

Research

With over R3 million worth of funds allocated towards cancer research annually, CANSA is one of the largest sponsors of this kind of research in South Africa. CANSA's Research Committee comprises of reputable researchers who review applications for funding and decide on research projects to be supported at various academic institutions around the country. Funds are obtained largely through bequests, trusts and fundraising through mailing initiatives and managed by fund managers via the Board of CANSA. All funds received from bequests and donations are earmarked solely for research. In the period under review, 16 researcher have been funded by CANSA.

Research Committee Members 2006-2007

- Dr Carl Albrecht: Research Advocate, CANSA
- Dr Muhammad Ali Dhansay: Director of the Nutritional Intervention Research Unit, Medical Research Council (joined June 2007)
- Prof Sharon Fonn: Head of the School of Public Health, University of the Witwatersrand (resigned Dec 2006)
- Prof Louis Goedhals, Head of the Department of Oncotherapy, National Hospital, Bloemfontein (joined April 2007)
- Mrs Sue Janse van Rensburg: National Executive Director of CANSA (joined June 2006)
- Dr Mary Kawonga: Public Health Specialist, School of Public Health, University of the Witwatersrand (resigned Dec 2006)
- Dr Greg Landers: Oncologist and Member of the CANSA Board of Directors
- Ms Salome Meyer: Development specialist, Chairperson, Member of CANSA Board of Directors (term of office ended Nov 2006)
- Ms Khathatso Mokoetle (Epidemiology), Community Liaison Director, Ekurhuleni Metropolitan Council, Office of the Executive Mayor (resigned Dec 2006)
- Ms Zanele Mthembu: Director of Health Promotion, National Department of Health (resigned Aug 2006)
- Ms Nokuzola Mqoqi: Director: Monitoring and Evaluation, Department of Health, Eastern Cape (joined April 2007)
- Prof Ann Müller, Associate Professor, Department of Nursing Science, University of Johannesburg
- Prof Gboyega Adebola Ogunbanjo: Director of Research and Associate Professor at the University of Limpopo (Chairperson from Nov 2006)
- Prof Hans Onya: Director of the Health Promotion Unit, University of the North (resigned April 2006)
- Mr Joel Perry: Head of Research & Health Programmes, CANSA (transferred to Gauteng Provincial Manager March 2007)
- Prof Paul Ruff, Head: University of the Witwatersrand Oncology Consortium (joined April 2007)
- Prof Krisela Steyn: Unit Director of Chronic Diseases of Lifestyle, Medical Research Council
- Prof Glynn Wessels: Head of the Paediatric Haematology/Oncology Unit, Department of Paediatrics and Child Health, Faculty of Health Science University of Stellenbosch (resigned Dec 2006)

Research Highlights

Dr Carl Albrecht, CANSA Research Advocate, was invited to serve on the International Affairs Committee of the American Association for Cancer Research (AACR) for three years starting in 2006. The committee has 18 members from the United States, Spain, France, Japan, China, Australia, Netherlands, Sweden, Switzerland, Singapore, England, Italy and South Africa. Dr Albrecht, who represents the interests of Africa, attended his first meeting was in Washington DC on 1 April 2006, which was part of the Annual Congress. The AACR is an organisation based in Philadelphia, Pennsylvania, that focuses on all aspects of cancer research including basic, clinical and translational research into the etiology, prevention, diagnosis, and treatment of cancer. Founded in 1907 by 11 physicians and scientists, AACR has over 24, 000 members, approximately a third of whom are outside the United States. It is the largest cancer research organisation in the world. The most important message Dr Albrecht brought back was that CANSA should focus research funding on projects that could lead to affordable early detection and prevention of cancers of national importance such as cervical, breast, colon, prostate and lung cancer as well as on optimal cancer palliation. "The central idea is to minimise risk factors so that cancers do not start and if they do happen to start, to eradicate them cheaply and as early as possible before it becomes exceedingly expensive and highly problematical to treat the cancers successfully. Furthermore, because less than 50% of cancer patients will be cured it is extremely important to focus on the scientific aspects of palliation to maintain the dignity of the patients through cancer care."

The A, B and C of CANSA sponsored research

Cancer will eventually be conquered through research and advocacy. To this end CANSA has been fortunate to receive magnificent bequests from individual members of the public over the years, specifically for funding cancer research. These funds have been grown with considerable success through excellent investment strategies by financial experts serving CANSA on the CANSA Investment Committee. For years CANSA has acted as the custodian of the funds and has made annual grants through a Research Committee of peer-review researchers.

