The National Medical Research Council (NMRC), established under the Ministry of Health in 1994, oversees the developments and advancement of translational and clinical research in Singapore. It provides competitive research funds to publicly funded healthcare institutions; awards competitive research funds for programmes and projects, supports the development of core critical research infrastructure, is responsible for the development of clinician scientists through awards and fellowships, and fosters interactions and knowledge exchange among researchers.

In 2006, the Ministry of Health established a new mandate to support translational and clinical research in areas where Singapore has great potential. With this in mind, NMRC’s role is ever more important in leading, promoting, coordinating and funding Translational and Clinical Research in Singapore. NMRC-funded research has led to inter-disciplinary partnerships and international collaborations, helping to boost the role played by Singapore biomedical sector on the global stage. Under the Research, Innovation and Enterprise (RIE) 2015 plan, Singapore has earmarked S$16.1 billion over a five-year period (2011-2015) to fund research and innovation in a variety of sectors, including biomedical and life sciences research. NMRC is one of the beneficiaries of this boost in funding, reinforcing the Council’s mandate as the champion for translational and clinical research. Human capital also plays a key role in the success of Singapore’s translational and clinical research industry.

Since its inception, NMRC has supported over 200 clinicians with scholarships, fellowships and various talent development awards. The council has also built up the translational and clinical research capabilities in Singapore through the funding of more than 1,750 competitive research projects and five Translational and Clinical Research Flagship Programmes. To ensure that its budget is appropriately managed and optimally utilised, NMRC evaluates the outcomes of the research projects it funds and facilitates the commercialisation of research findings.

For more information about NMRC, please visit [www.nmrc.gov.sg](http://www.nmrc.gov.sg).
INFORMATION SHEET ON TCR FLAGSHIP PROGRAMMES

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<tr>
<th>Title of Programme</th>
<th>Eye Surgery and Innovative Technologies (EyeSITe)</th>
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<td>Lead PI</td>
<td>Prof Donald TAN Tiang Hwee</td>
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<td>Theme PIs</td>
<td>Prof Roger Wilmer BEUERMAN, Prof AUNG Tin, A/Prof Jodhbir Singh MEHTA, A/Prof Tina WONG</td>
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<td>Amount Awarded</td>
<td>Tier 2- S$25M</td>
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**Background**

Corneal diseases and glaucoma are two of the major causes of blindness worldwide. The disease burden is considerable in Asia, affecting both children and adults alike. An estimated four to six million patients of infectious keratitis (corneal infections) have gone blind, about 12 million people suffer from corneal opacification, and about 60.5 million people are afflicted with glaucoma. In 2008, Prof Donald Tan and his team comprising Prof Roger Beuerman, Prof Aung Tin, A/Prof Jodhbir Mehta and A/Prof Tina Wong, were awarded the TCR Flagship Programme grant, worth $25m over five years, to run the Translational Research Innovations in Ocular Surgery (TRIOS) programme.

**Achievements**

In four years, the team has established five programmes that show promising scientific results, clinical outcomes and commercial potential. Notable achievements include:

**Invention of the “Tan EndoGlide”**

- A disposable surgical device and the first device marketed in the world with Food and Drug Administration (FDA) and Communauté Européenne approval for selective tissue transplantation of the cornea. It demonstrated less damage caused to vital corneal endothelial cells during Endothelial Keratoplasty (EK) surgery or Descemets Stripping Automated Endothelial Keratoplasty (DASEK), a new form of suture less, keyhole corneal transplantation, using the endoglde. Patients in Singapore had first access to the device in 2009. Currently, the device is used at the Singapore National Eye Centre (SNEC) for all patients undergoing the new corneal transplant procedure that is rapidly replacing conventional forms of corneal transplantation. SNEC is now one of the leading centres worldwide for such procedures.
EndoGlide 2 (enhanced EndoGlide 1) was released in September 2012. It aids the surgeon in donor tissue placement into the glide and for use with ultrathin donor tissue that has been shown to provide faster visual recovery. The team has now patented the Tan EndoGlide 3, which would be a new version for the latest form of corneal transplantation i.e. Descemets Membrane Endothelial Keratoplasty (DMEK). DMEK is the most recent form of EK surgery, whereby only Descemets membrane (DM) containing the endothelial monolayer of cells is stripped from the donor cornea, and inserted into the recipient cornea. Although DMEK surgery is still at an experimental stage, a licensing agreement with Network Medical has already been achieved. The team is currently unaware of any competing DMEK insertion device in existence; it is the hope that the Singapore Eye Research Institute (SERI) TRIOS will be the first to lead the field here. The team further hopes to manufacture the EndoGlide 3 in Singapore.

Defensins
This new generation of natural antibiotics has the potential to relieve the enormous burden of ocular morbidity due to infections from bacteria and fungus that is seen throughout South East Asia, as well as in the US and Europe. Defensins also show significant potential as a new class of antimicrobials in other fields of medical therapeutics such as systemic infections as a viable alternative to vancomycin for Methicillin-resistant Staphylococcus Aureus (MRSA), a type of Staphylococcus bacteria resistant to certain antibiotics, infections, as well as in applications such as the disinfective systems required in the cosmetics industry. The team is now testing their new Defensins in cell culture studies to assess its ability to kill bacteria, fungi and viruses in the lab and in animal eyes, with the ultimate aim to develop eye drop formulations for human clinical trials to prevent infection and scarring in the eye.

The three novel synthetic defensin molecules developed are:

(i) Broad spectrum antibiotic with excellent biocompatibility and effectiveness against gram positive and gram negative bacteria as well as fungus. It is safe to the eye, not susceptible to developing resistance and does not inhibit corneal wound healing.
(ii) Antifungal with excellent killing against fungus (within 15 to 30min) and yeast.
(iii) Modified natural product that is highly effective against all gram positive organisms and especially MRSA.

