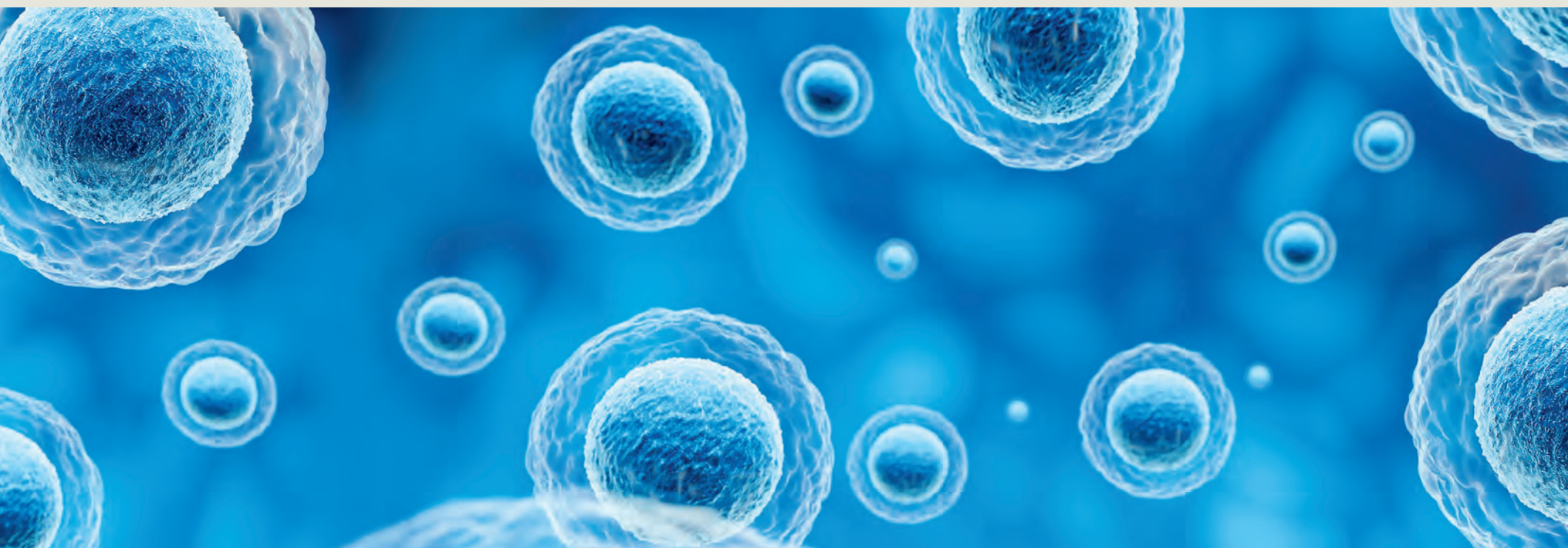


## 3

JOINT RESEARCH PROJECTS  
NON-COMMUNICABLE DISEASES*Human cell*

According to a review article in the *New England Journal of Medicine* (2013), non-communicable diseases (NCDs) will be the predominant global public health challenge of the 21st Century. The main goals of health policy will be to prevent premature deaths due to non-communicable diseases and reduce related healthcare costs. For clinical medicine, the main goals will be to improve detection and treatment of non-communicable diseases and prevent complications and catastrophic events. To achieve these goals, the primary mission of public health is a multilevel approach that integrates policy actions, regulations, health education, and efficient health systems. All countries can benefit by sharing experience and pooling expertise to prevent and control NCDs.

NCDs, also known as chronic diseases, tend to be of long duration and are the result of a combination of genetic, physiological, environmental and behaviours factors. According to the World Health Organization, these diseases kill 41 million people each year, equivalent to 71% of all deaths globally.

The main types of NCDs are cardiovascular diseases (like heart attacks and stroke), cancers, chronic respiratory diseases (such as chronic obstructive pulmonary disease and asthma), and diabetes.

People of all age groups, regions and countries are affected by NCDs. These conditions are often associated with older age groups, but evidence shows that 15 million of all deaths attributed to NCDs occur between the ages of 30 and 69 years. Of these "premature" deaths, over 85% are estimated to occur in low- and middle-income countries. Children, adults and the elderly are all vulnerable to the risk factors contributing to NCDs, whether from unhealthy diets, physical inactivity and exposure to tobacco smoke, or the harmful use of alcohol.

These diseases are driven by forces that include rapid unplanned urbanisation, globalisation of unhealthy lifestyles and population ageing. Unhealthy diets and a lack of physical activity may show up in people as raised blood pressure, increased blood glucose, elevated blood lipids and obesity. These are called metabolic risk factors that can lead to cardiovascular disease, the leading NCD in terms of premature deaths.

**Socioeconomic impacts of NCDs**

NCDs threaten progress towards the 2030 Agenda for Sustainable Development, which includes a target of reducing premature deaths from NCDs by one-third by 2030.

The rapid rise in NCDs is predicted to impede poverty reduction initiatives in low-income countries, particularly by increasing household costs associated with healthcare. Vulnerable and socially disadvantaged people get sicker and die sooner than people of higher social positions, especially because they are at greater risk of being exposed to harmful products, such as tobacco, or unhealthy dietary practices, and have limited access to health services.

In low-resource settings, healthcare costs for NCDs quickly drain household resources. The exorbitant costs of NCDs, including often lengthy and expensive treatment and loss of breadwinners, force millions of people into poverty annually and stifle development.

**Prevention and control of NCDs**

An important way to control NCDs is to focus on reducing the risk factors associated with these diseases. Low-cost solutions exist for governments and other stakeholders to reduce the common modifiable risk factors. It is thus important to monitor progress and trends of NCDs and their risk to guide policy and priorities.

To lessen the impact of NCDs on individuals and society, a comprehensive approach is needed requiring all sectors, including health, finance, transport, education, agriculture, planning and others, to collaborate to reduce the risks associated with NCDs, and promote interventions to prevent and control them.

Investing in better management of NCDs is critical. This includes detecting, screening and treating these diseases, and providing access to palliative care for people in need. High-impact interventions can be delivered through a primary healthcare approach to strengthen early detection and timely treatment. Evidence shows such interventions are excellent economic investments because, if provided early to patients, they can reduce the need for more expensive treatment.

**South Africa**

The accumulated losses to South Africa’s gross domestic product between 2006 and 2015 from diabetes, stroke and coronary heart

disease alone are estimated to have cost the country US\$1,88 billion (Abegunde DO, Mathers CD, Adam T, Ortegón M, Strong K. 2007). Employers face additional costs in the form of high staff turnover and absenteeism, because these conditions are not only a source of morbidity but a leading cause of death in our working-age population (Collins D L, Leibbrandt M. 2007).

Obese workers cost their employers 49% more in paid time off than their non-obese colleagues. Workplace wellness programmes are growing and show promise, but the urban poor, who are particularly vulnerable, have little access to them (Van Nuys K, Globe D, Ng-Mak D, et al 2014). The NCD epidemic in SA is an even greater burden because it is occurring concurrently with an ageing HIV-positive population.

**Switzerland**

Switzerland faces a growing burden of chronic NCDs. Currently, 2,2 million of a population of eight million is affected by NCDs, and this is responsible for 80% of health costs and nearly 60% of premature mortality. In early 2013 the Federal Council – Switzerland’s highest executive authority – approved a comprehensive healthcare strategy entitled “Health 2020”.

In 2016, a National Strategy for the Prevention of Non-Communicable Diseases was adopted after a year-long consultation process. This strategy has four overarching long-term objectives: “to control the global burden of disease due to NCDs; to contain rising costs in the health sector; to reduce premature mortality; to maintain and enhance the productivity and social participation of the population”. More specifically, the NCD strategy aims to “reduce behavioural risk factors; improve health literacy; develop a health-promoting environment; improve equity in access to health promotion and prevention; reduce the proportion of the population at increased risk of disease; improve the quality of life and reduce the need for care” (New England Journal of Medicine, 2013).

In 2017, specific measures were adopted to ensure a reduction of risk factors for chronic NCDs and a reduction of the burden of disease due to these conditions. The long-term success of this strategy will require the commitment of the many stakeholders in the health sector as well as cooperation between federal and cantonal authorities (Mattig T, Chastonay P. 2017:1002).

**OUTCOME OF THE NON-COMMUNICABLE DISEASES DOMAIN: ECONOMIC VALUE**

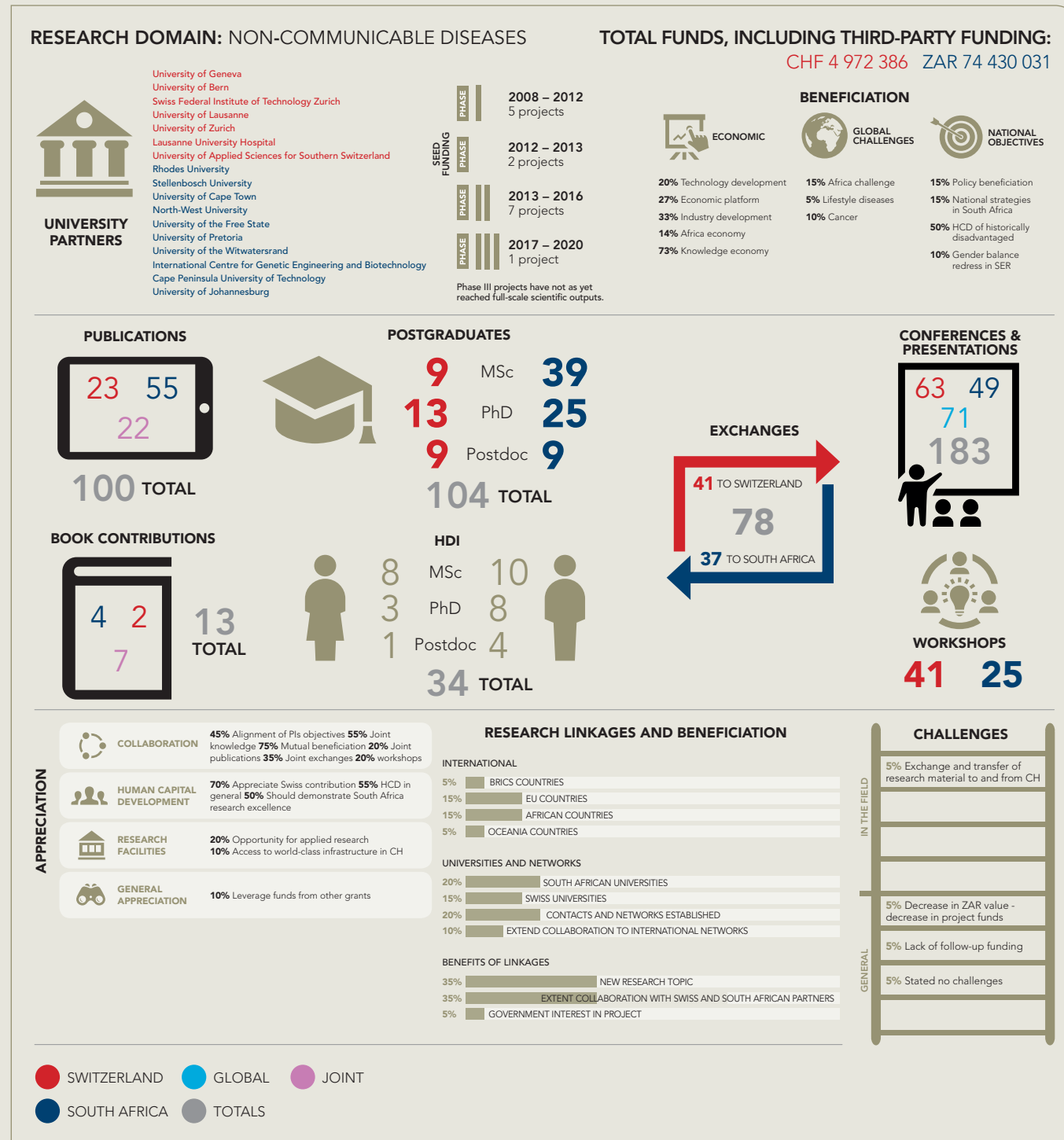
**More than half the research projects in this domain demonstrated innovation potential, which is important to curb the prevalence of NCDs and reduce the healthcare burden.**

INNOVATIONS	TOTALS	%
Projects achieved innovation	4	20
Impact innovation achieved	2	10
Projects have innovation potential	11	55
Innovation potential beyond projects	3	15

INDUSTRY LINKAGES	TOTALS	%
Research support from industry	2	10
Industry funding	3	15
Industry partner SA	3	15
Industry partner CH	2	10
Industry interested	3	15
SA Industry funds received	2	10
Swiss Industry funds received	1	5

INTELLECTUAL PROPERTY	TOTALS	%
Swiss IP	2	10
SA IP	1	5
Swiss IP protected	2	10
SA IP protected	1	5

## Outcomes of the Non-Communicable Diseases Domain (15 projects)





## Phthalocyanine-based smart probes for the molecular imaging disease-related proteolytic activity

This collaborative project has had a significant global impact due to its influence on the accuracy of disease diagnosis in the early stages. The project was based on the fact that the presence of disease-associated proteases can be detected via activation of specific fluorescence probes by the specific protease. The researchers developed novel phthalocyanine-based smart probes, inspired by previously optimised smart probes, by using unique complementary expertise of both the Swiss and South African researchers.

The inept nature of the human eye in detecting tissue deviations from the normal state poses a particular problem in disease imaging. Initially the manifestation of cancer led to the adoption of detection techniques that were both intrusive and cumbersome. These techniques involved procedures such as biopsies or explorative surgery, followed by histopathological analysis. The advent of imaging techniques such as ultrasound, whole body scans, CTs (CAT scan) and MRIs (magnetic resonance imaging) often averted these time-consuming and cumbersome techniques though they lacked the ability to detect internal tumours with diameters measuring less than two millimetres.

