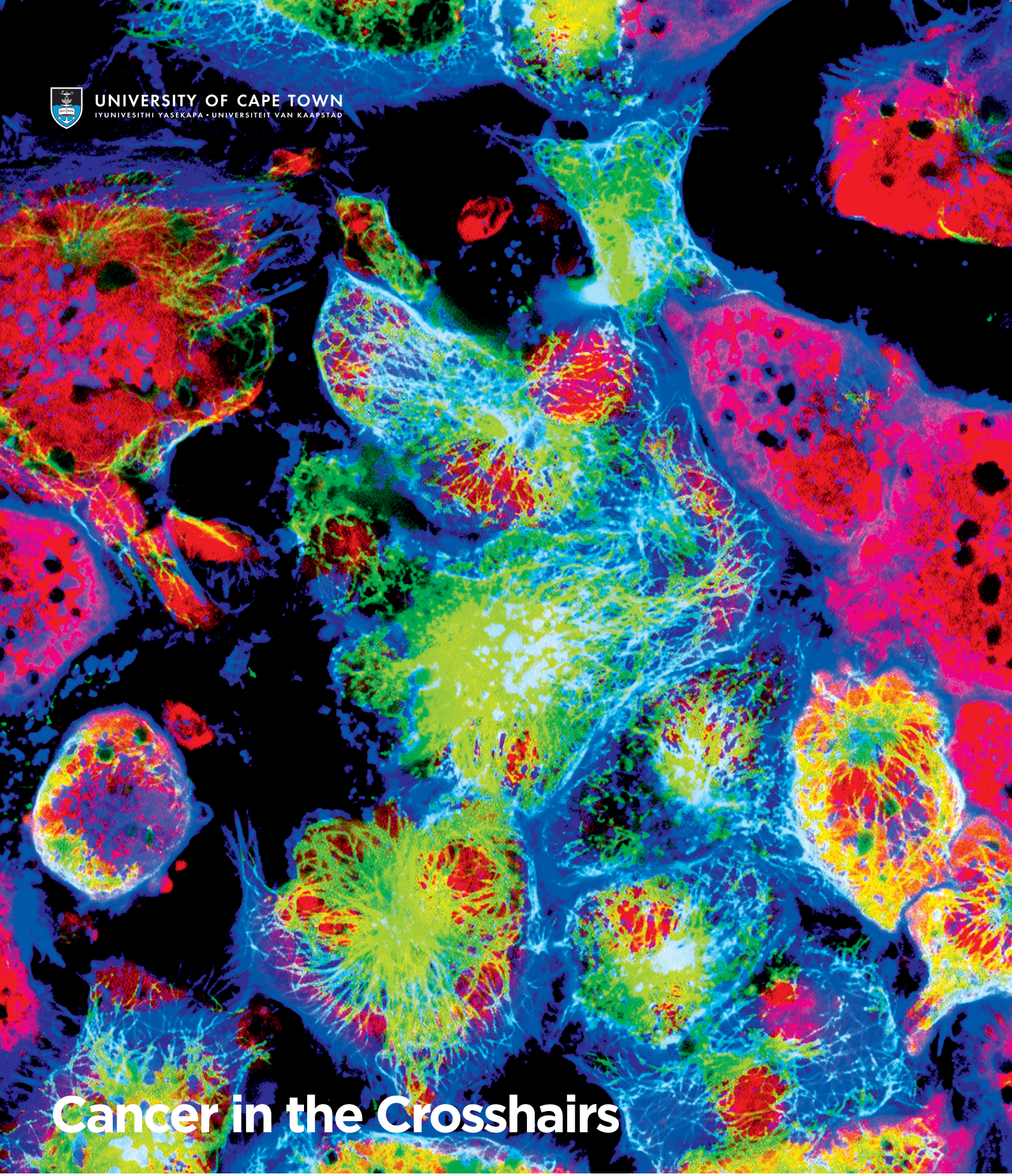


INNOVATION AT UCT 2018

Research Contracts & Innovation

Welcome to the 2018 edition of Innovation at UCT. This year we elected to profile the innovations happening in the cancer detection and treatment arena. Of note is the broad spectrum of involvement of inventors and researchers across three faculties (Engineering and the Built Environment, Science and Health Sciences).

