

Research

As part of its commitment to fighting cancer to save lives in all communities in South Africa, much of CANSA's work and resources are dedicated to research with a total of R3 391 553 spent on research for the period April 2005 to March 2006. This includes R500 000 for the Cancer Registry in the Western Cape and a provision of R500 000 for the Cancer Research Initiative of South Africa (CARISA). This is a joint project of CANSA and the Medical Research Council to raise the profile of cancer research by setting up national cancer research projects involving several Centres of Excellence in South Africa.

Regarding CANSA research, a Research Committee comprising of reputable researchers and development specialists, decides on research projects to be funded. 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. The organisation's Investment Committee releases an amount of money for research projects to the Research Committee on an annual basis with the former tasked to ensure that the research fund remains sustainable. During the period under review CANSA supported research consortiums for liver cancer; colon cancer and drug development.



Prof. Michael Kew, a world leader in liver cancer research, heads the Liver Cancer Consortium

Research Committee Members 2005-2006

- Salome Meyer: Development specialist, Chairperson, Member of CANSA Board of Directors
- Dr. Greg Landers: Oncologist and Member of CANSA Board of Directors
- Dr. Carl Albrecht: Research Advocate, CANSA
- Niamaat Gamildien: Chief Executive Officer CANSA (resigned December 2006)
- Elize Joubert: Acting Chief Executive Officer CANSA (January to March 2006)
- Joel Perry: Head of Health Programmes, CANSA
- Prof. Sharon Fonn: Head of the School of Public Health, University of the Witwatersrand
- Prof. Barry Mendelow: School of Pathology, University of the Witwatersrand, Technology and Outreach for the National Health Laboratory Service (NHLS) and Special Advisor: National Programme of Research in AIDS (MRC)
- Mary Kawonga: Public Health Specialist, School of Public Health, University of the Witwatersrand
- Khathatso Mokoetle (Epidemiology), Community Liaison Director, Ekurhuleni Metropolitan Council, Office of the Executive Mayor
- Zanele Mthembu: Director of Health Promotion, National Department of Health
- Prof. Ann Müller, Associate Professor, Department of Nursing Science, University of Johannesburg
- Prof. Hans Onya: Director of the Health Promotion Unit, University of the North
- 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

Research Projects

CANSA funds research consortiums or scientific teams on priority cancers for South Africa. These include breast, colorectal, liver and drug development. Non-group projects are also funded on other cancers.

Colorectal Cancer Research

Professor Raj Ramesar, Head of the Colorectal Cancer Research Consortium of the Medical Research Council (MRC) /University of Cape Town Human Genetics Research Unit in UCT's Institute for Infectious Diseases and Molecular Medicine, in the Faculty of Health Sciences

In line with the mission of CANSA, the Colorectal Cancer Research Consortium's research to date has led to the identification of disease-causing mutations, the establishment of a familial registry, genealogical tracking, cascade screening of families, and the ultimate provision of clinical screening services in the Western and Northern Cape, with work also being done in other centres in South Africa. The impact of this effort is the pre-symptomatic detection of those at highest risk for disease, an effort at health promotion and advocacy to prevent morbidity and mortality associated with disease, and genuine evidence (on Kaplan Meier curves) showing a significant difference in mortality between individuals identified with mutations in MMR genes and compliant with the clinical screening protocol, and those who were not compliant.



CANSA researchers from the Drug Development Consortium

Oesophageal cancer research

Research into oesophageal cancer is also supported by CANSA with one such consortium based at the Somatic Cell Genetic Unit in the University of the Witwatersrand's Department of Haematology and Molecular Medicine. The team, under the leadership of Dr. Pascale Willem, uses new tests on human genes developed by scientist Professor Rob Veale.

Oesophageal cancer is common in South Africa, particularly among African men. According to Professor Veale smoking and alcohol consumption play a significant role in this type of cancer. Extensive research conducted amongst people with this type of cancer shows the DNA to have gene damage. Dr. Willem added that certain genes like the fragile FHIT gene are particularly vulnerable when exposed to carcinogens. "This is a good example of acquired genetic aberration in which abnormalities develop in the genes during a person's lifetime. Cancer of the oesophagus highlights the importance of a healthy lifestyle and good nutrition," he concluded.

Oesophageal cancer is also the focus of research being conducted by Professor Wally Marasas, Head PROMEC Unit, MRC in Tygerberg, Cape Town on diet and other risk factors associated with this disease.