The need emerged for detection techniques that combined rapid results, high sensitivity and accurate disease identification. Molecular imaging, which is the biological process imaging in living organisms at the molecular and/or cellular level, addressed this need. Endoscopic fluorescence imaging uses the combination of genetic information, proteomics (the large-scale study of proteins), and new synthetic strategies in order to form new imaging probes, allowing the development of novel imaging techniques. The non-invasive nature coupled with high resolution and sensitivity make endoscopic fluorescence imaging ideal for treating patients suffering from cancer, ensuring that they can live as comfortably as possible.

In this study, researchers developed the synthesis and purification of a suitable, slightly water-soluble, mono-substituted phthalocyanine dye (fluorescent reporter) for the innovative smart probes that were being developed. These were then coupled to a polymeric carrier and quenched, with optimal quenching resulting from the strong interaction of phthalocyanine dyes when multimerised on a polymeric carrier.



**University of Geneva**  
Professor Dr Norbert Lange  
**Rhodes University**  
Professor Dr Tebello Nyokong



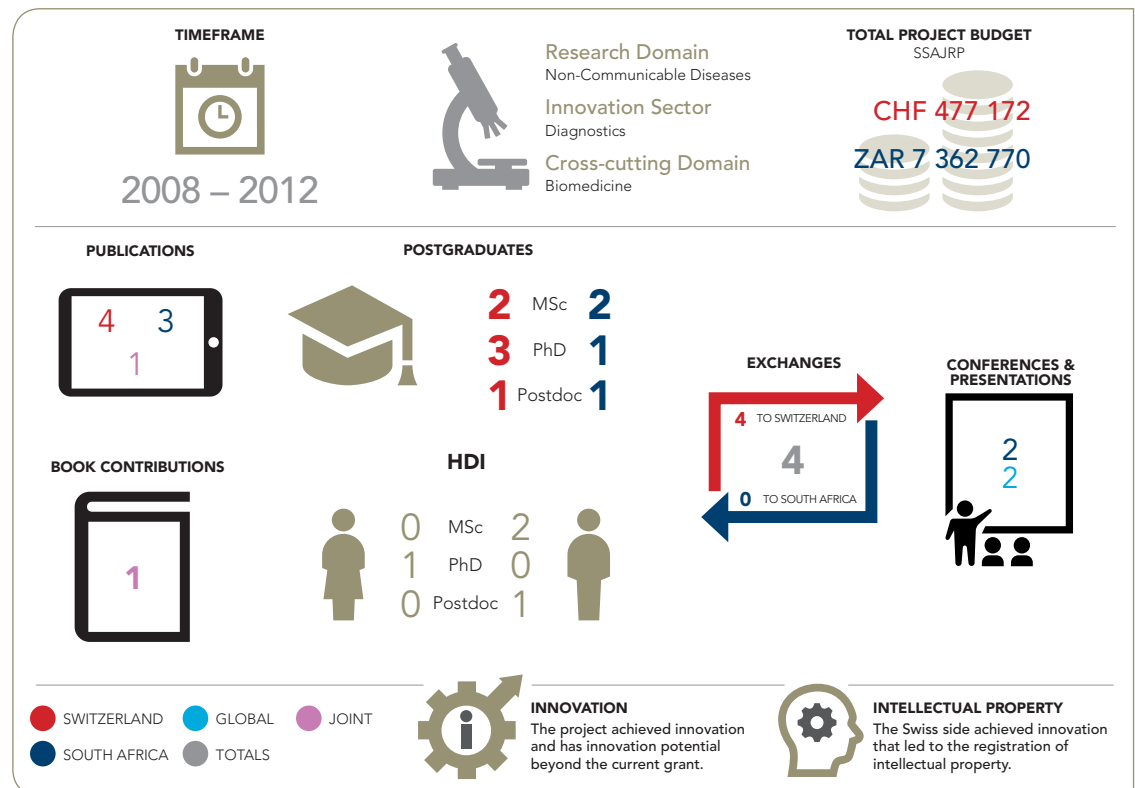
Photograph Courtesy Prof. T. Nyokong

Professor Tebello Nyokong

Professor Nyokong's laboratory and students.

*In vitro* and *in vivo* disease-associated proteolytic activity investigations were carried out in order to activate, characterise and optimise the probes. The response parameters at which the smart probes were aimed, for the purposes of optical fluorescence imaging, were the ability to absorb and emit light in

the near-infrared region (NIR) of the light spectrum; produce strong extinction and high fluorescence quantum yield; and a high versatility with respect to the target protease while possessing a very high specificity for the target tissue.



## Production and application of terbium radionuclides as a potential cancer diagnostic and treatment tool



**Swiss Federal Institute of Technology Zurich**

Professor Dr Roger Schibli

**The Cape Peninsula University of Technology**

Professor Tjaart Nicolaas van der Walt

This collaborative research project developed the technology to produce radioactive isotopes useful for medical purposes. It aimed to venture into the uncharted waters of the production and application of two extremely attractive tumour-labelling molecules in the form of the Terbium radionuclides Tb-152 and Tb-155.

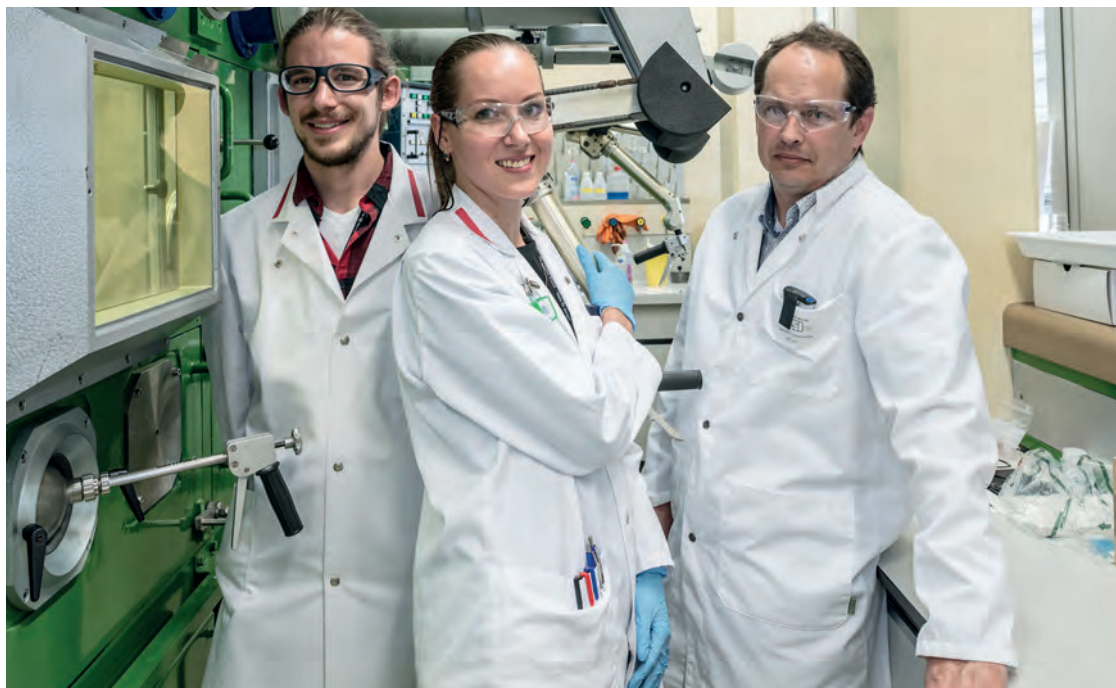
According to the WHO, 20% of deaths worldwide are as a result of cancer. Early detection and diagnosis, followed by effective treatment, is paramount to the increased quality of life provided to cancer patients. The use of radiopharmaceuticals in the cancer diagnostic tools of single photon emission computed tomography (SPECT) and positron emission tomography renders them non-invasive, and their ability to satisfy the abovementioned life quality enhancers makes them indispensable and increasingly used in oncology.

The results of the project are contributing towards the development of new and effective radiodiagnostics and therapeutics for the management of cancerous diseases.

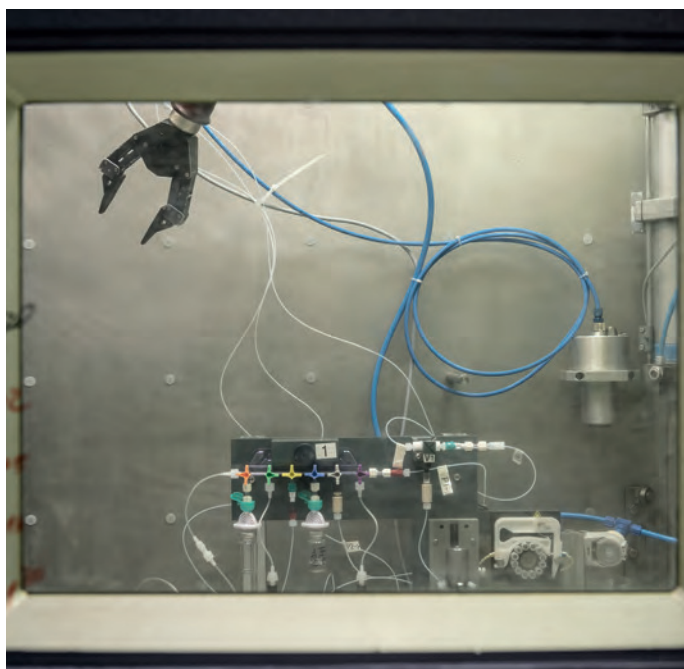
The researchers used state-of-the-art facilities that presented an outstanding environment to tackle this highly relevant, though thought-provoking, scientific endeavour at both the unique cyclotron facilities at iThemba LABS (South Africa) and the Paul Scherrer Institute (Switzerland). The studies mutually profited from capabilities of these unique sites and the know-how of local experts in the field of radiochemistry and radiopharmacy.

Terbium (Tb) is an element that has a number of radioisotopes that emit specific particles which can potentially provide a new dimension to the avenue of cancer therapy. This element also has potential use in positron emission tomography and SPECT diagnostic methods due to the radionuclides it possesses, and this necessitates the need to find effective extraction methods of these radionuclides from Gadolinium (Gd). The establishment of effective methods to acquire the radioisotopes Tb-152 and Tb-155 for potential cancer diagnosis, and Tb-161 for therapy, can have a significant impact globally in the treatment of cancer.

This project used ion exchange chromatography and other extraction methods to separate and



*Members of the Radionuclide Development Group in front of a hot cell at PSI: Roger Hasler (Technical Specialist), Nadezda Gracheva (PhD student) and Dr Nick van der Meulen (Group Leader).*



*Chemical separation system for Tb radionuclides.*



*Professor Dr Roger Schibli*





Close-up view of a mechanical hot cell manipulator.

obtain radioterbium nuclides from lanthanide elements such as Gadolinium and Dysprosium (Dy). Radioisotope separation from the lanthanides – a series of 15 metallic chemical elements that form part of the rare earth elements – required the compilation of a highly shielded tight casing in which highly radioactive substances could be remotely handled, called a hot-cell, and the instalment of the required equipment in a hot-cell at iThemba LABS. The researchers investigated the labelling of organic compound macromolecules, including monoclonal antibodies and peptides.

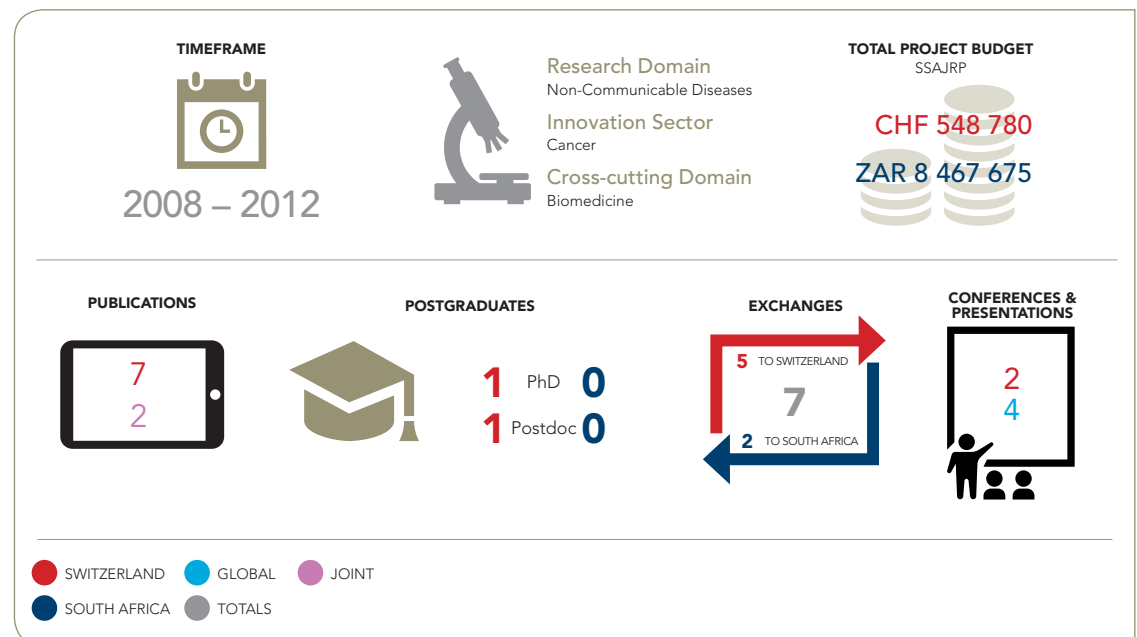
Significant advances in the field of radiotherapy were made with this project. Moreover, it served as a vehicle to capacitate Master's and Doctoral level students and junior faculty in the areas of radiochemistry, chemistry and biology. These scientists will serve to address the increasing demand of experts in these fields.

During the project, two key staff members left the Paul Scherrer Institute (PSI) in 2011 and 2012, thereby preventing development of chemical separations and preclinical work over this period. The issue was subsequently resolved when Dr N van der Meulen moved from iThemba LABS to PSI to cover this shortfall in 2013.

