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Centre for the Brain, Spine, Nerve and Muscle

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Spotlight On Brain Injury Research at NNI

Primary brain injury results in disruption of cellular function and structure leading to cell death. **Secondary brain injury** in the form of cerebral oedema and ischaemia further compounds the problem. Traumatic brain injury and stroke not only claim multiple lives each year but also leave a significant number of disabled survivors in the community.

At the **Acute Brain Injury Research Laboratory (ABIRL)** of the National Neuroscience Institute (at Tan Tock Seng Hospital), we strive towards a better understanding of cellular mechanisms underlying catastrophic brain injury in an effort to optimise patient management.

History of the ABIRL

The year 2000 saw Dr Ivan Ng returning from 2 years of neurosurgical training at Addenbrooke's Hospital in Cambridge, U.K. - a leading centre in head injury research. Inspired by his experience and previous work on apoptosis in traumatic brain injury, the ABIRL was conceived to carry out

further work in this field. He was joined by Dr Ng Puay Yong, a like-minded neurosurgeon who had then just completed a research fellowship at Yale in vascular neurosurgery.

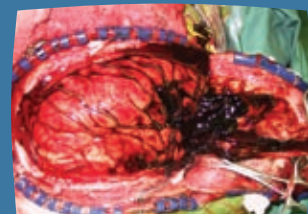
At present, the ABIRL is divided into a clinical/intensive care research arm, a translational research arm and a clinical trials research arm. These are co-ordinated by Dr Ang Beng Ti and Dr Ernest Wang with Dr Ivan Ng remaining overall principal investigator. Apart from the above, we have a vital support crew with Ms Lee Kah Keow, Neurotrauma Nurse Clinician, ABIRL Research Assistants (Ms Jill Wong, Ms Jasmine Lee, Mr Timothy Tan, Ms Tan Wan Loo), and Neurotrauma Clinical Fellows and Department Registrars.

ABIRL Activities

To date, we have been fortunate to secure up to S\$2 million in grant funding (*Table 1*) and have produced 15 publications in both local and international peer-reviewed journals. We are also involved in a number of clinical trials (*Table 2*).

Clinical/Intensive Care Research

The time-honoured approach of step-wise incremental interventions for raised intracranial pressures in the head-injured individual is undergoing more detailed scrutiny. With the ability to continuously monitor physiologic variables at the bedside, an individually tailored therapy may be more efficacious. As such, much of our work investigates the utility and relationship of multi-modality monitoring to patient outcome in conditions such as neurotrauma, spontaneous intracerebral haemorrhage and aneurysmal subarachnoid haemorrhage (SAH).



Acute Subdural Haematoma

>> HIGHLIGHTS

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Dr Ang Beng Ti
Clinician - Scientist
Neurosurgery

In concert with the vast amounts of data collected, IT methods to facilitate collation and analysis are also being devised. A sizeable patient database exists which allows for epidemiological analysis as well. Microdialysis to analyse the extracellular composition of metabolites to better appreciate secondary brain injury pathophysiology is an upcoming facet of our research.

Translational Research

Biomarkers reflecting severity of brain injury and the ability of these markers to predict patient outcome is another avenue of research. To this end, with ethics board approval, we have collated a library of peri-contusional tissue and post-SAH cerebrospinal fluid specimens. To foster recovery mechanisms following central nervous system injury, we have

investigated the use of DNA vaccination against neurite growth inhibitors in an animal model of ischaemic stroke.

Clinical Trials

Over the years, the Department of Neurosurgery at NNI (at TTSH) has had the opportunity to be a recruiting centre for a variety of clinical trials investigating the treatment of stroke and head injury (*Table 2*).

Current ABIRL members.

