Conference Booklet

11th Annual World Congress of SBMT

Breaking Boundaries of Science, Technology, Medicine, Art, and Healthcare Policy

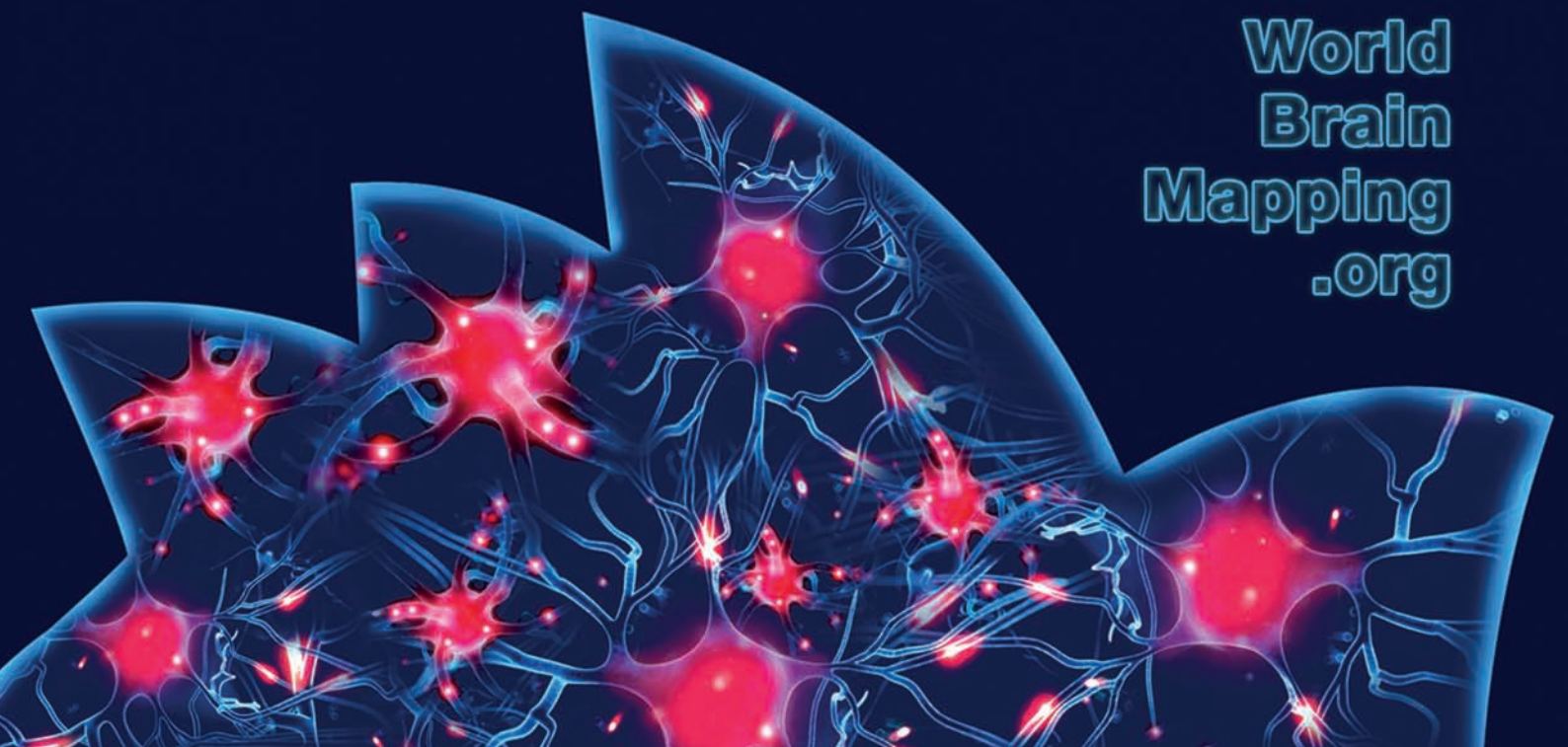
17 March – 19 March 2014

Four Seasons Hotel, Sydney, Australia

Society for Brain Mapping and Therapeutics
Breaking Boundaries of Science, Technology, Medicine, Art, & Healthcare Policy
SBMT

Congress organiser:

AusEvents
LIFE SCIENCE & TECHNOLOGY EVENTS



World Brain Mapping .org

Founder's Address

Dr Babak Kateb

Let me congratulate Dr. Kuldip Sidhu (the 11th President of SBMT) for his visionary leadership and for organizing a world class scientific meeting this year. I also thank Glenn Cross and Kirsty Grimwade from AusBiotech for coordinating such a magnificent convention. We could not have done this without the support of Dr. Alfredo Martinez-Coll and without the generous contributions and support of Brain Mapping Foundation, UNSW, Government of New South Wells, the US State Department, the US department of Commerce, the U.S. Department of Defense, Medtronic, Stryker, GE Healthcare, NeuroNexus, Rouge Research Inc., Neurologica, Integra, Synapse Biomedical Inc., Shining4Sharn Foundation and the members of the Society.