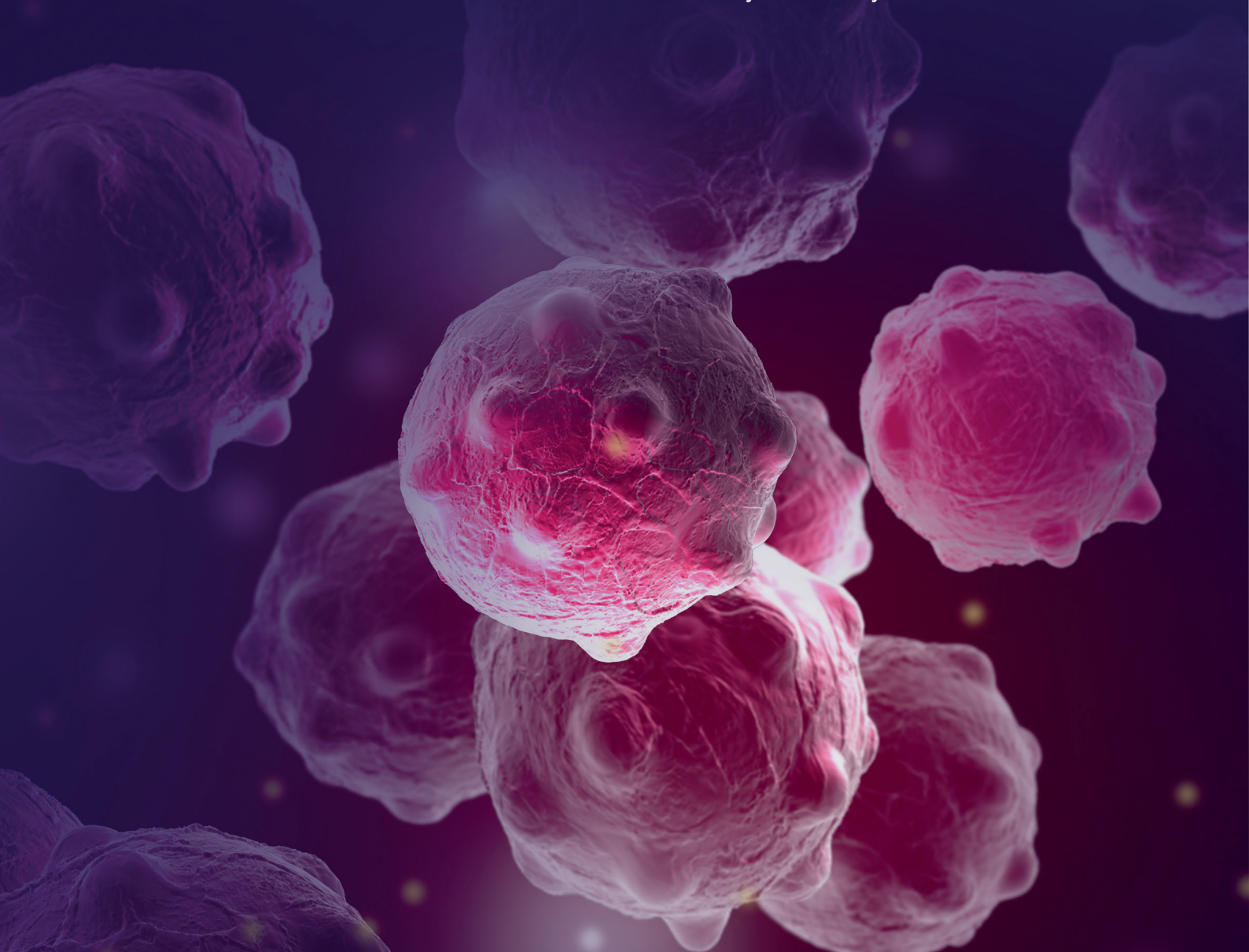
One of the reasons for our focus on cancer this year is recent World Health Organisation (WHO) reports that developing countries face unique challenges when it comes to diagnosis and treatment. Only 26% of countries with a lower than average GDP have pathology services available in the public sector, with similar rates of treatment. Cancer-causing infections, such as hepatitis and human papillomavirus, are also responsible for 25% of cancer cases in developing countries.