Much work was done to ensure preclinical success, with the data gained being used for a first-in-man injection of  $^{152}\text{Tb}$ -DOTATOC into a patient at Zentralklinikum Bad Berka, Germany, in 2016. This is currently paving the way for the introduction of the therapeutic  $^{161}\text{Tb}$  into clinics.



PSI's Radionuclide Development Group perform a Tb chemical separation from Gd target material.



## Imaging and therapy for cancer and other diseases using radioisotopes of rhenium and technetium compounds linked to biologically active molecules



University of Zurich

Professor Roger Alberto

University of the Free State

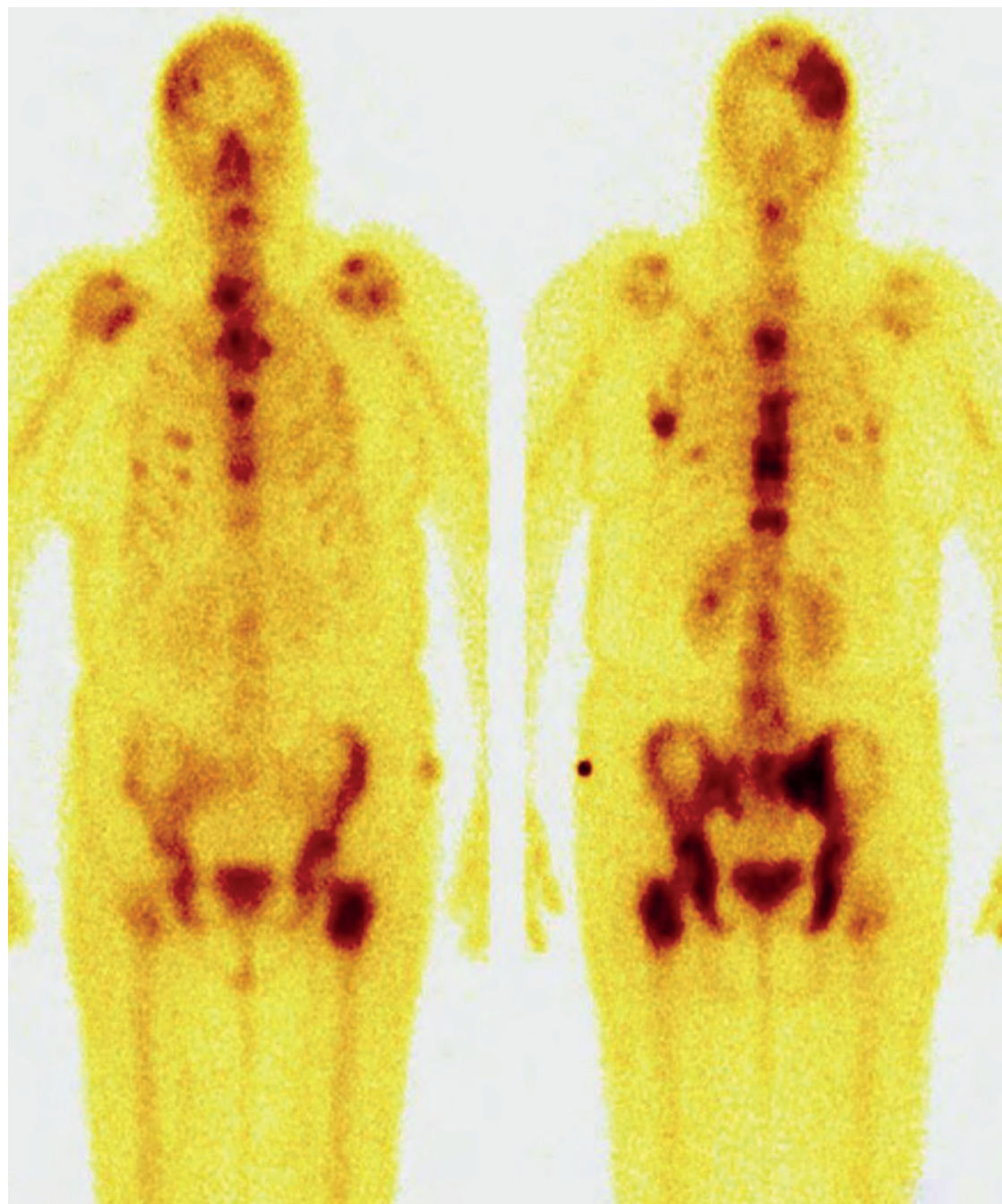
Professor Andreas Roodt

Researchers participating in this project aimed to bring together South African and Swiss expertise in fundamental nuclear medicine related to technetium (Tc) and rhenium (Re) to expand the drive in this complex field.

A fundamental principle of diagnostic nuclear medicine is to have a suitable radionuclide that is attached to a director-group system aimed at a specific target (disease-affected organ) in the body. Selected uptake of this compound is then evaluated via a detector, similar to normal X-rays, which produces an image from which physicians can plan future treatment.

Imaging with bioactive compounds comprising technetium-99m ( $^{99m}\text{Tc}$ ) is the most important modality of diagnostic nuclear medicine. To direct complexes of  $^{99m}\text{Tc}$  towards a targeted site (organ), e.g. cells with increased densities of particular receptors, compounds must be conjugated to a molecule with the corresponding biological recognition properties. Tc and Re belong to the same triad and, if homologous compounds are synthesised, the option of therapy arises wherein minute quantities of  $^{99m}\text{Tc}$  can be used for diagnosis and macroscopic amounts of Re for therapy. The researchers expanded the project successfully to include gallium coordination chemistry for potential radiopharmaceutical development.

The collaborative project formed part of the larger drive in South Africa towards creating a national collaborative platform, called the Nuclear Technologies in Medicine and the Biosciences Initiative (NTEMBI), to implement new strategic initiatives relating to R&D on nuclear technologies in medicine and the biosciences. NTEMBI was aimed to be managed by the South African Nuclear Energy Corporation (Necsa), as part of its legislative mandate and to function as a high-level Research, Development and Innovation (RD&I) initiative providing a framework to consolidate expertise and to implement new strategic initiatives relating to R&D on nuclear technologies in medicine and the biosciences. This overarching project with Switzerland was earmarked to form part of this broad initiative.



Scans of patient with bone cancer.





Courtesy Prof A Roodt

Professors Roger Alberto and Andreas Roodt.

A main outcome of the project was providing assistance to expand and/or establish international collaboration to routinely assess compounds containing Tc and Re for potential imaging and therapy respectively. The group arranged a Swiss-South Africa symposium, with a wide range of topics that included assistance via international networks to further the studies at South African Chemistry Departments, specifically at the University of the Free State and Nelson Mandela University as Centres of Excellence, to train students in radiopharmacy and nuclear medicine development. Major industry collaboration was established and is still being experienced under the project.

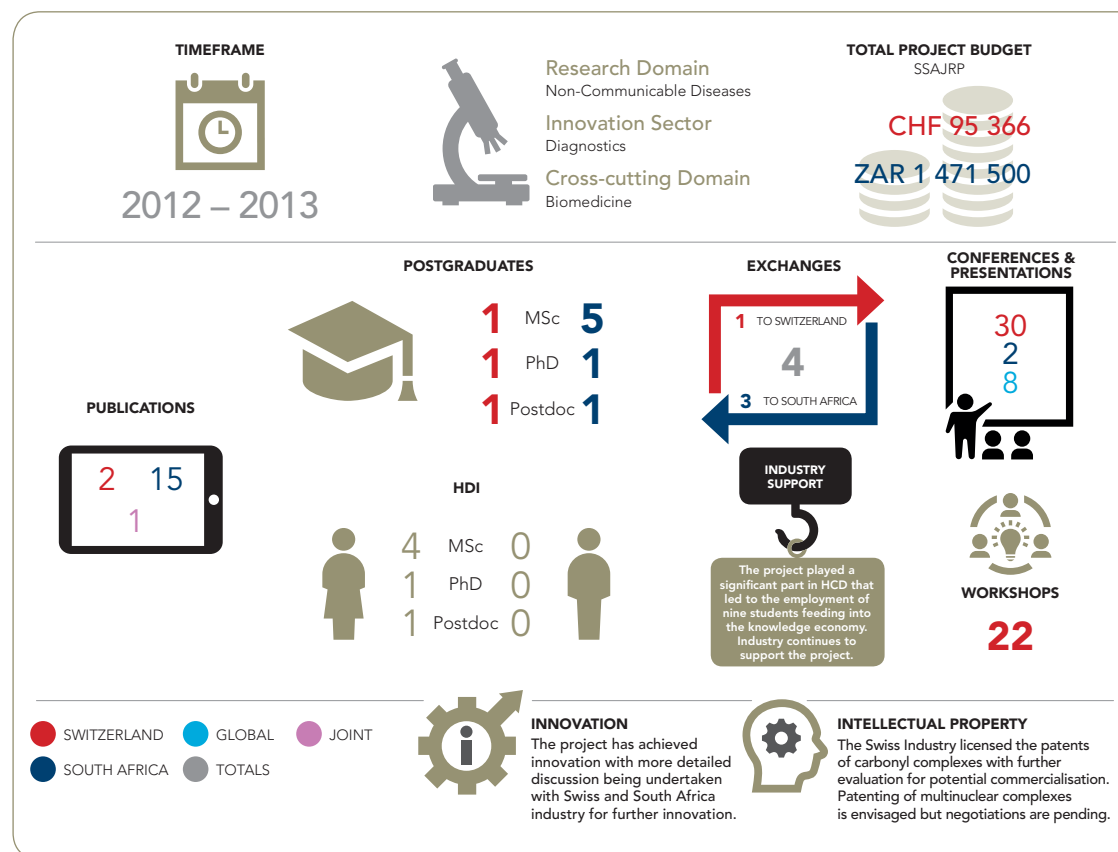
This project contributed significantly to expanding interaction between research groups from South Africa and Switzerland, and also established interaction with three African countries, India and Europe. It has consolidated the research cooperation between the groups beyond the actual project. The scientific accomplishments are mirrored in the human capital development and the scientific publications. A significant number of South African students benefitted from research visits to, and interaction with, the Swiss Principal Investigator and his students. Swiss students to South Africa experienced similar benefits.

The impact of this collaboration is far-reaching, and some outputs are still emerging. The project not only led to a substantial research output, but also enriched this field of science to pursue further. It resulted in significant interaction with industry in South Africa and research counterparts in other European countries and Africa.



Photographs courtesy of Andreas Roodt

PhD students of the University of the Free State of which three are from SSAJRP.





## Exploring the molecular basis of phenotypic spectrum of reproductive disorders in South Africa



**Lausanne University Hospital**

Professor Nelly Pitteloud

**University of Pretoria**

Professor Robert P Millar

Broadly, this collaborative proposal aimed to build a cohort of well-phenotyped South African GnRH-deficient patients to perform genetic studies using cutting-edge technologies and to examine the biology of the identified variants in appropriate *in vitro* models. A multidisciplinary strategy was employed that combined human genetics, bioinformatics, clinical studies, molecular biology and pharmacology.

Patients with rare diseases face a number of health disparities, including challenges in finding appropriate access to expertise and timely diagnostics. The project has been effective in developing links and collaborations between groups in South Africa and Switzerland with expertise in rare reproductive endocrine conditions. These increased capacities are expected to benefit patients by enhanced approaches to timely diagnosis, as well as consultation with clinical experts.

Through this collaboration, two previously undescribed mutations of the Luteinizing hormone receptor (LHR) and one follicle-stimulating hormone receptor (FSHR) mutation have also been identified. LHR and FSHR both play critical roles in human sexual development.

The researchers have characterised one of these mutations *in vitro* and confirmed its non-functionality, and are working up the others. Mutations in other hypothalamic GPCRs (G protein-coupled receptors that are of central importance in endocrine regulation) have also been identified. An MSc student is exploring these in more detail to confirm whether they are non-functional. This is a very exciting sub-project that has potential to identify novel genes and confirm whether they are non-functional. A member of the group at an academic hospital in Pretoria, South Africa, has collected blood from 15 South African patients suffering from reproductive dysfunction of unknown aetiology. Swiss participants in the project are exome sequencing these with the aim to identify further mutations of interest.

The collaborators have raised awareness of this project in South Africa and have set up collaborations with the relevant endocrinologists who are most likely to see these rare-disease patients. The collaboration has been most

productive with the reciprocal skills (South African receptor expertise for characterising GPCR mutations and rescue of function with pharmacochaperones and provision of patient DAN) and Swiss skills in whole exome sequencing. These novel discoveries position the partners to apply for international funding.

The impact on the patient community has primarily taken the form of raising awareness and creating avenues for patients to have consultations with experts in rare diseases. For the scientific community, the experiments involving the small molecule chaperones represent an important step forward in developing novel potential therapies for infertility. These scientific activities are likely of interest to industry, as they are unique pharmacological targets for an identified health need.

A number of female students and students from historically disadvantaged backgrounds are involved in the project.