During the past year a new system called "A, B and C" has evolved in CANSA and concerns the *modus operandi* of research funding. The Type "A" category defines research projects presented to CANSA by researchers at recognised institutions. In other words the researcher decides what to research. This has been the process until recently. Type "B" projects are similar to Type A except that the idea for the project comes from CANSA. Type "C" projects are also initiated by CANSA and concern the patient-oriented services of CANSA, such as palliation of cancer patients.

The reason for this innovation was that according to a CANSA survey of ten years of funding, researchers at institutions hardly ever chose topics dealing with early detection, prevention and palliation of cancer which are crucial key components of CANSA's mission statement. More than two-thirds of the research funded at institutions concerned cancer biology (basic research) and therapy (experimental and clinical).

The need for more cancer research

The Cancer Research Initiative of South Africa (CARISA) is a new organisation that is a joint initiative of CANSA and the Medical Research Council (MRC). The main idea behind CARISA is to obtain substantial new funding for cancer research especially from the South African government and from overseas.

CARISA will also focus more on cancer biology, cancer risk factors and therapy while CANSA will focus on early diagnosis, prevention, care, palliation and epidemiology. It is hoped that this initiative together with CANSA and the MRC will form a united and integrated platform for cancer research with substantially higher funding and activity.

South Africa is a natural laboratory for cancer research because of the great human genetic and economic diversity. There are numerous cancer incidence disparities which could be invaluable clues to understanding the causes of various cancers.



CANSA funded cancer researchers 2006/2007

<i>Researcher and institution:</i>	<i>Project:</i>
Prof P Arbuthnot, Medical School, University of the Witwatersrand	Signalling aptamers for the detection of HBV serological markers in patients at risk of hepatocellular carcinoma.
Dr O Ayo-Yusuf, Oral and Dental Hospital, University of Pretoria	Effects of life skills training on tobacco use and oral health in adolescents in Limpopo Province South Africa.
Prof G Brown, University of Cape Town	Role of Dectin-1 in beta-glucan mediated anti-cancer immunotherapy.
Prof W Gelderblom, PROMEC Unit, Medical Research Council	Therapeutic properties of rooibos and honeybush extracts against skin carcinogenesis.
Prof W Gelderblom, PROMEC Unit, Medical Research Council	A population-based cancer registry in the Eastern Cape Province.
Dr D Hendricks, University of Cape Town	Marine natural products as drug leads for oesophageal chemotherapy.
Prof and Dr Joubert, University of Pretoria	Differential cellular mechanism(s) and gene expression profiles of 2-methoxy -17 α -estradiol and estradiol metabolites in a breast cancer cell line and a non-tumorigenic epithelial breast cell line.
Dr D Katerere, PROMEC Unit, Medical Research Council	Biochemical and phytochemical evaluation of sutherlandia in anti-tumour assays.
Prof M Kew, University of the Witwatersrand	Aetiology and pathogenesis of hepatocellular carcinoma in Southern African black Africans.
Dr V Leaner, University of Cape Town	The role of nuclear transport proteins in the development of cancer.
Prof B Martincgh, University of KwaZulu-Natal	The photostability of sunscreen absorbers.
Prof C Medlen, University of Pretoria	Developmental and experimental chemotherapy of multidrug resistant cancer.
Dr E Murray, Groote Schuur Hospital, University of Cape Town	International Breast Cancer Study Group (IBCSG) trials, Adjuvant Tamoxifen Longer Against Shorter (ATLAS) study in breast cancer, Groote Schuur hospital breast cancer database.
Prof I Parker and Dr C Dandara, Medical School, University of Cape Town	Cancer epidemiology and the maintenance of a hospital-based registry at Groote Schuur Hospital.
Prof R Ramesar, University of Cape Town	Investigation of the clinical, pathological and molecular genetic basis of colorectal cancers.
Dr P Willem, National Health Laboratory Services, University of the Witwatersrand.	DNA profiling of oesophageal squamous cell carcinomas in the South African population.

Life Skills Training for the Prevention of Tobacco use and Promotion of Oral Health

Dr OA Ayo-Yusuf, BDS, MSc, DHSM, MPH, Senior lecturer/Senior Stomatologist, Dept. of Community Dentistry, School of Dentistry, University of Pretoria

In addition to the role of tobacco use and alcohol misuse, there is evidence supporting the association between changes in oral microflora associated with poor oral health and increased risk for cancers, especially oro-pharyngeal cancer.

While adolescents are less concerned about the development of tobacco-related cancers - long-term consequences of smoking or using oral smokeless tobacco (snuff) - the immediate effects such as stained teeth and bad breath are more salient to them. This innovative project, in collaboration with the Medical Research Council, was therefore designed to test the effectiveness of a Life Skills Training (LST) programme in preventing tobacco use and promoting oral health of adolescents in the Limpopo province. This three-year curriculum was developed to teach social competencies, such as decision-making, resisting peer pressure, managing anxiety and stress, among others. It further highlighted prominent short-term effects of tobacco use, such as bad breath, on social interaction/communication.