Seated L to R: Dr Ernest Wang, Dr Ng Wai Hoe, Dr Ivan Ng, Dr Ang Beng Ti, Dr Tran Minh Tri

Standing L to R: Mr Timothy Tan, Ms Lee Kah Keow, Ms Jasmine Lee, Dr Zhu Xing Bao, Ms Jill Wong

Absent: Dr Jayant Thorat, Ms Tan Wan Loo



• Determination of polyamines in cerebrospinal fluid of hemorrhagic stroke patients	NHG
• Influence of Head Posture in cerebral hemodynamics in acute brain injury	NMRC
• Poly (ADP-ribose) polymerase activation in Human Contusion Tissue and its relation with Outcome in Humans	NHG
• Vascular Endothelial Growth Factor and Receptor Expression in Cerebral Arteriovenous Malformations (AVM) of the brain	NMRC
• Brain tissue oxygenation in acute brain injury	NMRC
• Towards Evidence-Based, Cost-Effective Decision Making in Critical Care: Phase 1 - An Open Interface for Data Integration and Data Analysis in the Intensive Care Unit	TEC enterprising challenge award
• In-vivo microdialysis aid to defining and optimizing of cerebral perfusion pressure in head injury	NMRC
• Vascular endothelial growth factor and receptor expression in cerebral arteriovenous malformations (AVM) of the brain	NMRC
• Correlation between coma state and hypocretin levels in acute brain injury	SingHealth
• Poly (ADP-ribose) polymerase activation in human contusional tissue and its relation with outcome in humans	SingHealth

Table 1. ABIRL grant funding. (NHG: National Healthcare Group, NMRC: National Medical Research Council, TEC: The Enterprise Challenge)

“Our objective is to increase awareness of clinical neurophysiology, its relevance to clinical medicine and expanding role in neurology and neuroscience research.”

Dr Lo Yew Long
President, CNSS

F7ICH-1389 Randomised, Double-blind, Placebo-controlled, Multi-centre, Dose-escalating Study to Evaluate the Safety and Preliminary Efficacy of Activated Recombinant Factor VII (NovoSeven(r)) in Acute Intracerebral Haemorrhage	Novo Nordisk/ Quintiles East Asia Pte Ltd	Closed in 2002
F7ICH-1371 Randomised, Double-Blind, Placebo-Controlled, Multi-Centre, Parallel Groups, Study to Evaluate the Efficacy and Safety of Activated Recombinant Factor VII (NovoSeven(r)) in Acute Intracerebral Haemorrhage	Novo Nordisk/ Quintiles East Asia Pte Ltd	Closed in July 2004
SA-NXY-0006 SAINT-I (Stroke - Acute Ischemic - NXY Treatment) A Double Blind, Randomised, Placebo Controlled, Parallel Groups, Multicentre, Phase IIb/III Study to Assess the Efficacy and Safety of Intravenous NXY-059 in Acute Ischemic Stroke.	AstraZeneca	Closing
SA-NXY-0012 CHANT - A Double Blind, Randomized, Placebo Controlled, Parallel Groups, Multicentre, Phase IIb Study to Assess the Safety and Tolerability of 72 hour Intravenous Infusion of NXY-059 in Adult Patients with Acute Intracerebral Hemorrhage (ICH)	AstraZeneca	Ongoing
A1611005 A Double-Blind Placebo-Controlled, Multi-Centre Study to Evaluate the Efficacy and Safety of a 72-hour infusion of CP-101, 606 in Subjects with Acute Ischemic Stroke.	Pfizer	Closing
F7CBI-1600 A Randomised, Double-Blind, Placebo-Controlled, Multi-centre, Dose Escalation Study to Evaluate the Safety and Preliminary Efficacy of Recombinant Factor VIIa (NovoSeven(r)/Niastase(r)) in Subjects with Brain Contusions (Trial Phase II)	Novo Nordisk	Site Initiated; awaiting to CSA/FA to be signed

Table 2. ABIRL participation in clinical trials.