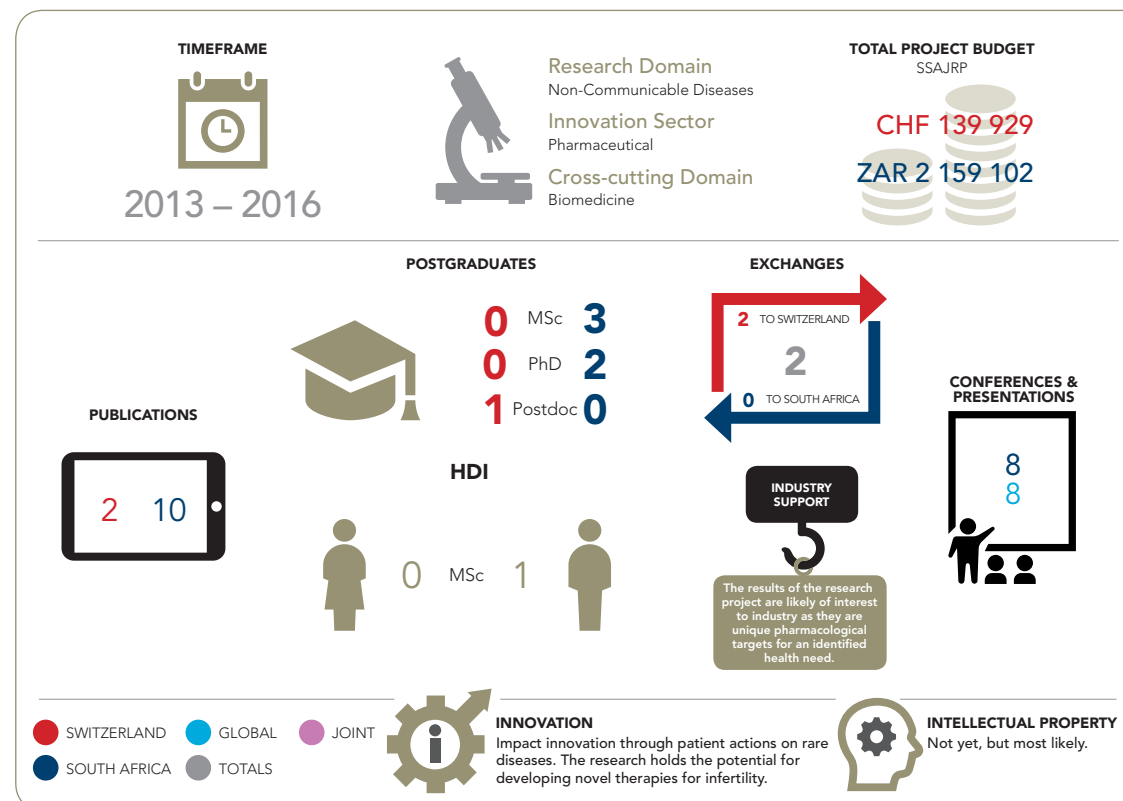
Professor Nelly Pitteloud

Photograph courtesy of LMNA



Professor Robert P Millar

Photograph courtesy of University of Pretoria



# Investigating the synergistic effect of Tat-RasGAP<sup>317-326</sup> in combination with hypericin-photodynamic therapy (hyp-PDT) on melanoma skin cancer cell death

The project used a novel approach by using a two-pronged strategy for the treatment of skin cancer. The first involved the pre-sanitising of the melanoma cells to death, which is achieved through exposure to the RasGAP-derived peptide, followed by the application of photodynamic therapy-induced cell death.

Specific objectives were to identify the mode of cell death induced via the combination therapy and the associated molecular and cellular mechanisms involved, and to investigate the effect of the optimised combination therapy (Aims 1) on melanoma cells and the role of the pigment, melanin, in cell death resistance.

The researchers previously performed a genome-wide CRISPR-Cas9 screen in order to identify regulators of hypericin PDT-induced cell death in A375 melanoma cells. While they did not identify any gene encoding protein involved in hypericin-PDT cell death, they highlighted FRYL (Fury Like Transcription Coactivator) as a putative gene involved in the resistance mechanism to this treatment.

Findings showed that FRYL does not independently modulate the manner by which hypericin-PDT exerts its anti-skin cancer effects.

The team did not manage to identify new regulators of hypericin-PDT-mediated cell death in A375 melanoma cells. Hypericin-PDT has been described to trigger different modes of cell death. Hence even if one death pathway is blocked, there is the possibility that another one can still be engaged to trigger cell death.

An African postdoctoral fellow, Dr Ajuwon, was given a Swiss fellowship and will work under the guidance of Prof Widmann. The Tat-RasGAP peptide does not enhance cell death triggered by the combination of the photo-sensitiser hypericin and photodynamic therapy (PDT). Dr Ajuwon will determine whether PDT synergises with the anti-cancer drug Cisplatin in a variety of skin cancer cell lines. This will bring important information on the usefulness of PDT in treating skin malignancies.

The study on the effect of photodynamic therapy as an adjuvant therapy for melanoma

and nonmelanoma skin cancers was potentially pertinent and applicable to industry. However, the project team's work determined that there is no benefit in combining PDT with the TAT-RasGAP peptide. This information is important for the private sector as it indicates that it would be unsound to invest funds to develop a therapeutic combination of PDT with TAT-RasGAP<sup>317-326</sup>. Rather, other combinations should now be investigated to try to improve current treatment of skin cancers.

The original objective of the project was modified because the Tat-RasGAP peptide did not enhance cell death triggered by the combination of the photo-sensitiser hypericin and photodynamic therapy (PDT). The team decided to take advantage of the CRISPR-Cas9 technology to perform a genome-wide screen to decipher the molecular mechanisms of hypericin-PDT mediated cell death.

The joint project between the South African and Swiss collaborators has helped acquire additional funds (a Swiss Government Excellence Scholarship to Dr Ajuwon) to support this work on PDT in the context of skin cancers.



**University of Lausanne**  
Professor Christian Widmann  
**University of Cape Town**  
Professor Lester Davids



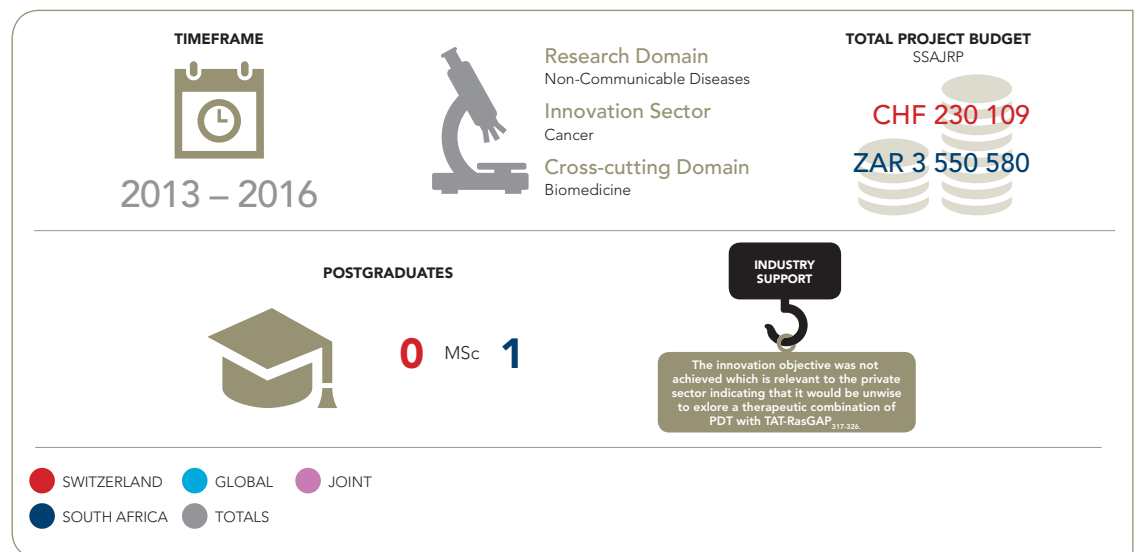
Photograph courtesy of Prof C Widmann

Professor Christian Widmann



Photograph courtesy of Prof C Widmann

Professor Lester Davids





## Stem cell activity in the adult human hippocampus



**University of Zurich**

Professor Dr Hans-Peter Lipp

**University of the Witwatersrand**

Professor Amadi Ogonda Ihunwo

The formation of nerve cells in the adult hippocampus, a brain region mediating memory and behaviour, is one of the most rapidly growing topics in neuroscience. Adult neurogenesis defies the previously held notion that the human body is unable to generate neurons after birth. The need to replace damaged or destroyed neurons propels the need to investigate why these neuron-producing stem cells are generated and if it is at all possible to stimulate neurogenesis.

Since researchers have obtained most data thus far by studying mice and rats only, studies in other species are of high importance for recognising the physiological and, with it, the potential clinical role of such newly-generated nerve cells.

The proliferation of these cells during the lifespan of an individual is paramount in this investigation since studies have indicated that cell formation and proliferation rate decrease with age. Another challenge is the significantly shorter lifespan of mice and rats, which are commonly used as laboratory animals, when compared to humans. This renders them inapplicable as animal models for the human conditions under investigation. However, some rodent species in South Africa have a lifespan of up to 20 years and may prove to be more accurate animal models for the adult human brain condition.

The Swiss-South African collaborators collected an interesting data set from a multitude of South-African rodents, documenting neuroanatomical and behavioural data.

In the quest to find an animal model for human adult neurogenesis, the researchers found that the common mole rat is the animal species that exhibits adult neurogenesis in regions of both the hippocampus and the cerebral cortices. This species would therefore be able to best represent an animal model for human adult neurogenesis. This study involved the four-striped mouse, common mole rat and the greater cane rat.

The South African researchers conducted the immunostaining in rodents. A postdoctoral fellow involved in the study stained the hippocampi of over 70 mammalian species, finding adult hippocampal neurogenesis to be present in all but two cetacean species. The pre-immunostaining of human brains



*From left: Drs Ajao, Meskenaite, Ola and Prof Amadi.*



*Mr A Becker from Zurich dissecting a brain in Pretoria.*

protocol for this study was reviewed in Zürich and approved for use in the Johannesburg laboratory.

The researchers believe the study can be further optimised by employing a combination of the study of the postmortem brain stem cell proliferation time course of children and young adults, and the use of the advanced modern stem cell activity visualising and quantification methods available in the Zürich laboratory.

The urgency for drugs that promote cognition or memory and restorative process has sparked interest in obtaining these by application of neuropsychology and neuroscience in studies of adult hippocampal neurogenesis (AHN). The distinct locality of the AHN has made it the prime focus in adult stem cell studies. AHN mechanistic studies have been performed in rats and mice, primates and humans with decreasing frequency in the mentioned order. Due to the high proliferation levels in rodents, the results are presently extrapolated to the human condition. In addition to the low AHN levels in monkeys and humans, the paucity of their use in studies is caused by expenses incurred in colony maintenance of monkeys due to their long lifespan, the toxicity of the stem cell proliferation marker substances injected into human subjects, and the lack of expertise in using postmortem brain stem cell proliferation and differentiation indication antibodies.

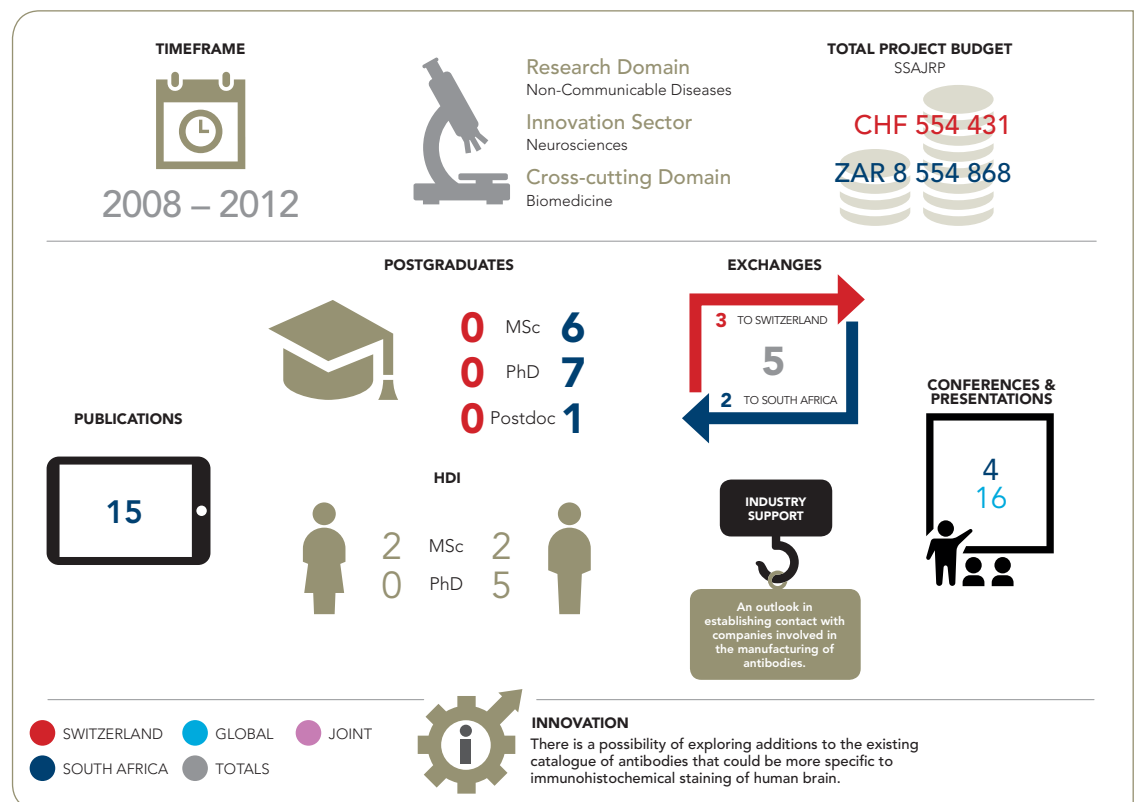
Studies using immunological markers at a Swiss laboratory have demonstrated the absence of AHN in many bat species and that there are remarkable AHN neuroanatomical and regulatory differences even among rodents living in the wild. The proliferation rate of AHN decreases monthly by 40% in standard laboratory mice. The danger in extrapolation to humans cannot be ignored. This has necessitated the need to find alternative rodent or entirely different species with AHN time course and age levels as close to that of the human condition as possible. Adult human neurogenesis is also amenable to future cell replacement therapy in the central nervous system repair.

The mutual benefits of the projects were many: there was a successful transfer of technology and know-how from Switzerland to South Africa; a close and ongoing cooperation between ecologists and neuroscientists from both countries; Swiss Master's students could experience the fascinating sides of South Africa both in the laboratory and the wilderness; and the Swiss partner could profit from the availability of native South African species that would have been inaccessible otherwise.



