity infrastructure as far as possible. However, high bandwidth connections will improve synchronisation between clinics."

Apart from enhancing the software functionality, Project PatHS also addressed many additional issues, such as physical security, backups, maintenance, remote support, change management, and continuous education to guarantee the ongoing success of the initiative.

Related research activities include designing alternative data input modalities, such as touch screens, to enhance the user experience, alternative business models for telemedicine in emerging economies, and the usage of mobile phones in healthcare delivery – more than 80% of the South African population already use mobile phones. SAP and its partners are currently following up on inquiries about these healthcare solutions from various countries in Africa.

"Project PatHS illustrates how public-private partnerships can play a major role in strengthening communities by introducing systems to assist working processes," comments Professor Eloff, SAP Meraka UTD research director. "In turn, the communities are empowered and exposed to technologies that they never thought they would be able to access."

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Goodhope Maponya, who is involved with interventions aimed at improved healthcare in remote rural areas

# Improving healthcare for patients in rural areas

THE SICK AND ELDERLY in remote rural areas experience severe constraints when they need medical attention. People who suffer from life-threatening and chronic diseases such as diabetes and hypertension need to have their vital medical signs checked on a regular basis. Due to the long distances between dwellings and local clinics or other medical facilities, this seldom happens. Rural hospitals and clinics are also often poorly equipped and understaffed, which does not bode well for improved healthcare services for terminally ill patients.

In the Lerero area near Graskop in Mpumalanga, the CSIR has piloted research to assist this rural community with improved healthcare through an intervention using information and communications technology (ICT). An informal community healthcare system exists in the area, albeit not very successful. Volunteer healthcare givers provide basic medical assistance to rural patients, visiting them at home on a daily to weekly basis.

"In the pilot area, these activities consume time; medical data are based on proxy observations and the experience of the healthcare givers, without any scientific measures. In addition, there is no reliable public transport available, thus volunteers have to walk long distances between the homes," explains Goodhope Maponya of the CSIR.

"The current pilot phase has not considered the use of bicycles or other forms of non-mo-

torised transport services such as donkey carts. Such options would require careful crafting so as to be aligned with the traditions of women in the Lerero community."

Healthcare givers in the Lerero area are the direct link between the patient and medical staff. Medical staff and institutions require data on the five vital signs of patients – blood pressure, pulse, temperature, blood sugar and weight – for effective patient monitoring and early diagnosis. "Blood tests are sophisticated and involve highly qualified medical staff. Such tests are thus not allowed to be done by the caregivers, with medical sisters opting for simple tests such as 'the urine dip-stick test'. This can be administered easily by the volunteer healthcare givers and has the potential of yielding an average of seven indicators, including blood sugar," adds Maponya. The challenge was to transfer the captured information to the nearest medical institution.

"Whereas telemonitoring has proven its value in developed areas, it has not yet been applied successfully in poor and rural areas," says Maponya, who heads the CSIR pilot project. "The system that has been designed is a robust and affordable ICT system. It allows for communication between 12 caregivers and medical staff at the two local clinics participating in the pilot. As caregivers interact with patients, they use their existing, familiar cell phones to send the vital-sign information via an ICT-enabled system with a preset menu that guides them through the process. In the interim, the CSIR has been supplying prepaid airtime, but a toll-free system is crucial for the success and sustainability of such a system."

The system uses USSD (unstructured service supplementary data) technology, which is accessible on all cell phones. USSD is an older protocol than SMS and easy to use. The 12 healthcare givers registered with the CSIR pilot project dial a dedicated number, prompting a pop-up menu screen, which is similar for all makes of cell phones. Once they have entered the patient data, these are sent to the medical sisters who use an access code to obtain the information via the internet.

"We were pleasantly surprised by the positive response of the sisters towards the web-based patient assessment tool. They can now access a large number of patients in a day without having physical contact with them," says Maponya. Patients are ensured of confidentiality as the information is sent directly to the sister who deals with specific patients. Thus early diagnosis is possible, with sisters advising caregivers when patients need to visit the clinic for assistance.

"An unexpected obstacle, however, was that healthcare givers were not even equipped with basic medical instruments such as thermometers, weighing scales or blood pressure meters to obtain data. For the pilot project, the CSIR provided essential equipment and training on its use to participating caregivers," Maponya notes.

"Factors such as the validity, reliability and timeliness of the patients' transmitted vital-sign data have a strong influence on decisions that medical sisters have to make. Trust between sisters and healthcare givers is strengthened by the quality and reliability of information transmitted. Even with some form of training provided prior to the pilot, caregivers still require continuous training. They have to be monitored on a weekly basis and evaluated on the activity-based processes of care and support for patients. A long-term commitment of weekly caregiver training workshops by medical sisters has been established. The CSIR is also frequently monitoring and assessing the flow of data between them."

"I believe this system can have a major impact on the healthcare sector in rural areas, not only in South Africa, but in many other developing countries. The CSIR is currently working on a roll-out plan, which includes developing a funding mechanism for the system," concludes Maponya.

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# RABIES

Tobacco plants for health. Pictured from left are CSIR researcher Nomali Zungu; research and development outcomes manager, Fanie Marais; CSIR chief researcher, Dr Rachel Chikwamba and project manager, Dr Ereck Chakauya.



# Tobacco plants become green factories to combat rabies

The CSIR genetically modified tobacco plants expressing the anti-rabies antibody, using *Agrobacterium tumefaciens*, a bacterium commonly used to introduce genes into plants.

Rabies is a viral disease, transmitted through the bite of rabid animals, most often dogs.

The virus infects the central nervous system, causing inflammation of the brain and is fatal once symptoms have developed.

Rabies is widely distributed across the globe. About 95% of human deaths occur in Asia and Africa.

(The World Health Organization)



A contract has been signed by South Africa's Innovation Fund for the final phases of development aimed at the establishment of a start-up venture that will produce rabies virus-neutralising antibodies through tobacco plants. This sees the formal birth of GreenPharm™, which is being incubated at the CSIR, from where the intellectual property originates and further development is being done.

GreenPharm™ hopes to bring its first product, a rabies drug (RabiVir™) that will be taken post-exposure, to the clinic by 2012. Over the next three years, the CSIR will conduct the research and development and intends to bulk up on the plant tissue needed and refine the extraction process; take into use a clinical supplies unit that complies with good manufacturing practices; as well as validate the product prototype and produce clinical batches of the product.

Rachel Chikwamba, principal investigator of the project, explains the significance of this development: "We intend bringing a safer and cheaper alternative to the market. The current rabies immune globulin uses either horse or human blood plasma, with the accompanying risk – in the case of human serum – of blood-borne infectious diseases such as HIV/Aids and the dependence on blood donations."

Preliminary data generated by the CSIR and St Georges, University of London, proved that the antibodies produced via tobacco were more efficacious in cell tests than plasma-produced counterparts and were cheaper to make.

Chikwamba says tobacco proved to have many advantages over other plants in terms of producing monoclonal antibodies. The plants produce lots of the protein needed (it has high expression levels); respond very well to genetic engineering and have a good public acceptance profile because the tobacco plant is a non-food crop.