Diet and other risk factors associated with oesophageal cancer in Transkei

Professor Wally Marasas - Head PROMEC Unit, MRC, Tygerberg, Cape Town

A culturally specific dietary assessment tool; the Ration And Portion size Picture (RAPP) tool was developed and validated in Centane, Eastern Cape Province. The RAPP dietary assessment tool includes life-size portions of traditional foods as well as a ratio of mixed dishes. This tool is aimed at providing reliable dietary and nutritional information on the rural population and can be of assistance to other nutritional researchers and dieticians to determine the dietary and nutritional patterns in a rural setting. The recipes that were used to prepare the food items should be included in the South African Food Composition Tables that will benefit all nutritional scientists in analysing nutritional intake. This project forms part of PhD in dietetics at the University of Cape Town. Analyses of beer samples that were collected during the validation studies of the RAPP tool showed the presence of high fumonisin levels, which could impact on setting risk parameters of this carcinogenic mycotoxin.

Cancer modulating properties of South African herbal teas (Rooibos and honeybush) in short-term in vitro and in vivo carcinogenesis assays

Dr. Wentzel Gelderblom, Head Somatic Cell Genetics Unit, University of the Witwatersrand

The chemoprotective properties of unprocessed and processed rooibos (*Aspalathus linearis*) and honeybush (*Cyclopia intermedia*) herbal teas, green and black teas (*Camellia sinensis*) were investigated against fumonisin B₁ (FB₁) promotion utilizing a rat liver carcinogenesis model. The relative amount of the larger pre-neoplastic lesions was significantly to marginally reduced by the

unprocessed herbal and black teas while a marginal increase was noticed with green tea. Unprocessed rooibos tea significantly and unprocessed honeybush tea marginally reduced the total number of pre-neoplastic lesions of each size category, respectively. The major polyphenolic components, which differ among the teas, may be responsible for the inhibitory effect of the herbal teas on cancer promotion of FB₁ in rat liver. This is the first report on the inhibition and/or delay of tumour development in the liver by unprocessed herbal teas. The mechanism involved is likely to be related to changes in the redox status of cancer cells that may inhibit their growth. A study in tissue culture utilising cancer cells showed that unprocessed rooibos exhibited the highest cytotoxic effects when compared to fermented rooibos and unfermented honeybush (*C. intermedia*) with fermented honey bush exhibiting the lowest effect. The high cytotoxic effect of unprocessed rooibos could be important in the selective removal of cancer cells *in vivo*.

City of Cape Town Cancer Registry Pilot

Patsy deLora, Project Manager, Cancer Registry

This pilot population-based cancer registry (PBCR) is the first urban population-based cancer registry in South Africa and its aim is to inform policy decision makers nationally about the implementation of a cancer registry; planning of cancer services and strategies; and the design of cancer prevention and control programmes in the City of Cape Town.

The function of the PBCR is to keep a register of all cancer cases occurring in Cape Town. Clinical and pathological data on cancers identified within defined geographic boundaries are collected continuously and systematically using a special computer programme developed by the International Agency for Research on Cancer (IARC).

Information collected by this registry will assist CANSA and policy makers to track trends in the incidence of cancers specific to this locality, as a strategy for planning, implementing and monitoring the impact of area-specific cancer control programmes. This type of registry is promoted as the future for development of cancer registries in South Africa.



The Hepatitis Vaccine and the reduction of liver cancer

Professor Michael Kew, Head of the Liver Cancer Consortium & Dora Dart, Professor of Medicine, Department of Medicine & Director of the MRC/University Molecular Research Unit, University of Witwatersrand

The public health benefits of the inclusion of hepatitis B virus vaccine in the Expanded Programme of Immunization in South Africa continued to be seen with further decreases in the incidence of chronic infection with this virus among the African children in the country. It is still too soon for a decrease in the incidence of the resulting liver cancer to be seen but there is very good evidence that this will occur after an appropriate time interval.

We have shown that the role played by the hepatitis B virus in high incidence of liver cancer in Southern Africa is even more important than was previously thought. With the availability of very sensitive molecular tests for the presence of the virus we have been able to show that a further approximately 30% of our patients with liver cancer that we previously thought not to be infected with the virus are infected with the virus. It is now evident that close to 90% of Africans are actively infected with the hepatitis B virus. This makes the potential to prevent this form of cancer by vaccination even greater.