Ocular Drug Delivery System
A novel drug delivery system utilising advanced nanotechnology and biomaterials that allows for timed-release of drugs to treat eye conditions. In collaboration with the School of Materials Science and Engineering at NTU, novel nano-drug carriers are bioengineered to deliver high concentrations of drugs over a sustained period of time via sustained release formulations. For instance, the team has successfully developed a sustained drug delivery formulation using a unique combination of nanoliposomes with Latanoprost (LipoLat), for lowering the intraocular pressure in glaucoma. A first in man Phase1/2 study on LipoLat is expected at the end of November 2012, at the SNEC on patients who suffer from ocular hypertension and primary open angle glaucoma.

The novel carrier systems have now been shown to enable a steady release of the drug over several weeks. Such early outcomes seem to indicate its great potential as the next generation of ocular drug delivery systems for all other ocular diseases, thus eliminating the need for frequent and long-term eye drops to control such conditions. Patients are therefore freed from the requirement to administer frequent, daily eyedrops for years on end, a requirement which often may last for a lifetime and result in non-compliance, can cease to carry multiple bottles of eyedrops, and potentially face reduced risk of disease progression. Overall, there is a notably improved quality of life.

**Femtosecond lasers in corneal surgery**

Two major outcomes were:

a) **The establishment of a new surgical procedure i.e. Refractive Lenticule Extraction (ReLEx), a new alternative to LASIK surgery.**

Clinical trials are confirming that ReLEx SMILE (SMall Incision Lenticular Extraction) laser treatment is highly effective and potentially safer than LASIK as there is no flap made on the cornea. Unlike LASIK, which uses two lasers and vaporises the corneal tissue to correct vision, ReLEx SMILE uses only one laser for the entire procedure and removes only an inner lens-shaped piece of cornea which corresponds to the patient’s myopia and/or astigmatism, through a keyhole incision in the cornea.

b) **Exploring a biological solution for Presbyopia via corneal lenticule re-implantation following cryopreservation**

Refractive lenticule from the ReLEx SMILE procedure have demonstrated that they can be cryopreserved and stored indefinitely. They have further shown in animal models that they can be re-implanted back into the cornea with retention of biological viability.
SERI has filed a patent for this technology, a \textit{potentially reversible} procedure that is the first of its kind, which adds a significant safety factor to laser corneal surgery. Similar to the concept of cord blood banking, the lenticules can be stored for the same patient, or can even be donated to other patients who require some forms of \textit{corneal transplant surgery}. The TRIOS program also aims to refashion these lenticules to treat \textit{presbyopia} ("lau hua"), which occurs in every person, and for which there is no treatment other than reading glasses.

This technology is due to be licensed to a new spin-off company, called \textit{Lenticor}, which will have the rights for this technology for the region. Lenticor will be a new local start up company that has prior expertise in cryopreservation and private cord blood banking. It will be able to offer patients undergoing ReLEx SMILE laser surgery the option of storing their own lenticules for future use. Working with A*STAR’s Exploit Technologies that is helping out with TRIOS commercialisation, the final licensing agreement is expected to be signed with Lenticor within the next few days, and this will be a true validation of the translational bench to bedside success of TRIOS. TRIOS SERI scientists and clinician researchers at SNEC will continue to work closely with Lenticor in a research collaboration to use this technology in developing new treatments for corneal transplants and for the treatment of presbyopia.

\textbf{Discovery of genes linked to Primary Angle Closure Glaucoma (PACG)}

Through an international consortium led by the team as well as inter-disciplinary collaborations established with local institutions such as the Genome Institute of Singapore (GIS), National University of Singapore (NUS) and Tan Tock Seng Hospital, a genome-wide association study (GWAS) identified three new susceptibility loci for Primary Angle Closure Glaucoma (PACG). Published in the Aug 2012 edition of high IF journal, Nature Genetics, this discovery will lead to further research to elucidate the full genetic architecture of PACG, eventually allowing the development of a clinically useful genetic profile for the identification, risk stratification and thus treatment of PACG patients in the future.

\textbf{Details of the Study}

The new programme “Eye Surgery and Innovative Technologies (EyeSITe)” will leverage on their past success with the aim to provide new clinical therapies diagnostic applications to aid in alleviating ocular morbidity from major eye diseases, including corneal disease, infection, glaucoma, refractive errors and retinal disorders. The specific objectives are:
1) The development of new classes of antimicrobial small peptide and peptoid molecules which will have a significant impact in treating corneal infections caused by Gram-negative, Gram-positive bacteria, as well as fungal infections and also for systemic infections.

2) The development of sustained drug delivery carriers to provide effective prolonged drug release without relying on patient compliance would improve therapeutic outcomes and overall healthcare and disease management in these patients who are generally elderly. This technology can clearly be applied across other ophthalmic conditions which require chronic medical treatment.

3) The bionic cornea programme aims to develop a carbon-fibre and titanium-based Artificial Cornea to treat severe corneal blindness. Other aims include the growing of corneal cells in the laboratory as a substitute for corneal transplantation, and developing new medical devices for transplantation surgery.

4) The femtosecond laser programme aims to provide a new treatment for keratectasia and keratoconus, and for presbyopia, and to develop new forms of cataract surgery with femtosecond lasers for Asian eyes which may provide more precise and safer clinical outcomes.

5) The PACG programme aims to develop new diagnostic and prognostic approaches to PACG, with a potential novel risk prediction algorithm combining ocular imaging and genetic markers to detect high risk patients (stratified medicine), which if successful, will be applicable not only in the clinic, but also at a population-wide level. In addition, the programme will provide new insights into the genetic basis of PACG as well as anatomical and physiological basis of angle closure, which in turn will lead to more targeted approaches to treating this blinding condition. As a first step towards this, the Singapore team has discovered the first three novel genetic loci associated with PACG. This information on the genes involved in PACG has now opened up new and exciting research areas that have the potential to culminate in new treatment modalities for angle closure glaucoma in the future.

These programmes, if successful, will result in better health outcomes for the above-mentioned ocular conditions, improve medical practice, and may also provide significant economic outcomes to Singapore.