A recent study published in the Lancet predicts that South Africa could see an increase in cancer cases of 78% by 2030. Early diagnosis is key to successful cancer treatment and our innovators have pushed forward novel ideas that are tailored to South Africa, specifically, and Africa as a whole.

In particular, Prof Stefan Barth, SARChI Chair in Cancer Biotechnology, and his Medical Biotechnology and Immunotherapy (MB&I) Research Unit are focusing specifically on African patients. The aim of the Unit is to develop local immune-oncology diagnostics and therapeutics as an alternative to the spiralling costs of leading therapeutics. Through novel techniques and approaches, a locally developed technology could help millions across the continent.

Included in our annual publication is an analysis of the UCT Intellectual Property (IP) portfolio as well as various annual metrics such as research income and new patent filings, among others. In terms of maturing the IP Portfolio post research, we have indicated the considerable funding that is going into innovation projects that are focussed on developing a new product or service.

We gratefully acknowledge the funding provided by the DST's National IP Management Office (NIPMO) that provides up to 50% co-funding of the IP protection expenses incurred by the university.



Impact Through Innovation 2017

2363 Research Contracts Signed

Value R 1.39 billion | Local R 399 million | Global R 989 million

41 Invention Disclosures

72 Patent Applications Filed in Different Countries

16 Patents Granted

125 IP Rights in Active Portfolio

37 IP License Agreements

R 3.58 m Total Income from IP commercialisation

4 new spin-off companies

>R 100 m value of UCT equity in spin-offs.

University of Cape Town • iYunivesithi yaseKapa • Universiteit van Kaapstad

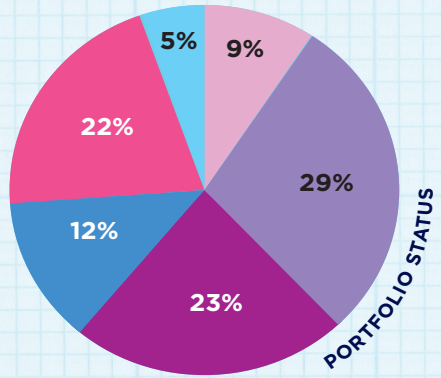
Funding Innovation*

UCT PreSeed Fund (2017) R 307k	TIA Seed Fund (2017) R 2.45 m	TIA Tech Dev Fund (5 years) R 43 m
TIA Platform / Infrastructure Funding (5yrs) R 75 m	MRC SHIP (5 years) R 152 m	dti THRIP (2017) R 61.5 m
UCT Evergreen Fund (2017) R 29.8 m		

* Technology Innovation Agency (TIA)
Medical Research Council (MRC)
Strategic Health Innovation Partnership (SHIP)
Department of Trade & Industry (dti)

UCT's IP Portfolio

There are 125 IP Rights that include copyright (software), patents and associated biological materials, trademarks and registered designs in the portfolio and the graphic shows the commercialisation status. Early cases are either new, needing a commercialisation strategy developed, or technologies that are being matured within the university using innovation funding.



Benchmarking

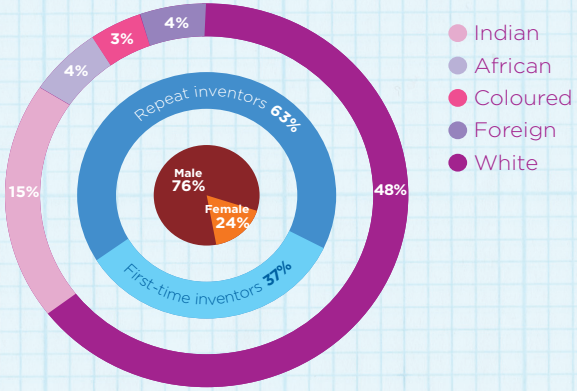
The Association of University Technology Managers (AUTM) determined the average number of invention disclosures, patents, licenses and spin-off companies one could expect per $ of research funding coming into an institution.