She explains that commercialisation requires both the development of upstream and downstream processes – scientists will continue with the development of a stable, genetically transformed line that produces the antibody in high concentrations while technologists will develop manufacturing facilities where the target molecules are isolated and purified. The company (GreenPharm™) is set to be spun out from the CSIR in three years' time.

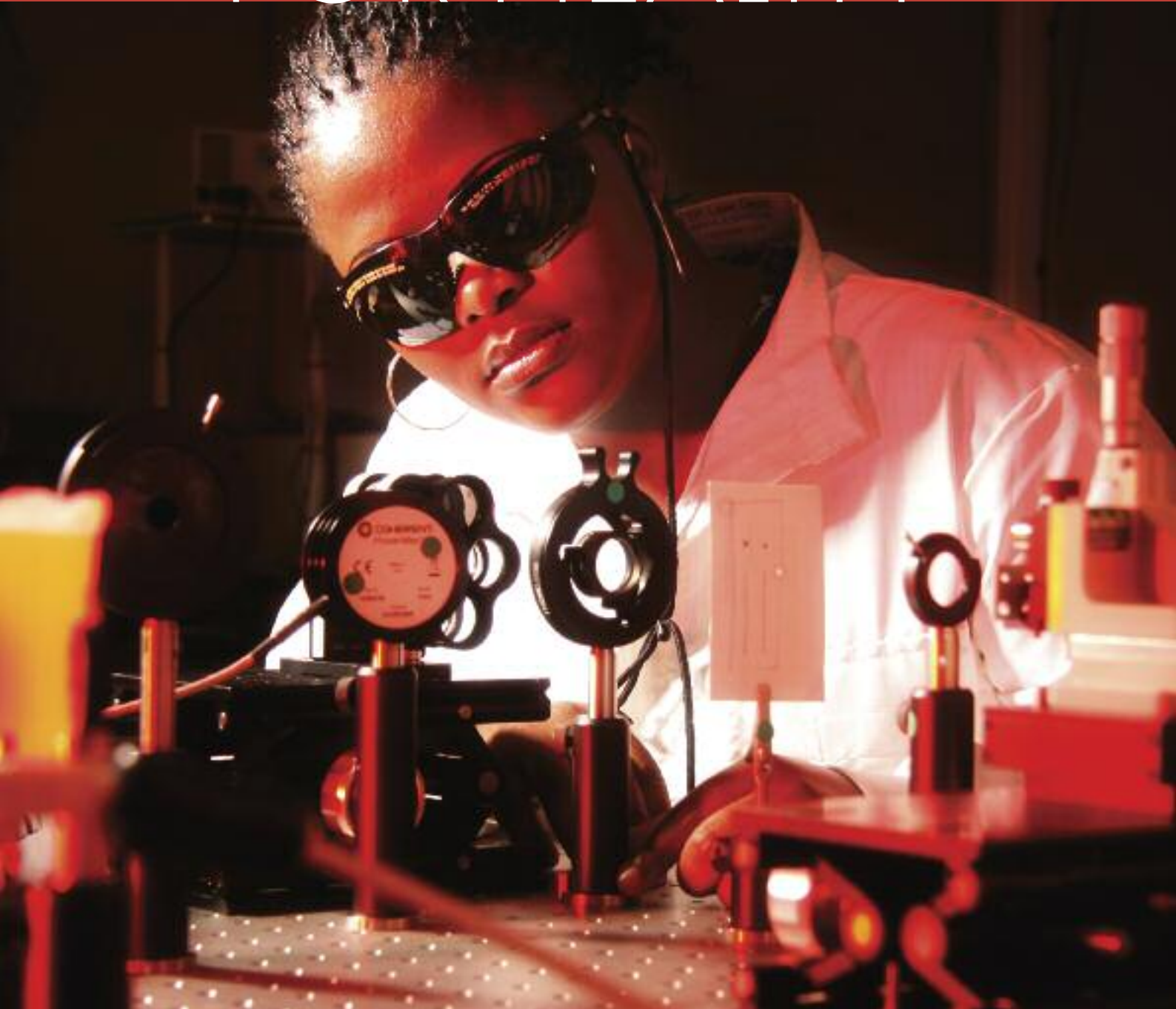
This research began in 2003 when the CSIR plant biotechnology research group entered the molecular farming arena and, with funding from the South African Department of Science and Technology, joined the international Pharmaplanta project. The knowledge gained during the five-year lifespan of the project is being extended to other areas.

Commenting on the investment decision, lead manager on the project for the Innovation Fund, Bethuel Nthangeni, says: "We are very excited to be associated with GreenPharm™. It is an excellent technology to showcase the investment aspirations of the Innovation Fund, which include investing in novel local technologies that have potential to be developed into sustainable businesses and contribute to the growth of the national economy."

In December last year, the project was named the inaugural winner of the SA Bio Business Plan Competition. The SA Bio Business Plan Competition is an initiative of the Innovation Fund in partnership with Emory University in the USA, with the ultimate aim of helping to promote the creation of new, venture capital-friendly biotechnology companies based in South Africa. The competition commenced in April 2008 and the entries were judged by an international panel of venture capitalists from the USA and Switzerland, most of whom have participated in biotechnology start-ups up to initial public offering. The R15 million investment is a direct result of being named the competition winner. – Alida Britz

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# ENABLING TECHNOLOGIES FOR HEALTH





Optical tweezing is on the rise as an enabling technology in medicine, biology

# CANCER CELLS SORTED FROM HEALTHY CELLS USING LASERS

BY DR ANDREW FORBES AND PATIENCE MTHUNZI

OPTICAL TWEEZERS permit trapping, moving and general manipulation of minuscule particles in the absence of any actual physical contact, opening the way to novel experiments at the micro scale.

In the late 1980s, Ashkin and co-workers showed that a laser beam can be used to create an 'optical trap' for microscopic particles. Once trapped, the particle can then be manipulated by controlling the laser beam; this is referred to as optical tweezing.

