

Professor Ling: his four decades of journey and passion for microglia research

By Madhuvika and Parakalan



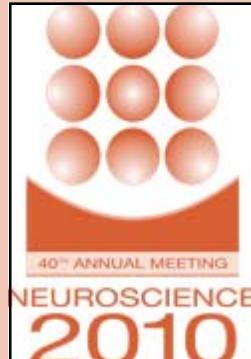
Back in the 1970s, neuroscientists were whacking their brains over the neurons but neglected the glial cells considering them merely as the supporting cells in the brain. Abundant research articles, however, are being published recently on the glial cells, especially the microglia, describing them as being an important mediator of neuroinflammatory response in neurodegenerative diseases. The roles of microglia in normal physiology and pathology are now greatly amplified with some recent studies suggesting that the cells are also actively involved in learning and memory in the healthy brain.

Prof Ling Eng Ang is a pioneer in glial research and has contributed greatly to the field of neuroglia. He has published over 300 research articles. He led the Department of Anatomy at NUS as the Head for about 10 years (1998-2008). During his tenure as the Head, he transformed the landscape of research environment in the Department of Anatomy. He also served as a member of the editorial board in several prestigious journals. But his journey to the top was not easy.

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SNA Travel Award 2010

SNA has set aside funds to support its members traveling to and presenting at the Neuroscience conference held annually by the Society of Neuroscience. This year the Travel Award was presented to three students— Ms Madhuvika Murugan, Ms Sukanya Shyamashundar and Ms Guru Girijha, to present their work at the Neuroscience 2010 conference at San Diego, 13-17th November, 2010.



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Editor's Message

The Singapore Neuroscience Association thought it would be valuable to issue a newsletter containing a brief account of some of the most eminent scientists, of what it was about science that captured their imagination as youngsters and kept it alive, what piece of knowledge they have added to the extraordinary lore of science and what message they have for budding scientists? In this issue, we have put together an interview of Prof Ling Eng Ang, a pioneer in glial research. His inspiring story will reflect the obstacles he faced as a young scientist and why he chose to take the road

less travelled.

The aim of the SNA Newsletter is to keep its readers aware of the events relating to neuroscience and to promote interaction and collaboration among neuroscientists from different backgrounds. We strongly encourage our members to actively contribute articles to the newsletter. Feedback on any aspect of the newsletter is welcome.

Editor

Announcements

We are proud to announce the achievements of our members.

A/Prof Charanjit Kaur , one of the senior committee members of our association received the **Research Excellence Award 2010**, Yong Loo Lin School of Medicine, for her outstanding contribution to Science.



Mr Parakalan Rangarajan and Ms Nimmi Baby won the Travel Award from the International Brain

A/Prof. Kaur

Research Organization (IBRO) and Federation of Asian Oceanic Neuroscience societies- Asia Pacific Regional Committee (FAONS-APRC) for attending the 5th FAONS Congress, November 2010.



Parakalan (L) and Nimmi (R) with Nobel laureate Torsten Weisel (center) at the 5th FAONS Congress.

Prof Ling (continued)

The beginning

Starting out from a 'kampong' (a small town called Ayer Tawar, Sitiawan) near Ipoh in Malaysia, Prof Ling did his schooling in a local Chinese High School. Coming from a humble family background of a rubber tapper family and being a rubber tapper boy himself in his school days and considering the financial constraints, he decided to join the National Taiwan University to pursue his undergraduate degree. "I decided to move there, my high school results helped and of course, the cost of living was lower in Taiwan then" he muses.

Inspiration

He and his brothers born in Malaysia to parents of Chinese descent were the first in their family to receive a formal education. At the National Taiwan University, he had to face stiff competition like any students who hail from small towns and joined the Department of Zoology where he found his love for Histology, influenced by a lecture given by a Professor from Emory University, Atlanta. After graduation, he moved to the University of Cambridge, England to pursue his doctoral degree (PhD) under the guidance of Professor E Neville Willmer (an FRS at the Physiology Laboratory, Downing Site), one of the best histologists and a pioneer in cell culture. "In Cambridge, what

surprised me most was that, the Histology was in the Physiology Laboratory and not Anatomy" - he vividly recalls.

Prof Ling's career has always been underpinned by a very strong research track record. Even now at the age of 66, he actively participates in research activities and encourages



young researchers to take the glial research to the next level with the advent of recent cutting edge technology. His active participation and contribution to research was readily recognised by the School of Medicine with the **Research Excellence Award**. He was conferred the degree of D.Sc. by NUS in 1989.