All photographs courtesy Amadi Ogonda Ihunwo

Professor Amadi Ogonda Ihunwo





## Epigenetic cross-talks and novel therapeutic strategies to prevent disease progression in ERG fusion-positive prostate cancer

By combining and integrating the expertise at the two leading institutions, progress is being made in understanding the mechanisms involved in prostate cancer progression. Their goal is to discover novel therapeutic approaches for a specific and highly frequent subtype of prostate cancer, called ERG fusion-positive tumours.

Cancer of the prostate is a leading cause of cancer deaths in men worldwide. While localised prostate cancer is highly curable, nearly all patients with metastatic disease progress to castration-resistant prostate cancer for which there are limited treatment options presently. Identifying factors and pathways that lead to tumour progression and castration-resistant prostate cancer is therefore critical. It can lead to the discovery of novel and more effective therapeutic strategies based on the molecular and biological characteristics of the tumour and improve the survival rate of prostate cancer patients.

The two groups have recently discovered a novel mechanism leading to oncogenic activation of ERG and contributing to prostate cancer progression.

Gene fusions involving ERG are found in about half of prostate cancers. This genetic rearrangement determines overexpression of full-length ERG in prostate epithelial cells. Both pre-clinical and clinical evidence indicate that multiple cooperating factors and cross-talks with signalling pathways are involved in the progression of ERG-positive tumours. However, the molecular details of these interactions are not defined yet. Understanding these mechanisms would be important to develop more effective therapies.

This project seeks to address the role of ERG in orchestrating and remodelling the transcriptional and epigenetic landscape in prostate tumours by examining the network of co-regulatory factors co-opted by ERG to activate the pro-tumorigenic and pro-metastatic programme. To this end, researchers from the two institutes are integrating molecular, genomic and functional studies *in vitro* and *in vivo* with human patient data to understand the events involved in the cross-talks between ERG, epigenetic effectors and transcriptional co-regulators and to examine their biological and clinical consequences. They will furthermore examine strategies aimed at reversing this pro-tumorigenic/pro-metastatic



**Institute for Oncology Research at University of Applied Sciences for Southern Switzerland**

Professor Dr Carlo Catapano

**University of Cape Town**

Professor Luiz Zerbini



Photograph courtesy of Carlo Catapano



Professor Luiz Zerbini



Photograph courtesy of Zerbini Group

Professor Luiz Zerbini (back) with students at an international workshop in October 2018.



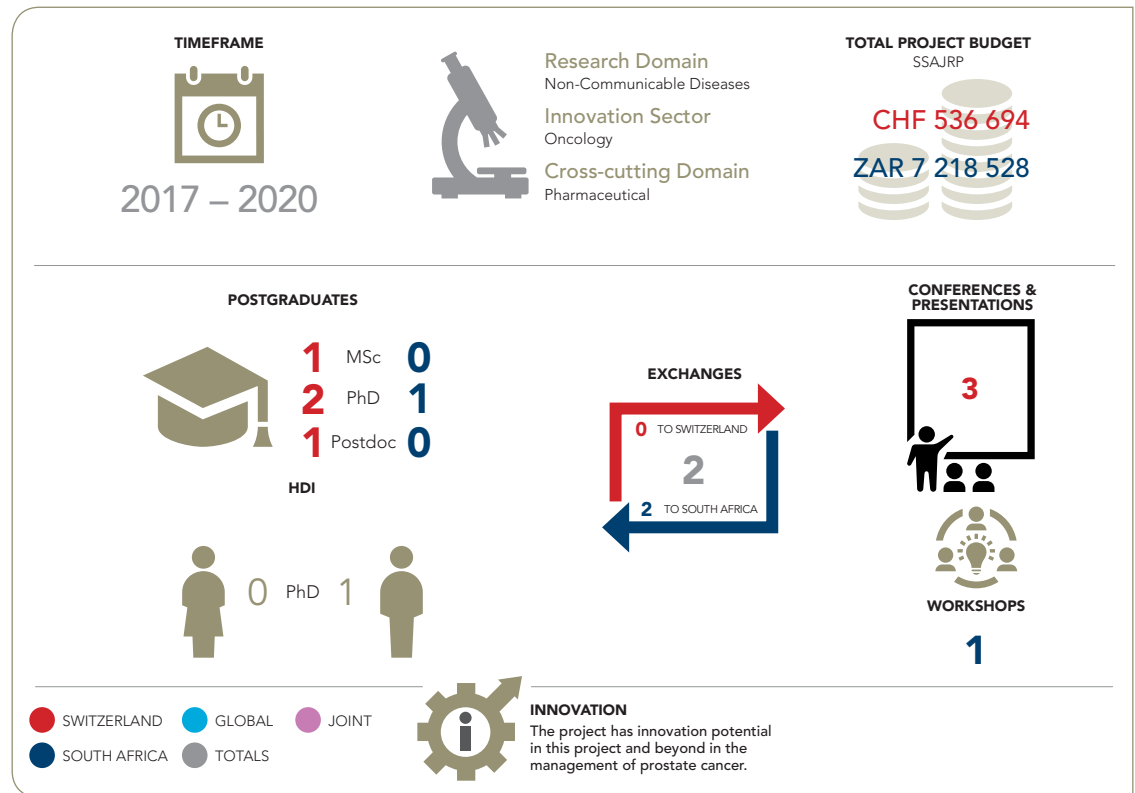
Photograph courtesy of Zerbini Group

Professor Pina Catapano, Mmboneni Muofhe from DST, Professor Carlo Catapano and Professor Luiz Zerbini.

programme by targeting the key components of the ERG-orchestrated epigenetic network.

During the first phase of this project they have combined molecular, genomic and functional studies in cell line and mouse models. They are dissecting the molecular events and identifying additional partners of the ERG epigenetic network. Both in cell lines and ERG transgenic mice they have found that epigenetic drugs such as inhibitors of EZH2 and other epigenetic effectors counteract the consequences of ERG-induced transcriptional deregulation and revert the tumorigenic and metastatic phenotype.

Ultimately, these studies will elucidate fundamental mechanisms leading to transformation and progression in ERG fusion-positive prostate cancers and will identify therapeutically actionable pathways whose modulation could have a broad impact on the management of prostate cancer.





## Flower code and cell competition: Understanding its role in cancer initiation, proliferation and tumour therapy

Cancer is a complex disease that places significant burden on individuals, families, health services and society. Early detection and treatment is still the best therapeutic option. In order to provide clinical significance, benefits to patients and society, along with high-tech advances in basic science, the collaborators in this project realised the need to foster cancer research that is relevant and translational.

Cell competition plays a major role in the initiation and progression of oncogenic stimulus in mammalian organs. Cancerous cells are super-competitive (winners) and they out-compete surrounding healthy cells (losers) for nutrition and extracellular growth signals, resulting in their death. Since cell competition between normal and transformed cells occurs from premalignant stages, the researchers exploited their knowledge of the cell competition molecular mechanisms to improve premalignant detection and treatment of cancer. They identified the Flower gene as a critical regulator of cell competition that, together with other cell competition regulators, can be used as a biomarker of cancer and for therapy purposes.

The collaborators analysed the importance of FlowerUbi and FlowerLose isoforms as regulators of cell competition in human cancer. Since Flower is a putative calcium channel, they hypothesised that the extrinsic signal that triggers cell competition via Flower might be calcium.

They found that the growth of cancer is significantly enhanced alongside a marked increase in the metastatic potential of cancer if FlowerUbi isoforms are overexpressed in the cancer tissue. On the other hand, over-expression of FlowerLose isoforms in the cancer tissue results in restricted tumour growth and metastasis. In addition, the Flower gene isoforms play a critical role in determining the aggressiveness of the cancer tissue.

The researchers also tried to address how these cells kill each other, i.e. on what the molecular mechanism of this cell competition is based. They identified a set of novel genes, which may play an important role in the regulation of cancer.

The Swiss team's research focuses on stable cell societies, cell competition and genetics, while the South African team has expertise in genomics and

proteomics approaches as well as translational cancer research. This laboratory has used cutting-edge technologies to address important questions in disease development and progression. Through the collaboration of these two groups, knowledge, expertise and resources were shared between Switzerland and South Africa, leading to a wide range of applications in both basic and translational research. Students and young scientists were also trained in an international setting and a high-quality research environment and increased infrastructure in both countries. The funding has greatly enhanced the exchange of knowledge and resources among the Swiss and South African laboratories.

The project trained and prepared team members for a future in this vital field of research and opened opportunities for the team members to pursue new research ideas. Interactions of young scientists help strengthen the current and future relationship and cooperation between South Africa and Switzerland.



**University of Bern**

Dr Eduardo Moreno

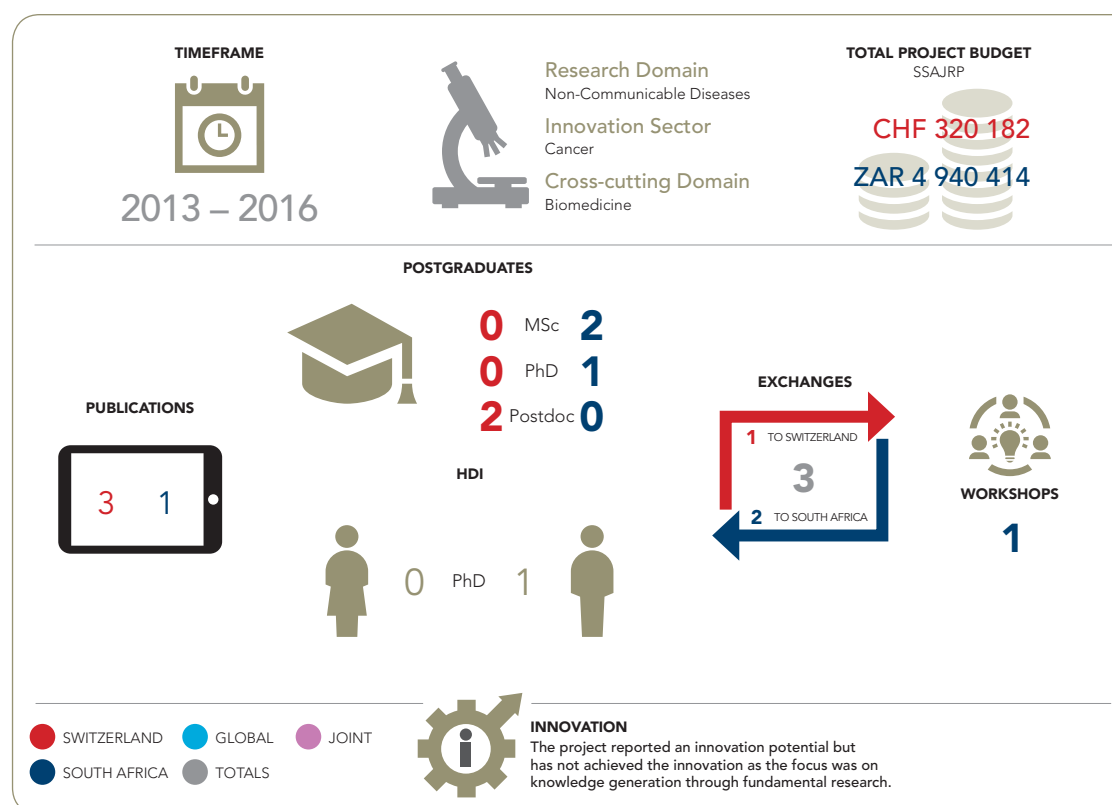
**International Centre for Genetic  
Engineering and Biotechnology (ICGEB)**

Dr Luiz Zerbini



Photograph courtesy of Champalimaud Foundation

*The Moreno laboratory team.*



# Relations of the job demands-control-support model of job strain with personality attributes: A cross-national study in Switzerland and South Africa



**University of Lausanne**  
 Professor Jérôme Rossier and Dr Koorosh Masoudi  
**University of Johannesburg**  
 Professor Gideon de Bruin

The research team's objectives were to examine the moderating effects of personality - as described in the Big Five model of personality - and culture in the demands-control model of job strain. The model posits three principal causes of job strain, namely high job demands, low job control or autonomy, and poor social support in the workplace. Hence, the model is successful in explaining when or under what conditions people are likely to experience job strain. However, the model is less successful in explaining who will be most likely to experience job strain.

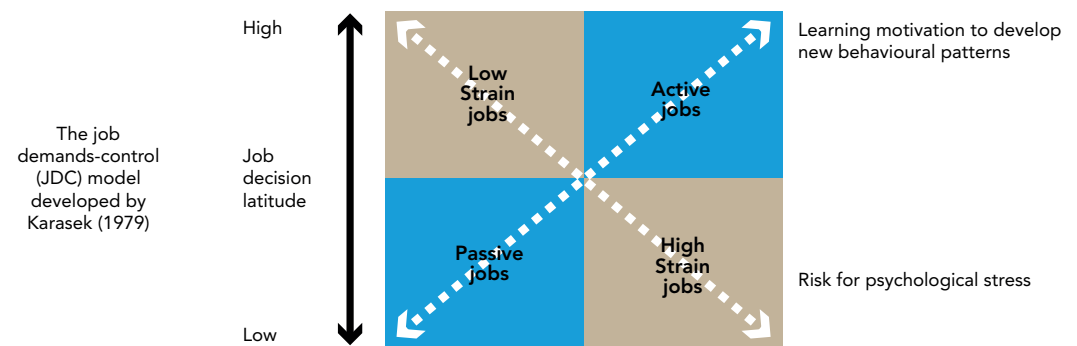
### The job demands-control (JDC) model developed by Karasek (1979)

The research team expected the findings of this project to shed new light on the cross-cultural validity of the demands-control model, which may serve to identify cross-cultural universalities and cultural specificities in the experience of job strain. In addition, they expected that the findings would show that individual differences in personality will either augment or diminish the effects of job demands, job control and social support on job strain. This would lead to a better understanding of who is most likely to experience high levels of job strain.

