

HUMPHREY OEI INSTITUTE CANCER RESEARCH NEWS

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**Today's Research
Tomorrow's Cure**

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of Cancer Research for the community*

RESEARCH IN THE LIMELIGHT

THE ROLE OF P73 IN CANCER GROWTH

Prof Kanaga SABAPATHY



While a significant amount of research has been conducted on p53, a tumour suppressor gene discovered in 1979, its close relative p73 has received much less attention. Discovered a decade ago, p73 belongs to the same family of tumour suppressors and has a complex role in cell cycle regulation and death. Like p53, expression of p73 induces cell death. However, contrary to p53, p73 is typically not mutated but is over-expressed in cancers. Even more puzzling is the fact that p73-deficient mice are viable, and only rarely develop spontaneous tumours (unlike p53-deficient mice).

To shed light on this puzzle, a team from the National Cancer Centre Singapore (NCCS) led by Prof Kanaga Sabapathy decided to look more into p73's role in cancers. They found that under certain cellular growth conditions, p73 relinquishes its tumour suppressor role and instead promotes cell growth. Scientists have found that p73 exists in two forms. One is called the 'Full Length' form, consisting of the whole protein, and this acts as a tumour suppressor. The other is the ' ΔN ' form, which is a shorter version lacking the front portion of the gene. This does not act as a tumour suppressor. Researchers have previously shown that the ΔN form is able to inhibit the 'Full Length' form, and is therefore an oncogene.

"The expression of p73 alone inhibits cellular growth and leads to cell death. However, when it is co-expressed with a proto-oncogene called c-Jun, p73 actually enhances cell growth in the long term. This suggests that c-Jun somehow collaborates

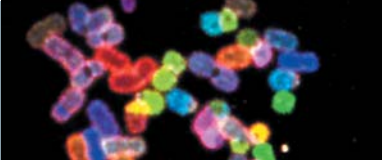
with p73 to negate the latter's tumour suppressor function," explained Prof Sabapathy.

The team's findings were recently published in the prestigious Nature Cell Biology journal in May 2007. Their findings are significant because it is the first time that scientists have shown that this tumour suppressor is able to support cell growth, contrary to previous research.

"This suggests the possibility of p73 becoming a drug target. Many cancers have hyper-expressed p73 levels. So if scientists are able to develop the right conditions to shut down p73, they may be able to stop the growth of the cancer cells. But obviously developing new drugs that can do this is still a long way off," said Prof Sabapathy.

Moving forward, the next steps are to move this research beyond cell culture studies and into animal studies. This will help the team see whether shutting down p73 activity will stop tumour growth.

"I started researching into p73 in year 2000, not long after it had been discovered, as it was a new field and there were many things that were not well understood in the area," said Prof Sabapathy. "I knew that p73 was over-expressed in cancers and this is directly relevant to patients. Everyone in the team works with the motivation of trying to find a cure for cancer. I wanted to know more about the regulation and function of p73, and this continues to drive me and my team forward."



GETTING TO KNOW YOU



Jelissa CHENG A PASSION FOR BRAIN CANCER RESEARCH

At just 29, Jelissa Cheng recently won the Young Investigator's Award (Basic Science) at SGH's 16th Annual Scientific Meeting held in April 2007. This was for her research in identifying a new drug target for treating brain tumours. Jelissa shares more on her research passions.



"...Even though we had been expecting this result to happen, the first time that we actually witnessed it was definitely a "wow" moment for me!"

MISS JELISSA CHENG

Q Tell me more about your research, which won you the recent Young Investigator's Award

The research in my lab focuses on brain tumours, specifically managing their resistance to conventional treatments, such as radiotherapy and chemotherapy. Gliomas are high-grade brain tumours. These are highly aggressive and lethal – patients rarely survive beyond two years. Treatment includes a combination of surgery, radiation and chemotherapy. Unfortunately, patients often relapse, indicating that resistance has developed against radiotherapy and chemotherapy. Our research investigates the underlying reasons for this resistance, and how we can use this knowledge to overcome chemo-resistance and improve patients' response to treatment.

Past research has shown that a gene, called Ect2, has a unique role in glioma biology. I found that Ect2 is necessary for cells to proliferate, and without the Ect2 protein, brain tumour cell growth is arrested. I combined Ect2 depletion with

conventional treatments like chemotherapy and radiation, to see if this is a viable strategy against tumour resistance and was thrilled to observe a more than 40% decrease in tumour viability in a treatment-resistant brain tumour cell line. Even though we had been expecting this result to happen, the first time that we actually witnessed it was definitely a "wow" moment for me!