UCT's metrics have been analysed and compared to figures that are 15% above the AUTM average. The targets are being exceeded except for provisional patent filings.

	OUTPUT TARGET AUTM AVE. +15%	ACTUAL
Funded Research (5 yrs)		$532m
Inventions Created (5 yrs)	215	218
Inventions Created (2017)	32	41
Provisional Patents Filed	16	12
IP Licenses	8	37 (10*)
Start-ups Created	0.8	4

*excluding poisons database licenses

Invention disclosure demographics

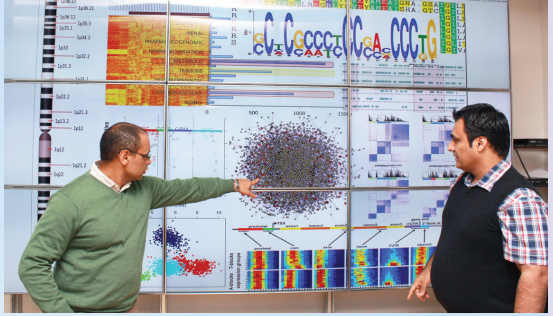


1 A PALLADIUM-BASED DRUG SHOWING LOTS OF PROMISE

One of the greatest drawbacks of most current cancer treatments are the brutal side- effects that many patients suffer while in therapy. Research suggests that one of the reasons for this could be the use of the metal platinum as the core element in most of these drugs. There is evidence that the side-effects could be minimised by replacing it with a close metal relative, palladium.

Professor Sharon Prince and her lab have teamed up with Professor Selwyn Mapolie from Stellenbosch University to investigate a range of palladium complexes for their anticancer uses. After extensive *in vitro*, as well as *in vivo* tests, they discovered a palladium-based drug called AJ-5 which showed high anticancer activity with very little effects on normal cells. Importantly, AJ-5 was able to clear tumours in mice with negligible side effects. Its effectiveness also manifested at a 50 times lower concentration than the commonly-used platinum-based anticancer drug, cisplatin.

To increase its water solubility, the structure has been tweaked slightly to produce a derivative drug called BTC2 that promises to be equally, if not more, effective. It is currently being prepared for pre-clinical testing.



2 CANCER CLASSIFICATION THROUGH BIOINFORMATICS

Along with early detection, the accurate classification of cancer type can be crucial in providing patients with a relevant and successful treatment regime. Through genomic and bioinformatic methods, Professor Kevin Naidoo and his research team have identified glycogene biomarkers that reveal information about the type of cancer in patients. They've also established that these biomarkers can take clinicians a step further in revealing specific subtypes as well.

This is a major breakthrough as almost every cancer has various subtypes, which all require a different treatment approach. Breast cancer, for instance, has four known subtypes, which Naidoo and his team were able to identify accurately through each one's unique gene expression. The research group is taking the study even further in an effort to establish whether these same gene expressions in tumour tissue samples can be identified in a blood sample so as to minimise invasiveness of the test and to facilitate screening for cancer at a much earlier stage of the disease.

The significance of the research is that Naidoo and the team's work can assist oncologists in selecting the most effective cancer therapy for specific cancer subtypes, instead of using a sledgehammer approach that treats all subtypes with the same therapeutic regimens.

3 DENDRITIC CELL VACCINES TO TREAT CANCERS AND INFECTIOUS DISEASES

In the field of immunotherapy, which utilises a patient's own immune system to fight disease, there have been significant advancements over the past decade to treat various cancers. Its impact and interest has resulted in the discovery of new forms and combinations of immunotherapies.

