FACTSHEET – PROFILE OF INVESTIGATORS
Clinician Scientist Awards 2009

Dr Joseph Wee – CSA (SI)

Senior Consultant, Department of Radiation Oncology,
National Cancer Centre Singapore (NCCS)
Adjunct Associate Professor,
Duke-NUS Graduate Medical School Singapore

Area of research: Nasopharyngeal Cancer

Nasopharyngeal Cancer, or NPC, affects about 400 Singaporeans each year. It ranks sixth in cancer incidences among all male Singaporeans, and is endemic in Southern China and Southeast Asia. It is unique in afflicting southern Chinese individuals at the prime of their lives. Although NPC is among the more curable cancers, there remains a substantial core of 30% of patients who will subsequently recur and die.

Dr Wee and his team are embarking on a Phase III clinical trial, which will test the effectiveness of treating locally advanced Stage 3 and 4 NPC patients using a combination of 3 new chemotherapy drugs administered before chemo-radiotherapy.

This research builds on previous trials on incurable NPC patients conducted at NCCS. The results of these trials using these new 3 drug combinations showed an improvement in median survival of 12 months previously to 18.5 to 24 months currently for this incurable cohort of patients.

This study hopes to increase the cure rate and overall survival by about 15% for those with locally advanced but potentially curable NPC.

A/Prof Tai E Shyong – CSA (SI)

Associate Professor
Department of Medicine
NUS Yong Loo Lin School of Medicine
Senior Consultant
Division of Endocrinology, University Medicine Cluster
National University Health System

Area of Research: The causes and effects of obesity, high blood pressure, diabetes and high cholesterol in Singapore

Heart disease is the second most common cause of death in Singapore and the most common cause in developed countries, accounting for over a quarter of all deaths. It has been estimated that about 90% of heart attacks can be prevented by altering the levels of risk factors such as smoking, high blood pressure, diabetes and high cholesterol.

As part of an overall research programme, Prof Tai hopes to find answers to the following questions:

- What causes some individuals to develop high levels of risk factors for heart diseases?
- Who are those at high risk of developing these disorders and how do we identify them?
- What is the effect of these risk factors on the risk of heart disease?
- How do they affect the quality of life of Singaporeans?

Two specific projects are proposed:

- A study to look for new genes involved in high cholesterol, obesity, blood pressure and abnormalities of blood vessels. The team will carry out genetic analysis in over 3000 individuals to achieve this.

  This information will then be combined with that from other investigators in Singapore and internationally to try to better understand some of the biological processes leading to the development of these disorders. It is expected that knowledge of these pathways will contribute to the development of novel treatments for these disorders.

- In the second project, the team will look at how high density lipoprotein (HDL) protects individuals from heart disease. HDL particles circulate in the blood and are responsible for transporting excess cholesterol from the blood vessels back to the liver to be discarded. High levels of HDL-cholesterol are associated with lower risk of heart disease, which is why HDL cholesterol is called the ‘good cholesterol’.

  However, this is not always the case. Some people with high levels of HDL cholesterol are not protected because their HDL does not function well. There are many proteins present in HDL that affect its function. By studying the role and functions of these proteins, the research team will be able to assess the risk of heart disease for an individual more precisely than by measuring HDL cholesterol alone, which is the current standard practice.

Dr Mahesh Choolani – CSA (SI)

Associate Professor
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Senior Consultant
Department of Obstetrics and Gynaecology,
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Area of Research: Prenatal diagnosis

Globally, 1 in 50 babies is born with serious physical or mental handicap, and as many as 1 in 30 with some form of congenital malformation. Such abnormalities, ranging from mild cases such as extra digits to other more severe structural or chromosomal disorders, may have significant consequences if detected only after birth.

Currently, prenatal diagnosis for fetal abnormalities such as Down syndrome and thalassaemia usually require invasive testing by amniocentesis (taking fluid from the womb) and chorionic villus sampling (sampling a small segment of the placenta). As both tests are invasive, they carry a small but significant risk of fetal miscarriage. This risk causes considerable parental anxiety and in many cases parents choose not to opt for the test based on this fear.

Fetal DNA is known to circulate in the mother's blood but in minute quantities. While techniques are being developed to use this fetal DNA in maternal blood for prenatal diagnosis, there will always be some doubt of its accuracy due to the small quantities obtainable.

On the other hand, if fetal cells that circulate in the mother's blood could be harvested, this would represent a pure source of fetal DNA not unlike that actually obtained at amniocentesis and chorionic villus sampling. More certain and accurate genetic diagnoses could be made using this fetal material.

So far, the team has identified the ideal fetal cell type for non-invasive prenatal diagnosis (NIPD), this is the fetal erythroblast (red blood cell). Research by the team has shown that this cell contains epsilon-globin which is not present in adult cells, and therefore represents an ideal fetal cell identifier. These cells can also be enriched from maternal blood, but only in very few numbers.

The team would like to take their work further by determining the accuracy of new methods they have developed to harvest these cells from maternal blood. In addition, the team plans to develop novel ways to multiply these cells by special culture methods, and to multiply this material many fold. This will enable doctors to use advanced technology to diagnose fetal abnormalities while still in the mother's uterus without an invasive procedure that carries the risk of miscarriage.

Dr Ling Khoon Lin – CSA (INV)

Consultant
Department of Gastroenterology & Hepatology
Singapore General Hospital

Area of Research: Helicobacter pylori gastritis and gastric cancer

Gastric cancer is one of the common causes of cancer deaths in Singapore and in the world. It is thought that about 90% of all gastric cancers are caused by the bacterium *Helicobacter pylori*.

About 50% of the world's population and about 30% of all Singaporeans have an active *H. pylori* infection. It causes a chronic inflammation in the stomach. While all patients with *H. pylori* infection will develop a chronic gastritis, only 2-3% of them will go on to develop gastric cancer. It is thought that the exact composition of immune cells and proteins which contribute to this inflammation varies from one person to another and it is this which determines a person's risk of developing gastric cancer.

The research will study the patient's immune response to *H. pylori* and if certain immune cells or proteins can be used to identify patients at risk of developing pre-malignant or malignant gastric lesions. This would then identify high risk patients who may benefit from surveillance endoscopy. The research also aims to identify immune pathways which could be targeted by therapeutic agents to reduce patients' cancer risk.

The work will be done in collaboration with researchers from the Singapore Immunology Network, the National Cancer Centre and the Singapore Gastric Cancer Consortium.

Dr Dan Yock Young – CSA (INV)

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Area of Research: Harnessing liver cells for the treatment of liver diseases

Liver disease as a whole, including liver cancer, is among the top ten causes of death in Singapore. Hepatitis B is endemic in Singapore and may affect up to 4% of the unvaccinated population.

Liver disease can be fatal if the liver fails. To date, the only cure for progressive severe liver failure is liver transplantation. However, liver transplantation in Singapore is limited by the availability of donors. Advances in medical research allow us to isolate and grow liver "stem" cells in the laboratory. The team's hope is to harness these cells from various sources such as placenta, bone marrow and fetal liver. These cells can then be

expanded to meaningful numbers and induced to work as useful functional liver cells. They can then be used in direct transplantation where sufficient cells grown in the laboratory can be injected into the liver to replace part of the injured liver and support the essential functions needed to sustain life. In addition, they may also be incorporated in an artificial liver dialysis device to take over the functions of the liver, much like the kidney dialysis machine we have today, while waiting for the injured liver to recover or stabilize.

More importantly, the availability of these cells will allow us to better understand diseases such as Hepatitis B and C infections, drug induced liver diseases and even liver cancer. It will also assist in drug development to treat many of these conditions.

The research team expects that the knowledge generated from this work will facilitate development of better treatment for liver disease.

Dr Chen I-Cheng Mark – CSA (INV)

Registrar
Communicable Disease Centre,
Tan Tock Seng Hospital
Duke-NUS Graduate Medical School Singapore

Area of research: Epidemiology and modelling the transmission of infectious diseases such as SARS and influenza within the hospital environment.

Infectious diseases can cause explosive outbreaks and the first time Singapore experienced it was during the Severe Acute Respiratory Syndrome (SARS) crisis in 2003. There are also concerns that similar outbreaks might occur with pandemic influenza. In addition, non-pandemic / seasonal influenza has also been shown to cause substantial illness and mortality on an annual basis.

Singapore, being a major hub of international trade and travel, is particularly vulnerable when new infectious diseases or new strains of existing infectious diseases emerge. Moreover, the recent emergence of the new 2009 H1N1 influenza strain underscores the need to be constantly improving our understanding of infectious disease threats and the best way to deal with them.

Simulation models have been used to help us understand infectious disease transmission, and how best to prevent outbreaks, or reduce the amount of illness and severe illness that might result when an infectious disease spreads. Simulation models have been built which deal with the spread of respiratory infections like SARS and influenza within communities, as well as the spread of such diseases between countries.

However, while hospitals in Singapore were the most severely affected during the SARS crisis in 2003, there have been very few models which deal specifically with understanding the spread of such infections within hospitals.

In this study, the research team aims to develop simulation models that allow us to simulate how an infectious disease like SARS or pandemic influenza might spread within the hospital. The research brings together a multidisciplinary team of clinicians,

epidemiologists, laboratory scientists, statisticians and computer scientists in a multi-disciplinary approach to the problem. The work will involve collecting data from staff and patients, and then integrating such data into a computer simulation model, looking specifically at how best to protect the hospital environment from such infectious disease threats. By exploring various intervention strategies such as vaccination, drug treatment, and use of protective measures, these simulation models will help to design strategies which best protect the staff and patients of the hospital as well as the wider community in the event of another outbreak.

Moreover, the efforts can also be extended and combined with other work which models transmission in the community to look in totality at how best to protect Singapore and to reduce the impact from new and existing infectious disease threats. This in the long run, will translate to better understanding of infectious diseases and the options available for protecting the public health.