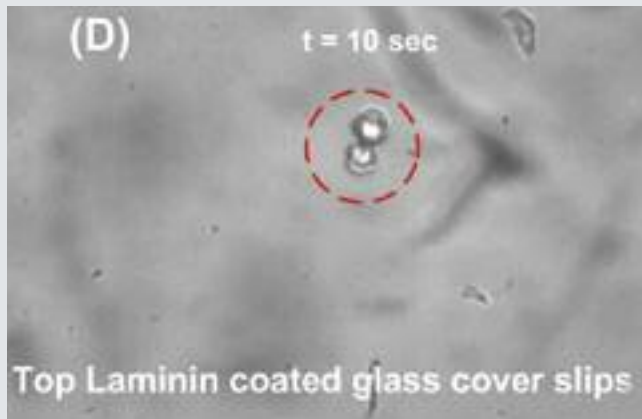
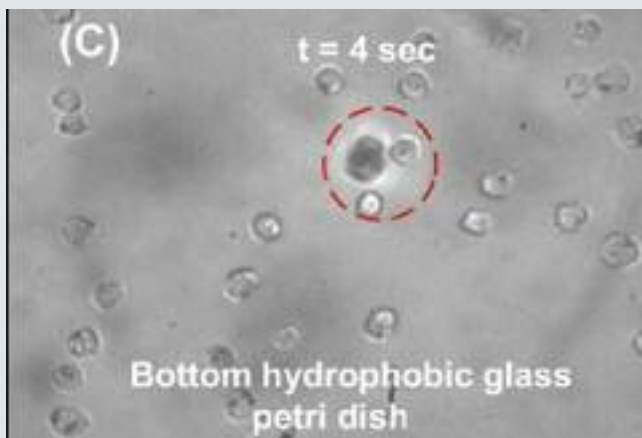
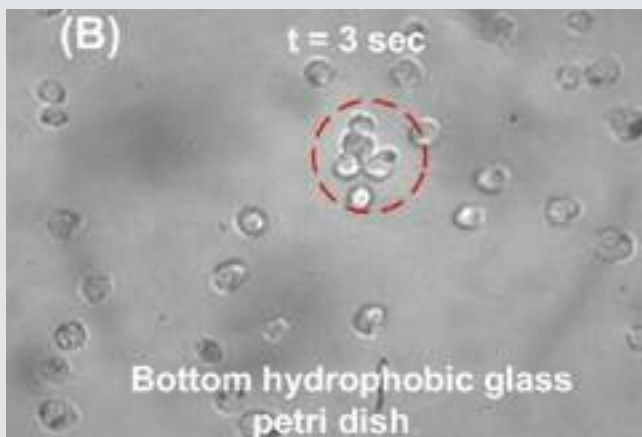
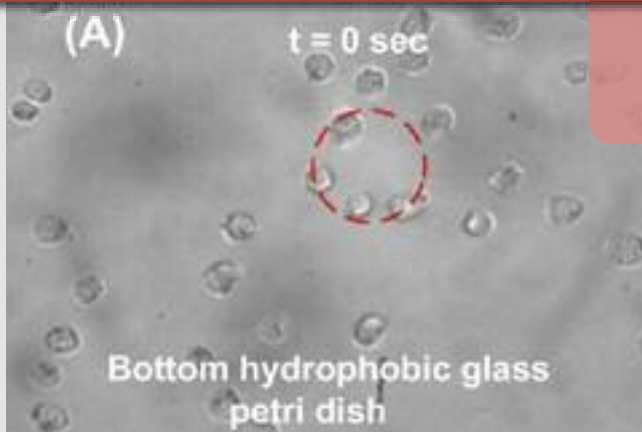
The principle is analogous to conventional tweezers, except here the trapping and control of the particle is purely with light and not with any mechanical device. Since these light-matter interactions occur at such a small size scale, optical tweezers hold massive potential for novel scientific developments

and applications in the biomedical and the biotechnological research arenas.

Even though the forces involved are typically in the pico-Newton range, this is sufficient for control of biological cells and strands of DNA, opening the way to controlled non-invasive biomedical experiments at the micro-scale.

The physics of optical trapping and tweezing is very simple, and is based on the familiar bending of light (refraction): when light passes through a biological cell, there is a change in its propagation direction due to refraction.

Since light carries momentum, this change in direction also corresponds to a change in momentum, which results in a force acting on the cell that moves it away from its original



Over time the optical tweezer separates two different cell types - to the top and bottom of the disk. They then can be cultured separately.

position. In order to control this movement, tweezers also exploit the intensity distribution of laser beams: the strongest force is directed towards the most intense area of the beam, causing the cell to always move to this region, essentially 'trapping' it by the laser beam. We have demonstrated this in the laboratory with embryonic kidney cells.

Once trapped, particles can be manipulated easily by simply moving the laser beam. By focusing the laser beam on a very small spot, these effects are accentuated, allowing cells to be trapped in a precise location in all three dimensions. To avoid damage through the absorption of light by a trapped specimen, particularly in biological samples, most optical tweezers use monochromatic (near infrared) continuous wave sources.

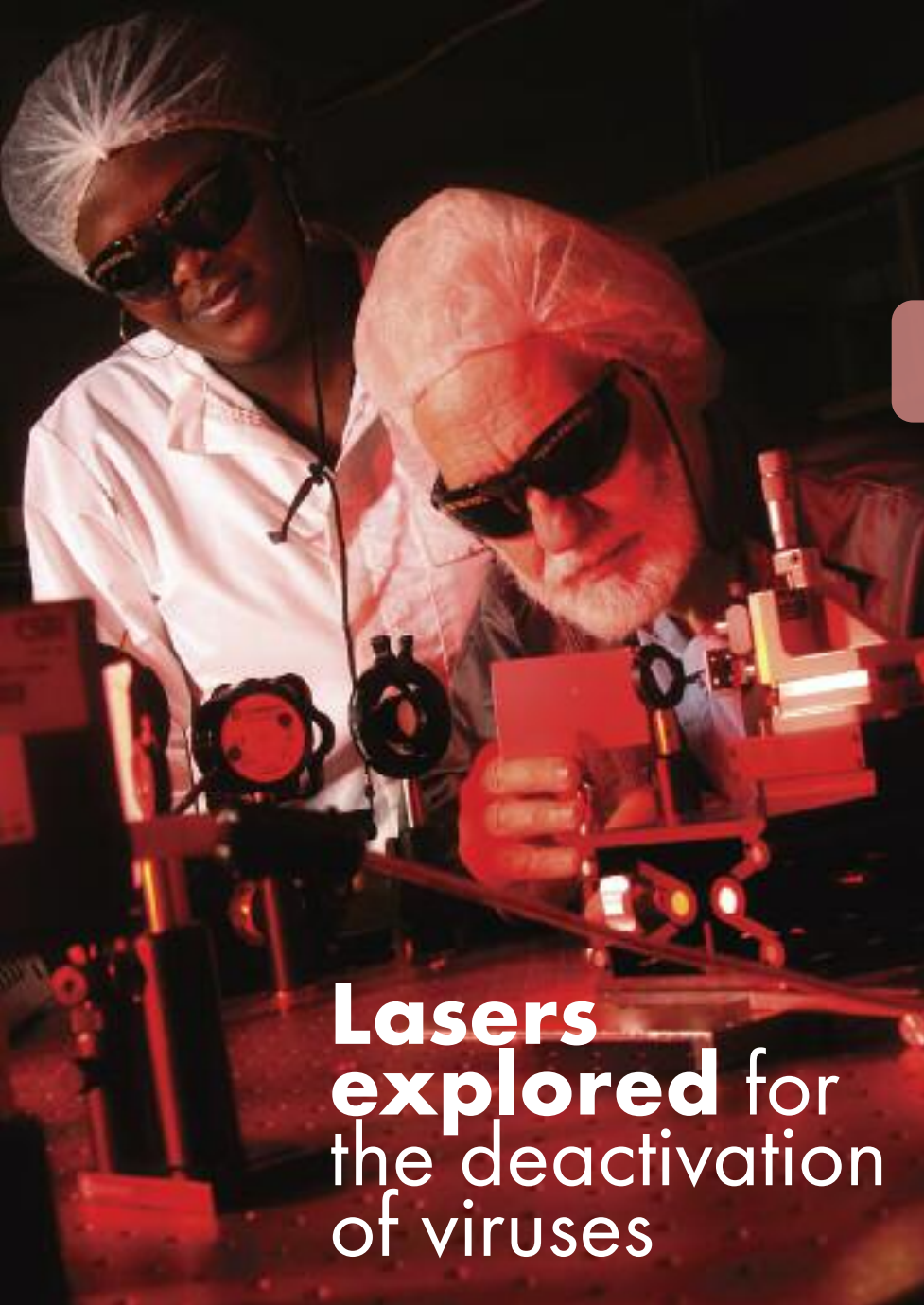
Initially, optical tweezers only made use of basic laser beams with Gaussian profiles, thereby generating basic optical traps capable of basic manipulation. However, by changing the shape of the beam, more versatile movement can be obtained. In particular, we can cause cells to rotate due to the transfer of angular momentum from the beam to the cell. Once rotating, optical tweezers can also control the rate of rotation by simply controlling the amount of angular momentum carried by the photons.