TEAM’S PROFILE
**Donald TAN Tiang Hwee (LEAD PI)**  
*Medical Director, Singapore National Eye Centre (SNEC)*  
*Chairman, Singapore Eye Research Institute (SERI)*  
*Professor, Dept. of Ophthalmology, National University of Singapore (NUS)*  
*Chair, Eye Academic Clinical Programme, Duke-NUS Graduate Medical School*  
*Medical Director, Singapore Eye Bank*

Involved primarily in clinical and translational research in cornea, refractive surgery and myopia, he has published over 300 peer-reviewed articles (h index = 42), contributed 18 book chapters and holds 13 patents in stem cell culture, myopia prevention, refractive corneal implants and surgical devices for endothelial keratoplasty, and has also trained 22 corneal fellows from 13 countries. He is the recipient of over 20 awards, which include the APAO 2001 De Ocampo Award, the AAO 2006 Distinguished Achievement Award, the ISRS/AAO 2009 Casebeer Award, the Saudi Ophthalmological Society 2010 Gold Medal, the Australia and New Zealand Corneal Society 2011 Doug Coster Award, the Canadian Society of Ophthalmology 2011 W. Bruce Jackson Award, the EuCornea 2012 Medal, and the Portland, Oregon Arthur Devers 2012 Lecture.

Prof Tan established the Asia Cornea Society in 2007 and the Association of Eye Banks of Asia in 2009, and is currently President of both societies. In 2012, he assumed the Presidency of the US based Cornea Society, its first International President.

**AUNG Tin**  
*Senior Consultant & Head of Glaucoma Service, Singapore National Eye Centre (SNEC)*  
*Deputy Executive Director, Singapore Eye Research Institute (SERI)*  
*Professor, Dept. of Ophthalmology, National University of Singapore*

Prof Aung is a pre-eminent clinician-scientist and his research interests are angle closure glaucoma and the molecular genetics of eye diseases. Prof Aung and his team were the first in the world to discover the SLC4A11 gene responsible for Congenital Hereditary Endothelial Dystrophy (CHED), published in Nature Genetics. Recently Prof Aung and his team were the first to study PACG genetics using a genome-wide perspective and results were published in the prestigious scientific journal, Nature Genetics, on 26 August 2012. This was a major achievement for the Singapore team, which led the largest international consortium of doctors and scientists involved in glaucoma research.

Prof Aung has more than 300 publications, has been an Invited Lecturer to more than 80 International Conferences in 30 different countries and has received numerous awards.
including the Singapore NMRC-BMRC Clinician Scientist Awards in 2005 and 2008, the Nakajima Award from the Asia Pacific Academy of Ophthalmology in 2006 and the Singapore President’s Science Award in 2009. Prof Aung has been awarded more than US$15 million in research grant funding and has set up collaborations with many centres worldwide in the US, UK, India, China, Myanmar, Thailand, Indonesia and Japan. Prof Aung is a member of the Editorial Board of the following journals: Ophthalmology, Eye, Journal of Glaucoma, International Glaucoma Review and Asian Journal of Ophthalmology.

Roger Wilmer BEUERMAN
Senior Scientific Director, Singapore Eye Research Institute (SERI)
Professor, Duke-NUS, SRP, Neuroscience and Behavioural Disorders
Director, Singhealth Medical Proteomics Centre

Prof Roger Beuerman is adjunct Professor of Ophthalmology, Yong Loo Lin at NUS, School of Medicine; Adjunct Professor of Chemical and Biomedical Engineering at NTU; and Adjunct Senior Scientist at the Bioinformatics Institute. He is a clinical scientist with more than 25 years of experience in ophthalmology research working on the development of refractive surgical procedures, corneal preservation medium, the clinical confocal microscope used in ophthalmology, biomarkers of eye disease and peptide based antimicrobials.

He is an expert in epithelial wound healing and internationally known in the area of ocular surface disease. He is developing new antimicrobial peptides for topical applications, and in ocular proteomics he has developed new biomarkers focusing on the diagnosis of dry eye and inflammation. He has co-edited three books in ophthalmology, the latest on myopia. Overall, he has more than 220 publications, sits on several editorial boards, such as “Cornea” and “Ocular Surface” and reviews grants for the SingHealth Foundation, the National Medical Research Council and is on the Association for Research in Vision and Ophthalmology (ARVO) Program Planning Committee. Prof Beuerman was recently made a Fellow of ARVO and has received the 2009 President’s Award in Science and Technology.

Jodhbir Singh MEHTA
Co-Head, Cornea and External Disease, and Senior Consultant, Singapore National Eye Centre (SNEC)
Head, Tissue Engineering and Stem Cell group, Singapore Eye Research Institute (SERI)

A/Prof Jod S Mehta joined the SERI faculty as a Clinician Scientist and is also a Consultant Ophthalmologist at SNEC since 2008. He has academic affiliations with DUKE-NUS
Graduate Medical School and is also an Adjunct Associate Professor with NUS. Dr Mehta received his general ophthalmic training at Moorfields Eye Hospital, London. He also completed a Corneal External disease and Refractive fellowship with Moorfields and SNEC. He has won awards at the American Academy of Ophthalmology (AAO), ARVO and recently the Nakajima Award at the Asia Pacific Academy of Ophthalmology.

His corneal interests lie in corneal transplantation – penetrating keratoplasty, lamellar keratoplasty and endothelial keratoplasty, femtosecond laser technology, corneal imaging, corneal infections, corneal refractive surgery, keratoprosthesis surgery, ocular drug delivery systems and corneal genetics. Dr Mehta is author of over 140 peer-reviewed publications, seven book chapters and six patents.