We have continued with our research showing that the different genotypes of hepatitis B virus found in Southern Africa differ in their ability to cause disease. This is seen most impressively in liver cancer caused by the virus which is 4.5 times more likely to occur with genotype A (by far the predominant genotype in Southern Africa) than the other genotypes. Research at a molecular level as to the why this genotype is more likely to cause liver cancer than the other genotypes is continuing.

In view of the very limited options for treatment of liver cancer it is essential to make the diagnosis as early as possible. Our research into a new tumour marker for liver cancer in the form of an unusual protein in the serum of the great majority of our liver cancer patients is thus very encouraging with respect to improving the chance of successful treatment until such time as prevention by immunization comes about.

Population-based cancer registry in the Eastern Cape

Nthuthu Somdyala, Researcher MRC, Project Leader

A population-based cancer registry in the Eastern Cape is the oldest South African cancer information source that has been serving local needs by monitoring variations in trends and patterns with regards to oesophageal cancer. Recently the registry was further developed and upgraded to serve national and international needs. It is one of the reliable infrastructures available in the country for planning cancer intervention programmes at local, provincial and national levels.

Awareness about cancer has increased with particular reference to the former Transkei region. Specific cancer control plans are underway including improved service delivery by training more doctors and nurses in oncology. The Provincial Non-communicable Diseases Directorate in collaboration with CANSA planned cancer awareness campaigns to areas with high incidence of specific cancers including oesophagus, breast and cervical during 2005-2006. The registry links closely with the Provincial and National Health Departments and project leader, Nthuthu Somdyala made a presentation to the MEC of Health in Bisho in November 2006.

In February 2006, the PROMEC Unit Cancer registry was visited by Deputy Minister of Health Nozizwe Madlala-Routledge. Capacity development, skills and knowledge transfer are some of the important components used in improving data collection methods thereby improving the quality of data collected. Two oncology nurses were selected to attend an IARC training course for cancer registries in Africa held during March 2006 in Benoni, South Africa.



Nthuthu Somdyala, a researcher at the Medical Research Council, is project leader for the Cancer Registry in the Eastern Cape

Cancer Registry at Groote Schuur Hospital (GSH)

Professor M. I. Parker, MRC/OC Research Group, Institute of Infectious Disease and Molecular Medicine, University of Cape Town

Cancer is a major national burden in South Africa. In the year 2002 alone, an estimated 18 504 South Africans died of cancer, amounting to about 51 deaths per day. Of these, 1137 (6%) died of oesophageal cancer. Cancer results in major losses in the economy in health care expenditure and lost productivity.

Reducing the nation's cancer burden requires a multidisciplinary approach involving physicians, researchers, epidemiologists, public health planners, legislators and others. We are therefore crucially dependent on accurate cancer statistics to learn more about the causes of cancer and for early detection. Cancer specialists make treatment decisions based on accurate cancer data from sources such as reports from pathologists and cytologists. Even after treatment, cancer specialists still need cancer data to follow up on patient response in order to determine whether the treatment has worked and if not, to determine why not. Because the GSH cancer registry will provide this type of data, it will be a valuable research tool for those interested in the aetiology, diagnosis, and treatment of cancer. In our efforts to contribute on the "War on Cancer" we have identified changes in certain genes that make people who harbour them more susceptible to the risk of developing oesophageal cancer. The data in the cancer registry is being used to understand environmental risk factors or high-risk behaviours that are associated with each cancer, so that preventive measures can be taken to reduce the number of cancer cases and the mortality rate. Data from the preliminary analysis of the cancer database at GSH shows that individuals who start smoking at an early age (less than 20 years of age) are three times more likely to develop oesophageal cancer. The consumption of home-brewed beer is also associated with increased risk. Once the registry at GSH has accumulated enough information for all cancers, the data mined from this cancer registry could be used to make public health decisions that maximize the effectiveness of limited public health funds by prioritising the screening or preventive programmes. Should we obtain sufficient funding, a lifetime follow-up of patients will be pursued. Patient follow-up allows us to understand the dynamics of survival associated with each cancer. The importance of the GSH cancer registry lies in the collection of accurate and complete data sets that can be used for cancer control and epidemiological research, public health programme planning, and patient care improvement. These activities can lead to a reduction of the burden of cancer.