Using the same techniques, one can also trap and control multiple cells at once, opening research into cellular interactions. Similarly, multiple optical traps can be used to study the interaction of a single infectious agent and an antibody, or a chromosome and a drug. Such single-molecule reactions would not be possible without the aid of optical tweezers.

Some special classes of laser beams - Bessel beams - have the potential to reconstruct their shape after trapping a cell, allowing for the trapping of multiple cells along the laser beam's axis. When combined with conventional trapping, this leads to the possibility of creating three-dimensional structures in a controlled manner.

To date, optical trapping and tweezing has found numerous applications in biology and medicine, including measuring the mechanical properties of molecular motors and biopolymers, stimulating neuronal growth, studying the dynamics of DNA and sorting white and red blood cells. In particular, specific areas of interest in the cell biology and biomedical field include the identification, characterisation and subsequent isolation of individual cells and/or cell sub-populations from a complex mixture of different cell types. We have recently demonstrated this technique with Chinese hamster ovary cells. In an experiment by PhD student Patience Mthunzi, Chinese hamster ovary (CHO) cells - with and without ingested microspheres - were separated such that only cells that had internalised microspheres were propelled axially to the top of the sample chamber, attached to the laminin-coated glass cover slips and thereby sorted and separated from the surrounding cells without spheres, allowing the two groups to be cultured separately (see cell sorting figures). This technique can be applied to any class of cell types, for example, separating cancer cells from healthy cells, or stem cells from ordinary cells, and is expected to be an enabling technology in the future in clinical oncology and related biomedical research fields.

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Palesa Molukanele and Dr Ted Roberts eradicate a virus with a laser beam

## Lasers explored for the deactivation of viruses

MANY VIRUSES can be harmful and a nuisance to mankind, plants and animals. In human beings, they destroy or alter living cells and cause diseases. In plants, viruses damage plant cells and ruin crops. CSIR scientists are hard at work on a multidisciplinary project titled *Femtosecond laser deactivation of viruses*. The project is the brainchild of CSIR laser scientist, Dr Anton du Plessis.

The aim of the research is to selectively deactivate certain viruses, while leaving the sensitive materials, such as the host cells, unharmed, by manipulating and controlling with a femtosecond laser system. This group is repeating experiments conducted in the USA to see if they can deactivate viruses under the same conditions. Further experiments will then be conducted to see if they can optimise the

process by using a very large variation of laser parameters that can be achieved at the CSIR National Laser Centre.

PhD student Palesa Molukanele elaborates: "Scientists in the USA managed to deactivate the M13 virus with lasers. M13 is a virus composed of circular, single-stranded DNA that infects bacteria. It is a non-lytic virus, in other words, it does not kill infected cells by disrupting their plasma membranes. Infection is not lethal; however, the infection causes turbid plaques in *E. Coli*, a gram-negative bacterium that is commonly found in the lower intestine of warm-blooded organisms.

"Given the success of the American scientists, we feel that we have a contribution to make in improving the laser parameters," she says.

"Once we are able to deactivate the M13 virus, there's a variety of viruses we would be interested in experimenting with, opportunistic viruses that attack immuno-compromised individuals like people infected with HIV or pregnant women."

Molukanele says the advantage of using laser therapy as opposed to drug delivery, is that laser therapy would not evoke problems of drug resistance. "With this technique, we would be able to be very selective and deactivate only the affected areas," she says.

CSIR laser scientist Dr Ted Roberts says laser technology is one of many possible ways of deactivating viruses. "The research we are working on at the moment will allow the laser beam to interact with the virus and subsequently deactivate it," he says.

The project draws on expertise in laser science and biosciences. "[The virus] M13 is useful for tests because it does not infect or pose harm to humans," says Dr Roberts. "It thrives or multiplies on *E. Coli* and what we are hoping to do is to put it in a solution with a certain concentration. We then apply it to *E. Coli* bacteria and see if it infects the normal cells."

The idea, according to him, is to find out how effective this particular concentration is and to use the same concentration for the laser irradiation. "We vary the laser parameters such as laser intensity and exposure time in our efforts to find an optimum condition for deactivating the virus," says Dr Roberts.

He says limited work is done worldwide in this area of research. "It is exciting to be working on a multidisciplinary project, where biological and physics scientists share their knowledge in pursuit of a common objective."  
- Mzimasi Gcukumana

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Pictured in front are Dr Colin Kenyon, research group leader; Anjo Steyn, PhD student. Pictured back are Caroline Kunene, laboratory assistant; Marli Botha, PhD student; Michael Mathomu, intern; Clement Nkosi, intern; Robyn Roth, senior researcher and Silindile Zunngu, intern.

# Upsetting the nitrogen metabolism of infection-causing bacteria

PhD student Anjo Steyn loads a sample for analysis by high pressure liquid chromatography



RECENT BREAKTHROUGHS by the CSIR in the understanding of the biochemistry of infection-causing organisms, such as the tuberculosis (TB)-causing bacteria, will potentially enable the development of therapeutics that will specifically target the bacteria. This could significantly impact the disease burden of TB, HIV/Aids and other infectious diseases in South Africa and around the world.

The CSIR's structural biology group focuses on identifying, elucidating and clarifying potential new drug targets, primarily in infectious diseases such as TB, HIV/Aids and malaria. Part of the process of developing new drugs involves identifying a 'target' in the organism causing the disease. This can include specific enzymes or reactions that can be 'upset'. The CSIR research is focusing on developing novel anti-infectious agents that target these specific enzymes or reactions within the causative organism – and specifically inhibit or 'upset' the target organism. Once identified, these drug targets form a basis for rational drug design and lead drug identification and modification programmes.

One project within the structural biology group is focused on clarifying and understanding the reaction mechanisms and regulation of the enzyme glutamine synthetase (GS). GS is a central enzyme involved in nitrogen

metabolism. It catalyses the reaction of three molecules, L-glutamate, adenosine triphosphate (ATP) and ammonia, to L-glutamine, adenosine diphosphate (ADP), and inorganic phosphate. This process is important because glutamine acts as a precursor for the synthesis of a number of other amino acids as well as purines and pyrimidines, which are vital precursors to the synthesis of nucleic acids.

Of the three distinct forms of GS that occur, only GSII occurs in higher organisms (eukaryotes). GS I is found only in bacteria (eubacteria) and archaea (archaeobacteria). Within GS I, two significant bacterial sub-divisions exist: GS I- $\alpha$  and GS I- $\beta$ . The TB-causing organism, *Mycobacterium tuberculosis*, has the GS I- $\beta$  enzyme, which is crucial for the fitness of TB and is related to its pathogenicity. The enzyme is regulated or controlled via a complex adenylation/deadenylation cascade. The difference between the bacterial and human GS enzymes enables scientists to target the bacterial enzyme specifically, without interfering with the functioning of the human host enzyme.