Formation of CNSS

Dr Lim Li Ling
Consultant
Neurology

The **Clinical Neurophysiology Society (Singapore) (CNSS)** announced its formation in January 2005 with the election of its first committee, comprising neurologists from the National Neuroscience Institute (NNI) and the National University Hospital (NUH). According to its founding president Dr Lo Yew Long, a senior consultant at the NNI and a prolific researcher in the field: “Our objective is to increase awareness of clinical neurophysiology, its relevance to clinical medicine and its expanding role in neurology and neuroscience research.”

The CNSS was welcomed as an affiliate to the International Federation of Clinical Neurophysiology (IFCN) at the IFCN-supported Asian and Oceanian Symposium on Clinical Neurophysiology (AOCNP) on 2-4 February 2005 in Chiang Mai, Thailand. The AOCNP was attended by members of the Executive Committee of the IFCN, including its Past President, Professor Marc Nuwer, and more than 300 international delegates. The scientific programme comprised lectures, workshops and Meet-The-Expert sessions. Among the international teaching faculty were several NNI staff, including Dr Umapathi Thirugnanam, Dr Yee Woon Chee, Dr Lim Shih Hui, Dr Lo Yew Long and Dr Lim Li Ling, who shared their experience in autonomic function studies, EMG, EEG and polysomnography.

As the Singapore Chapter of the IFCN, the CNSS hopes to be one of the future hosts of the AOCNP and aims to expand its membership. All who are interested in clinical neurophysiology, please call 6326-5003 for more information.



Dr Lo Yew Long, President, CNSS (2nd from L), with the Singapore contingent at the AOCNP Gala Dinner in Chiang Mai, northern Thailand.

Department Of Neurology (at SGH) Weekly Teaching Schedule

EVENT	DATE & TIME	VENUE	CONTACT PERSON	CONTACT NO.
* Neurology Grand Round	Monday 12:00pm - 1:00pm	SGH Ward 74 Meeting Room	Dr Puvan Ms Serene Lee	6326 5003
* Sleep Medicine Lectures	Monday 1:00pm - 2:00pm	SGH Ward 74 Meeting Room	Dr Lim Li Ling Ms Serene Lee	6326 5003
* Electrophysiology Round	Tuesday 12:15pm - 1:15pm	Neurodiagnostic Laboratory	Dr Andrew Pan Chua SK	6326 5003
* Dementia Round	Tuesday 1:00pm - 3:00pm	Brain Centre R2 Room	Dr Christopher Chen	6326 5003
Neuro-ophthalmology Teaching	1st Tuesday of the month 5:15pm - 6:15pm	SNEC Level 4	Dr Alvin Seah	6326 5003
* Neurology Mortality Round/Journal Club	Wednesday 12:00 - 1:00pm	SGH Ward 74 Meeting Room	Dr Pavanni	6326 5003
* Clinical Neurology Teaching	2nd & 4th Thursday of month 1:00pm - 2:00pm	SGH Ward 74 Meeting Room	Dr Lim Shih Hui	6326 5003
* Neurosonology Round	Thursday 1:00pm - 2:00pm	Neurovascular Lab	Dr Chang Hui Meng	6326 5003
Neuro-ophthalmology & Orbital Radiology Rounds	1st Friday of the month 7:30pm - 8:15pm	Radiology Department Level 1 Conference Room	Dr Alvin Seah	6326 5003
* Neuroradiology Round	Friday 8:15pm - 9:30pm	Radiology Department Level 1, Conference Room	Dr Winston Lim Dr Chan Ling Ling	6326 5003
Video/Movement Disorder Rounds	Last Friday of month 1:00pm - 2:00pm	SGH Ward 74 Meeting Room	Dr Tan Eng King	6326 5003
Neurology Foundation Course	Weekly	SGH Ward 74 Meeting Room	Dr Andrew Pan Ms Serene Lee	6326 5003

The Programme is open to all doctors.

* CME points awarded

NEW FACES

Drs Lim Li Ling, Lee Seng Swim, Shahul Hameed and Aris Catur Bintoro recently joined the clinical staff at NNI (at SGH).