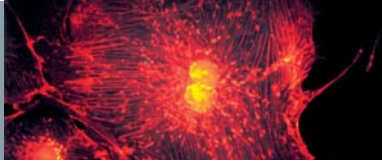
Q Why did you choose to enter cancer research? Is this something that you want to make a career of?

I find research in brain tumours both very interesting and clinically relevant. I am currently pursuing my PhD. in cell biology at the National University of Singapore. Upon completing this, I would like to continue my research in brain tumours for at least a few more years. I have received good support from my lab at NCCS, and there are excellent opportunities here. Looking into the future, I would like to venture into neurobiology and research on other diseases with unmet medical needs. At the same time, I am also keen on teaching. I like to seek knowledge and enjoy making new discoveries and presenting my findings to the world.

"I have received good support from my lab at NCCS, and there are excellent opportunities here."

MISS JELISSA CHENG





NCCS SMF SCHOLARSHIP AWARD WINNERS

Seven researchers and three associate investigators from the National Cancer Centre Singapore (NCCS) received scholarships from the Singapore Millennium Foundation (SMF) this year. This is a first for NCCS clinicians to win the scholarship. In 2006, 12 NCCS post-doctoral fellows and PhD. students received similar awards from SMF.

The presentation ceremony was held at NCCS on 24 August 2007. They were amongst 34 recipients who received their awards from Mr Tan Gee Paw, member of the SMF Board and Chairman of PUB.

SMF is a non-profit charitable organisation funded by Temasek Holdings as part of their community outreach programme to promote and advance scientific progress in Singapore.

This year's recipients will be pursuing research work in the field of tumour suppressor network in hepatocellular carcinoma, radio-resistance of brain tumour stem cells, miRNA expression profiling and functional analysis in gastric cancer, among others.

The NCCS recipients are:



1. Dr Mei-Kim ANG

Supervisor: Prof Bin Tean TEH /
Dr Wen Hsin KOO

Research Title: Immunohistochemical analysis and gene expression profiling in peripheral T-Cell Lymphomas



6. Dr Aik Seng OOI

Supervisor: Prof Bin Tean TEH /
Dr Wen Hsin KOO

Research Title: The effect of the Hepatitis B Virus X protein on the expression profile of microRNAs in hepatocellular carcinoma



2. Mr William CHIN

Supervisor: A/Prof Malini OLIVO

Research Title: Targeted delivery of photosensitizer using biomedical polymers for biophotonic therapeutics and diagnostics of cancer



7. Dr Felicia TAN

Supervisor: Prof Bin Tean TEH

Research Title: Analysis of Immunohistochemistry and gene expression in human



3. Mr Muhammad Iqbal DULLOO

Supervisor: Prof Kanaga SABAPATHY

Research Title: Elucidating the mechanisms regulating the stability of p73, the homologue of the tumour suppressor p53



8. Dr Min-Han TAN

Supervisor: Prof Bin Tean TEH /
Dr Wen Hsin KOO

Research Title: Molecular genetics of clear cell renal cell carcinoma



4. Dr Khong Bee KANG

Supervisor: Prof Meng Cheong WONG

Research Title: Radioresistance of brain tumour stem cells



9. Dr Poi Kiang TAN

Supervisor: Prof Kam Man HUI

Research Title: Selective gene transfer into human brain tumours by using MG11-mediated adenoviral vectors with native tropism



5. Mr Siew Hong LEONG

Supervisor: Prof Oi Lian KON

Research Title: miRNA expression profiling and functional analysis in gastric cancer

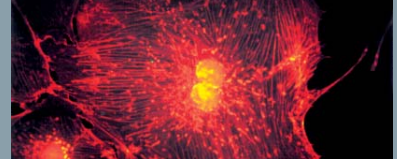


10. Dr Marissa TEO

Supervisor: Dr Han Chong TOH

Research Title: Tumour suppressor network in hepatocellular carcinoma

KEEPING YOU POSTED



UPCOMING DISTINGUISHED LECTURE SERIES



Prof Arnold LEVINE TO DELIVER THE 3RD HUMPHREY OEI DISTINGUISHED LECTURE

Renowned researcher and molecular biologist, Prof Arnold Levine will deliver the 3rd Humphrey Oei Distinguished Lecture later this year. His lecture is titled: "Single Nucleotide Polymorphisms in the p53 Pathway: Cancer, Gender and Fecundity."

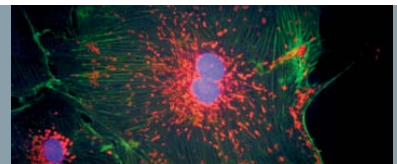
This public lecture will be held at the National Cancer Centre Singapore (Level 4, Lecture Hall) on Monday, 12 November 2007, from 11.45 a.m. to 1.00 p.m.