It is amazing how far we have come in the last 11 years. I am very proud to oversee the progress of our organization in the last 11 years. It is amazing how SBMT and Brian Mapping Foundation (BMF) has impacted the way the clinical translational neuroscience is practiced through our conventions, policy advocacies such as our involvement in the BRAIN initiative and the G20 World Brain Mapping and Therapeutics Initiative.

SBMT/IBMISPS started as a small summit of near 20 scientists, physicians, and engineers 11 years ago. We went from a small conference room to a larger hotel space to a conference center in France, UCLA, Harvard, and UCSF. Our first international convention was held in the Metro Toronto Convention Centre in 2012, followed by a successful 2013 w]World b]Brain Mapping Congress at the Baltimore Convention Center last year with near 370 speakers over 3 days. We have now successfully accredited our programs across multiple disciplines thanks to American Association of Neurological Surgeons (AANS), International Society for Magnetic Resonance Imaging in Medicine (ISMRM) and American College of Radiation Oncology (ACRO).

The Foundation and the Society published the first inaugural textbook of Nanoneuroscience and Nanoneurosurgery last year and now working on two additional textbooks scheduled to be released in 2015. The Society has established a new publication in collaboration with PloSOne (world's largest open access publisher) called NeuroMapping & Therapeutics. The collection is now accepting papers online at PlosOne-NeuroMapping and Therapeutics. We also teamed up with our publishing partners, Taylor and Francis and PLosOne, at the Society for Neuroscience (SFN) in order to introduce the SBMT to SFN's membership.

Our record of accomplishment in the past 11 years has been stellar including 11 successful world congresses, two satellite conferences, 1 textbook, 3 special issues of Neuroimage, 1 brand new journal publication with PlosOne, 1 congressional report language and involvement in many initiatives worldwide including President Obama's BRAIN initiative.

We have successfully brought together diverse scientific, medical, and engineering communities to tackle complex neurological disorders such as brain cancer, brain and spinal cord trauma, ALS, Alzheimer's disease, and Parkinson's disease.

SBMT members have pioneered in the field by introducing a new retinal imaging to diagnose 1`Alzheimer's disease, introduce microwave device to treat cancers (brain, breast, prostate, lung, liver, and head and neck), invented new nano-drugs to treat brain diseases and pioneered policies that could support such game-changing approach.

I congratulate the Honorable Prime Minister Abbott and the Congressman Fattah for their Pioneer in Healthcare Policy Award. They have been the force behind the sound policies that impacted the care and well-being of millions of Americans and Australians. I also congratulate the pioneering work done by Dr. Kuldip Sidhu in the field of stem cell research and applaud the humanitarian work of Dr. Charlie Teo. I also congratulate Sharn McNeill for her Beacon and Courage and Dedication Award. We all learn from Sharn's unwavering, courageous fight against ALS that gives hope and strength to the leaders in scientific/ medical research and people in the ALS community.

Let's celebrate our past achievements but don't lose the sight for the future. However, we still have many works to be done. Although we made some progress, we are still lacking in effective treatments for majority of common neurological diseases, such as ALS, autism, brain cancer, Alzheimer's, Parkinson's, and traumatic brain injuries to name a few. We have to work together and start defeating these diseases that are killing and disabling millions of people and cost world economy in trillions of dollars.

I hope you will enjoy this remarkable scientific meeting and hope to see you in 12th annual World Brain Mapping Congress at the Los Angeles Convention Center in California (March 6-8th, 2015).

Respectfully yours,

Dr. Babak Kateb

Founding Chairman of the Board of SBMT, President of Brain Mapping Foundation, Director of National Center for NanoBioElectronics (NASA/JPL), Research Scientist, Department of Neurosurgery, Cedars-Sinai Medical Center.

Welcome Address

A/Prof Kuldip Sidhu

On behalf of the Society for Brain Mapping and Therapeutics (SBMT) and its executive board including the local chapter, it is my great pleasure as a president to extend our warm welcome to you all to Sydney, Australia for the 11th Annual World Congress of the SBMT 2014 – Bringing Together Engineering, Art, Science and Medicine. Australia as a multicultural society is also the home for multidisciplinary neuroscience research and has a worldwide recognition.

Brain Sciences UNSW Sydney provides a strong platform for such meetings to facilitate collaborative research and access to relevant technologies and expertise. It encompasses an inter-disciplinary approach drawing together researchers with diverse backgrounds like engineering, science and medicine from the various schools, hospitals and Institutes nationally and internationally with a collective interest in various aspects of the function and structure of the brain in both a normal and dysfunction state. Similarly the Melbourne Brain Centre, Queensland Brain Institute at Brisbane, Brain and Mind Institute in Sydney, The Australian Neuro-muscular Research Institute in Perth, Australian Brain Bank Network, the Australian Society for Medical Research, the corporate and disease related foundation memberships, are other icons in Australia creating specific niche in neurosciences.

It has been a great journey over the last two years as a team to accept this responsibility and to host the SBMT World Congress in Sydney. This has been made possible only because of tremendous support first from SBMT HQ particularly through Dr Babak Kateb, Founding Chairman of the board and CEO of SBMT and president of Brain mapping Foundation based in California, AusEvents a division of AusBiotech, the most professional agency managing this meeting, the high profile program committee for bringing this excellent state-of-the-art program to you. Our great sponsors, NSW Health, Medtronic, GE Healthcare, Brain Sciences, UNSW and others supporting various sessions. My heart goes out to all those colleagues and friends and associations particularly the Australasian society of stem cell research, NSW stem cell network, UNSW, NSW Health Department and many others who promoted this congress through their networks.

The SBMT under the leadership of Dr Kateb is playing a very significant role worldwide to promote the cause of clinical translational neurosciences, strategically liaising with both the government agencies and philanthropic institutions which can make a difference in this field. Last year we made presentations to the White House in Washington DC under the auspices of Brain Mapping Foundation and The US Congressional neurosciences caucus that lead to the release of 100 million dollars 'BRAIN Initiative' from the president Obama. We prepared and submitted a white paper on this initiative and currently we are working together with various agencies like NIH, DOD, NSF, NASA developing strategies how to make the best of this initiative. This year I proposed to Dr. Kateb that we submit a proposal to the G20 Summit for the cause of neurosciences and prioritise resource allocation for research towards neurodegenerative diseases and other neuropsychiatric ailments. We presented this proposal to the honorable PM Abbott and the honorable President Obama as well as the US Congressional Neuroscience caucus.

The hosting of the meeting of SBMT here in Sydney, the first one in Australasia signifies its vision and policy to open out to the world and engage top brains to find solution to ever increasing burden of the neurodegenerative disease and other related ailments of the brain and promote new frontiers of science in this area. Therefore, neurological research should not be views only as scientific discovery but rather as an economical necessity.

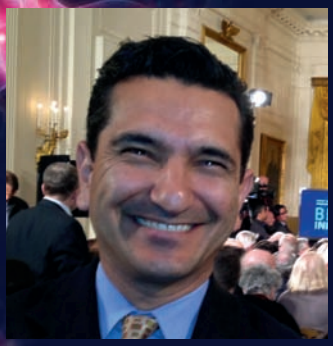
I sincerely hope that you enjoy the ambience of this world class scientific event and our hospitality in Sydney, the most beautiful, model harbour city, the state capital of New South Wales. It offers spectacular beauty, landscape and variety of tourist attractions. The Four Seasons Hotel, the venue is superb for this meeting ensuring your comforts. I look forward to future collaboration through SBMT with all of you and hope together we can rapidly find solutions for devastating neurological disorders.