Dr Lim joined the NNI in August 2004 after spending 6 years in the United States with the Cleveland Clinic Neurology Residency and Clinical Neurophysiology fellowship programmes, and an additional year on the staff of the Department of Neurology there. Her subspecialty interests are Sleep Medicine, Clinical Neurophysiology and Neuromuscular Disorders.

Dr Lee joined us as a registrar in November 2004 having trained initially at the University of Sydney. He worked at the Royal North Shore Hospital where his interest in the diagnostic approach to Neurology was sparked by an inspiring mentor. When he does find time in his hectic schedule, he enjoys reading comics and novels.

Dr Hameed went to medical school at the University of Madras and spent several years training in Sabah, eventually getting his MRCP there. He worked for a year in General Medicine at the Fremantle Hospital in Perth before joining us as registrar in January this year. He also enjoys reading and plays cricket and golf.

Dr Catur Bintoro comes from Semarang, Central Java in Indonesia, having trained at Diponegoro University there. He completed his diploma in Neurology in 2000 and plans to spend 6 months here gaining experience in Epilepsy and EEG, under the supervision of Dr Lim Shih Hui.

From Left to Right:
Dr Lee Seng Swim,
Dr Shahul Hameed,
Dr Lim Li Ling,
Dr Aris Catur Bintoro.



“SEF is a non-profit organisation dedicated to promote public awareness and education on topics surrounding epilepsy for the welfare of people with epilepsy.”

In Support of Epilepsy

Ms Stella Wang
Nurse Clinician
Nursing

The NNI and Singapore Epilepsy Foundation's 1st support group meeting on 19 Feb 2005 brought a group of 7 patients and relatives together, to share on their encounters and experiences on living with the condition of epilepsy.

Dr Nigel Tan spoke to the group on **“Refractory Epilepsy”** and Dr Thomas Sim, a lecturer from Nanyang Polytechnic, spoke on **“Depression and Coping in Epilepsy”**.

The support group meeting plays an important role in bringing patients and caregivers from different walks of lives together. Through this sharing, patients will realise that they are not alone and help is always available.

Singapore Epilepsy Foundation (SEF) is the Singapore Chapter of the International Bureau for Epilepsy. SEF is a non-profit organisation dedicated to promote public awareness and education on topics surrounding epilepsy for the welfare of people with epilepsy.

Its objectives are:

- to provide an organisation for the benefit and service of people with epilepsy and others interested in epilepsy and associated conditions
- to promote the study of the causes and treatment thereof and the diffusion of information concerning the same

SEF plans to have monthly support group meetings at NNI, SGH and NUH. For further details, please visit www.epilepsy.com.sg

Encouraging Overseas Experiences



Nurse Clinician (Epilepsy), Stella Wang, sharing her overseas experiences with nurses from other hospitals & institutions.

The NNI Nursing department gathered more than 60 nurses from different hospitals on 27 Jan to share on their HSDP overseas experiences (*Health Services Development Program*). Our Nurse Clinicians Emily Ang (*Brain Tumour*) and Stella Wang (*Epilepsy*) shared what they observed and learnt during their two-month attachment in the United States, while Lee Kah Keow (*Head Injury*) shared her enriching experiences in Sweden. We encourage more of such programs to enhance the knowledge of our staff in their areas of specialities.



Nurse Clinician (*Head Injury*), Lee Kah Keow, sharing her knowledge and experiences in Adelaide, South Australia.

“So, is Lewy body formation a cause or consequence of the neurodegeneration process?”

Lewy body in Parkinson’s disease: Good, Bad or Both?

Dr Yu Wei-Ping
Principal Investigator
NNI Research Faculty

The presence of Lewy body (LB) inclusions is a signature characteristic of Parkinson’s disease (PD) recognised nearly a century ago. However, it is only in recent years that the molecular composition of LB began to be uncovered. Several components of the LB have now been identified, including synuclein, synphilin-1 and parkin. Interestingly, all of these proteins are encoded by genes whose mutations are closely associated with the familial form of PD, thus implying a common pathological mechanism for both familial and idiopathic PDs. Surprisingly, proteins deposited within the LB inclusions are often enriched with ubiquitin. Ubiquitin attachment on a protein generally tags it for degradation via the proteasome. How these proteins could have escaped from the proteasome degradation machinery remains obscure.