Prof Levine has made significant contributions in the field of oncology through his research on the causes of cancer in

both humans and animals. He was the first to discover the p53 tumour suppressor gene, which acts to protect individuals from developing cancer. Following Prof Levine's discovery, thousands of researchers have followed in his footsteps, seeking to focus on the p53 gene, which is the most commonly mutated gene in cancer.

For more details, please visit the website www.nccs.com.sg or email Carol.Ang.S.Y@nccs.com.sg

CORRIDOR CONVERSATIONS

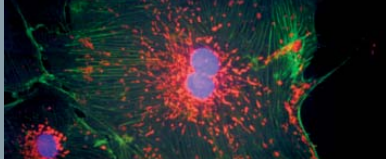


NCCS RESEARCHERS GET GRANTS FROM SINGHEALTH FOUNDATION

Ten researchers from the Humphrey Oei Institute of Cancer Research (HOICR) have received grants to further develop their work in various areas of cancer research.

The awards were given out by the SingHealth Foundation in March as part of their aim to promote research and medical breakthroughs that can generate positive impacts on society.

The research grants allow recipients to work individually or collaboratively, with awardees coming from different medical and science divisions in the National Cancer Centre Singapore (NCCS).



CORRIDOR CONVERSATIONS

Continued from previous page

The recipients are:

1. Prof Kanaga SABAPATHY

Title of Project: Clinical implications of MDM2 and p53: prediction of cancer susceptibility and prognosis.

Grant duration: Two years

Project Summary: p53, the most important tumour suppressor gene is mutated in about 50 per cent of all human cancers, underscoring its importance in preventing malignant transformation. Prof Sabapathy's research will prove significant as his work will help to shed light on the numerous questions still unanswered, where efforts are made to predict and hopefully prevent or manage the disease at its earlier stages of development.

2. Prof Kam Man HUI

Title of Project: Hepatocellular carcinoma validation studies

Grant duration: One year

Project Summary: Hepatocellular carcinoma (HCC) is one of the most prevalent lethal human malignant cancers worldwide. With the highest incidence rates occurring in parts of Asia and Africa. Prof Hui's research works have shown a better prediction of the recurrence of HCC, through combining clinicopathological information and novel molecular markers. In using these readily-available features, Prof Hui's work could help accurately predict, at diagnosis, recurrent disease for all HCC patients, to facilitate the clinical management of HCC.

3. Dr Ganesan GOPALAN

Title of Project: Isolation and validation of peptide aptamers targeting antizyme inhibitor.

Grant duration: Two years

Project Summary: Dr Gopalan's study looks into the development of specific peptide aptamer(s) with the potential to perturb Azi function(s) to modulate polyamine homeostasis and thus tumorigenicity. This is done through a systematic screening of a peptide aptamer library in yeast. Polyamines, are small aliphatic cations present in all living cells and are involved in many biological functions such as cell growth and proliferation, synthesis of proteins and nucleic acids and immunity. A strong correlation between high levels of polyamines and rapid cellular proliferation has placed the cellular polyamine metabolism in the focus of efforts for the development of anti-neoplastic therapy.

4. Dr Ivy AW HO

Title of Project: Identification and characterisation of factors produced by human mesenchymal stem cells that influence glioma progression.

Grant duration: Two years

Collaborators: Paula YP LAM, Kam Man HUI, Chang Ming GUO, Winston SHIM

Project Summary: Gliomas are malignant tumours, which are highly invasive. Clinical gene therapy trials for gliomas have been disappointing. Emerging evidence indicates that human mesenchymal stem cells (MSC) play an important role in tumorigenesis. However, its exact contribution in tumour growth remains poorly defined. Dr Ho's proposal is the team's first attempt in investigating the relationship of MSCs and glioma cells in their micro-environment. Further understanding the underlying mechanism of the interactions will also be of enormous value in the design of therapy for gliomas.

5. Dr Grace Y WANG

Title of Project: Driving non-selective bystander effect of Fas Ligand towards Glioblastoma Multiforme and exploring the potential regulatory effect of Interleukin-13 receptor alpha 2 (IL-13R α 2).