A/Prof Kuldip Sidhu

President & co-convener
11th Annual World Congress of SBMT
Centre for Healthy Brain Ageing
UNSW Medicine Sydney

Society for Brain Mapping and Therapeutics Program Executive Program Committee 2014

A/Prof Kuldip Sidhu (Co-convener)
Stem Cells Specialist,
UNSW Medicine,
Sydney NSW



Dr Babak Kateb
SBMT Chairman & CEO
(Ex-officio)
Maxine Dunitz
Neurosurgical Institute
CA USA

Dr Alfredo Martinez-Coll
Senior Business
Development Manager
NewSouth Innovations
UNSW Sydney NSW

Glenn Cross
COO
AusBiotech,
Melbourne VIC

A/Prof Charlie Teo (Co-convener)
Director, Centre for
Minimally Invasive
Neurosurgery
Prince of Wales Private
Hospital, Sydney NSW

Kirsty Grimwade
Events Manager,
AusBiotech,
Melbourne VIC

Society for Brain Mapping and Therapeutics Program Program Committee 2014

Professor George Paxinos
NHMRC Australia Fellow
Neuroscience Research Australia, Sydney NSW

A/Prof Caroline Gargett
Deputy Director,
The Ritchie Centre
Monash Institute of Medical Research
Clayton, Victoria

Professor Gary F Egan
Professor & Foundation Director, Monash Biomedical Imaging, Monash University
Deputy Director, National Imaging Facility, Australia

Mr Glenn Cross
Chief Operating Officer
AusBiotech,
Melbourne VIC

Professor John Justin Gooding
Director of the Australian Centre for NanoMedicine
Head, Biosensors and Biointerfaces Research Program, School of Chemistry, University of New South Wales, Sydney NSW

Professor Perminder Sachdev
Director,
Neuropsychiatry Institute
UNSW Medicine, Sydney

Professor Perry Bartlett
Director, Queensland Brain Institute University of Queensland, Brisbane

A/Prof Megan Munsie
Stem Cell Australia,
Melbourne VIC

11th World Congress of SBMT Sponsors and Exhibitors

Major Partner:

NSW Ministry of Health: Office for Health and Medical Research (OHMR)

Health and medical research play a vital role in the continued growth and better health of our community and economy. From increased life expectancy and new treatments for disease, and technologies that change the way we live and work, to addressing environmental challenges - scientific research and the knowledge it generates affects us all.

As a part of the NSW Ministry of Health, the Office for Health and Medical Research (OHMR) plays a crucial role in supporting the State's leading health and medical research efforts. OHMR works with the health and medical research communities, the higher education sector and business to promote growth and innovation in research to achieve better health and environmental and economic outcomes for the people of NSW.

OHMR is responsible for the delivery of a range of programs and policies including:

- Medical Research Support Program
- Medical Devices Fund
- Biobanking
- Bioinformatics
- Research Hubs
- Clinical trials
- Clinical research networks
- Research ethics and governance

For more information please email ohmr@doh.health.nsw.gov.au

Web: www.health.nsw.gov.au\ohmr

Gold Partner:

Medtronic

At Medtronic, we're committed to *Innovating for life* by pushing the boundaries of medical technology and changing the way the world treats chronic disease. Driven by our deep understanding of the human body and our collaboration with physicians, we're transforming technology to treat patients across the entire care continuum. Our innovations help physicians diagnose diseases earlier, treat patients with the least amount of disruption possible, and help alleviate symptoms throughout the patient's life. Today, we're improving the lives of millions of people worldwide each year across numerous conditions - including heart disease, diabetes, neurological disorders, spinal conditions, and vascular diseases. But it isn't enough. So we're innovating beyond products. We're breaking down barriers, challenging assumptions, and looking beyond the status quo - to continually find more ways to help people live better, longer.

11th World Congress of SBMT Sponsors and Exhibitors

Session Partner:

GE Healthcare

GE Healthcare provides transformational medical technologies and services that are shaping a new age of patient care. Our broad expertise in medical imaging and information technologies, medical diagnostics, patient monitoring systems, drug discovery, biopharmaceutical manufacturing technologies and performance solutions services deliver better care to more people around the world at a lower cost.

Healthymagination is GE's $6 billion commitment to bring high-quality health care at lower cost to more people around the world through our advanced technologies and research and development capabilities. Just as ecomagination applies our scale and innovation toward tackling environmental challenges, healthymagination offers dramatic new investments toward achieving sustainable health

Session Partner:

Neurologica

Session Partner:

Brain Sciences UNSW

11th World Congress of SBMT Sponsors and Exhibitors

Exhibitors:

Stryker

Stryker is a leading medical technology company and together with our customers, we are driven to make healthcare better. Stryker offers innovative reconstructive, medical, surgical, neurotechnology, spine and robotic arm assisted technologies to help people lead more active, satisfying lives. We are committed to enhancing quality of care, operational effectiveness and patient satisfaction.