Recently, a lab led by Dr Lim Kah Leong at the NNI, in collaboration with Professor Ted Dawson at the Johns Hopkins University School of Medicine, have discovered that parkin could mediate a non-classical ubiquitination, which distinguishes from the classical lysine-48 (K48)-linked ubiquitination in that an alternative lysine residue on the ubiquitin molecule, lysine-63 (K63) is used instead (J. Neurosci. 2005, 25:2002-2009). It has been well documented that proteins modified by K48-linked ubiquitination are the primary targets for proteasome-mediated degradation. Thus, this finding offered a simple speculation on how ubiquitinated proteins (K63-linked) could have escaped degradation by the ubiquitin-proteasome system. Indeed, when coexpressed with synuclein and synphilin-1 in transfected cells, parkin promotes LB-like inclusion formation, suggesting a role of parkin in LB biogenesis. This notion well aligns with the observation that LBs are frequently absent in the familial PD patients with parkin mutations. It thus appears that parkin is a dual-function ubiquitin ligase that mediates both K48- and K63-linked ubiquitination, presumably under different cellular conditions.

How does parkin choose between the two types of ubiquitination?

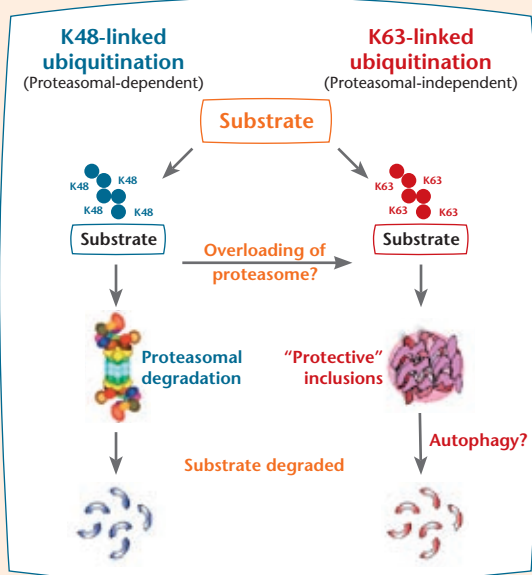
Dr Lim and colleagues found that when the substrates are expressed at a very low level relative to parkin expression, they are predominantly modified

by K48-linked ubiquitination. However, as the ratio of substrates to parkin increases, the modification of substrates began to switch from K48-linked to K63-linked ubiquitination. This finding is intriguing as it implies that parkin-mediated K63-linked ubiquitination only occurs when accumulating substrates reach a significant (toxic) level, due to, for example, overloading or impairment of the proteasome.

Taken together, these findings suggest that parkin serves multiple neuroprotective functions and thus could be a potential target for neuroprotective drugs. Certainly, there are several questions to be addressed, for example, how or why proteins modified by K63-linked ubiquitination are sequestered to form inclusion rather than being sent to other cellular processes as it has been shown that the K63-linked ubiquitination is usually associated with protein sorting, trafficking and endocytosis.

So, is Lewy body formation a cause or consequence of the neurodegeneration process?

While a persuasive answer is still some distance away, current findings have a strong bias towards its neuroprotective function. This notion is important, as it urges a strong precaution for those who attempt to develop neurodegeneration-protecting drugs by preventing LB formation, because, after all, they may be aiming at a wrong target.



Brain Awareness Week is dedicated to just that - **brain awareness**. BAW was initiated in the USA and is promoted widely as a week-long, world-wide series of educational events in March. The pathway to greater awareness of the brain begins with education. Among the BAW activities organised, public education programs are the best way to connect with our community to increase knowledge and understanding of the wonders of our brain and nervous system.