About 2 000 learners from 21 randomly selected secondary schools across the province were enrolled in this study for annual surveys and oral examination. To date, over 20 educators from 10 intervention schools have been trained in teaching the life skills programme and, over 2 000 learner workbooks have been supplied to learners. Early results have provided us with deeper understanding of what makes learners start to smoke or use snuff. Some of the prominent factors include peer influence, exposure to other family members' smoking and the inability to cope with stress. This study has also illustrated for the first time, the effect of exposure to second-hand smoke on oral health of adolescents. Part of our results have been recently published in the online version of the Journal of Adolescent Health and part of the study's results was also recently presented at the 2007 scientific meeting of the International Association for Dental Research, in New Orleans, USA. The analysis on the early effects of the intervention itself is currently being prepared.

Tumour immunotherapy

Gordon D Brown, PhD, Associate Professor / Wellcome Senior Fellow Institute of Infectious Disease and Molecular Medicine Division of Immunology, Faculty of Health Sciences, University of Cape Town

We are examining the role of Dectin-1 in β -glucan-mediated tumour immunotherapy, looking both in vivo and in vitro. So far CANSA funding has contributed towards the characterization of the Dectin-1 knockout mice and the determination of the signalling mechanism by which beta-glucans mediate their immuno-modulatory activity. We are currently examining the role of this receptor in a tumour immunotherapy in vivo. There have been 17 peer reviewed publications and nine conferences attended during the period under review.

Breast cancer gene study

Annie Joubert, University of Pretoria

The project is examining differential cellular mechanism(s) and - gene expression profiles of 2-methoxy-17 β -estradiol and estradiol metabolites in a breast cancer cell line and a non-tumorigenic epithelial breast cell line.

In this study a breast carcinoma cell line (MCF-7), as well as the MCF-12A cells will be included to determine the differential cellular mechanism(s) and - gene expression profiles of 2ME and estradiol metabolites. MCF-7 cells are derived from a pleural effusion of human breast adenocarcinoma and the MCF-12A cell line is a non-tumorigenic epithelial cell line produced by long-term culture of normal mammary tissue. Obtaining a global impression of the influence of the above-mentioned substances on these cells will contribute to the understanding of molecular mechanisms and cell signaling events associated with 2ME and its metabolites during antitumor responses, enabling researchers to focus on affected cellular mechanisms and contribute to the clarification of, and the extrapolation to breast tissue in vivo with possible diagnostic and/or prognostic value. This knowledge will prove essential in the understanding of breast cancer etiology and may also set new targets for other disciplines such as gene therapy.

Outcomes/results progress made: Dose- and time-dependent studies were conducted. Influence on cell growth and metabolic activity was investigated spectrophotometrically by means of crystal violet as a DNA dye and the 3-[4,5 dimethylthiazol-2-yl]-2, 5-diphenyl tetrazolium bromide assay, respectively. Influence of 2ME on morphology was determined by means of light and fluorescent microscopy.

The IC₅₀ was established at 10⁻⁶ M 2ME for both MCF-7 and MCF-12A cells and the influence of 2ME on cell morphology was assessed after 24, 48 and 72 hours of exposure. Haematoxylin and eosin staining revealed that the vehicle-treated control had no influence on the morphology of the MCF-7 and MCF-12A cells. However, 2ME-treated MCF-7 cells showed hallmarks of apoptosis including abnormal metaphase cells, membrane blebbing and apoptotic bodies. Abnormal (metaphase block and apoptotic) MCF-12A cells were observed after 24 hours of exposure when compared to the vehicle-treated control cells. Propidium iodide and Hoechst 33342 staining confirmed results obtained from light microscopy demonstrating membrane blebbing and apoptotic bodies in 2ME-treated cells. In MCF-7 cells, flow cytometry using Annexin V indicated 3.8% cells to be in early apoptosis compared to 0.5% of the control cells after 24 hours exposure to 2ME at a concentration of 10⁻⁶ M 2ME. In contrast to the MCF-7 cells, Annexin V indicated 1.9% cells to be in early apoptosis compared to 1.7% of the control cells after 24 hours exposure to 2ME at a concentration of 10⁻⁶ M.

Agilent's Human 1A Oligo Microarray slides with 20,173 known human 60-mer oligonucleotide probes were subsequently employed to study the influence of 2ME on gene expression profiles in both MCF-7 and MCF-12A cells. A possible mechanism of action of 2ME in MCF-7 cells was deduced from microarray results. Three peer-reviewed papers were published and five conferences attended.