Tina WONG
Senior Consultant, Glaucoma Service, Singapore National Eye Centre (SNEC)
Head, Ocular Therapeutics and Drug Delivery Research Group, Singapore Eye Research Institute (SERI)

A/Prof Tina Wong holds an adjunct faculty position at the School of Materials Science and Engineering, NTU. Previously, A/Prof Wong was a Glaucoma Fellow at Moorfields Eye Hospital in London, UK, where she completed her general Ophthalmic training. She was awarded the highly competitive Wellcome Trust Vision Research Fellowship in 1999 for which she completed a PhD on “The role of matrix metalloproteinases in conjunctival wound healing” at the Institute of Ophthalmology, University College London in the laboratory of Prof Peng T. Khaw. Her research resulted in her receiving several national prestigious awards.
Title of Programme

Singapore Gastric Cancer Consortium – Re-defining the Management of Gastric Cancer

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<tr>
<th>Lead PI</th>
<th>A/Prof YEOH Khay Guan</th>
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<td><a href="mailto:mdcykg@nus.edu.sg">mdcykg@nus.edu.sg</a></td>
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| Theme PIs        | Prof Patrick TAN, Prof Yoshiaki ITO, Dr YONG Wei Peng |

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**Background**

Gastric adenocarcinoma, or gastric cancer, is a leading cause of global cancer mortality that accounts for 700,000 deaths worldwide annually. It is particularly common in East Asia countries such as China and Korea, as well as in Singapore where males have a 1.50 lifetime risk for it. Prevention, including early detection, and treatment options for the disease are clinically challenged at present. For most countries, screening efforts are directed towards population subgroups that are at highest risk of developing gastric cancer because it is not practical to carry out mass population screening programmes which are cost-effective in Japan and South Korea where incidences of gastric cancer are comparatively higher. In terms of treatment, surgery, chemotherapy and targeted therapies - newer treatment option which uses small molecules and antibodies to inhibit the pathways of specific oncogenes (genes that potentially cause cell to turn cancerous) - have not been highly effective as they yield varying responses in patients.

In 2007, a national translational research group of clinicians and scientists from universities, research institutes and hospitals across Singapore working in gastric cancer research, the Singapore Gastric Cancer Consortium (SGCC), was the awarded the TCR Flagship Programme to solve important clinical questions to improve the care of gastric cancer patients. Since the group’s inception in 2006, it has grown to comprise more than 31 members, led by A/Prof Yeoh Khay Guan and the theme PIs A/Prof Patrick Tan, Prof Yoshiaki Ito, and Dr Yong Wei Peng who form the group’s steering committee.

The current award will be a continuum for SGCC to transit from “Improving Outcomes for Our Patients” to “Re-defining the Management of Gastric Cancer”. Over the past five years, the team has excelled in translating basic research to clinical research and vice versa. Notable achievements that will cast positive impacts in future healthcare for gastric cancer
includes robotic endoscopy, genomic-guided personalised treatment that yields better patient response and decreased drug toxicity, early detection of gastric cancer in clinical settings through diagnostic kits, and improved therapeutic strategies.

**Notable Achievements**

- New genomic classification of gastric cancer (*published*) that may be superior to the classic Lauren classification. It is the basis for genomic-guided personalised treatment (undergoing prospective proof-of-concept (POC) international clinical trial; as of Oct 2012, a total of 50 patients have been recruited) with the aim of achieving improved patient response rate and decreased drug toxicity.

- Robot endoscope system – first group in the world to perform robotic Natural Orifice Transluminal Endoscopic Surgery (NOTES) in human patients (2011). This work recently received the President’s Technology Award and has led to a spin-off company (EndoMaster Pte Ltd).

- First in Singapore to diagnose early stage 1 or stage 0 gastric cancer through endoscopic screening of a pre-disease high risk cohort (Gastric Cancer Epidemiology Programme, GCEP cohort comprising 3,000 subjects). From this cohort, 17 patients were detected with early cancers.

- Publications being prepared for (1) whole-genome sequencing project completed in 2011 in collaboration with GIS, and (2) for key genetic changes identified in early stage (I & II) gastric cancer completed in collaboration with Illumina.

- Biomarker discovery projects have resulted in the protection of two novel biomarkers for gastric cancer detection. A commercialisation grant was secured to produce novel reagents (aptamers, monoclonal antibodies or peptides) against one of these biomarkers, C9, and the team is in the process of developing a diagnostic kit for clinical applications.

- In the reportedly largest study of genomic copy number alternations in gastric cancer to identify novel drug targets, results indicate that close to 37% of the gastric cancer cases diagnosed may be treatable by drugs targeting a single cell signaling pathway. For one of these targets (FGFR2), we found that FGFR2-amplified gastric cancers exhibited sensitivity to dovitinib, an orally bioavailable targeted therapy. These findings were translated into a first-in-man industry supported clinical trial in Singapore.
- Deepened understanding of molecular pathways leading to gastric cancer development: found two genes, FAT4 and ARID1A to be mutated in 5% and 8% of stomach cancers, respectively. Functional experiments demonstrated that disrupting the activity of FAT4 and ARID1A is likely important for gastric cancer to develop.

- Discovered a way to overcome resistance to cisplatin, a commonly used chemotherapeutic agent: target BMP4 (Bone morphogenetic protein 4) as a promising therapeutic strategy for improving the efficacy of cisplatin treatment.

Details of the Study
In this new five-year run, the programme will maintain its focus, with expanded scope on:

(i) EARLY DETECTION- as the principle strategy to improve gastric cancer clinical outcomes.
   The theme will be led by A/Prof Yeoh (lead PI) and supported by Prof Patrick Tan, to identify suitable blood-based diagnostic biomarkers, from candidate biomarkers identified in a previously assembled pre-disease high-risk cohort (Gastric Cancer Epidemiology Programme, GCEP), to develop a cost-effective screening strategy for Singapore patients.

(ii) THERAPEUTICS- to improve treatment.
   The theme will be led by Dr Yong Wei Peng, supported by Prof Patrick Tan, to firmly establish the clinical usefulness of the genomic classification of gastric cancer previously discovered by the team to be able to predict patient survival and drug responses in cell lines and patients, through an ongoing prospective clinical trials, as well as to test the efficacy of new treatment options, e.g. peptide vaccines, through new clinical trials.