Creating **Brain** Awareness



In conjunction with Brain Awareness Week (BAW), the NNI and the National University of Singapore organised a BAW lecture at Raffles Junior College on 17 March, aimed to increase knowledge and understanding of the brain and nervous system.

Singapore faces an ageing population that will be more prone to suffer from neurological diseases. Through research and technological breakthroughs, doctors and researchers will be able to understand and treat patients more effectively, thereby softening the economic and social impact of neurological diseases.

Dr Ivan Ng, Consultant Neurosurgeon, NNI, spoke to his alma mater on **“Neurosurgery for the New Millennium”**. New innovation in the operation theatres and neurocritical care units were outlined, with emphasis that the goal of any technology in neurosurgery is to effectively balance good patient outcomes with neurosurgical deficits. Dr Liou Yih-Cherng, Assistant Professor, NUS, highlighted the growing concerns of Alzheimer’s disease with **“Pinning Down ‘tangles’ and ‘plaques’ in Alzheimer’s Disease”**.

The pathway to greater awareness of the brain begins with education. Through such public lectures, we hope to inspire students’ interest in the neurosciences, and strengthen the foundation for ongoing education and research breakthroughs in this field.



Dr Yee Woon Chee, Chairman of BAW 2005, with Dr Ivan Ng (L) and Dr Liou Yih-Cherng (R)

“I have always been interested in science, and I feel that the seminar complements what I have studied in school well. It is interesting to learn that the brain, while weighing only 2% of our body weight, actually contains 100 billion neurons! The seminar has made me think more deeply about the issues presented. I will not rule out the possibility of a career in the neurosciences one day.”

*Magdalena Koh, Vice-Head Prefect,
Methodist Girls’ School*

“The lecture was generally interesting and clear. It covers quite a wide view and range of subject matter, especially the presentation on neuro-surgical research.”

*Alex Ang, Raffles Institution,
Chairman of the Science Club*



The interactive session possibly fuelled the students’ ambitions of entering the field of neurosciences.



Magdalena (extreme right), sharing her thoughts with Neus-link.



POLYSOMNOGRAPHY COURSE & SLEEP MEDICINE REVIEW

17-18 SEPTEMBER 2005
Health Promotion Board Auditorium

TARGET AUDIENCE

Medical and healthcare professionals interested in the Laboratory Evaluation and Management of Sleep Disorders

OBJECTIVES

This 2-day course will give an Overview of Sleep Medicine from a multidisciplinary perspective, with an emphasis on Practical Polysomnography with Clinical Correlation: -

- **Basic Mechanisms of Normal Sleep**
- **Overview of Common Adult & Paediatric Sleep Disorders**
- **Management of Sleep Related Breathing Disorders, including CPAP Therapy and Upper Airway Surgery**
- **Laboratory Evaluation of Sleep with Clinical Correlation**
- **Fundamentals of Polysomnography Technology & Interpretation of Sleep Studies (including Staging of Sleep, Scoring Rules, MSLT and MWT)**
- **Demonstration of Common Adult & Paediatric Polysomnographic Abnormalities, Pitfalls in PSG Interpretation (including Recognition of Physiologic & Non-Physiologic PSG Artifacts)**

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REGISTRATION FEES

Early Registration (before 15 July 2005):

Symposium Only

Physician: SGD\$150.00

Trainee: SGD\$100.00

Paramedical Staff: SGD\$75.00

Symposium & Workshop

Physician: SGD\$400.00

Trainee: SGD\$325.00

Paramedical Staff: SGD\$200.00

Normal Registration (from 15 July 2005 onward)

Symposium Only

Physician: SGD\$200.00

Trainee: SGD\$125.00

Paramedical Staff: SGD\$100.00

Symposium & Workshop Only

Physician: SGD\$500.00

Trainee: SGD\$350.00

Paramedical Staff: SGD\$250.00

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(registration form & programme details available on www.singaporesleepsociety.com)

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