He started his research carrier at the age of 21 and worked on invertebrate histology, trying to link cytology and evolution. "We were pioneers in using the electron microscope for the ultrastructural study of nemertine worms, a protochordate. I really turned the electron microscope inside out", he commented. Cambridge undoubtedly gave him great opportunities to meet with eminent scientists like Prof Alan L Hodgkin (a Nobel laureate for discovery of action potential in neurons). Such exposure, coupled with his own drive and zeal, enabled him to complete his PhD within three years.

Remarkable discoveries in the field of Glia biology

Prof Ling embarked on post-doctoral training at McGill University, Canada under the supervision of Prof Charles P Leblond, who was then the top histologist in North America. There, he started working on neuroglial cells using techniques such as electron microscopy and radioautography. He was one of the pioneers to characterize the glial cell types, their dynamics and origin. By stereotaxic intraventricular injection of radioactive thymidine into the lateral ventricles, he was able to show the stem-cell origin for oligodendrocytes and astrocytes in the developing brain.

Embarking on the ambitious journey to discover the source of microglia

Prof Ling in his twenties, joined the Department of Anatomy, University of Singapore (on 2 July, 1972), as one of the youngest faculties. With the limited resources available, he meticulously planned and executed his research to understand the origin and morphology of microglia from the post-natal rat brain. He also extended his research on brain microglia to the spinal cord and retina of the primate.

As a Visiting Professor at McGill University, he re-joined Prof Leblond in 1978-79 and discovered the origin of microglia from the circulating monocytes using carbon labeling. This has been a landmark discovery in the field of microglia and he proudly coined the phrase ‘from blood to brain’ referring to the origin of microglial cells from peripheral blood monocytes. He then received accolades widely for his breakthrough results from the microglia research community and was invited for the first microglia conference in 1992 held in Munich, Germany. He wrote his first review on the origin and nature of microglia, a highly cited article. Another review was published in *Glia* in 1993 and has been cited 425 times to date (Web of Science). This remains one of his proudest contributions to Science.

Further down the road

Having studied extensively the structure and origin of microglia, he delved into the functional aspects of microglia with support from a number of his ‘disciples’. Despite being at the helm for more than four decades, the 66 year old shows no sign of slowing down. Besides guiding his students (who are now noted scientists and professors themselves), Prof. Ling also nurtures young scientists from Asia (China, India, Malaysia etc.) inspiring them to take part in solving the microglia puzzle. He also urges current neuroscientists to focus on the cerebrospinal fluid as it might give us insights into different neurodegenerative diseases. He says with thousands of papers now on microglia, “a cell type that



L to R: Prof Ling with A / Prof Dheen (President,SNA), Prof Tay (Former President, SNA) and Prof Bay Boon Huat (Head, Department of Anatomy) at the International Anatomical and Cell Biology Conference conducted by the Anatomy Department, NUS.

nearly drowned 40 years ago is now a rising star in neuro-pathology!”

Advice to neuroscientists from a non-medicine background

He believes that the knowledge of human anatomy, the cyto-architectures of organs and connectivity between different organs are essential for the success of biomedical research yielding useful outcome to the health care industry. He offers valuable advice to all young researchers – “Research must be self-driven and not driven by incentives or promotions, which is why even at my age with so many publications I am interested to know more about microglia”. Being a life science graduate, he filled the gaps in his knowledge about Histology and Anatomy by extensive reading and research. This made him extremely successful in this area of research and even led to publication of his EM images in some of the best Histology textbooks. He also urges life science graduates to attend lectures delivered by Anatomy staff to medical students. ‘If you do not speak the language of anatomy, you will never understand the script of Neuroscience’.

**“Research must
be self-driven
and not driven
by incentives or
promotions”**

When asked about the importance of scientific communications and knowledge sharing, he says attending conferences and participating regularly in journal clubs are the best ways to stay connected with both departmental and international scientific communities. He also says that students must read thoroughly each and every article that is cited in their papers and thesis.

Neuroscience in Singapore and the Department of Anatomy, NUS

Prof Ling is extremely satisfied with the growth of neuroscience research in Singapore. He believes in ‘team effort’ in doing research and hence advises all researchers to be a part of large research groups rather than doing research as individuals.