(iii) GASTRIC CARCINOGENESIS- to understand the molecular biology of gastric cancer.
   The theme will be led by Prof Yoshiaki Ito, supported by Prof Patrick Tan to identify new therapeutic targets and early detection biomarkers, through the use of animal models that faithfully recapitulate various aspects of gastric cancer development including transitions from normal gastric tissue, to precancerous states and eventual cancer.
**TEAM’S PROFILE**

**YEOH Khay-Guan (LEAD PI)**  
*Associate Professor of Medicine*  
*Yong Loo Lin School of Medicine*  
*National University of Singapore*

Dr Yeoh is a clinician-investigator and gastroenterologist at the National University Hospital, Singapore. His research interest is in the early detection of gastric and colorectal cancers by screening and the use of molecular markers. He is the Lead-Principal Investigator for the Singapore Gastric Cancer Consortium, a national translational-clinical research programme focused on improving outcomes for gastric cancer.

He has published over 100 peer-reviewed papers in international journals. Dr Yeoh serves in several leadership roles including Dean in the Yong Loo Lin School of Medicine. He also chairs the National Colorectal Cancer Screening Committee of the Health Promotion Board, Ministry of Health which recommends guidelines for the national colorectal screening programme in Singapore.

**Patrick TAN**  
*Professor, Duke-NUS Graduate Medical School*  
*Group Leader, Genome Institute of Singapore (GIS)*  
*Program Leader, Cancer Science Institute of Singapore*  
*Research Associate Professor, Institute of Genome Sciences and Policy, Duke University*

Dr Patrick Tan holds a joint appointment as a Professor at the Duke-NUS Graduate Medical School and a Group Leader at GIS. He is a Program Leader in Genomic Oncology at the Cancer Science Institute of Singapore, National University of Singapore and a Research Associate Professor in the Institute of Genome Sciences and Policy at Duke University, USA.

His research focuses on the application of genomics to cancer and infectious disease. He received his B.A. (summa cum laude) from Harvard University and MD PhD degree from Stanford University, where he received the Charles Yanofsky prize for Most Outstanding Graduate Thesis in Physics, Biology or Chemistry. Locally, he has received the President’s Scholarship, Loke Cheng Kim foundation scholarship, Young Scientist Award (A-STAR), Singapore Youth Award (twice), and the Singhealth Investigator Excellence Award.
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<th>Yoshiaki ITO</th>
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<td>Programme Leader and Senior Principal Investigator, Cancer Science Institute Singapore</td>
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<td>National University of Singapore</td>
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<td>Yong Loo Lin Professor of Medical Oncology</td>
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<td>Department of Medicine, Yong Loo Lin School of Medicine,</td>
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Prof Ito obtained his MD PhD from Tohoku University, Japan, and studied in Duke University, USA, Imperial Cancer Research Fund Laboratories, UK and National Cancer Institute, USA. He became a Professor in 1984 at the Institute for Virus Research, Kyoto University, and served as Director between 1995 and 2001. His area of research is in the elucidation of the molecular mechanism of carcinogenesis. He discovered the major oncoprotein of polyomavirus, middle T antigen that triggered the discovery of well known tumor suppressor, p53.

More recently, he discovered the RUNX family of genes which are critical regulators of developmental and cancer. In particular, he discovered RUNX3 is a tumor suppressor of gastric, colon and many other solid tumors.

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<th>YONG Wei-Peng</th>
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<td>Senior Consultant</td>
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<td>Department of Haematology-Oncology</td>
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<td>National University Cancer Institute, Singapore (NCIS)</td>
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Dr Yong obtained his medical degree and postgraduate training from the University of Aberdeen, Scotland. After completing an oncology fellowship at the National University Hospital, he was awarded the A*STAR international clinical pharmacology fellowship at the University of Chicago. His clinical interest is in gastrointestinal cancers and his research interests are pharmacogenetics and epigenetics in cancer.
Title of Programme
Genetic Predilection, Epigenetic Change, MicroRNA Profiling and Experimental Therapies in Heart Failure

Lead PI
Prof Arthur Mark RICHARDS
Email: arthur_mark_richards@nuhs.edu.sg

Theme PIs
A/Prof LIU Jianjun, Prof Kandiah JEYASEELAN, Prof Colin Lawson STEWART

Amount Awarded
Tier 1- S$9M
Funding Duration Five Years

Objective of the Study
To improve understanding of inherited factors for risk of heart failure, through genetic studies and the identification of specific gene products, with a view to improving prediction of heart failure and identifying new treatments.

Details of the Study
Heart failure is the final common pathway of a myriad of cardiovascular diseases. It is a major health problem worldwide and is projected to afflict one in five people now in middle age at some point in time in their remaining lifetime. According to the World Health Organisation (WHO), the largest increase in incidences of cardiovascular disease is reportedly seen in Asia. While this is in part due to rising rates of smoking, obesity, dyslipedemia and diabetes, the global shift in the burden of heart failure to the developing countries of Asia suggests that ethnicity is related to differences in the incidence and outcome of heart failure observed in multi-racial Asia.

For Singapore, heart failure is the most common cardiac cause of hospitalisation, with only 32% of cases surviving five years. About 30% to 50% of heart failure patients have small, stiff hearts that are not dilated, can still pump with reasonable strength, but fill poorly (heart failure with preserved ejection fraction where ejection fraction refers to the fraction of blood pumped from the heart with each heartbeat) while the remaining have enlarged hearts that pump weakly (heart failure with reduced ejection fraction). There appears to be no difference in background factors (high blood pressure, coronary artery disease, diabetes and cholesterol) detected for both types of heart failure. However, inherited factors, specifically genetic variants, are postulated to be associated with the type of heart failure developed.
Awarded the National Medical Research Council's (NMRC) first Tier 1 grant to run a TCR Flagship Programme, the research team, led by Prof Mark Richards and comprising co-PIs A/Prof Liu Jian Jun, Prof Kandiah Jeyaseelan, and Prof Colin Stewart, brings together essential skills and experience in both basic science and clinical care of heart failure from team members based in four sites – the National University Heart Centre, Singapore (NUHCS), the Genome Institute of Singapore (GIS), the faculty of Biochemistry, Yong Loo Lin School of Medicine and the Institute of Medical Biology (IMB).