Phytochemical and Biochemical investigation of Sutherlandia frutescens in short term in vitro and in vivo carcinogenesis assays

Dr David R Katerere, MRC, Cape Town

The project is investigating the cytotoxic, antimutagenic, antioxidant, antiproliferative and cancer modulating properties of *Sutherlandia frutescens* in short term in vitro and in vivo carcinogenesis assays. It will also isolate the compounds responsible for these activities.

This far, anti-mutagenic activity has been shown in the ethylacetate and aqueous methanol extracts. Anti-oxidant activity using various spectrophotometric assays has also been demonstrated. A publication on the results of the two studies is now under preparation. Two conference presentations have been made at SAAB and SAfost.

Breast Cancer Research

Dr Elizabeth Murray, University of Cape Town & Groote Schuur Hospital

This project includes looking at international studies aimed at improving cure rates from breast cancer and also quality of life of patients receiving breast cancer treatment. There are many publications from the international studies. Since the beginning of 2007 there have been seven peer reviewed papers with authorship from the University of Cape Town or no listed authors. The Principal Investigator at the University of Cape Town is a member of the Scientific Committee. University of Cape Town investigators have collaborated in many other publications and conference presentations. International and local protocols are based on results of studies and discussion at meetings.

The second aspect is the breast cancer database which is used for educational talks and research projects e.g. recently two theses have been published and many talks presented which have used results from the database.

The Aetiology and Pathogenesis of Hepatocellular Cancer in Southern African Black Africans

Professor Michael Kew, Dora Dart Professor of Medicine & Director of the MRC/University Molecular Research Unit, University of the Witwatersrand

Aim: Although much is now known about the main causes of hepatocellular cancer in southern African black Africans, information on the pathogenetic mechanisms by which the risk factors cause the tumour is still limited. Much of our present research is therefore directed towards determining these pathogenetic mechanisms.

Outcomes/results: The role of occult (silent) hepatitis B virus infection in the causation of hepatocellular cancer in southern African black Africans has hitherto not been studied. We have completed such a study, which shows that the majority of our patients with evidence of past but not present hepatitis B virus infection on seriological testing only are in fact actively infected with the virus as shown with highly sensitive molecular tests for detecting viral DNA in serum. The association between chronic hepatitis B virus infection and hepatocellular cancer in black Africans is thus even stronger than was initially thought.

Information on the level of hepatitis B viral infection (number of viral particles in the blood) as a factor in the causation of hepatocellular cancer in southern African Black Africans has been obtained and is being statistically analysed. The role of the mutation at position 1653 of the hepatitis B virus genome in causing hepatocellular cancer has been completed.

The number of peer-reviewed articles was nine. Prof Kew attended three international conferences. In recognition of his outstanding role in medical research, he was appointed as Founder Member for Africa of International Liver Cancer Association. He delivered the first Madangopalan Memorial Lecture at the Indian National Association for the Study of the Liver meeting in Vellore, India.

Oesophageal Cancer Research Group

Professor Iqbal Parker, DST/NRF Research Chair in Cancer Biology, Director: MRC/UCT Oesophageal Cancer Research Group, Division of Medical Biochemistry, Faculty of Health Sciences University of Cape Town.

In 2006, Professor Parker was awarded DST/NRF Research Chair in Cancer Biology in the first round of the prestigious DST/NRF Research Chairs programme. In August 2006 he was also appointed as the Director of CARISA, a joint initiative between CANSA and the MRC to address the imbalance in statutory funding for cancer research. On the international front, he was elected onto the executive committee of the International Union for Biochemistry and Molecular Biology (IUBMB) and Chair of the Committee on Symposia during the triennial congress in Kyoto, Japan in June 2006.

His team started a hospital based cancer registry at Groote Schuur. In the past year they concentrated on collecting data and biological samples from oesophageal cancer patients and hope to include other major cancers such as breast, gynaecological and GIT cancers. Collected information included age, race, gender, degree of dysphagia, chest and back pain, duration of symptoms, performance status, size of the tumour, and site of the tumour, histology, stage of the disease and treatment decisions. In the past year, approximately 200 new patients were added to the database. For these patients, questionnaires were completed; blood sample taken (for DNA preparation and plasma) and biopsies were taken in those who were taken for surgery.

In order for the analysis to be of scientific value, blood samples from control individuals were also collected. Age, race and geographically matched controls were collected. The required ratio of patients to controls is at least 1 to 2, thus we also collected 200 control samples. Preliminary analysis of our data, indicated that the bulk of the patients with oesophageal cancer are aged between 40 and 80 years (~90%), more than 85% present at the clinic when they have lost at least 5kg, > 60% are bed-ridden to some extent and >90% present with squamous cell carcinoma (SCC) as apposed to adenocarcinoma (ADC).