Having been around since the early 1990s, dendritic cell vaccines are hardly a new form of immunotherapy. However, following a decline in popularity during the 2000s, newer cell maturation technologies and biomarker approaches have led to their revival, with many clinicians working hard to increase their efficacy.

Dendritic cells are a subset of white blood cells that act as messengers, rather than fighters, gathering information about antigens in the body and presenting it to other immune cells. When extracted from a cancer patient, these cells can be trained to identify the specific pathogen or cancer antigen present, and draw the immune system's attention to fighting it once back inside the patient. The challenge for clinician scientists lies in preparing these cells adequately for the task ahead.

In an effort to meet this challenge, Professor Keertan Dheda and Dr Michele Tomasicchio from UCT's Centre for Lung Infection and Immunity have developed a maturation 'cocktail' to prepare dendritic cells *in vitro*. The technology utilises the patient's own dendritic cells which are 'trained' in the laboratory with a cancer or infectious disease antigen, together with a maturation cocktail, to relay danger signals to other immune function cells to specifically target and kill the cancer or infectious disease affecting the patient. Their approach is being tested against breast cancer and infectious diseases (extensively-drug resistant tuberculosis in particular).

They have recently shown, in a preclinical trial involving breast cancer patients, that the vaccine had high efficacy against primary breast cancer cells *in vitro*. They will now test the vaccine in a phase I/II clinical trial involving stage 3 and 4 breast cancer patients. This is the first study of its kind in Africa, and they have filed two patents based on their work.

4 CAPERAY: SAVING LIVES, TIME AND MONEY WITH DUAL-MODALITY BREAST IMAGING

A sobering and significant statistic when discussing cancer is that 1 in 8 women will be diagnosed with breast cancer. Fortunately, if caught early enough, this disease can be treated successfully. Since the 1960s, mammography has served as the primary diagnostic tool for clinicians, becoming the first step in successful diagnosis and treatment. There is, however, one big drawback: it fails to detect early stage tumours in dense breast tissue. To minimise these chances, women at risk are often sent for further ultrasound screenings, racking up costs and delaying diagnosis.

But what if the two imaging systems could be combined into one efficient solution? This is the question that led UCT spin-of company CapeRay's Professor Kit Vaughan and his team to develop the Aceso imaging system, which combines full-field digital mammography and automated breast ultrasound into a single device. The fact that the breasts remain in identical orientation and compression for both images also assists in more accurate and speedy diagnosis. In addition to saving patients' time, it also reduces the clinic's costs associated with diagnosis.

The Aceso device recently received CE certification, which means it can be marketed throughout Europe, the Middle East and here in South Africa. It is currently also being used in a large clinical trial under supervision of Dr. Kamila Padia at Two Military Hospital in Wynberg.

5 FIGHTING HPV WITH SURFACTANT A

Surfactant and associated surfactant proteins are most commonly associated with the integral role they play in maintaining lung function and protecting the lung from infection. In fact, the first thing neonatologist paediatricians do to boost a premature infant's chances of survival is to treat them with a surfactant protein.

Based on this, Professor Bill Horsnell and Doctor Georgia Schäfer (both from the Division of Immunology) started wondering whether these proteins could be used to fight infections in other mucosal sites within the body. This eventually led to research around human papillomavirus (HPV), focusing specifically on the female reproductive tract, where HPV infection may cause cervical cancer.

They looked at Surfactant Protein D and A and whether these proteins actually bound to the virus. Both did, but Surfactant Protein A (SPA) showed a tighter binding to the virus. Along with this, they had found that the levels of surfactant protein in the female reproductive tract are relatively low to start off with. These two findings gave rise to the idea, then, that raising the level of SPA in the female reproductive tract could enhance its ability to protect against this type of viral infection. During *in vivo* tests in mice using HPV pseudovirion, it was found that adding SPA to the female reproductive tract did indeed reduce infection. Horsnell believes that while SPA might not end up being used as a treatment in its own right, it could be used to enhance the efficacy of existing vaginal gels to stave off HPV infection.

6 THE RISE OF THERANOSTICS IN CANCER TREATMENT

The term 'theranostics' has been coined to describe agents that can be used for diagnosis via imaging and/or therapy. Fast becoming the norm in personalised medicine, UCT recently made an important contribution to this field with the development of GluCAB™, which was designed to be radiolabelled with either a diagnostic or therapeutic radioactive isotope for both imaging and treatment of cancer. Considered to be next generation chemotherapy, it was developed by Profs. Iqbal Parker and Roger Hunter and their then PhD student Cathryn Driver in collaboration with a team at the South African Nuclear Energy Corporation (NECSA).

The now Dr Driver has subsequently joined NECSA and the drug development is progressing through *in vivo* pre-clinical trials to investigate the uptake and distribution of the molecule in the body and especially how it is taken up by a tumour. The molecule has also been designed to include a linker that is cleaved near or inside the tumour providing efficient release of the toxic payload to attack the cancer. These cancer-focused approaches will hopefully minimise general toxicity to health cells and side effects that are experienced by patients. The hope is that it is taken up preferentially (often due to the proliferation of blood vessels in the tumour), concentrating the dose of radiation in the tumour.

As proof of just how promising this innovation is considered to be, BGM Pharma has come on board as commercial partner to fund the pre-clinical trials and ultimately hopefully the commercialisation of this new pharmaceutical.

7 HARNESSING ANTIBODIES AS BOTH DIAGNOSTIC TOOLS AND TREATMENT VEHICLES FOR CANCER

Surgery, radiation and chemotherapy are by far the most common cancer treatments available today. While all three have proven success rates, they also have major drawbacks. Radiation and chemotherapy, especially, may be effective in killing off cancerous cells, but in most cases also cause damage to normal cells. Obviously, the ideal would be to target diseased cells only.

Interested in how antibodies can be harnessed to, firstly, recognise diseased cells and secondly, guide tailor-made treatments to said cells, Professor Stefan Barth from the Medical Biotechnology and Immunotherapy (MB&I) research Unit, Dr Shivan Chetty, head of MB&I's research strategy and innovation, and their team of biotechnology researchers have made important progress in developing more effective means of cancer diagnosis and treatment.

The basic premise is that specific antibodies will bind with specific pathogens. By attaching a diagnostic label to the antibody, the clinician will be able to track its activity through various imaging techniques. If this label is fluorescent, they will be able to track it through microscopy. If it is a radio label, clinicians would be able to see the antibody-labelled tumour using molecular imaging. This means once the antibody binds to a diseased cell, a diagnosis can be confirmed.

This same antibody can then also host a therapeutic label, which can be activated with a simple switch in wavelength. To do this, an appropriate therapeutic label would need to be attached to the antibody, in addition to the diagnostic label. As soon as diagnosis has been confirmed, the therapeutic label can be activated by the clinician. The therapeutic label would depend on the type and stage of cancer in question.

Globally JAMA Oncology report that there are over 8.7m deaths from cancer. In South Africa, 2015 figures indicate that lung, cervical and oesophageal cancer accounted for 19 160 deaths. Breast cancer is the most prevalent for South African women, but cervical the deadliest. In men, prostate cancer is the most common, but lung cancer is the biggest killer.

Researchers at UCT inventing new approaches and are attacking cancer on a number of frontiers using ingenious, novel tools. These innovations will significantly impact the health of South Africans, as well as others globally.

8 IDENTIFYING NOVEL CANCER BIOMARKERS AND THERAPEUTIC TARGETS

In the past decade, there has been a substantial shift in cancer research toward a more targeted approach to specific cancers. As Professor Virna Leaner, Head of the Medical Biochemical Division at UCT explains, "The current thinking is that if you can target a cell specifically, you will have fewer side effects on the non-cancer cells".

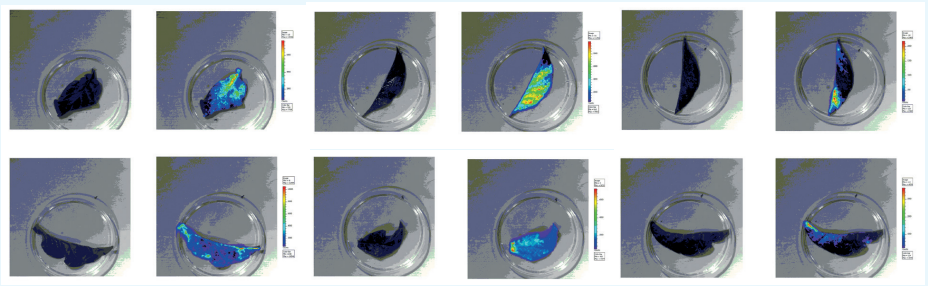
Through the application of this approach, Leaner and Dr Pauline van der Watt are hoping to find novel cancer biomarkers in the form of proteins that could also serve as therapeutic targets. The hypothesis is that if you are able to inhibit or block the function of a protein that is essential to a cancer by using a drug, then the cancer cells should die. During a recent study using a small cohort of cervical cancer patients at Groote Schuur Hospital, the researchers identified a protein called Kpnb1 as a potential biomarker and therapeutic target for this kind of cancer. Knowing the structure of the protein, Leaner and her group worked with Prof John Trent from the University of Louisville to scan in silico libraries for chemical compounds with structures matching Kpnb1 in a lock-and key manner. The idea is that these drugs will attach to the protein and hopefully impede its function.

The group has identified a number of promising compounds, which are now being tested in the laboratory to see if they are, firstly, effective in killing cancer cells and, secondly, killing the specifically targeted cells.

9 IMPLANTS TO REPLACE TUMOUR-DAMAGED BONES

When tumours start eating into bone, it can drastically affect a patient's quality of movement and, as a result, also life. Associate Professor of Mechanical Engineering, George Vicatos, has made it his life's work to create implants that replace damaged bone. During his career, Vicatos has designed a number of noteworthy products, to name a few: **a)** implants for limb-salvage surgeries that include modular long-bones and joints replacements, and custom implants that are uniquely designed for a specific patient, to replace a part or an entire bone; **b)** Within the many modular long bones, joints, and customised implants, Vicatos has patented a constrained rotational knee with a special bearing that allows patients to rotate and flex this joint; **c)** an extendable implant that allows a child's limb, where a big chunk of bone has been lost to tumour, to 'grow' at the same pace as its counterpart.

Vicatos and his student James Boonzaier also teamed up with Dr Rushdi Hendricks, a private Maxillofacial Surgeon, to design a device that assists in recreating bone and soft tissue where tumour has eaten away at the maxilla. Using the century-old method of distraction osteogenesis, (surgically breaking the bone and pulling the two pieces a fractional amount apart per day to enable new bone and tissue to form in the gap), they are able to reproduce the patient's upper jaw bone, gums and palate. This device is the first that successfully navigates the curvature of the upper jaw enabling teeth to be implanted in the newly formed bone. The team has recreated a healthy maxilla for six patients with the final outcome being a significant improvement over current alternatives.



10 SHEDDING LIGHT ON DEEP TISSUE CANCERS WITH BIOLUMINESCENCE

A major challenge in the detection and diagnosis of deep-tissue cancers is that it largely relies on invasive methods, such as surgery. The reason for this is that current non-invasive imaging systems cannot penetrate human tissue to the necessary depth. In recent years, there have been a number of studies focused on employing fluorescence technology for deep-tissue imaging in pre-clinical mouse cancer models. However, natural molecules and proteins do have some inherent fluorescence of their own and this causes a measurable background interference, which compromises the quality of the image.

In an effort to solve this problem, Dr Anwar Jardine and his PhD student Marwaan Rylands have been looking at advancing ways in which deep tissue bioluminescence imaging (BLI) can be more effective. Jardine and Rylands' research focuses on the enzyme luciferase and its substrate, D-luciferin, which is known to enable the firefly to glow in the dark due to a process of bioluminescence.

The technology is focused on producing modified versions of luciferase's natural substrate, D-luciferin. This builds on the long-established technology of incorporating the gene sequence responsible for luciferase production into the expression system of cancer cells. Modified luciferins itself is not unique, as various derivatives of D-luciferin are known and already applied in BLI. However, what makes their research different is the fact that they identified a novel D-thioluciferin derivative that is sensitive to cellular stress biomarkers and also maintains an extended output of light. It also leans toward the red-light wavelength, which is known to increase the depth of tissue visualisation. This enables biomedical research scientists to non-invasively watch tumours shrinking on treatment in pre-clinical mouse tumour models.

11 HPV VACCINES MADE FROM PLANTS

Human papillomaviruses (HPV) have been identified as the cause of cervical and other cancers, which has made it possible to create vaccines targeting them specifically. In the past, most HPV vaccines were created using expensive mammalian tissue culture or yeast fermentations. With production in mammalian cells, however, there is a problem of cost as well as an inherent risk of contamination with human pathogens.

In an effort to avoid this, Prof Edward Rybicki and the Biopharming Research Unit (BRU) have created HPV vaccines expressed in plants instead. They were among the first to demonstrate the feasibility of making an HPV vaccine in plants and were also the first to publish use of a transient method instead using transgenic plants. This has made the turnaround time for creating the vaccine a lot quicker. "It takes only up to seven days to see results, which is a huge difference. If you use transgenic plants, it can take up to six months," explains Dr. Inga Hitzeroth, Deputy Director of the BRU. The team has produced many different HPV vaccine candidates in plants, several at a very high yield. The IP has also been successfully licensed sequentially to two major pharmaceutical companies for different periods and is now under consideration by a new potential commercial partner.

Furthermore, a key element of any HPV vaccine development is the use of a neutralisation assay to test efficacy through the detection of serum neutralising antibodies. A pseudovirion-based neutralisation assay (PBNA) using mammalian cells is the current golden standard for testing candidate HPV vaccines. Additionally, HPV pseudovirions can deliver DNA vaccines which can be used to treat infected individuals. Production of PsVs is, however, very expensive and time-consuming, and also holds the risk of contamination with mammalian DNA. The BRU has demonstrated that producing HPV and other virus pseudovirions in plants can solve all these issues as the production is relatively cheap, quick, and contamination by mammalian DNA is altogether eliminated.

13 PLANT-BASED HPV PSEUDOVIRION

Similar to their work in creating human papillomavirus (HPV) vaccines, Prof Edward Rybicki and Dr Inga Hitzeroth of the Biopharming Research Unit (BRU) at UCT have been at the forefront of manufacturing HPV pseudovirions (PsVs) in plants. Resembling a native virus, but containing no infective DNA, these plant-produced HPV PsVs could be used as delivery vehicles for DNA vaccines used in gene- or other therapy, such as for HPV-induced cancers.

The idea is that the HPV PsVs would be taken up by cells and the therapeutic DNA would be released, resulting in synthesis of recombinant protein that could invoke an immune response. This would ultimately kill infected cells or act therapeutically. Production of HPV PsVs in plants, as opposed to the conventionally used mammalian cell culture, allows for more cost-effective production of PsVs at scale. Since they don't contain any infective or mammalian DNA, they also circumvent safety concerns associated with mammalian cells.

The application of the HPV PsVs as a DNA vaccine delivery vehicle also shows promise in extending beyond cervical cancer. HPV is present in all cutaneous tissues and is also implicated in other cancers such as skin, throat and lung cancer. Therefore, HPV PsVs could serve as a delivery mechanism of treatments of most if not all cutaneous cancers, as well as of a number of other human and animal diseases.

UCT Spin-off Companies

DRONESAR · Cell-Life · curitbiotech · ATTRI · Antrum Biotech · CapeRay · AngioDesign · tuluntulu · SAT · Nurture Restore Innovate · CAPE catalytiX · abalobi · HyPlat · IMPULSE · sonic · LUMKANI · PST SENSORS · Cape Bio Pharms · Elemental

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