Prof Richards is the director of the Cardiovascular Research Institute (CVRI) at NUHCS. He has over 25 years of experience in clinical care for heart failure patients in New Zealand, and many years of research experience, alongside basic scientists, investigating new biochemical pathways in heart failure. His work has led to the establishment of new blood tests for diagnosing and monitoring heart failure which have improved care and survival in this condition. Under his oversight, the co-PIs, as experts of their respective research domain, will be leading investigations focused upon (i) differences in genetic backgrounds, (ii) different activation and de-activation of genes (“epigenetics”), (iii) the role of intermediate gene products (“microRNAs”) and the (iv) potential of gene targets, to improve understanding of inherited factors for risk of heart failure so that the overall aims of improving prediction and progression of heart failure and identifying new treatments can be fulfilled.

Specifically, cardiac ultrasound scans will be used to measure changes in heart function to determine any relation to genetic variation. The team will also explore the use of microRNAs that are detected circulating freely in the blood of patients with heart failure or afflicted with heart valve disease and heart attacks, as potential biomarkers for the diagnosis of heart failure and as pointers to new therapeutic targets in heart failure. Animal studies using mice with genetic modifications which lead to heart failure or after experimental induction of heart failure will be conducted in parallel to human studies. Corroboration of findings from both subject groups opens up the plausibility of using genetically engineered mice to find new treatments for heart failure at the first instance.

In this run of the grant, Prof Richards will also be joined by internationally experienced clinical colleagues from NUHCS, namely A/Prof Carolyn Lam, A/Prof Ling Lieng His and Dr Mark Chan. They will be providing essential input into management of patients with heart failure and serious heart valve disease and coronary artery disease. Dr Roger Foo, who has over 15 years of experience in the UK and recently joined CVRI, will be sharing his special
knowledge in the epigenetics of human heart failure to potentially develop gene-targeted treatments.

TEAM’S PROFILE

Arthur Mark RICHARDS (LEAD PI)
Professor in Medicine, National University of Singapore (NUS)
Director, Cardiovascular Research Institute (CVRI)
National University Heart Centre, Singapore (NUHCS)
National University Health System (NUHS)

Prof Mark Richards graduated from the University of Otago, New Zealand, and was trained in cardiology in both New Zealand and the United Kingdom. He has directed NUHC’s CVRI since October 2009. He has held clinical responsibilities in Cardiology for over 25 years and for many years has also worked alongside basic scientists in researching new biochemical pathways in heart failure. He established the Christchurch Cardioendocrine Research Group (now Christchurch Heart Institute) which has conducted integrated research into the pathophysiology, diagnostics and therapeutics of cardiovascular disease in the four disciplines of clinical observational and therapeutic trials, molecular biology, pre-clinical physiology (models of heart failure) and biomarker discovery and immunoassay.

His group contributed original work on the role and application of circulating vasoactive peptides and in particular was the world’s foremost pioneering group in elucidating the bioactivity of the cardiac natriuretic peptides and applying measurement of plasma cardiac peptide levels as diagnostic and prognostic tests in heart failure. The improved understanding of heart failure from Prof Richards and his team has led to the establishment of new blood tests for diagnosing and monitoring heart failure which have improved care and survival in this condition. Prof Richards will work alongside eminent researchers with expertise in the genetic and epigenetic aspects of cardiovascular disease.

LIU Jianjun
Deputy Director
Senior Group Leader, Human Genetics
Genome Institute of Singapore (GIS)

Dr Liu Jianjun obtained a PhD in Quantitative Genetics from Duke University in the US, and has held scientific appointments in New York and subsequently in Singapore, with positions held in NUS, NTU and GIS over the last 10 years. He has carried out a series of genome-wide association study (GWAS) studies in Chinese populations and identified susceptibility
loci for a range of infectious and autoimmune diseases. There is value in the GWAS data collected from an Asian population in helping to understand the genetic heterogeneity of disease susceptibility between Asian and European populations. In addition, he has a powerful track record in cancer genetics, e.g. nasopharyngeal carcinoma and non-Hodgkin lymphoma, and in particular breast cancer.

As a member of the Breast Cancer Association Consortium (BCAC), his group worked on the first GWAS study on breast cancer, which identified five common susceptibility loci for breast cancer. Other areas of research include neurological and neuropsychiatric disorders such as stroke, Parkinson's Disease (PD), Schizophrenia and related psychoses. His team discovered that genetic variation of the LRRK2 gene influences the risk for PD in Asian populations but the mutation spectrum of LRRK2 is different between Asian and European patients. G2385R was identified as a common risk mutation in Asian populations, but absent in European population.

Dr Liu and his team will now direct their expertise at genetic variation influencing onset and evolution of heart failure.

Kandiah JEYASEELAN

Professor in Biochemistry and Molecular Biology
Department of Biochemistry, Yong Loo Lin School of Medicine, National University of Singapore

Genetic engineering, especially gene cloning and expression has been the passionate area of research for Prof Kandiah Jeyaseelan. Prof Jeyaseelan obtained his PhD and DSc in Molecular Biology from the University of Sheffield, England. He is also a Chartered Biologist and a Fellow of the Society of Biology (FSB), London. As a pioneer molecular biologist in Singapore since 1984, he has published many international research articles and conducted workshops and scientific meetings on molecular biology and biochemistry. In the early 90's his laboratory at NUS was the first to clone a cardiotoxin gene. His ability to keep abreast with the advancement in molecular genetics has enabled him to carve a niche area of research; RNomics in Translational Medicine.