They hoped that the joint study of personality and culture within the context of the demands-control model would open up new avenues of research in the job strain domain.

Results indicated that equivalence cannot be assumed and that steps need to be taken to establish equivalence before cross-national comparisons can be made. The results showed that partially equivalent measures can be obtained by employing latent trait theory methods; however, full equivalence is difficult to achieve.

Another result they reported was that personality traits indeed moderate the relationship between job characteristics and strain outcomes. Overall, the results were similar across the two countries and in line with theoretical expectations, but some interesting anomalies appeared that require further investigation.

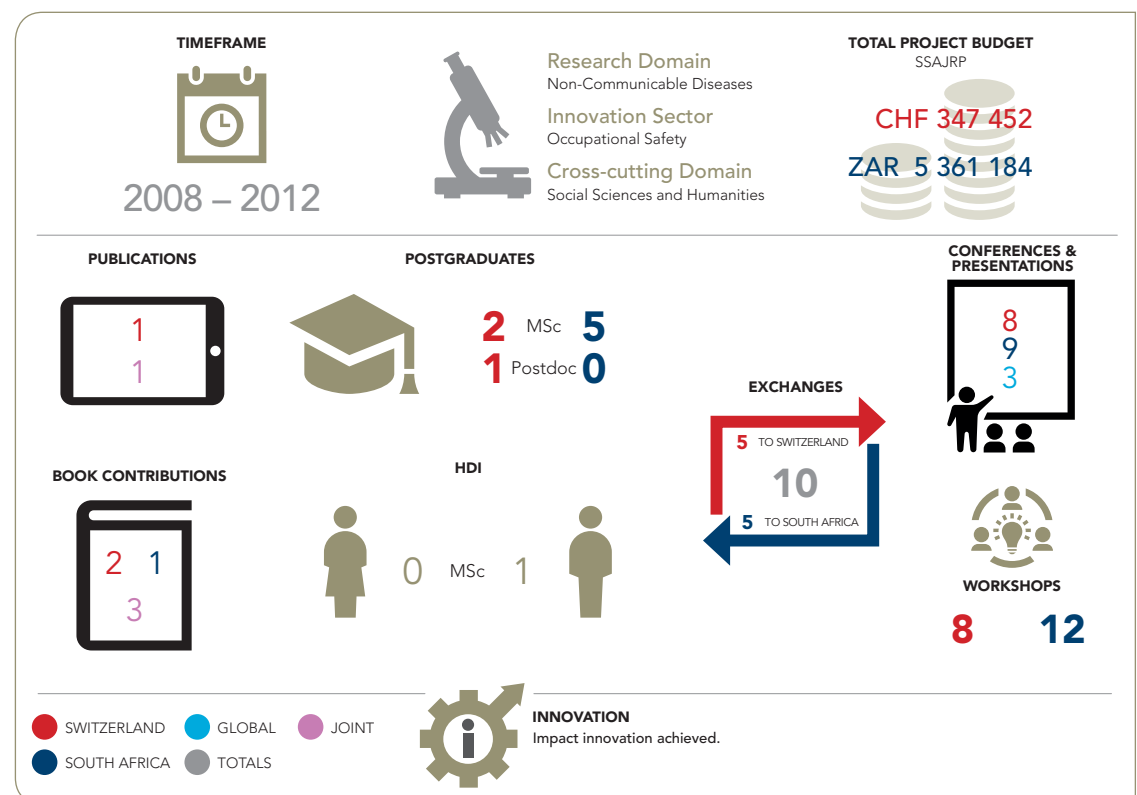


The demands-control model the researchers used was developed in North America and has been mostly studied in America and Europe. Little was known about the cross-cultural validity of the model. In particular, almost no research had been done in the African context.

The project allowed for theory testing and theory building in a cross-cultural context. This is likely to stimulate further research in the important areas of

job stress and occupational well-being, which in turn might lead to the development of innovative interventions aimed at the treatment and/or prevention of job strain and the facilitation of job growth.

Moreover, a review article on the topic of this joint research project was published in a special issue about personality and culture of the *Swiss Journal of Psychology*, co-edited by Prof Jérôme Rossier.



Footnotes:  
 1. [https://doc.rero.ch/record/305061/files/Gy\\_rk\\_s\\_C.-Impact\\_of\\_Personality-20170830.pdf](https://doc.rero.ch/record/305061/files/Gy_rk_s_C.-Impact_of_Personality-20170830.pdf)  
 2. Christina Györkösi<sup>1</sup>, Jurgen Becker<sup>2</sup>, Koorosh Massoudi<sup>1</sup>, Gideon P. de Bruin<sup>2</sup>, and Jérôme Rossier  
 3. Diagram sources Toolshero



## Using novel nano- and Pheroid-technologies to enhance calcium delivery for food and nutrition applications: production, characterisation and *in vivo* efficacy

The project entailed the synthesis, characterisation and optimisation of nanostructured calcium (Ca) oxides, phosphates and carbonates (NCCs) by flame spray pyrolysis (a process that produces nanoparticles), the packaging of the nanostructured Ca oxides in different Pheroid carriers, and the evaluation of the effect of both in an *in vivo* study.

A Pheroid is a vehicle responsible for delivery and can be used to package a number of applications such as medicines, lotions and creams, food supplements and cosmetics. Pheroids also assist with absorption. NWU is the patentholder of the technology.

During the course of the project, the following were investigated: various factors that contribute to optimal synthesis of the nanostructured calcium compound; the various types of Pheroid carriers that can be used; the stability of the formulated Ca; and the compound:carrier ratios. *In vivo* studies were used to evaluate the value of Ca phosphate and Ca phosphate entrapped in Pheroid as intervention for bone density diseases. The researchers also tested to what extent customers would accept such formulations through sensory testing of the different Ca compounds/delivery systems in different foods.

The bioavailability of nanostructured Ca versus micron-sized Ca, including Pheroid/biomineralised Pheroid structures, were also evaluated in an animal model, with concurrent assessment of potential toxicity in histopathology studies using a rat feeding study.

Even though the project started out with negative results due to the inability to produce the raw materials that would have been investigated, it enabled intensive sharing of knowledge about analytical methods and experimental procedures and knowledge transfer between the two participating institutions. It further involved a plant nutrition research company with equal shareholding by German and South African shareholders. The inclusion of a study leader from New Zealand further broadened the research linkages.

Since the problems with the production of nanopowders could not be solved in a reasonable



Swiss Federal Institute of Technology Zurich

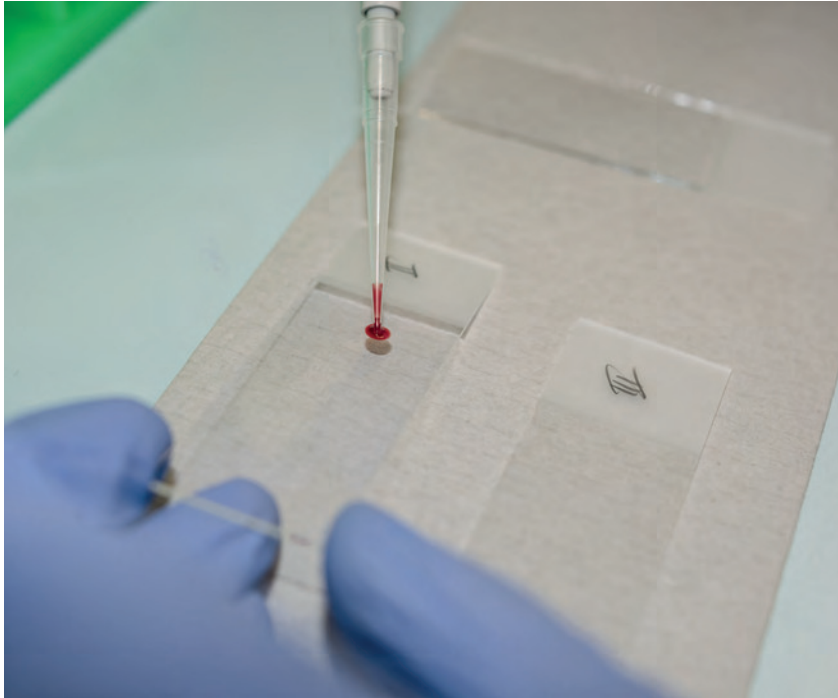
Professor Dr Michael Zimmermann

North-West University

Professor Anne Grobler



Desktop manufacturing for the novel liquid capsule dosage form of a Pheroid®-containing product now commercially available.



Photograph courtesy of Prof A Grobler



Photograph courtesy of ETH Zurich



Photograph courtesy of Prof A Grobler

Professor Dr Michael Zimmermann

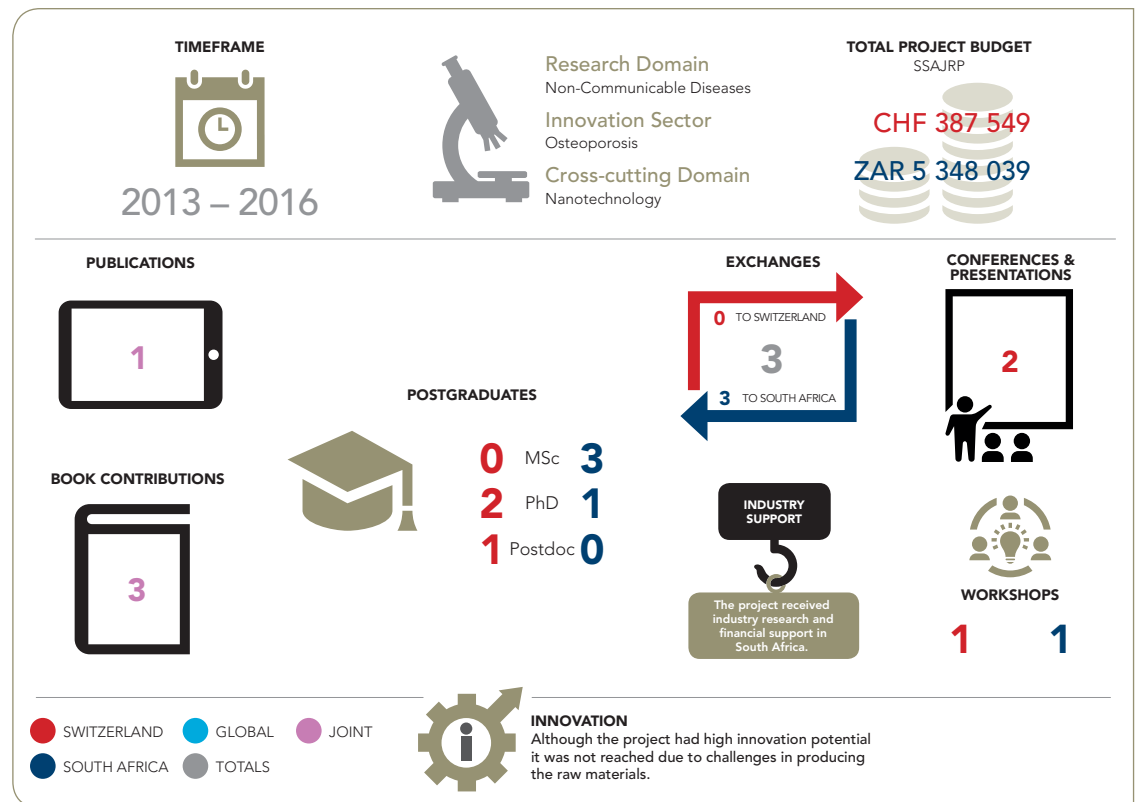
Professor Anne Grobler

Research conducted in the Grobler laboratory.

timeframe, commercially available compounds with the desired composition and specific surface area were used for compound carrier studies. Size and composition effects were investigated in a rat balance study and the results were compared to a previously published dissolution method for Ca to compare both *in vitro* and *in vivo* experiments.

The project contributed to knowledge on flame-assisted spray pyrolysis (FASP) as a promising new approach to produce nanopowders and has stimulated the search for a more suitable dissolution method with a possible correlation with *in vivo* absorption. The results of the studies also highlighted the possibility of an alternative Ca uptake mechanism in the animal model used, which needs to be further investigated.

This project enabled intensive sharing of knowledge about analytical methods and experimental procedures, as well as knowledge transfer between the Human Nutrition Laboratory at ETH Zurich and the Preclinical Drug Development Platform at NWU. The methods used to determine the effect of compound administration on harvestable yield was transferred to Dr Jesper Knijnenburg of ETH, who has since continued his career in this discipline.





## Genetic analysis of the role of Hsp70-Hsp90 organising protein in the development of cancer



University of Geneva

Professor Didier Picard

Rhodes University

Professor Adrienne Edkins

The Swiss and South African research groups aimed this collaborative, three-year study at analysing the role of the putative oncoprotein, Hsp70-Hsp90 organising protein (Hop), in mammalian cell and cancer biology using a combination of genetic and molecular techniques. The overall purpose was to determine whether Hop is involved in fundamental cellular processes that underpin cancer biology, analyse these processes at the molecular level and evaluate whether or not Hop may be a drug target for cancer.

The role of Hop was evaluated by depleting the levels of the protein by ribonucleic acid. RNA is one of three major macromolecular molecules essential for all forms of life, interference or through CRISPR/Cas9 mediated deletion of the gene. CRISPR is widely used to disrupt gene function by inducing small insertions and deletions. Hop was either depleted or knocked out of several established cancer cell lines and the effect on the biology of the cell evaluated. From the knockout lines, it was clear that Hop was not required for any essential cellular functions. Similar to the knockout lines, depletion of Hop by RNA interference (RNAi – a process used by organisms to regulate the activity of genes) did not result in a major growth defect. However, global analysis of proteins in Hop-depleted cells provided an insight into biological pathways that were perturbed and may account for the adaption of Hop-depleted cell lines.