The theory behind the research involves examining the reaction mechanisms deployed by GS as well as the adenylation/deadenylation control mechanism of GS in biochemical detail to identify a way to inhibit specific as-

pects of the *M. tuberculosis* GS functionality. In practice this has involved comparing adenylylated and deadenylylated GS in *Escherichia coli* and *M. tuberculosis* (four functionally distinct enzymes in total). This is of particular value since as humans, we do not have the adenylylation/deadenylation cascade in our GS, meaning that potential therapeutics could target the adenylylated GS of TB or other causative organism without interfering with normal bodily functions.

CSIR researchers have discovered a specific mechanism in which ATP binds to enzymes, which is controlled and regulated in a number of ways. Dr Colin Kenyon, who leads this research says, "This breakthrough in the understanding of the related biochemistry can now be exploited to produce specific classes of therapeutics that will target this mechanism for potential control in TB as well as malaria and possibly cancer."

The biochemistry of this research has now extended into a new area, including the identification of novel mechanisms targeting specific kinases to control TB, malaria and cancer.

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Rudzani Muthabane formats components into a 96-well microtitre plate

# WELCOME TO MOTHER NATURE'S AFRICAN CHEMISTRY TREASURE CHEST

BIOSCIENTISTS AT THE CSIR are set to develop one of the largest libraries of purified natural compounds for pharmaceutical use based on the country's unique plant biodiversity – thereby translating South Africa's rich biodiversity into chemical diversity.

Using modern technologies, they hope to create a compound library of more than 15 000 purified natural compounds in the immediate future. Such a library would be the first of its kind in the world – based on South Africa's biodiversity – and of significant commercial value.

According to CSIR researchers Drs Vinesh Maharaj and Nivan Moodley, no synthetic chemist can ever rival the creativity or ingenuity of Mother Nature: "Small molecules found in plants and living organisms have intrinsi-

cally been selected through natural evolution to exert biological effects. This offers a structural variety without any rivals."

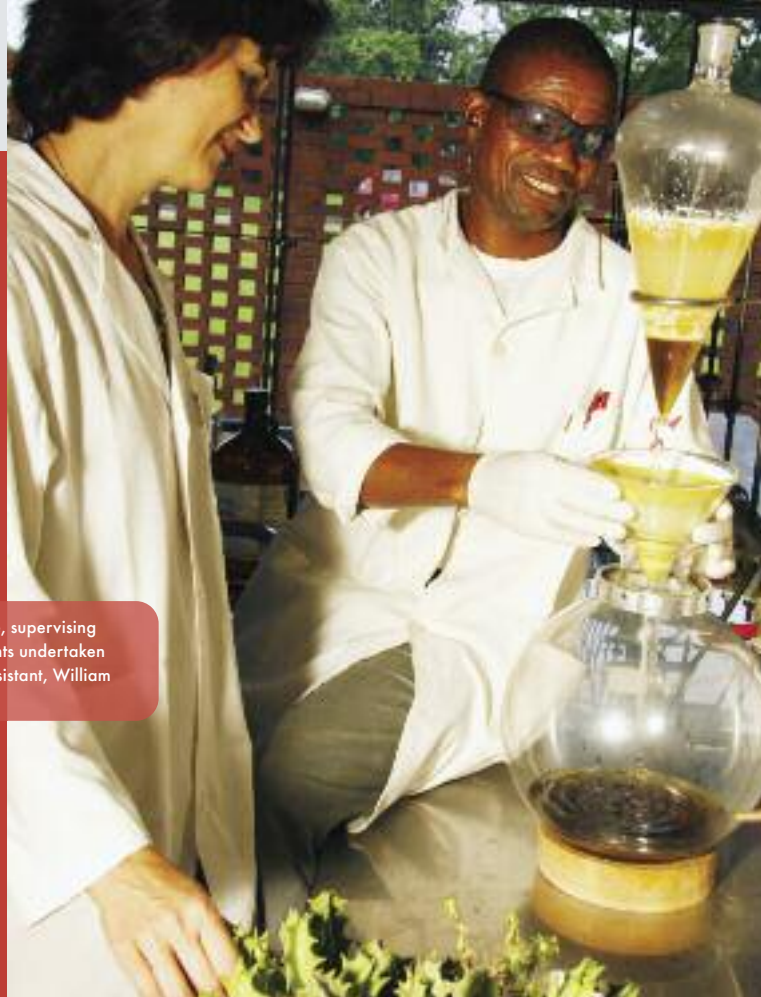
However, until quite recently it was too expensive to search for these compounds, let alone develop a pharmaceutical product ready for distribution. Prior to the 1990s, more than 80% of drug substances were either natural products or inspired by a natural compound. With the advent of high-throughput chemistry and the availability of large libraries of synthetic compounds, the percentage of drugs developed from natural compounds dwindled to almost half of all drugs approved since 1994.

"Plant extracts are exceedingly complex mixtures of different classes of chemicals, and their isolation and purification in a format suitable for screening is often quoted as one of

According to the World Resources Institute, the market for medicines derived from plants was worth \$14 billion annually in the US and \$40 billion worldwide in 2001. The commercially most successful product derived from a plant is a cancer product called Taxol, derived from the Pacific yew tree. Its sales reached \$1,481 million in 1999.

the main bottlenecks for their use. Moreover, the creation of a truly diverse library of natural compounds for screening would require access to a significant number of truly diverse plant species to be subject to the separation of individual natural compounds," explains Maharaj.

"The advantage of a compound library will be that no further purification will be required, which enables active compounds to be evaluated on an equivalent basis to synthetic compound libraries. At the moment there is no



Dr Gerda Fouche, supervising extraction of plants undertaken by laboratory assistant, William Maboŧja



“WEIRD, PECULIAR, WONDERFUL, strange, bizarre, fascinating, and of course, unique, are the kind of words that are used to describe the welwitschia. It is one of the few things on Earth that can truly claim to be one of a kind. There really is nothing like it”. So starts SANBI’s description of the welwitschia. It is also called *tweeblaarkanniedood* (Afrikaans), *nyanka* (Damara), *khurub* (Nama) and *onyanga* (Herero).

single research organisation or pharmaceutical company in South Africa that can boast a pure compound library derived from the botanical specimens available in this country.”

So far the CSIR’s bioprospecting research group already boasts the largest repository of South African plants, with 32 000 plant extracts representing 11 000 plant species. This existing library will form the basis of a greatly enhanced chemical library. The group works closely with the South African National Biodiversity Institute (SANBI) to conduct the botanical research and keep samples in its herbarium (a collection of dried, pressed, or preserved plants specimens like leaves, flowers, seeds and stems).

According to Maharaj the selection of plants will be based on existing knowledge of the chemistry of different groups of plants. For example, it is already well known in botany that certain plant families such as Apocynaceae and Euphorbiaceae contain high levels of alkaloids, which are known for their unique biological activity, e.g. the vinblastine anti-cancer alkaloid drugs isolated from the Madagascar periwinkle.