As a recent landmark discovery, his laboratory has shown that microRNAs originating from injured brain can be detected in the peripheral blood samples and hence can be used as diagnostic and prognostic biomarkers in stroke patients. Subsequently, he has demonstrated that circulating blood microRNAs form ideal biomarkers in other related
diseases such as diabetes, hypertension and hyperlipidaemia. Thus far, Prof Jeyaseelan has supervised 38 PhD graduates and has held several research, academic and administrative positions in various universities including the University of Melbourne. At present he also holds an Adjunct Professorship at the Monash University, Australia. Since 2011, his laboratory has been working closely with Prof Richards on microRNAs in heart diseases. Under this TCR flagship program that is funded by NMRC, in collaboration with several eminent clinical colleagues at NUHS and scientists in A*Star institutions, Prof Jeyaseelan will be developing microRNAs as novel biomarkers for early diagnosis and possibly as new therapeutic agents for cardiovascular diseases.

Colin Lawson Stewart  
*Senior Principle Investigator and Assistant Director*  
*Institute of Medical Biology (IMB)*

Prof Stewart graduated with a D Phil from the University of Oxford, UK, and has held scientific posts in prestigious institutions in Germany and the US. He has pioneered many techniques and made pivotal discoveries in stem cell and gene science. He developed the technique of aggregating EC/ES cells with embryos to make chimeras and discovered that EC/early embryos have a powerful de novo DNA methylation activity. He was instrumental in discovering the role of the cytokine LIF in maintaining mouse embryonic stem (ES) cells. Subsequently he demonstrated that, paradoxically, LIF was not essential for embryonic development but was essential at regulating embryo implantation.

His long-standing interests include epigenetic regulation of gene expression, particularly genomic imprinting. He developed the first androgenetic and parthenogenetic ES lines and used these to identify novel imprinted genes and elucidate the role of imprinting in regulating cell proliferation. He also determined the functions of three imprinted genes in the Prader-Willi disease region. His current focus is the functional architecture of the cell’s nucleus in stem cells, regeneration, aging and disease, particularly with regard to how the nuclear functions integrate with cytoskeletal dynamics in development and disease.

Prof Stewart is a long-standing leader in the field of the laminopathies which underlie a significant proportion of inherited heart disease.
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<th><strong>Title of Programme</strong></th>
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<td>Non-Small Cell Lung Cancer: Targeting Cancer Stem Cell and Drug Resistance</td>
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<th><strong>Lead PI</strong></th>
<th>A/Prof TAN Eng Huat</th>
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<th><strong>Theme PIs</strong></th>
<th>A/Prof LIM Bing, Dr Axel HILLMER</th>
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<th><strong>Amount Awarded</strong></th>
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**Objective of the Study**

The study is targeted primarily at never-smokers with lung cancer. The objectives are four-fold:

1) To conduct a comprehensive analysis of the cancer genome of never-smokers with lung cancer in order to have a complete or near-complete view of the genomic mutations.

2) To look for novel genomic mutations other than those already known (refer above) that can potentially be treated by new targeted agents. These new targeted agents can be used in combination with standard treatment in order to enhance the efficacy of standard therapies thereby prolonging quality survival.

3) To determine the spectrum of acquired genomic alterations that can contribute to the onset of resistance to targeted agents and to design rational clinical studies combining newer targeted agents with standard therapies to address these mechanisms of resistance in patients.

4) To understand more deeply the behaviour of cancer stem cells that are believed to be the source of cancer cell proliferations and to develop strategies to target this subset of cancer cells that may lead to more durable remission of lung cancer and therefore improve survival outcome.

To achieve these objectives, close collaboration amongst the researchers and with the patients will be crucial. This is because patients need to understand the importance of undergoing repeat biopsies, which can be invasive, in order to carry out the analysis of the cancer genomes to aid the team in designing the clinical studies in a more rational manner. Close collaboration has also been established with major pharmaceutical companies that have a rich pipeline of new targeted compounds undergoing early phase clinical trials. As a result, the team has put in place several clinical trials that may potentially benefit patients in terms of tumour control.
Details of the Study

Lung cancer is a highly fatal disease and accounts for the highest cancer-related mortality in Singapore and other developed nations. However, lung cancer is peculiar in Singapore and other East Asian countries in that never-smokers comprise about a third of all lung cancer diagnosed each year. The cause of lung cancer in never-smokers is still unknown. Most of these patients are females and tend to be about a decade younger than the smokers. Unfortunately, like smokers, less than 15% are diagnosed at an early stage. Therefore, the majority of these patients would have an incurable disease when first diagnosed and the treatment intent is palliative in nature.

Over the past decade, technological advances in analysing the genetic makeup of cancer cells (or cancer genome) have led to the uncovering of alterations in genome that are largely confined to never-smokers. These alterations have been shown to drive the growth of the cancer cells. More importantly, we have drugs that target these alterations and block their functions, thereby causing some of the cancer cells to die or stop growing temporarily. These so-called targeted drugs are taken orally and tend to be associated with lower side-effects than standard chemotherapy. Studies have also shown that these targeted agents are more effective than chemotherapy in slowing down the growth pace of lung cancers that showed the relevant genomic alterations.

However, physicians and patients continue to face significant challenges when confronting the disease. Firstly, these targeted drugs are limited in efficacy. Not all patients with the relevant genomic alterations respond equally well to these drugs. A minority do not respond to these drugs at all. Moreover, the duration of the responses also varied greatly amongst the responders with resistance setting in within one year of starting treatment for the majority of responders resulting in regrowth of the cancer. Over the past five years, there has been increasing understanding of the mechanisms of the acquired resistance to these targeted agents. However, the understanding is still far from complete. More intensive research is needed to address the shortcomings of the currently available therapies for lung cancer.

Another challenge is the lack of effective therapies for a significant proportion of never-smokers who do not have the known cancer genomic alterations that can be treated with targeted drugs. It is likely that these patients carry unknown genomic mutations in their cancer cells that are yet to be discovered. Therefore detailed genomic studies of this group of patients have to be urgently conducted in order to expand the treatment options for them.
There are currently two cancer genomic alterations found mainly in never-smokers with lung cancer that can be treated with oral targeted drugs. The most common type is called the epidermal growth factor receptor (EGFR) mutations which can be effectively treated by targeted drugs known broadly as EGFR tyrosine kinase inhibitors or EGFR TKI for short. Examples of EGFR TKI include gefitinib (Iressa™), and erlotinib (Tarceva™).