Grant duration: Two years

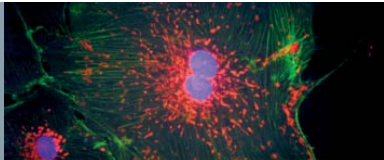
Collaborators: Kam Man HUI, Wai Hoe NG, Paula YP LAM

Project Summary: Glioblastoma Multiforme (GBM) represents the most malignant brain tumour in humans with a mean survival time of 12 to 18 months after diagnosis. Despite surgical resection and post-operative treatment, these tumours will recur and subsequently cause neurological deterioration and death. Over the past years, the large-scale gene expression profiling technology through Affymetrix GeneChip arrays has emerged as a promising research strategy for analysing thousands of genes simultaneously. Various studies have identified target genes as well as novel molecular pathways by this technology, which was not otherwise possible by conventional means.

6. A/Prof Balram CHOWBAY and Dr Charles CHUAH

Title of Project: The impact of hOCT1 (SLC22A1), ABCG2 and ABCB1 pharmacogenetics on pharmacokinetics and pharmacodynamics of imatinib in Asian chronic myeloid leukaemia patients on imatinib therapy.

Grant duration: Three years



CORRIDOR CONVERSATIONS

Collaborators: Yeow Tee GOH

Project Summary: Chronic myeloid leukaemia (CML) is a malignant haematopoietic stem cell disorder. The introduction of imatinib, a selective Abl kinase inhibitor in 2000 has revolutionised the treatment of CML, leading to highly effective responses with low toxicities. However, resistance to imatinib has also been observed. The proposed study by both researchers is expected to provide insights into mechanisms of resistance to anti-cancer agents among patients suffering from malignancies, particularly chronic myeloid leukaemia.

7. A/Prof Ann SG LEE

Title of Project: Molecular mechanisms of isoniazid resistance in Mycobacterium tuberculosis isolates from Singapore.

Grant duration: Two years

Collaborators: Sin Yew WONG, Yong Jiang SUN

Project Summary: Mycobacterium tuberculosis (MTB) is the world's leading cause of mortality, due to an infectious agent with global estimates of two billion people currently infected worldwide. Complicating this scenario is the emergence of multi drug-resistant (MDR) tuberculosis, causing great concern and need for the understanding of the molecular mechanisms and its epidemiology of drug resistance. However, increasing resistance to Isoniazid (INH), the treatment for latent tuberculosis has sparked concern. Understanding the mechanism of drug action and resistance mechanisms may assist in the discovery and development of newer and more effective anti-tuberculous drugs.

8. A/Prof Oi Lian KON

Title of Project: Human umbilical cord lining cells for haemophilia A treatment.

Grant duration: Two years

Collaborators: Toan Thang PHAN, Jaichandran SIVALINGAM

Project Summary: Haemophilia A is a blood-clotting disorder characterised by factor VIII (FVIII) deficiency that affects one in 5,000 – 10,000 live male births, making it one of the most prevalent genetic disorders. The life-threatening nature of severe haemophilia and the lack of safe and affordable treatment are some of the factors that propelled A/Prof Kon and her team to develop an approach aimed at restoring the ability of haemophilia patients to produce FVIII *in vivo* safely and durably. The research could also mean the correction of other genetic disorders.

9. Dr Gopalakrishna IYER and Prof Khee Chee SOO

Title of Project: Identification of gene expression profiles and molecular pathways that predict the progression of oral dysplasia to invasive cancer.

Grant duration: Two years

Collaborators: Kam Man HUI, Ranjiv SIVANANDAN

Project Summary: Head and neck squamous-cell carcinomas represent a significant public health problem, both worldwide and locally. Despite advances in surgical and other treatment modalities, survival rates remain disappointingly low. Hence, it has been suggested that strategies to improve prevention and early diagnosis of pre-malignant lesions are high priorities for reducing death secondary to an otherwise mutilating disease. Using this approach, both Dr Iyer and Prof Soo's eventual aim is to apply the collected data into future prospective studies and to prognosticate patients identified to have dysplastic lesions through opportunistic or population-based screens.

10. Dr Alethea CP YEE and Dr Terina YY SEOW

Title of Project: To assess health-related quality of life (HRQoL), functional status and survival of high risk End-Stage Renal Disease (ESRD) patients on dialysis and ESRD patients on conservative management.

Grant duration: Three years

Collaborators: Cynthia Ruth GOH, Kok Seng WONG, R. AKHILESWARAN, Fei GAO

Project Summary: Little is known about the health-related quality of life (HRQoL) and functional status in the local end-stage renal disease (ESRD) patients. Both Dr Yee and Dr Seow's objectives are to assess HRQoL, its functional status and survival of high-risk ESRD patients on dialysis and those on conservative management. This study is planned to shed light on appropriate delivery of healthcare services by addressing issues still unanswered, and by providing a guide on the best use of limited resources in the local population.

Grants sponsored by:

