# neus-link

Centre for the Brain, Spine, Nerve and Muscle

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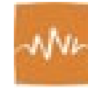

National Neuroscience Institute

SingHealth

# *Spotlight On*

## Neurogenetics Laboratory

Among medical disorders which are inherited or genetic, the greatest numbers are neurological diseases. In October 2005, the NNI added yet another specialised service for the care of patients with neurological diseases when its Neurogenetics Laboratory began offering gene tests for eight genetic neurological diseases, with more anticipated.

Increasingly, the value of molecular gene testing for genetic diseases is being recognised in clinical medicine. Molecular gene testing can identify the specific genetic disease when several genetic diseases share a common clinical presentation, eg. among the hereditary motor and sensory neuropathies (or Charcot Marie Tooth diseases) or the limb girdle muscular dystrophies. It can also help the physician confirm the diagnosis of a specific genetic disease when that disease shows variant or atypical clinical features, a not uncommon problem. When disease features are very mild, diagnosis may remain uncertain without confirmation by molecular gene testing. In managing patients with genetic diseases and their families, molecular gene testing is usually necessary for genetic counselling and always necessary for pre-natal diagnosis. As science advances and management options increase, and as society requires that patients be better informed, we can expect a rising need for molecular gene testing.

*>> HIGHLIGHTS*


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*"When disease features are very mild, diagnosis may remain uncertain without confirmation by molecular gene testing."*

Currently, the genetic diseases for which the Neurogenetics Laboratory offers molecular gene testing include:

| DISEASE | GENE |
|---|---|
| 1. Charcot Marie Tooth disease type IA | PMP22 |
| 2. Hereditary Neuropathy with Liability to Pressure Palsies | PMP22 |
| 3. Charcot Marie Tooth disease type IB | P0 |
| 4. X-linked Charcot Marie Tooth disease | GJB1 |
| 5. Transthyretin related Familial Amyloid Neuropathy | TTR |
| 6. Familial Amyotrophic Lateral Sclerosis | SOD1 |
| 7. Hereditary Torsion Dystonia | DYT1 |
| 8. Dystrophia Myotonica (Myotonic Dystrophy) type I | DMPK |

Since the Laboratory first offered these tests, we have added another gene test:

| DISEASE | GENE |
|---|---|
| 9. Kennedy's disease (X-linked spinal bulbar muscular atrophy) | AR |

The following tests will be offered in the coming months:

| DISEASE | GENE |
|---|---|
| 10. Hypokalemic periodic paralysis | CACNL1A3, SCN4A, KCNE3 |
| 11. Hyperkalemic periodic paralysis | SCN4A |
| 12. Hereditary Spastic Paraplegia 4 (SPG4) | SPAST |
| 13. Limb Girdle Muscular Dystrophy type IIB | DYSF |
| 14. Hereditary inclusion Body Myopathy/Distal Myopathy with rimmed vacuoles | GNE |

Because of the broad and sensitive implications of genetic testing, and with guidelines recently issued by the Bioethics Advisory Committee of Singapore, advice to patients and doctors is appropriate. Physicians intending to refer patients for molecular gene tests should be prepared to counsel the patient on the purpose and issues involved in testing when obtaining informed consent required for the test. They should be prepared to counsel the patient on the test results. Hence, these tests are best applied by specialists in the field or doctors familiar with the disease and its genetic issues. The Laboratory will ensure full confidentiality and careful quality control in the testing and reporting process. Test results will be forwarded solely to the referring doctor.

**Dr Yee Woon Chee**
Deputy Director (Research)
*NNI Research Faculty*

**USEFUL INFORMATION**

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Sat, Sun and Public Holidays: Closed

*"...a team of 4 neurologists to compete, in a quiz-format contest that tests neurological knowledge from the straightforward to the downright esoteric."*

# The Tournament of the Minds

**Dr Nigel Tan**
Consultant
*Neurology*

From left to right: Dr Nigel Tan, Dr Nagaendran Kandiah, Dr Kevin Tan & Dr N.V Ramani.

The World Congress of Neurology is held every 4 years, and this year, it took place in Sydney. The Tournament of the Minds is a competition held during the Congress. Each country sends a team of 4 neurologists to compete, in a quiz-format contest that tests neurological knowledge from the straightforward to the downright esoteric. Previous questions from the 2001 Tournament had included obscure neurological diagnoses, mysterious eponymous neurological signs and neurological diseases in polar bears!

This year's contest was no different. Hosted by previous champions Australia (who were exempt from this year's contest as they were the organisers), the questions were an interesting mix of the obscure, the common and the eccentric. This was Singapore's first time in the contest. Being a somewhat slack team captain, I entered our nation into the contest 3 months before the Congress, but only formed the team 30 minutes before the competition began!

Given the quiz format, we opted to go with a mix of youth and experience. The team thus consisted of Dr NV Ramani, Dr Kevin Tan, Dr Nagaendran and myself. Going into the contest hall for the contest heats, we found ourselves surrounded by many senior luminaries in the field of neurology, men and women who had published in august journals like the New England Journal of Medicine when I was a teenager!

We refused to be intimidated and were pleasantly surprised when we found ourselves overall 3rd at the end of the heats, behind New Zealand and Canada, and just ahead of the UK. The top 4 teams advanced to the semi-finals the next day.

During a closely-fought semi-final with Canada, we were neck-to-neck the Canadians for most of the contest. At the end of the contest, we were tied. It came down to the wire with a winner-takes-all sudden death question. Unfortunately, the Canadians came to the diagnosis a few seconds ahead of us, and thus advanced to the finals. The UK team eventually beat the Canadians to take the trophy.

Overall, it was terrific fun to have made it to the final 4 of the competition, and we made many new friends during the contest. I think we surprised many for being the only Asian country to make it into the final 4. For a first time attempt, I felt we acquitted ourselves very well. We'll definitely be back for the 2009 Tournament in Thailand!

# The Right Stuff:
# A Clinician-Scientist's Journey

**Dr Lim Li Ling**
Consultant
*Neurology*

In this issue, we feature an interview with Dr Tan Eng King, Senior Consultant Neurologist and a pioneering SingHealth Clinician Scientist. He is the recipient of numerous research awards, most recently this year, the prestigious BMRC-NMRC Clinician Scientist Investigator Award and the SingHealth Excellent Researcher Award.

He shares with us the story of his trailblazing journey in an unconventional career path, his unique insights and some advice for budding young clinician scientists.

***Q. You were one of only 4 physicians selected when the SingHealth Clinician Scientist scheme was started in 2002 to promote a research culture in hospitals. What made you decide to pursue this career track?***

I came away with my clinical and research fellowships in the States hugely inspired by the drive, motivation and diligence of my mentors Prof Jankovic and Prof Ashizawa. I returned to SGH in 2000 and started the Movement Disorders programme. At the time I was mostly focused on my clinical work, and regarded my laboratory experience as an interesting exposure. The Clinician Scientist scheme provided me with an opportunity to take on a different challenge.

Dr Tan Eng King, seated 2nd from right, with his PD multi-disciplinary team at SGH campus.

***Q. It sounds like your priority after returning to Singapore after your fellowship at Baylor was setting up a clinical service. What obstacles did you encounter along the way and how did you finally end up a clinician scientist?***

Providing a value-added service in the subspeciality was and still is my top priority. Fortunately there was generous support from the head of department and our colleagues, and our service was started in 2000. We were up and running within a year of starting out. With a thriving clinic which now sees about 1,000 patients on regular follow-up, we now had a large potential study population. The next step was to implement our research ideas, which was tough initially as we had no funding or laboratory space. Again, we were supported by the generosity of colleagues who loaned us research space in their own laboratories. Finally in 2001, I received my first research grant of $90,000 from NMRC and set up a Neurogenetics Laboratory. We set up a gene bank, studying the genetics of Parkinson's Disease, screening for genetic mutations and polymorphisms.

***Q. You have clearly made significant strides in your relatively short career so far as a clinician scientist, achieving international recognition, publishing prolifically and winning numerous awards in the 3 years since you were appointed in the pioneering clinician scientist scheme. What drives you and keeps you motivated?***

Our Movement Disorders Programme is now about 5 years old. Being able to surmount all the initial problems and provide a comprehensive and valuable service has given me renewed inspiration to continue in our efforts. My priority remains with our patients and the quality service we provide. I see myself as a clinician foremost, and also enjoy my work as a clinician scientist, which is why I persevere in spite of the sometimes long hours and numerous challenges.

My exposure to great mentors in the United States, who were very hardworking, showed me that we could achieve similar great things in research given the right environment, opportunities and the capacity to work hard.

***Q. What are some of the downsides to life as a clinician scientist and how have you overcome these challenges yourself?***

In the budding stage, there will be financial issues as research cannot be sustained without funding. Money will continue to be important to continue one's research and there will be regular pressure to secure grants for ongoing research or new projects.

Even when grant funding is secure, there is also the potential stress of "failing the grant", as in not meeting the research project objectives for whatever reasons. There will inevitably be the pressure of meeting deadlines and timelines for the completion of the project.

*"Dr Tan is an internationally recognised expert in his field of molecular genetics in Parkinson's Disease. He trained with Dr Joseph Jankovic at the Parkinson's Disease Center and Movement Disorders Clinic at Baylor College of Medicine in Houston, one of the world's leading clinical and research institutions focusing on Parkinson's disease and related movement disorders."*

Financially, one must be prepared to make sacrifices as a clinician scientist, rather than a clinician providing hospital patient care services. For example, my pay did remain stagnant when I became a clinician scientist. Depending on the amount of time spent in and type (laboratory or clinical) of research, there is the risk of losing touch with one's general clinical skills if one becomes too subspecialised or spends time predominantly as a bench scientist. This may be a problem should one eventually choose to return to clinical practice.

On the other hand, if one chooses to maintain a clinical practice, one may at times be overwhelmed by having too many patients, and running laboratory experiments concurrently. With clinical practice there will be the inevitable demands of patient care, whether it be patients calling or referrals from other physicians and dealing with clinical management issues.

Another downside is that research experiments may not turn out as you expected and papers may be rejected, which can be very discouraging. And finally, since clinician scientists are a new breed of physicians, there are no clearly set out precedents for those who may choose in the future to return to a clinical path. So there is uncertainty not just in terms of whether continued funding is feasible, but also what options are available should one decide to return to being a full-time clinician.

***Q. What do you think are some of the problems facing budding clinician scientists and how do you think the scheme can be improved in the future?***

One of the limitations is the lack of mentoring opportunities available to aspiring clinician scientists. This problem will take time to resolve as our pool of clinician scientists grows in the years to come. For now, junior scientists could look to senior physicians within their departments for guidance as a start, until more formal mentor-mentee schemes become available.

I also feel that due to funding limitations, many worthy clinician scientists are being turned away. Hopefully this will improve so that more deserving candidates are given the opportunity to carry out their research ideas and contribute to the progress in medical science locally.

There also seems to be a discrepancy in the amount of funding available for clinical research as compared to basic science research, which should be addressed. This may be related to the impact factor, which is highly regarded by funding committees, and tends to be higher in basic science journals compared to clinical ones. Clinical researchers are therefore disadvantaged.

More dialogue between policy makers and clinician scientists who experience the teething problems first-hand could help address some of these issues.

***Q. What advice do you have for younger colleagues interested in exploring the career path of a clinician scientist?***

Although being a clinician scientist seems to be the "in-thing" these days, I would strongly advise younger physicians to pursue a research track only if you have a genuine interest and burning desire to perform research in a particular field, rather than for other reasons such promotions, bonuses and recognition. Life as a clinician scientist is tough, and is not sustainable without a passion for research.

While I do suggest that you find a niche for yourself in the area you are interested in, I have myself been told that I have too wide a range of interests, encompassing clinical practice with a heavy patient load, clinical studies and laboratory research. This could potentially prevent the single-minded focus that some believe to be essential to research excellence. However I find that as long as I enjoy what I am doing, I can manage my clinical and laboratory responsibilities and achieve my goals. This also allows me to stay in touch with my clinical skills while performing useful research at the same time.

Besides doing what you like, you also need to be smart in deciding what research to do in terms of feasibility and availability of resources. There will be many obstacles and you have to be patient. Although some luck is involved, I believe good luck is created by those who work hard and are prepared to seize opportunities when they come your way.

In the end, success means different things to different people, whether it be international recognition, financial rewards or something else. To me, life is a marathon and winning is to achieve happiness in what you do. So please choose to do what you truly enjoy.

***Q. What are your future plans?***

I am taking things 1 step at a time. For now I am busy with my clinics, clinical and laboratory research, teaching and mentoring junior scientists. It gives me pride to be a part of the medical excellence Singapore has achieved.

*"We are currently investigating the mechanisms of cellular response to chemotherapeutic drugs of choice in clinic. Our team has succeeded in isolating these putative cancer stem cells which we demonstrate to be resistant to temozolomide, and increase in cell numbers upon drug treatment."*

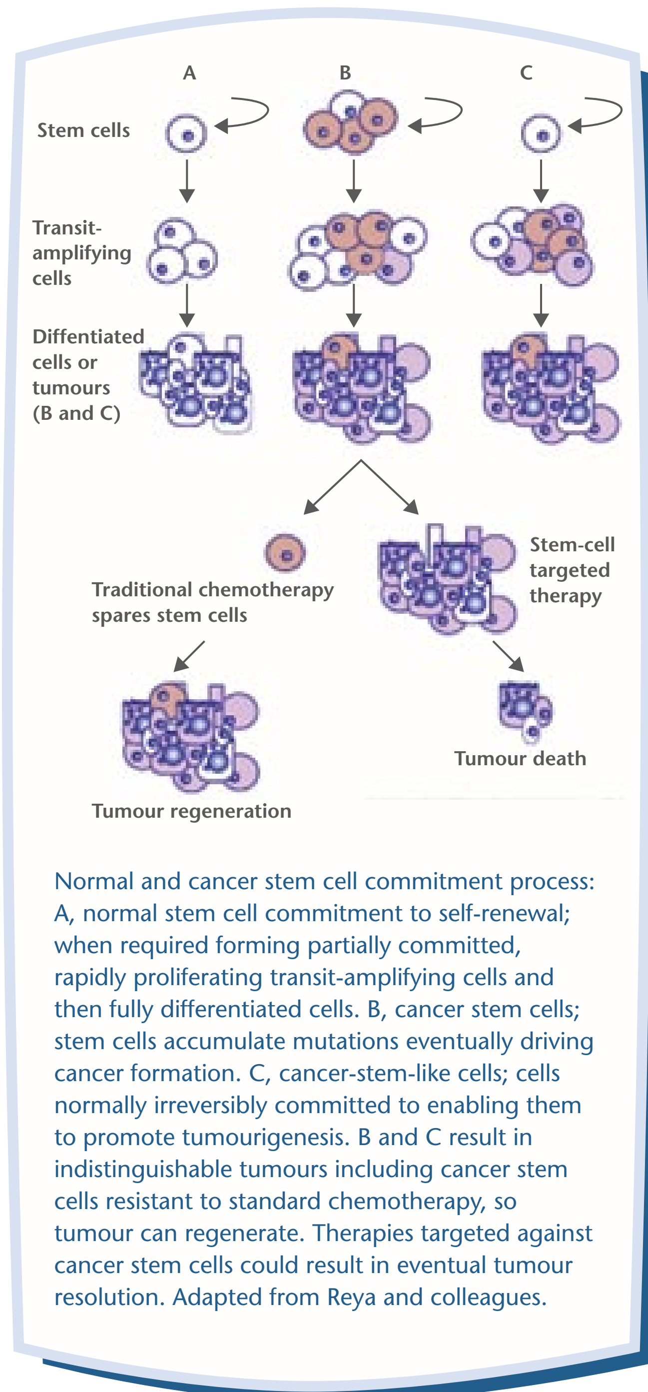
# Neuro-Oncology: Cancer as a Disease of Stem Cells

**Dr Carol Tang**
Principal Investigate/Head
Neuro-Oncology Research Lab
*NNI Research Faculty*

July 2005 marks the beginning of the Neuro-Oncology Research Lab at the National Neuroscience Institute. Our team comprises a NMRC Medical Scientist awardee-PhD student, Research Officer, and a clinical team of neurosurgeons, a neuro-pathologist based in Canada, and a neurologist. Our team's initial focus deals with the study of chemoresistant brain tumour stem cells from primary malignant brain tumours.

Stem cells have acquired a golden glow in the past few years as a possible tool for reversing tissue degeneration. Many researchers predict that stem cell transplants will one day heal the damaged heart, or brains under attack by Alzheimer's or Parkinson's disease. But the very qualities that make these cells so attractive for therapy, especially the ability to replicate ad infinitum, also hint at a dark side. Recent evidence in leukemia, breast and brain tumours indicate that stem cells may be the source of mutant cells that give rise to cancerous tumours and maintain their growth. As these cancer stem cells with distinct properties form the minority population of the heterogeneous tumour mass, they escape the cytotoxic effects of drug treatments, thus the disease-causing cancer stem cell population is left behind, which subsequently leads to tumour recurrence.

Our team's initial focus is the isolation and characterisation of putative brain tumour stem cell sub-populations from astrocytic tumours, notoriously known for their chemoresistance. We are currently investigating the mechanisms of cellular response to chemotherapeutic drugs of choice in clinic. Our team has succeeded in isolating these putative cancer stem cells which we demonstrate to be resistant to temozolomide, and increase in cell numbers upon drug treatment. We have also shown the multidrug resistance transporter ABCG2, present on brain tumour stem cells, to be the molecular determinant for temozolomide cellular efflux. Establishing homogeneous cell lines from these cancer stem cell sub-populations remain our priority in enabling further studies on cancer etiology and mechanisms. Such well-characterised brain tumour stem cell lines would also find great importance in the screening for novel drug




Normal and cancer stem cell commitment process: A, normal stem cell commitment to self-renewal; when required forming partially committed, rapidly proliferating transit-amplifying cells and then fully differentiated cells. B, cancer stem cells; stem cells accumulate mutations eventually driving cancer formation. C, cancer-stem-like cells; cells normally irreversibly committed to enabling them to promote tumourigenesis. B and C result in indistinguishable tumours including cancer stem cells resistant to standard chemotherapy, so tumour can regenerate. Therapies targeted against cancer stem cells could result in eventual tumour resolution. Adapted from Reya and colleagues.

*Non-pharmacological, physical therapy as well as psychological and social support continue to have an important complementary roles in the optimal management of patients with PD.*

# Parkinson's Disease:
# Nursing Management and Treatment Strategy

**Jennie Lee**
Nurse Clinician (Parkinson's Disease)
*Nursing*

A nursing workshop "Caring for the Parkinson's Disease Patient- A Nursing Perspective" was conducted by our very own Parkinson's Disease & Movement Disorders Nurse Clinicians, Jennie Lee (NNI@SGH) & Lau Puay Ngoh (NNI@TTSH) on the second day of the 3rd Singapore International Parkinson's Disease & Movement Disorders Symposium held from 9-10 September.

When a patient is being diagnosed with Parkinson's Disease (PD), the neurologist will offer some explanation of the illness. Some of the common terms patients and health care workers will always hear are chronic, progressive, dopamine and deep brain stimulation.

In simple term, Parkinson's Disease (PD) is a chronic, slowly progressive disease of the nerve cells (neurons) in the part of the brain (substantia nigra) that control muscle movement. Normally, these nerves cells produce a substance called dopamine, a chemical messenger that is responsible for transmitting signal from one group of cells to another, allowing co-ordinated functions of the body's muscles and facilitating smooth muscle movement. When the cells die and dopamine production is correspondingly reduced, patients may experience tremors and movement problems such as bradykinesia (slowness), rigidity and impaired balance. Problems with thinking and behavior may also occur.

Pharmacological and surgical advances have resulted in increasingly symptom relief for persons with PD. Non-pharmacological, physical therapy as well as psychological and social support continue to have an important complementary roles in the optimal management of patients with PD. Those patients with advanced PD can opt for an alternative therapy- Deep Brain Stimulation (DBS) to control the symptoms.

At this workshop, topics discussed included Non-pharmacological treatment for PD, Surgical Treatment in PD ( DBS Surgery), Neuropsychiatry of PD and Exercises PD patients.

Participants from various local and overseas institutions, including overseas doctors were present at this workshop. The workshop offered an interesting overview from the nursing perspective on the treatment options given to PD patients. There were interesting video clips for the viewers and interactive discussions between the speakers and the participants. Feedback given was overwhelming, with many commenting that they had enjoyed the session.

therapeutics aimed at complete eradication of tumour chemoresistance and recurrence.

The new year brings many aspirations to our team and we remain focused in our aim to develop this science in light of medical advancement. Our message for the coming year? The human spirit and the process of scientific endeavor are as important as the actual discovery!

Clinical team includes:
Ang Beng Ti, Neurosurgery
Ng Wai Hoe, Neurosurgery
Yeo Tseng Tsai, Neurosurgery
Seow Wan Tew, Neurosurgery
Ivan Ng, Neurosurgery
See Siew Ju, Neurology
Ang Lee Cyn, Pathology, Canada

Research team from left to right:
Constance Chua (PhD student), Norazean Zaiden (Research Officer), Carol Tang (Principal Investigator/Head, Neuro-Oncology Research Lab).

# 1st Neurosurgical Instructional Course *featuring* Virtual Reality

## 2-5 May 2006
## National Neuroscience Institute

The Department of Neurosurgery has been involved in the development and usage of virtual reality technology with our academic and commercial partners for almost a decade and the system has been a permanent feature in our department teaching and surgical planning. It is an extremely useful tool in helping our colleagues and residents in understanding the nuances of neurosurgery with regards to applied neurosurgical anatomy. This course is an extension of our commitment to share our experiences and insights in modern neurosurgery.

A stellar programme has been planned, which includes distinguished faculty in the likes of Professor Albert Rhoton and Dachling Pang, who will with our local faculty, will offer a programme which will detail specific relevant neurosurgical anatomy supplemented with virtual reality demonstrations and specific nuances of a particular approach. The topics covered are immense, ranging from skull base approaches to concepts of neurovascular surgery, spine surgery, functional and minimally invasive neurosurgery.

**For more information, contact the Course Secretariat at nni_secretariat@nni.com.sg or visit www.nni.com.sg for course details.**

# 3rd SINGAPORE INTERNATIONAL NEUROSCIENCE CONFERENCE

"From Brain Research to Brain Repair"

**23-24 May 2006**
**National Neuroscience Institute**
TTSH Theatrette & Conference Rooms

**Main Symposium**
* Epilepsy & Cognition
* Neurogenetics & Neurodegenerative Disorders
* Ion Channel & Receptor Function
* Developmental Neurobiology & Neural Stem Cell

SINC constitutes one of the most important neuroscience meetings held in Singapore and the South East Asia region. This year's theme "From Brain Research to Brain Repair" aims to stengthen the bonds between basic neuroscientists and clinicians, and narrow the gap between basic neuroscience research and clinical application. In the 2-day conference, internationally renowned neuroscientists and local experts will cover important current topics in Epilepsy and Cognition, Neurogenetics and Neurodegenerative Disorders, Ion Channel and Receptor Function, Developmental Neurobiology and Neural Stem Cell.

**For more information and registration, please call 6357 7163, email nni_secretariat@nni.com.sg, or visit www.sinc.com.sg**

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