“We already have a flying start with our collection of extracts from South African plants. A funding partner will, however,

South Africa is a 'hot spot' for biodiversity with more than 24 000 plant species – representing 10% of the world’s species. The Cape Floral Kingdom, for example, is the smallest of the world’s six Floral Kingdoms, but it contains 8 700 species of which 68% are endemic (occur only in South Africa and nowhere else).

enable us to progress much faster in this regard,” says Maharaj. “Southern Africa has some truly ancient plants. Just think of the *Welwitschia mirabilis* found in the Karoo and Namib Desert. Some of those plants are 600 to over a thousand years old,” he says.

The natural compounds from a truly unique, ancient plant like the *Welwitschia* could be the world’s next wonder drug – or perhaps not. – Wiida Basson

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# USING YEAST TO MAKE DRUGS FOR HUMAN USE

THE USE OF YEAST TO PRODUCE NOVEL HUMAN HEALTH TREATMENTS COULD BE ONE OF THE ANSWERS TO THE CURRENT LACK OF CAPACITY IN THE PHARMACEUTICAL INDUSTRY.



Ntsane Moleleki

CSIR SCIENTISTS are developing and modifying yeast to produce human therapeutic proteins and peptides, as well as building human capacity in this area. The limitations of the current manufacturing processes of the pharmaceutical industry are largely due to the use of chemical synthesis for the production of human therapeutic peptides. As a result, demand is exceeding supply for a large number of drugs and therapeutics globally. The use of recombinant DNA technology is becoming the most effective way for producing therapeutic proteins and peptides.

For the past three years, the CSIR has focused on glycoengineering, and has developed strategies to produce therapeutic proteins and peptides at high levels in the yeast *Yarrowia lipolytica*. For proteins to work optimally as therapeutic drugs, they often need to be post-translationally modified, i.e. after they are synthesised. Glycosylation is one of the most common modifications, and it involves the addition of a sugar or a sugar chain to specific parts of proteins. This affects numerous properties of the modified proteins, including biological activity, function, clearance from circulation and antigenicity.

Within the context of this CSIR research on yeast, glycoengineering involves genetically modifying yeast to 'humanise' its glycosylation pathway by replacing it with the human glycosylation pathway. The group has demonstrated the ability of *Y. lipolytica* to produce various therapeutic proteins including anti-HIV therapeutic peptides and human erythropoietin (EPO). EPO is a hormone that controls red blood cell production and is used to stimulate increased density of red blood cells. It is also used in surgical procedures to reduce allogeneic blood transfusion requirements, as well as for the treatment of anaemia associated with chronic kidney disease, cancer and HIV infection.





The research team – Pictured (back) are Donald Kahari, Siyavuya Bulani, Zawadi Chipeta; (middle) Ntsane Moleleki, Lebogang Nkuna, Ananias Kgopa, Faranani Ramagoma; (front) Nokukhanya Mfumo, Wendy Limani, Puseletso Manyapye and Nozipho Zulu

Traditionally, glycosylated human therapeutics are produced using mammalian expression systems, such as the Chinese hamster ovary cell lines. However, the use of animal-derived cell lines has proved to be more expensive, less safe, complex and more susceptible to viral contamination. The use of yeast offers significant advantages over current methods using animal-derived cell lines, as well as chemical synthesis. It is cheaper – due to the shorter fermentation time, safer, with a higher quality and quantity and is also locally manufactured. According to CSIR researcher Ntsane Moleleki, "it could contribute significantly to the biotechnology sector by revolutionising the way that therapeutic proteins are made". To date, one group at Dartmouth College in the US has successfully humanised the glycosylation pathway in a different yeast.

The CSIR started work on *Y. lipolytica* in 2006 with support from BioPAD. The overall aim is to humanise the glycosylation pathway in this yeast while at the same time improving and customising it as a host for expression of human therapeutic proteins and peptides. The yeast *Y. lipolytica* was selected specifically due to findings of a comparative study which demonstrated the superior nature of *Y. lipolytica* as a secretion host of active heterologous proteins (i.e. proteins that are not normally found in yeast). This yeast has

also been studied extensively by key CSIR partners such as the French National Institute for Agricultural Research (INRA), which is part of the National Centre for Scientific Research (CNRS) in France.

The first phase of this project has resulted in a number of significant outputs. The primary aim has been fulfilled through the development of extensive human capacity in yeast genetic engineering, glycobiology techniques, protein expression and, in the long term, customised yeast strains that can express humanised biotherapeutics. In addition to the establishment of a core group of 11 scientists, a number of additional students (PhDs and MScs) have also benefited. In the next cycle of funding, intensive workshops will be conducted to train research students from previously disadvantaged universities around the country in techniques such as protein purification, yeast genetic engineering and glycan profiling.

Other outputs of the project include the development of standard operating procedures, protocols on how to analyse N-linked glycans, and a 'toolkit' of *Y. lipolytica* strains that glycosylate proteins to different extents. Intellectual property is also being generated for the methodology used to produce proteins and peptides.

These achievements provide a good foundation for extending this research into a protein-production platform based on *Y. lipolytica*, which is being supported by BioPAD for an additional three years. This future phase of research will focus on glycoengineering and developing the yeast for the production of therapeutic peptides and proteins.

As Moleleki says, "Something great has been started here. More time is needed to refine the process. This could be a potential way to produce glycosylated proteins cheaply while simultaneously contributing to the scarce skills set in South Africa and further afield, through a number of PhDs."

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**bi·o·ma·te·ri·al**

*n.*

A biocompatible material that is used to construct artificial organs, rehabilitation devices, or prostheses and replace natural body tissues.

THEY ARE HOLLOW, spherical microparticles with single port-like openings and pores covering their entire surface. They are at the heart of a CSIR innovation in soft tissue filler material, primarily because they are designed to be conducive to the in-growth of human cells and are completely resorbable. They've been named Dermapearl™, and CSIR researchers are now embarking on preclinical trials to substantiate their claims conclusively. The researchers believe that their invention could quite literally change the face of cosmetic surgery, and over a longer period, an array of medical conditions.

Lara Kotzé, CSIR researcher and project leader, says the particles are the perfect dermal filler, because the hollow, ported particles serve as both a tissue bulking substance and a tissue harbour for cells. "The inside cavity and port of the particle provide space for the cells to proliferate and for sufficient nutrient and oxygen exchange," she explains. The material from which the microparticles are made also displays favourable resorption properties.

"There is documented evidence that long-term implants have adverse tissue reactions, therefore you wouldn't want a foreign material in your body permanently. While these particles are completely resorbable, they take longer to be absorbed back into the body than some other dermal fillers and their proposed effect of increased cell proliferation therefore gives longer-lasting and more permanent results," she says.

Lara Kotzé

## CSIR injectable dermal filler progresses to preclinical trials

# MICROPARTICLES WITH UNIQUE CELL HARBOUR CONCEPT in the biomaterials domain

Kotzé says biomaterials are any material, synthetic or natural, that is used as a structural component that comes into contact with biological systems. It could be artificial skin, contact lenses, joint replacements, tooth implants or dermal fillers and it could be made of ceramics, polymers, both synthetic and natural, or metals. "The demand for biomaterials is rapidly increasing, one reason being the rise in human life expectancy," says Kotzé.

Dermal fillers have an obvious use in reducing the signs of facial aging through non-invasive cosmetic surgery. Such a soft tissue bulking product is also suitable to correct a condition called lipoatrophy, which is the loss of fat under the skin – specifically in the cheeks, causing hollow and sunken facial features. It is caused by aging and diseases and is often associated with Aids sufferers. "Treatments for HIV/Aids will continue to progress, and then the focus will shift to improving the associated conditions, such as lipoatrophy," says Kotzé. These types of applications for the microparticle platform are achievable in the short term and the team will pursue this objective.

But soft tissue fillers also hold promise as a remedy for medical conditions, such as velopharyngeal inadequacy, often caused by congenital defects such as a cleft palate. Bulking of the soft palate with a soft tissue filler can help correct this condition, enabling better speech and swallowing. Similarly, Kotzé says it could play a role in correcting gastroesophageal reflux disease (chronic heartburn) and bulking of the urinary sphincter in urinary

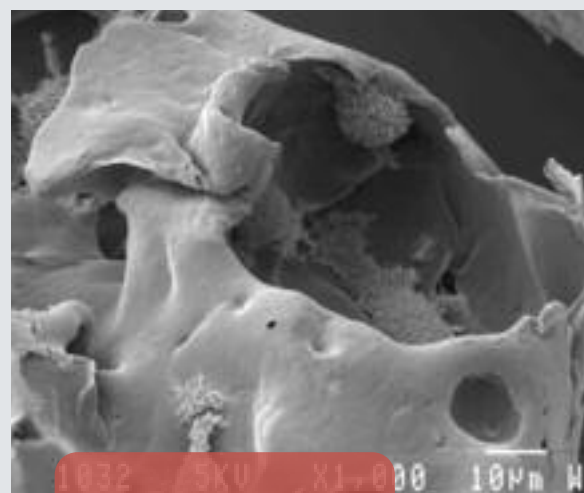
incontinence. Finalising a product for these applications is a longer-term aim.

Using an emulsion process, the Dermapearl™ microparticles are made of polycaprolactone, a polymer commonly used in implant applications. Hyaluronic acid (a substance naturally occurring in the human body) is used as carrier medium.

The Dermapearl™ business plan was a runner-up in the 2008 SA BioPlan Biotechnology Business Plan Competition. The team outlined plans to produce the microparticles in South Africa and then partnering with an established company in the dermal filler market. There are currently no producers of dermal fillers in South Africa, and "with a new industry comes new job opportunities," says Kotzé. She says the review panel – comprising international venture capitalists – all commented extremely favourably on the potential of the invention. The new dermal filler stems from earlier CSIR research in which a ceramic biomaterial was developed to encourage the regeneration of bone. Trials showed that bone cells regenerated rapidly when using this product with its similar geometric shape to the shape now used in the dermal filler.

With patent applications in place; an upcoming internship in the United States for SA Bio Plan semi-finalists; and CSIR funding for preclinical studies, Kotzé is optimistic about the future of their invention, even though it will take several years to bring it to market.

– Alida Britz



A microscopic view of a Dermapearl™ microspheres, with the pores covering its surface clearly visible. To the right, cells can be seen growing on and in the microparticle after 72 hours.

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## When engineering meets biology

# SYNTHETIC BIOLOGY EMPLOYED TO FIND SOLUTIONS TO SOME OF AFRICA'S KILLER DISEASES

BY DR MUSA MHLANGA

FIFTY YEARS of tremendous progress in molecular biology, genomics and biochemistry has identified many key cellular components and processes common to all life. In parallel, rapid advances in information technology, optics, physics and other enabling technologies have permitted the manipulation and monitoring of biological systems. The combining of the two fields of progress have given birth to synthetic biology, an emerging discipline that exploits advances in our biological knowledge with enabling technologies to construct – from the molecular level upwards – new biological systems and devices.

Dr Musa Mhlanga, research leader of the synthetic biology emerging research area, pictured with a new super-resolution microscope that enables researchers to see detailed structures at the level of single molecules within cells. This investment is one of several investments by the Department of Science and Technology in synthetic biology over the past two years.



Key to this, is the application of principles normally found in engineering, to biology. To better understand the unique intellectual and strategic ambitions of the CSIR's synthetic biology emerging research area, one needs not look further than a few projects in the newly established research groups.

The molecular biomaterials group, under the direction of Dr Justin Jordaan, focuses on the bottom-up construction of bio-molecular systems from a combination of biological and polymer precursor materials.

The group aims to be a leading developer of synthetic biological systems, using a bottom-up manufacturing approach. This can be achieved by using the superior technical advantages of their technology enabling and proprietary ReSyn™ technology platform. They have developed a novel protein immobilisation matrix consisting of cross-linked polyethyleneimine strands that enable the construction of advanced biological systems.

These matrix particles are produced in an emulsion, enabling size control, an important characteristic for their intended applications. The advantages of this technology are the extraordinarily high biological-binding capacity and high enzyme activity maintenance after immobilisation. These properties allow for the immobilisation of combinations of proteins to the particles and have uses in areas as diverse as industrial enzymes and clinical diagnostics.

One of the broad aims of the gene expression and biophysics research group is to enhance the study of synthetic biology by developing single-molecule technologies that will revolutionise the study, modelling, engineering and imaging of gene expression *in vivo*. Led by Dr Musa Mhlanga, who is also the leader of the synthetic biology emerging research area, they intend to use a number of model systems to achieve this goal. One important focus is on developing advanced optical imaging approaches to achieve super resolution of biological objects. Such studies can be used to examine infectious diseases and host pathogen-induced transcription, to screen for natural compounds, drugs or small molecules than can 'engineer' transcription and to study stochasticity and 'noise' in gene expression. Decrypting gene expression, and thus enabling its fine control, is one of the fundamental aims of synthetic biology's bottom-up approach.

This group works very closely with the high throughput biology group lead by Dr Neil Emans. High-content screening (an extension of high-throughput biology techniques) allows for the evaluation of multiple biochemical and morphological parameters in cellular systems, if biological readouts in the system are amenable to quantitative data collection *in vivo*. Using automated imaging and microscopy techniques, as well as cell-based assays developed with the gene expression and biophysics group, the high-throughput

biology group aims to identify genes and chemical compounds which are implicated in infectious chronic diseases. By combining the imaging of cells with image analysis algorithms, individual components of the biological system are assigned quantitative properties.

Recently the CSIR acquired an siRNA genome-wide library that will enable the ability to screen the entire human genome for genes implicated in HIV infection, for example. With innovative technology developed within this CSIR group, several genome-wide screens are planned.

The CSIR synthetic biology group has set itself the goal of developing the foundation technologies and research development capacities that cover the entire synthetic biology workflow. Through a new human capacity development programme, and by training graduate students and postdoctoral fellows, it aims to be the leading synthetic biology centre in South Africa and among the leaders worldwide. In doing so, it also hopes to play an influential role in developing the field in South Africa through local and international partnerships and contribute to finding basic research solutions to the diseases affecting South Africa and Africa today.

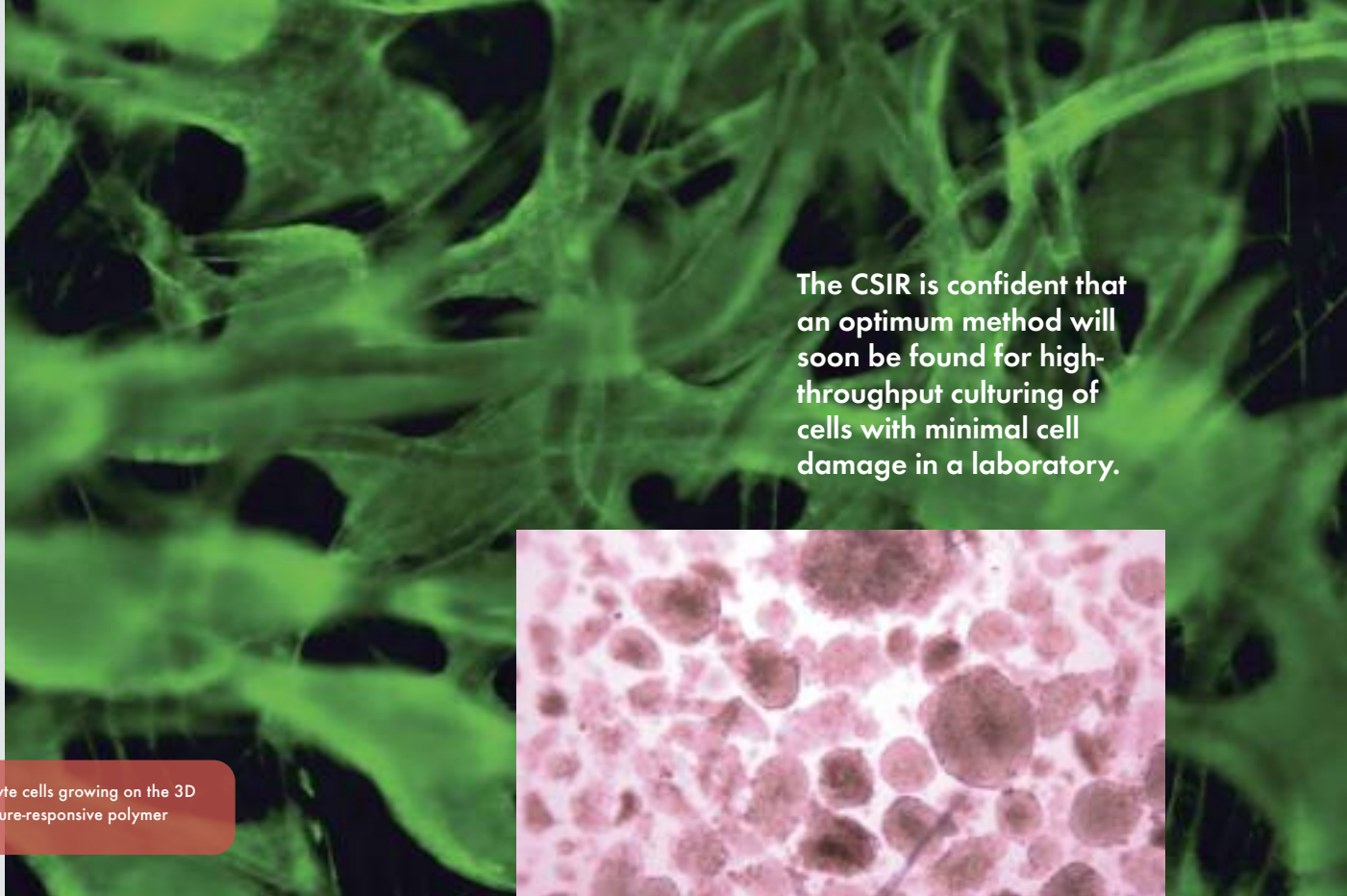
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## Treating internal bleeding on the spot with ultrasound waves

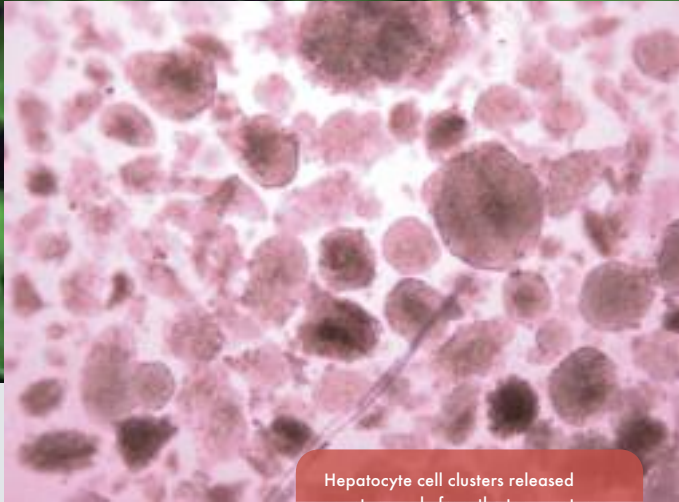
CSIR SCIENTISTS PLAYED A PART in the development of a transportable device for the treatment of internal bleeding. Immediate treatment after sustaining an injury and before an equipped medical facility can be reached, can make the difference between life and death. *ScienceScope* reported in March 2009 that high intensity focused ultrasound (HIFU) is at the heart of an American-developed device in which ultrasound waves are directed towards a specific point within the body, resulting in rapid heating of diseased or injured tissues. When heated, the biological tissues shrink and fuse, stopping bleeding in deep tissue and within organs such as the liver, spleen, pancreas, etc. One currently approved application of HIFU in the medical field is for the treatment of prostate cancer, while approval is also being sought for the treatment of pancreatic cancer and uterine fibroids.

The CSIR's contribution related to the development of transducers, in collaboration with the University of Washington in Seattle, USA. Transducers convert electric pulses to ultrasound waves. **For the full story, See *ScienceScope*, March 2009, page 53.**



The CSIR is confident that an optimum method will soon be found for high-throughput culturing of cells with minimal cell damage in a laboratory.

Hepatocyte cells growing on the 3D temperature-responsive polymer



Hepatocyte cell clusters released spontaneously from the temperature-responsive scaffold at 25°C

# POLYMER SCIENCE CALLED UPON IN CELL-CULTURING BREAKTHROUGH

A breakthrough in the culturing of human cells on a mass scale with use of a temperature-responsive polymer has led to the filing of an international patent application.

ScienceScope reported in March 2009 that researchers at the CSIR have developed a cell-culturing device that would greatly reduce the human factor in cell culturing, while allowing cells to grow in an environment that closely resembles conditions within the human body.

One aspect of the innovation featured a temperature-responsive polymer used as a coating on 3D fibre scaffolds. This means that cells can grow in a 3D, natural state – rather than on a flat surface. The scaffolds are porous, allowing for oxygen and nutrients to reach the cells, yet they contain enough surface area for the cells to bind to and proliferate.

When the temperature is changed, the cells are released without harming them. In this way one can harvest and release cells by merely changing the temperature of the media, and without damaging the cells’ surface proteins. Since March 2009, the project team has made substantial progress and has now demonstrated proof-of-concept for non-invasive thermal cell culturing.

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