Developmental and Experimental Chemotherapy of Multidrug Resistant Cancer

Professor C. E. Medlen, Department of Pharmacology, Faculty of Health Sciences, University of Pretoria

This group identified a riminophenazine (a derivative of clofazimine used in the treatment of leprosy) that can sensitize resistant cancer cells for chemotherapeutic drugs such as paclitaxel. A combination of the new drug and paclitaxel will be tested in a liver cancer model at the University of New South Wales. Liver cancer is one of the most difficult cancers to treat and the successful treatment thereof is therefore a challenge to many researchers in this field.

Methotrexate is one of the most potent classical antitumour drugs in clinical administration, both alone and in combination regimens. However, severe toxic side effects and induction of drug resistance continue to restrict its therapeutic use. Excellent *in vitro* performance was shown by a series of methotrexate conjugates, which exceeded methotrexate in activity by factors of 10-200. Pt-polymers with



Margo Nell (research assistant) & Prof. Medlen at work in the lab

impressive and selective anti-proliferative effects on tumour cells have also been identified. This polymer had no pro-oxidative interactions with human neutrophils as is the case with cisplatin. Studies investigating the effects of these polymers in tumour bearing nude mice are underway.

New osmocene-containing betadiketones with potential antineoplastic activity were designed and synthesized by this group. Results obtained with these complexes clearly indicate that the introduction of a metallocene group in the ligand coordinated to titanium makes it more stable, and more active in eradicating cancer cells and provide the basis to obtain drugs that can bypass resistance in the setting of minimal toxicity in normal cells. A new class of chloroquine-derived hybrid molecules with promising *in vitro* anti-tumour activity has also been identified. A simple and cost-effective method to synthesize these agents, which can be produced in large quantities if required, is in place. Novel silver-containing organic compounds were also designed, synthesized and tested by this group. These compounds have activity against cancer cells at very low concentrations.

The consortium has formed an alliance with BioPAD, who will provide the necessary funds to do preclinical and clinical studies of the most promising compounds. Hopefully this will enable us to bring a new anticancer drug into the market with improved activity against resistant cancers in the setting of decreased toxicity.

Pancreatic Cancer

Professor P. C. Bornman, Head Surgical Gastroenterology Upper Gastrointestinal Hepatopancreato-Biliary Unit, Grootte Schuur Hospital and Department of Surgery, University of Cape Town

Pancreatic cancer is one of the most dreaded gastrointestinal malignancies with an overall 5-year survival of 0.4%. In reality the average survival is only three to six months and even patients who undergo resection seldom live beyond two years. Therefore most patients will receive some form of palliative treatment to alleviate jaundice, gastric outlet obstruction and intractable pain. Several palliative treatment options are available today, which include open and laparoscopic bypass operations, non-operative biliary and duodenal stenting, nerve plexus blocks and chemo-radiation. The choice between these treatment options requires careful consideration with the emphasis on minimizing the risks associated with these procedures while ensuring that patients enjoy maximum quality of life (QOL).

To this end the Unit has been involved with several studies since 1999 assessing *inter alia* the role of minimal access laparoscopic bypass procedures comparing this to non-operative stenting in a randomized control study and, assessing QOL after various palliative treatment options. The results have been presented at various national and international meetings and publications are pending.

Ten-year Audit on research funding: 1994 to 2003

During this year an audit on outputs on research funded by CANSA was undertaken by Dr Carl Albrecht. During this period of analysis from 1994-2003, 129 researchers obtained research grants from CANSA totaling R28 178 961 (\$4 776 095). The funds were used for 192 projects, which yielded 570 peer-reviewed publications in 253 different journals listed in the PubMed database. The overall mean impact factor of all of the publications was 3.8.

In the conclusion of his analysis Dr Albrecht states: "This analysis shows that the CANSA-funded research output between 1994 and 2003 was excellent in terms of the number of publications, mean impact factor, cost per publication and overall bibliometric productivity which has been expressed in a novel, rational and uncomplicated formula for comparative purposes. About two thirds of the projects concerned laboratory and/or clinical research while only a third involved psycho-social aspects of cancer. A third of the grantees did not publish a single paper and a stringent new agreement is being formulated to counteract this in future. While South Africa needs far more excellent research on cancer prevention the paramount need for merit when selecting projects is re-emphasized".

By highlighting some of the work done by CANSA-funded researchers a common double thread becomes evident. The benefits of research are crucial now and in the future to increase the knowledge on cancer diagnosis and treatment but also for appropriate measures for cancer control.



Dr. Carl Albrecht