The second type, which is found in about 5% of lung cancer in never smokers, is called anaplastic lymphoma kinase (ALK) translocation, which predicts for good responses to a targeted drug broadly known as ALK inhibitors. There is currently only one ALK inhibitor approved for clinical use, which is crizotinib. These targeted agents have been shown to be superior to standard chemotherapy in terms of proportion of good responders and duration of responses. However as stated above, the majority of these patients will eventually develop resistance to these agents within one year of treatment. Under such circumstances, chemotherapy will be recommended as a second-line treatment option.

For patients that lacked EGFR mutations or the ALK translocations in their cancer genomes, standard chemotherapy is generally recommended as the first-line therapy.

The key to understanding the behavior of cancer cells and the ways to counter them is through a deeper understanding of the cancer genome. The next step would involve relating the cancer genome information to the outcome of the therapies applied to the patients. By doing so for a sufficient number of patients, we could derive information that can help to predict which patients would respond to the particular treatment or not. These are deemed the best steps to take, to make cancer treatment more personalised and optimised for response and outcome.

To carry out this strategy, collaboration between scientists and clinicians is needed. More importantly, the degree of collaboration between these researchers and patients is extremely crucial to the success of this strategy. The patients need to be willing to contribute tumour specimens and participate in clinical trials involving the newer targeted agents. The former usually requires an invasive procedure to obtain fresh tumour specimens prior to commencing on the new therapies. At times, a repeat biopsy may be needed to determine changes in the cancer genome as a result of the therapies in order to better understand the mechanisms of the drug action on the cancer cells.
Overall, this study brings together experienced scientists and clinicians who are experienced researchers in lung cancer to look deeper into the above challenges facing never-smokers with lung cancer.

TEAM’S PROFILE

**TAN Eng Huat (LEAD PI)**

*Associate Professor Tan Eng Huat, Senior Consultant, Department of Medical Oncology, and Head, Division of Clinical Trials and Epidemiological Sciences, National Cancer Centre Singapore*

A/Prof Tan Eng Huat has been practicing medical oncology in Singapore since 1992 and has been actively involved in lung cancer clinical trials since 1994. He has led several international phase 2 and 3 clinical trials in lung cancer and is currently the head of the Division of Clinical Trials and Epidemiological Sciences at the National Cancer Centre, Singapore.

He is also one of the directors of a regional oncology research cooperative group called the Cancer Therapeutics Research Group that comprises centres in Singapore, Hong Kong, Taiwan, South Korea, and Australia. Dr Tan is also the principal investigator of Theme 3 of this study, which is the conduct of translational clinical studies.

**LIM Bing**

*Senior Group Leader, Stem Cell and Developmental Biology, Genome Institute of Singapore (GIS)*

Dr Lim Bing is Senior Group Leader for Stem Cell and Developmental Biology group at GIS. Dr Lim’s research interest has centred around the biology of Stem Cells, beginning at the University of Toronto studying blood stem cells followed by post doctoral work on gene transfer into stem cells at Harvard Medical School where he is currently also Associate Professor of Medicine. He took on a joint appointment at GIS in 2003 to develop a stem cell program. Using a genomic approach in studying mouse and human embryonic stem cells, he has sought to identify genetic factor controlling growth and transformation of stem cell. More recently, significant parallel efforts have been made to study stem cells in diseases such as cancer. As Director of Cancer Stem Cell Biology at GIS, and working with doctors across Singapore, he seeks to accelerate the application of basic research discoveries in clinical practices.
Dr Lim sits on several research, educational and ethics committee responsible for charting research focus and efforts in Singapore. He also sits on review committees for research grants in major international institutions and is on the editorial board of several research journals.

Axel HILLMER  
*Senior Research Scientist, Genome Institute of Singapore (GIS)*

Dr Axel Hillmer is a biologist with a human genetics background. He obtained his PhD at the University of Bonn, Germany, in 2006 when he worked on the genetic causes of hair loss disorders. Dr Hillmer joined GIS in 2008 and got a faculty position in 2011. His research interest is in the genetic basis of cancer. His group uses modern next generation massive parallel sequencing approaches to analyse patient tumor samples. He explores which genes or chromosomal regions show mutations which in turn cause the disease and which might be useful as drug targets. The identification of new drug targets is crucial for the development of new therapeutic approaches against cancer. Dr Hillmer’s studies provide insight into the processes which are involved the development of cancer.

Other participating clinicians and researchers

**A/Prof GOH Boon Cher**  
*Head, Dept. of Haematology- Oncology*  
*National University Health System (NUHS)*

A/Prof Goh has vast experience in early phase clinical trials and holds several research grants including the coveted Clinician Scientist Award.

**Dr Ross SOO & Dr CHIN Tan Min**  
*Senior Medical Oncologists, Dept. of Haematology- Oncology*  
*National University Health System (NUHS)*

Dr Soo and Dr Chin have long established records in running clinical trials in lung cancer, having published widely on this topic in top-tier international journals.

**A/Prof Darren LIM & Dr Daniel TAN**  
*Senior Staff Members, Dept. Medical Oncology*  
*National Cancer Centre (NCC)*

A/Prof Lim and Dr Tan are key clinician-researchers in upper aerodigestive tract cancers including lung cancer. Both are experienced translational and clinical trial investigators holding Individual Research Grant (IRG) grants in important translational research lung cancer.
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<td>Dr Agasthian, A/Prof Koong Heng Nung, and Dr Su Jang Weng</td>
<td>Thoracic Surgeons at National University Heart Centre, Singapore (NUHCS), National Cancer Centre (NCC) and National Heart Centre (NHC) respectively</td>
<td>They are crucial co-investigators for this study which is multidisciplinary in nature.</td>
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<tr>
<td>Dr Angela Takano</td>
<td>Senior Consultant Thoracic Pathologist, Department of Pathology</td>
<td>Singapore General Hospital</td>
<td>She will be handling the pathological aspect of this study and will work closely with the scientists in optimising the tissues for sequencing and analysis.</td>
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