The group's analysis did identify new roles for Hop in the cell. Taken together, these studies increase the fundamental understanding of Hop in mammalian cell biology and indicate that Hop may have important cellular functions. Some of the findings suggest that Hop may be a putative drug target and therefore there is the potential for future translation of the group's fundamental research findings. Research into the mechanisms by which Hop affects the cell is ongoing.

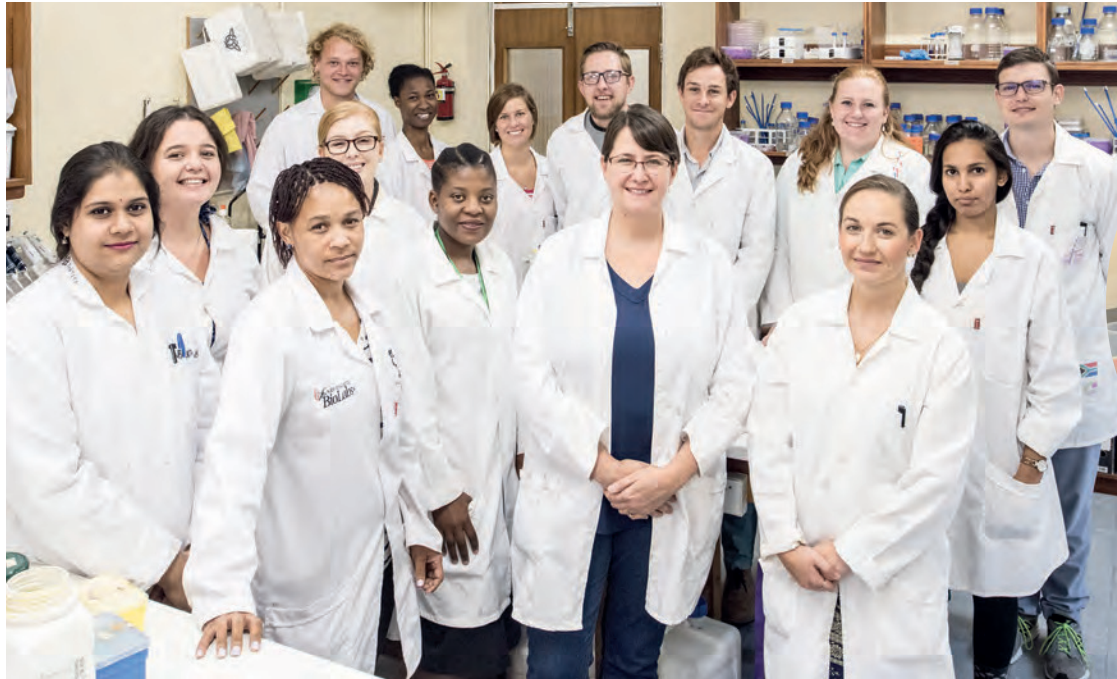
The project has made a substantial contribution towards the human capacity pipeline through the training and involvement of a number of postgraduate students who will receive advanced degrees through this training, and postdoctoral/emerging researchers. In addition to the students trained during the grant, the project generated



Professor Didier Picard



Professor Adrienne Edkins



Professor Edkins with her laboratory team.



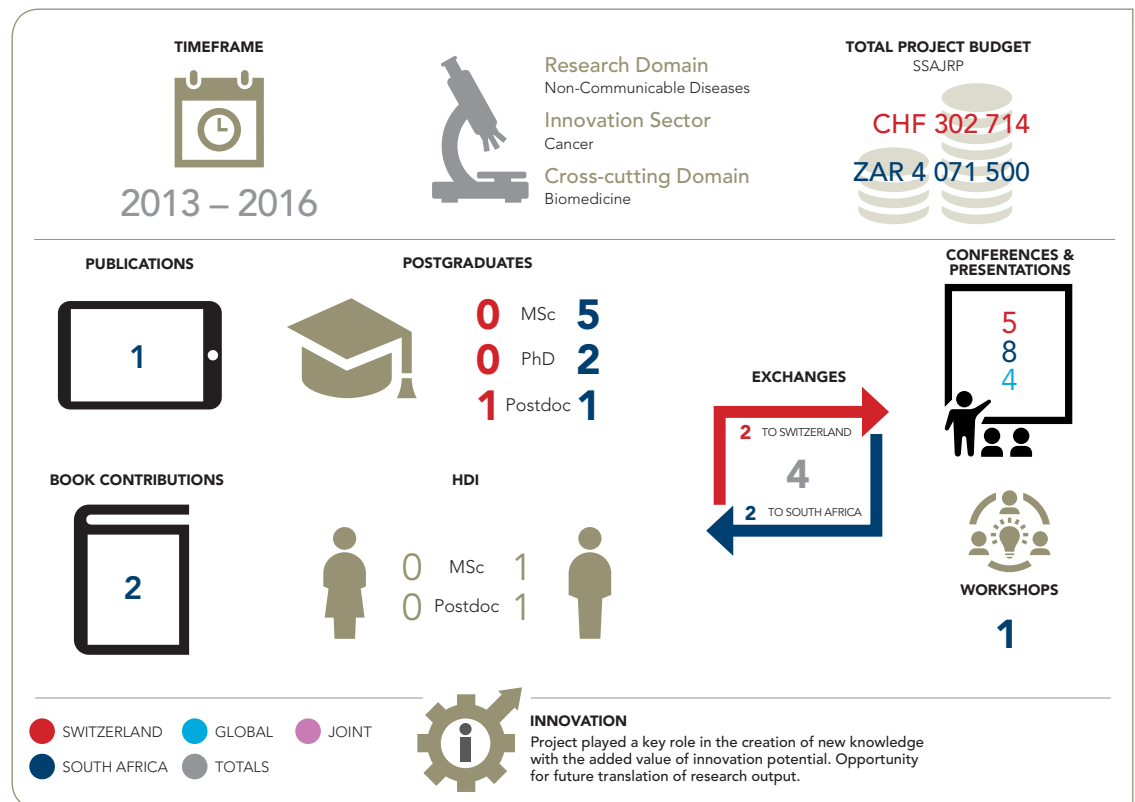
Kaushik Bhattacharya

Photograph courtesy of Didier Picard

new avenues of research for training of other postgraduate students beyond the funding cycle. The postgraduate students of the South African partner are almost all female and a number of them are from historically disadvantaged groups, which makes a major contribution towards promoting redress in terms of equity from a student training perspective.

This project has also involved mentoring and developing postdoctoral and emerging researchers who have recently been appointed in independent academic positions. In addition, the South African Principal Investigator is a young female scientist whose research trajectory has been developed through the mentorship of her Swiss counterpart.

This project led directly to the establishment of a new collaboration between the South African and Swiss research groups. Due to the joint research interests, sharing of resources and complementary research expertise the collaboration is proposed to continue beyond this grant.





## Investigation of natural and synthetic high-density lipoproteins as a therapeutic vehicle for cardio protection



### University of Geneva

Professor Dr Richard James (retired)

Dr Miguel Frias

Professor Nicholas Vuillemier

### University of Cape Town

Professor Dr Sandrine Lecour

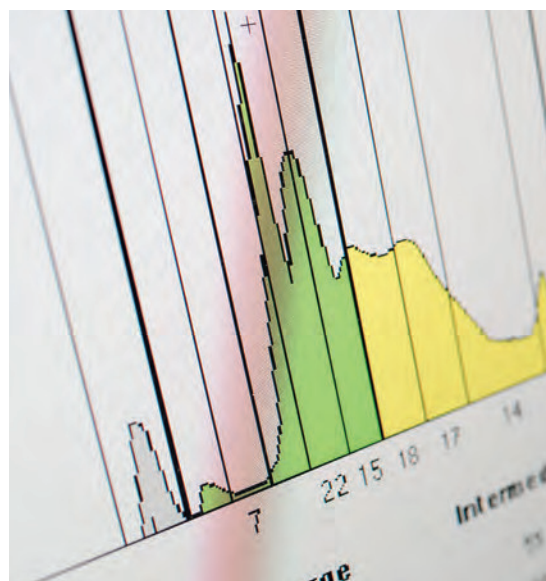
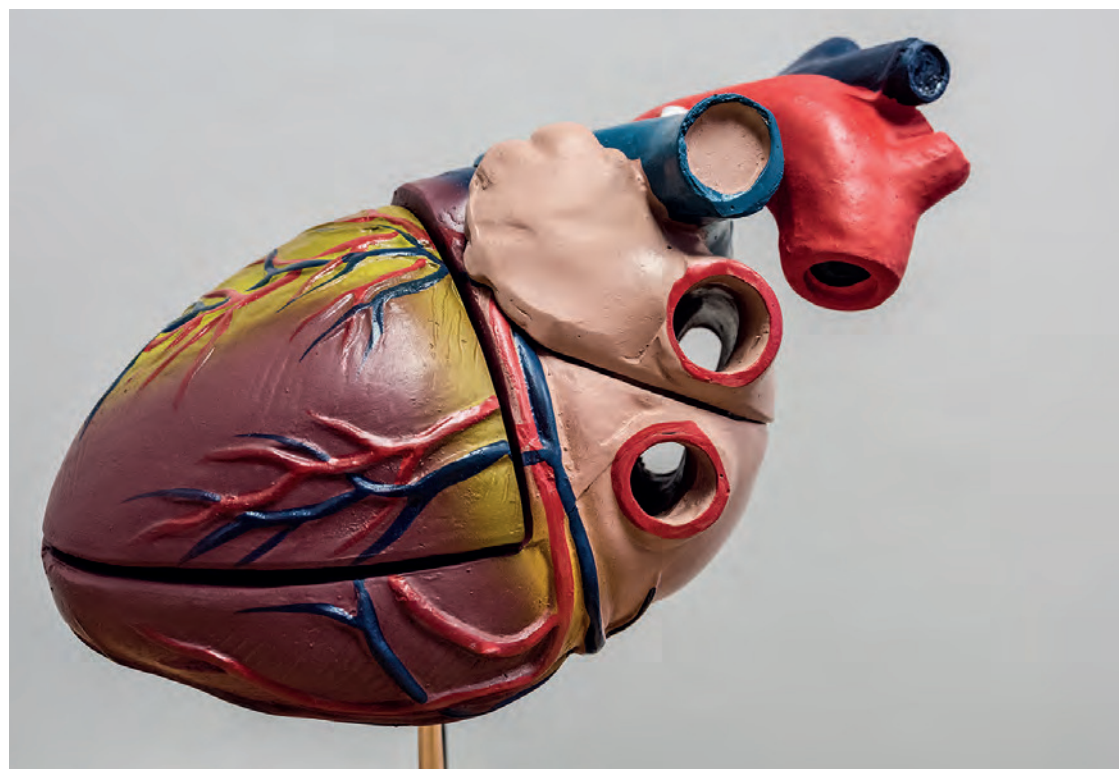
The researchers involved in this project investigated the therapeutic potential of natural and artificial high-density lipoprotein (HDL), commonly referred to as the good cholesterol, and explored the mechanisms that they could undertake to use synthetic HDL for cardioprotection in a clinical setting. As the risks of cardiovascular diseases are increased by decreased plasma HDL levels, the development of an effective synthetic HDL will benefit patients affected by myocardial infarction, diabetes, obesity and other associated pathological conditions worldwide.

Underutilisation of high-density lipoproteins (HDL) as a therapeutic target against cardiovascular disease is of particular concern. It appears that HDL offers a wide range of cardiovascular benefits ranging from modulation of lesion development to cardiomyocytes and eventually that of heart function.

The researchers used an isolated mouse heart model to show that HDL administered in a dose-dependent manner protected the animal from myocardial infarction. Genetically modified animals that lacked tumour necrosis factor (TNF) and the cardiomyocyte transcription factor signal transducer and activator of transcription 3 (STAT3), allowed them to confirm the means by which HDL is protective.

The replacement of HDL with its major component, sphingosine-1 phosphate, yielded similar results. They noted a significant increase in the cardioprotective nature of HDL when they used a specially designed sphingosine-1 phosphate-enriched synthetic HDL in the animal models in place of the native HDL.

The data researchers obtained through this collaboration brought novel insight into the knowledge of cardioprotection with HDL. The design of their synthetic HDL as a novel therapy for cardioprotection is promising. Furthermore, their data clearly suggest the relevance of measuring HDL subclasses rather than total HDL as a more sensitive approach to measure cardiovascular risk in the clinical practice.



Lecour laboratory research tools and results.



PhD student with Professor Sandrine Lecour.

This project has assisted in the capacity building of previously disadvantaged students and the acquisition of new research skills in South Africa. In collaboration with the Swiss partners, novel techniques to assess HDL sub-fractions, composition and functions were successfully established in South Africa. In return, the Swiss partners learned the isolated heart perfusion technique from the South African partners and managed to establish this technique in their laboratory in Switzerland.

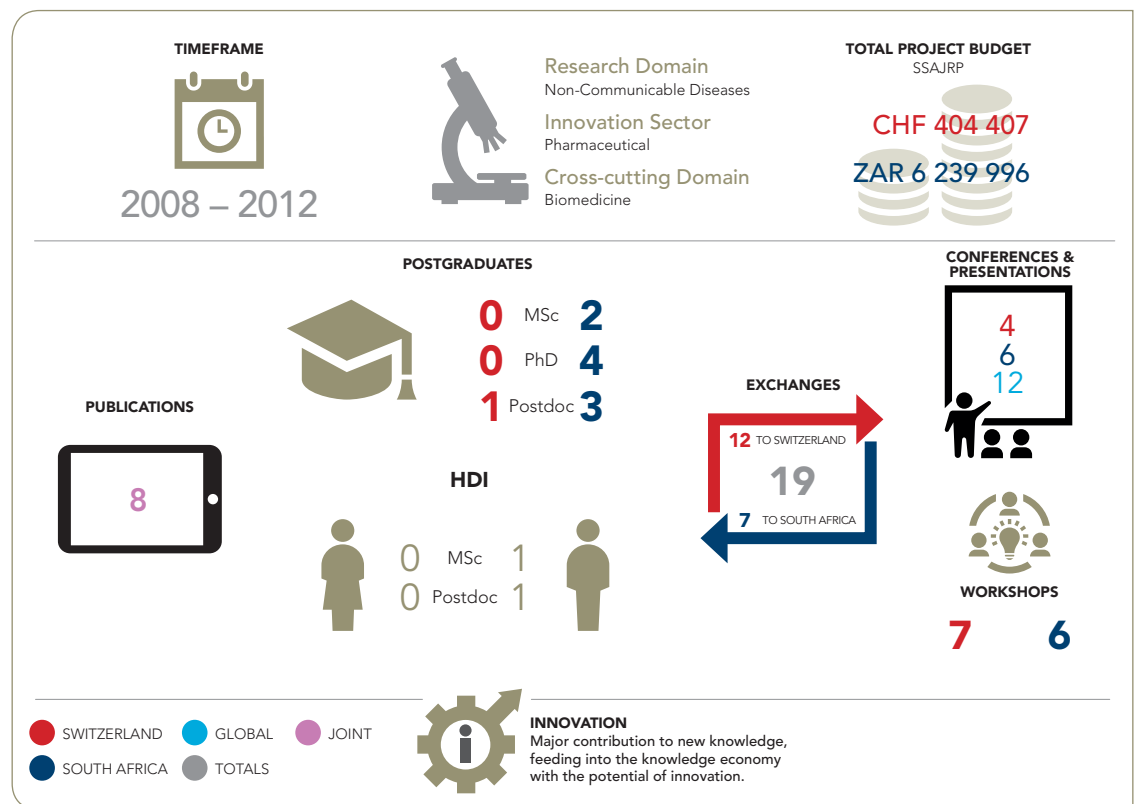
A major impact of the collaboration has been the raised awareness and potential of South African medical research among Swiss scientists. South African students participated in the Swiss national meetings of the Cardiovascular Research and Clinical Implications Network that bring together young Swiss scientists working in the cardiovascular domain to present and discuss their studies. This underlined that fruitful scientific exchanges with South Africa are possible beyond those promoted by focused programmes.

Over the years, the collaboration has been extended to additional Principal Investigators and research facilities in both Switzerland and South Africa, and researchers from the Stellenbosch University and the University of Lausanne are involved in the continuation of this project.

“The SSARJP has allowed us to build a successful collaboration between South Africa and Switzerland. However, it has been challenging to grow this

collaboration at the end of the programme due to lack of funding. Luckily, the excellent relationship between Swiss and South African partners has allowed us to pursue this collaboration with

minimal funding (via a joint PhD student) and we also managed to extend it to other collaborators in Switzerland, South Africa and Germany,” said Professor Dr Sandrine Lecour.





## A translational model for the role of amygdala in fear behaviour



**University of Lausanne**

Professor Ron Stoop

**University of Cape Town**

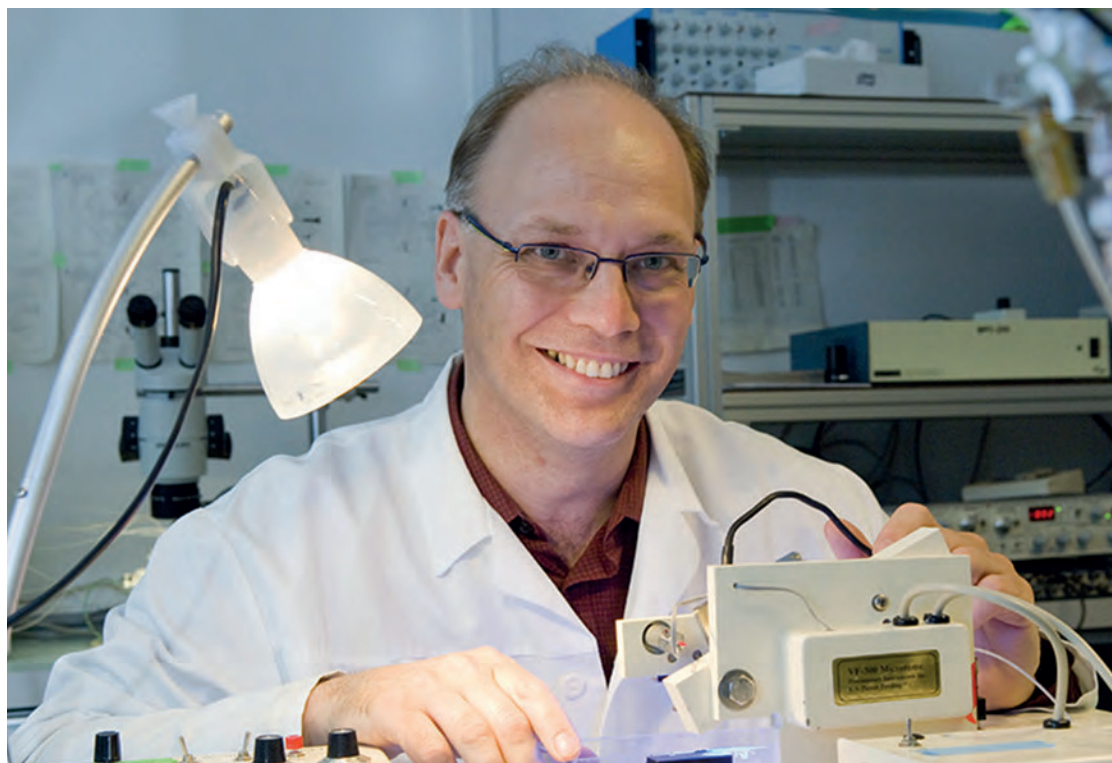
Professor Jack van Honk

The participants in this project aimed to initiate translational research on rodents (in Lausanne) and humans (in Cape Town) to investigate the role of the amygdala in fear behaviours. The amygdala is an almond-shaped set of neurons located deep in the brain's medial temporal lobe, shown to play a key role in the processing of emotions such as fear. In humans, the amygdala has been and still is being investigated and discussed as a single unit. Rodent research has, however, clearly demonstrated that the amygdala has structurally and functionally separate subdivisions, with even antagonistic properties.

The researchers showed selective bilateral basolateral amygdala (BLA) damage in a group of subjects from the Northern Cape, South Africa, caused by a rare fault of the EMC1 gene (Urbach-Wiethe Disease (UWD), a rare recessive genetic disorder). Using neuroimaging techniques, the South African group showed that in these subjects the central nervous system (CNS) remains functional. Moreover, data on these UWD subjects correspond to animal models in showing that instrumental behaviours (subserved by the BLA) shifted to impulsive (subserved by the central-medial amygdala - CMA). These findings broadly agree with recent rodent models of the Swiss group at the University of Lausanne, but there are many unknowns requiring joint research to bridge the translational gap. In this bilateral project, the researchers for the first time used a truly translational approach in a project to construct a translational amygdala-centred neurobiological model of fear.

The researchers at UCT started new neuroimaging experiments with UWD subjects. Together with the Swiss collaborator, new translational tasks (for fear and socio-economic behaviours) were developed for further testing and translational research with amygdala patients and hormones. Several peer-reviewed papers were published in top scientific journals.

The project resulted in capacity development in terms of expertise in psychophysiological, neuroimaging and neuroeconomic research, which is evidenced in high-impact publications and international collaborations. The South African Master's and PhD students who worked on the



*Professor Ron Stoop*



*A plastic model of the right hemisphere of the human brain, with the amygdala on the left (anterior) of the hippocampus (in blue).*



Photograph courtesy of Prof. J von Honk

Professor Jack van Honk



Entrance to the Center for Psychiatric Neurosciences of Lausanne University Hospital.

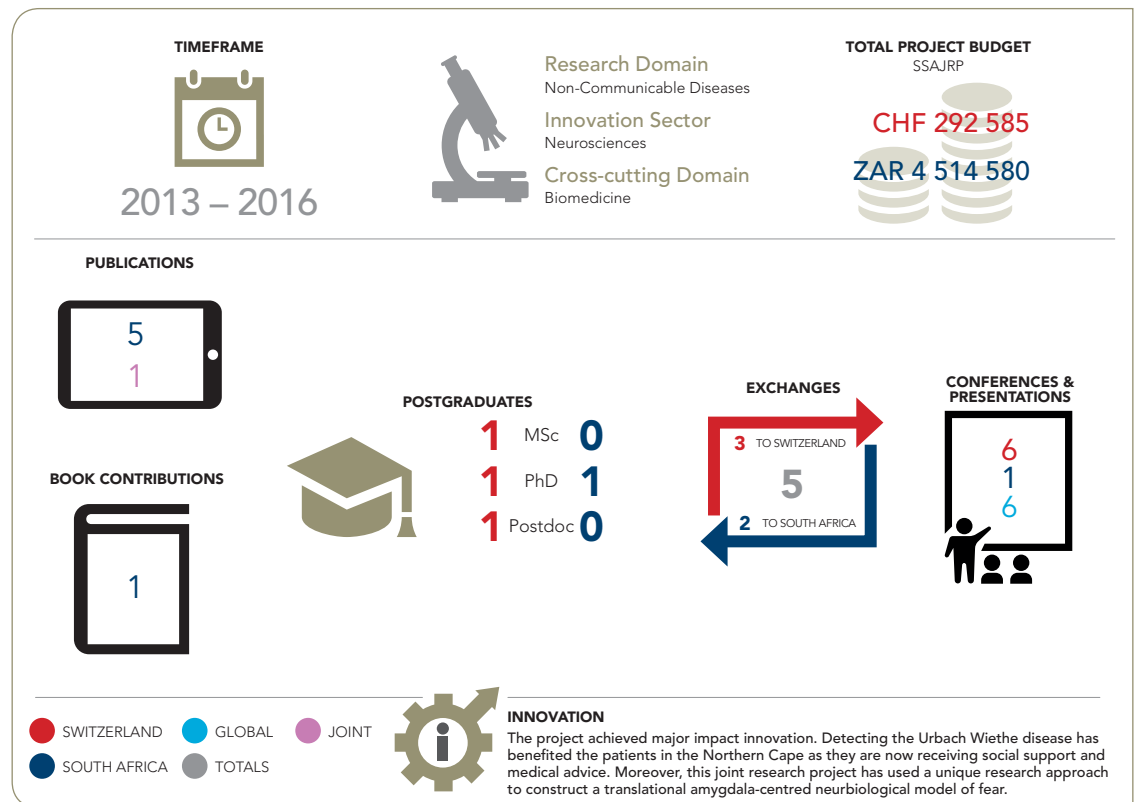


Yvonne Blake, graduate student from South Africa, financed by the Swiss-South Africa programme.

project were trained at top universities in Europe (Lausanne and Utrecht).

A new collaboration with Professor Michael Naeff, an expert in neuroeconomics at the University of London, supported the experiments on UWD.

Research on UWD has benefitted the patients and also some of the control subjects in the Northern Cape in that they received social support and medical advice and support. Most patients are now supported by disability grants. Children suffering from UWD, and control subjects in the Northern Cape, received support and small scale funding for education.





## Multi-functional cyclopentadienyl and carbonyl complexes for theranostic applications



**University of Zurich**

Professor Roger Alberto

**University of the Free State**

Professor Andreas Roodt



Photograph courtesy of Andreas Roodt

Supervisors in UFS RadioLab.

Imaging with bioactive compounds comprising Technetium-99m ( $^{99m}\text{Tc}$ ) is the most important modality of diagnostic nuclear medicine. To direct complexes of  $^{99m}\text{Tc}$  towards a targeted site (organ), e.g. cells with increased densities of particular receptors, the complex must be conjugated to a molecule with the corresponding biological recognition properties. The complex itself must be stable under physiological

conditions, i.e. not trans-metallate to other sites or be metabolised by enzymes. If the attached biological molecule is cytotoxic, the metal-containing compound can be used for therapy. Technetium and Rhenium (Re) belong to the same triad. If homologous compounds are synthesised, the option of theranostics arises: minute quantities of  $^{99m}\text{Tc}$  for diagnosis and macroscopic amounts of Re for therapy.

The research teams participating in this collaboration aimed their work at the preparation and biological study of such homologues. Considering the demand for physiological stability and structural flexibility, they focused their study on two well-known classes of ligands: cyclopentadienyls (Cp) and Schiff bases. Besides the synthetic challenge, they were interested in ligand exchange kinetics and substitution mechanisms, since both parameters are decisive for the success of  $^{99m}\text{Tc}$  labelling. The project thus encompassed fundamental organometallic and coordination chemistry aspects, as well as physicochemical studies in solution and biological investigations.

Experiments with radionuclides such as  $^{99m}\text{Tc}$  provided the project with special analytical and educative opportunities. They ultimately achieved their objectives of combining Re and  $^{99m}\text{Tc}$  with functionalised ligands of both types; and accomplished complexes with two conjugation sites for binding one or two equal or different targeting/cytotoxic portions.

Through the intense mutual exchanges, discussions and collaborations, new innovative ideas emerged from this project. The two described tracks resulted in unexpected findings so far unknown in the inorganic medicinal and radiopharmaceutical community. The researchers will jointly develop these results, which will make an impact in the global community. The current project not only led to a substantial research output but also fertilised this field of science and makes it a necessity to pursue further.

The SA students involved in this project are critical for the development of capacity in radiopharmacy, specifically from a fundamental chemistry point of view. Some South African hospitals employed students who were involved in the project.

The South African participants initiated significant interaction with industry in South Africa as well as with iThemba LABS under the overarching programme. Research interaction and expansion has been initiated with other countries and will be expanded further.

A number of compounds for theranostics (Re and  $^{99m}\text{Tc}$ ) prepared under the umbrella of this project were, or will be, subjected to biological studies at different laboratories in Germany and in France. The researchers are envisaging patenting multinuclear complexes, with negotiations pending.



Photograph courtesy of Andreas Roodt

Professor Andreas Roodt (right) with two students in the Fast Kinetic Laboratory.