Award Winning Abstracts - SNA Travel Award

Analysis of epigenetic factors in mouse embryonic neural stem cells exposed to different glucose concentrations

Ms Sukanya Shyamasundar

Maternal diabetes induces patterning defects in the developing brain during embryogenesis. We hypothesize that maternal diabetes alters the epigenetic mechanisms (namely, histone modifications, DNA methylation and microRNA mediated) and expression of genes involved in various signalling pathways resulting in brain defects in embryos of diabetic mice. These findings would provide novel insights into how maternal hyper- or hypo-glycaemia influence the fate of stem cells during development and also ascertain possible therapeutic strategies to prevent functional disturbances in the brain of infants exposed to maternal glucotoxicity or glucose deprivation.



Hypoxia-induced oligodendrocyte death is mediated by N-methyl D-aspartate receptors expressed in amoeboid microglia via NF- κ B signalling pathway

Ms Madhuvika Murugan.

The present study was focused on identifying the expression of N-methyl D-aspartate receptor (NMDAR) subunits on activated microglia and to determine their role in the pathogenesis of periventricular white matter damage (PWMD) in neonatal rats following hypoxia. The expression and functionality of NMDAR in primary microglial cultures was ascertained. Hypoxia induced the nuclear translocation of NF- κ B which was suppressed by administration of MK801, an NMDAR antagonist. MK801 also down regulated the hypoxia-induced expression of tumor necrosis factor-alpha, interleukin-1beta, inducible nitric oxide synthase (iNOS) and nitric oxide (NO) production by microglia which may be mediated by the NF- κ B signalling pathway. Hence microglial NMDAR might be a novel therapeutic target to ameliorate PWMD.

Role of iron and iron regulatory proteins in hypoxic periventricular white matter damage in the neonatal brain

Ms Guru Girijha R

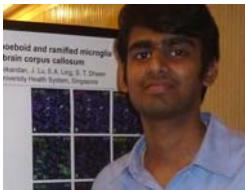
In the present study, we examined the role of iron in causing periventricular white matter (PWM) damage following a hypoxic injury in the developing brain.



Iron regulatory proteins and transferrin receptor which are involved in iron acquisition were found to be increased following hypoxia in oligodendrocytes in the PWM and Perls' iron staining showed an increase of intracellular iron in the oligodendrocytes. In primary oligodendroglial cultures' administration of deferoxamine reduced the ROS level and reduced the cell death. The present results suggest that excess iron might mediate oligodendrocyte death in PWM following hypoxia.

IBRO Travel Award

Transcriptome analysis of amoeboid and ramified microglia isolated from the rat brain corpus callosum



Mr Parakalan Rangarajan

Microglia are the resident immune cells of the central nervous system (CNS). Early postnatal brains harbor agglomerates of amoeboid microglia, which gradually transform into ramified microglia of the adult CNS. Upon activation, the ramified microglia assume the amoeboid form and involve in phagocytosis. We aim to study the mechanisms of transformation of amoeboid to ramified morphologies. To achieve this, we isolated amoeboid and ramified microglia from the 5 day and 4 week rat brain corpus callosum (CC) respectively using laser capture microdissection and performed microarray analysis. The transcriptome profiling revealed novel molecules associated with amoeboid and ramified microglia, which may be useful therapeutic targets in pathophysiology.

Analysis of RUNX1T1 expression in microglial cells of the rat brain

Ms Nimmy Baby

Microglia, which participate in the innate immune reaction of the brain, have been shown to arise from peripheral blood monocytes of the haematopoietic lineage. RUNX1T1, a member of RUNX family is involved in transcriptional regulation of genes required for proliferation and differentiation of haematopoietic stem cells. We identified a four-fold upregulation of RUNX1T1 in amoeboid microglia in comparison to that of the ramified microglia from our microarray analysis and was confirmed by immunohistochemistry. Our study suggests an important role for RUNX1T1 in microglial proliferation and differentiation in association with neuroinflammation.

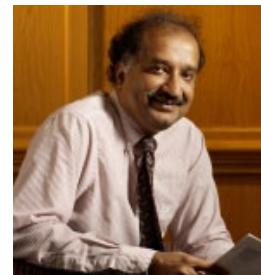


Events and Seminars

The primary goal of SNA is to promote the exchange of information among researchers. For this purpose, SNA holds seminars and workshops throughout the year. The talks are delivered by prominent scientists from around the globe. Such seminars offers graduate students and young researchers an opportunity to learn about the latest advances in neuroscience research and to meet and network with fellow neuroscientists from different parts of the world.

Professor Ranga Krishnan R is the Dean at the Duke-

NUS Graduate Medical School. He is widely recognized for his contributions to the understanding of the neurobiology of late life mental disorders and he was among the first investigators to establish a link between "silent" strokes and depression in the elderly. He presented his work on "**Broken Heart and Silent Strokes**" in a seminar organized by SNA.



From L to R: Dr He Beping, A/P Samuel Tay, Prof .Ranga Krishnan, A/P Charanjit Kaur, Prof Bay Boon Huat, A/P Thammem Dheen, Dr Sivakumar Vishwanathan, A/P Sanjay Khanna and A/P Ong Wei Yi at a seminar organized by SNA.

Professor Ling Eng-Ang shared his "microglia" experience with young researchers at an SNA conducted event. As a pioneer in glial research he spoke in length about his findings and the future prospects of studying the microglia, which he calls "**The rising star in neuropathology**".



Prof. Bay Boon Huat (left) acknowledging Prof. Ling (right) for his inspiring talk.

In response to Prof. Ling's presentation - "Your presentation on the origin and role of microglia in the central nervous system is one of the best talks in recent time. Members of the audience have really appreciated the wonderful presentation of your work done over the last 40 odd years. We have all got a lot to learn from your good self, a truly world class leader in Microglial Research!!!" - A/P Samuel Tay

"I cannot agree more with Sam !I would like to add that it is not just Prof Ling's reputation that is inspiring but also his mentorship of staff and students." -**Prof Bay Boon Huat**

Dr Judy Sng, Principal Investigator at the Singapore Insti-

tute of Clinical Sciences, was an invited speaker at the Neuroscience Seminar organized by SNA. She presented her work on "**Epigenetic control of the critical period in sensory development**".



A/P Charanjit Kaur (left) presenting a token of appreciation to Dr Judy Sng (right).

Three winners (Ms Madhuvika Murugan, Ms Sukanya Shyamasundar and Ms Guru Girijha R) of the SNA travel grant also presented their research work at the Neuroscience Seminar.



Prof G Raisman

Prof Geoffrey Raisman, Professor and Chair of Neural Regeneration at University College London, UK presented his work on "**Repair of the Central Nervous System**". The seminar was co-organized by SNA along with the Department of Pharmacology, NUS.



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Neuroscience.org.sg



Dr Wai.T.Wong Head of the Unit on Neuron-Glia Interactions in Retinal Disease at the National Eye Institute, NIH, shared his work on “Microglia in retina” in a seminar organized by SNA.

Dr. Wai T Wong



A/Prof Lu Jia (second from left) and **Dr He Beiping** (second from right) with students at IASCB Conference.

The International Anatomical Science and Cell Biology (IASCB) Conference was conducted between the 26th-29th May 2010 by the Department of Anatomy, Yong Loo Lin School of Medicine and co-organized by the Singapore Neuroscience Association and

Microscopy Society (Singapore). The primary focus of the conference was



Participants at IASCB conference

to act as a platform for the exchange of knowledge and information on Anatomical Sciences which encompasses morphology, neuroscience, developmental biology, molecular biology, biochemistry, toxicology and cancer biology. Eminent researchers and educationists from all over the world showcased their work at the conference.



Prof Satkunanantham, Director of Medical Services, Ministry of Health, Singapore and **Prof John Wong**, Dean, Yong Loo Lin School of Medicine, NUS at the opening ceremony of IASCB conference.

SNA contact :
A/Prof. ST Dheen
President

Department of Anatomy
Yong Loo Lin School of Medicine
National University of Singapore.
thameem_dheen@nuhs.edu.sg



Prof Satkunanantham delivering a lecture on “Anatomy— the foundation of good clinical practice and biomedical research” at the IASCB Conference 2010.

SNA Travel Fellowships

Singapore Neuroscience Association is pleased to announce the **SNA Travel Fellowships** for Young Investigators (Graduate Students and Post-doc Fellows) to attend the “Neuroscience 2011” conference to be held in Washington DC, USA from 12th to 16th November 2011. The applicant :

1. should be a SNA member (for at least 1 year),
2. should have submitted an abstract as a presenting author,

3. should submit a letter/email of recommendation from his/her supervisor.

The number of fellowships (\$\$ 500 each) is limited.

Applicant should submit the abstract to Dr. He Beiping (anthebp@nus.edu.sg) on or before 13 May 2011.

The Fellowship recipients will be notified as soon as decision is made.

Neuroscience Meetings



8th World Congress of

Neuroscience IBRO

Florence, Italy, July 14-19, 2011.



Society for Neuroscience

Neuroscience 2011

Washington DC , Nov 12-16, 2011.

Membership Form

Name :

Designation:

Institution/ Department:

E-mail:.....HP:

Address:

Please complete the form and submit to Dr.Sivakumar, Department of Anatomy, NUS along with a membership fee of 15\$ per annum.