Medtronic

At Medtronic, we're committed to *Innovating for life* by pushing the boundaries of medical technology and changing the way the world treats chronic disease. Driven by our deep understanding of the human body and our collaboration with physicians, we're transforming technology to treat patients across the entire care continuum. Our innovations help physicians diagnose diseases earlier, treat patients with the least amount of disruption possible, and help alleviate symptoms throughout the patient's life. Today, we're improving the lives of millions of people worldwide each year across numerous conditions - including heart disease, diabetes, neurological disorders, spinal conditions, and vascular diseases. But it isn't enough. So we're innovating beyond products. We're breaking down barriers, challenging assumptions, and looking beyond the status quo - to continually find more ways to help people live better, longer.

Rogue Research

Rogue Research has brought the advantages of modern frameless neuronavigation to the neuroscience research world. Our product, Brainsight, allows you to use the principles of frameless stereotaxy to perform a variety of neurosurgical procedures with accuracy, simplicity and improved subject comfort when compared to stereotactic frames.

Integra

Integra is a world leader in medical technology, is dedicated to limiting uncertainty for surgeons, so they can concentrate on providing the best patient care. Integra offers innovative solutions in orthopaedic extremity surgery, neurosurgery, and reconstructive and general surgery.

Integra's orthopaedic products include devices and implants for foot and ankle, hand and wrist, shoulder and elbow, tendon and peripheral nerve protection and repair, and wound repair. Integra is a leader in neurosurgery, offering a broad portfolio of implants, devices, instruments and systems used in neurosurgery, neuromonitoring, neurotrauma, and related critical care.

Founded in 1989 Integra is headquartered in Plainsboro, New Jersey and has over 3,500 employees worldwide.

Obituary

Dr. Lucien Maurice Levy
(Age 67)

Dr Lucien Levy passed away December 19, 2013, peacefully at his home in Columbia, Maryland. Lucien was a great supporter of SBMT and was an important member of its board.

He played a significant role in SBMT brain initiative proposal that was submitted to the White House, the US congress and NIH. The whole scientific community is sending condolence messages.

'He was our beloved colleague and member of this distinguished board' said Dr Babak Kateb, CEO, SBMT.

Lucien's Doctor of Medicine degree was from the Johns Hopkins University in 1981 and after fellowship in neuroimaging he attained a full position of Professor of Radiology at The George Washington University since 1999. He served as a Senior Editor of AJNR since 2007 and was an Associate Editor of Radiology since 2009 and he was passionate about it. His breadth of knowledge was spectacular, and as Editor Emeritus of AJNR, Dr Robert Quencer once said, "One could learn more from reading Lucien's evaluations than from the actual articles he was reviewing."

Lucien was a great teacher and researcher and attracted fellows for mentorship from throughout the world. He was a decorated person with many accolades. Lucien will be remembered for his wit and humor. He brought smiles from all of those, whom he mentored, even on the most mundane of subjects. He was very unassuming, quiet, and private man. He will be missed immensely by his colleagues, his family, his trainees, and all those who encountered him.

Gala Dinner

The IVY Ballroom
1/330 George Street Sydney

Pre Dinner drinks from 7.00pm
Dress: Black Tie

Award Winners:

Award 1:
Pioneer in Healthcare Policy Award

PM Tony Abbott and **US Congressman Chaka Fattah**

Award 2:
Humanitarian Award Winner

Charlie Teo

Award 3:
Pioneer in Medicine Award Winner

Kuldip Sidhu

Award 3:
Beacon of Courage and dedication Award

Sharn McNeill

1 Program

MONDAY 17 MARCH 2014

7.00am – 5.00pm	**Delegate Registration**
	Grand ballroom 1
8.35 – 8.40am	**Conference Welcome** **Kuldip Sidhu,** President of SBMT
8.40 – 8.55am	**Conference Welcome** **PM Envoy,** Australian Government
8.55 – 9.10am	**Babak Kateb** Founder, Chairman, CEO of SBMT & President of Brain Mapping Foundation
9.10 – 9.25am	**Keynote Address** **Consul General Hugo Llorens,** Embassy of the United States of America
9.25 – 9.40am	**Keynote Address** **Kirsty Duncan,** Member of Canadian Parliament Video Address
9.40 – 9.50am	**Keynote address** **Congressman Chaka Fattah,** Senior Member of the House Appropriations Committee Video Address
9.50 – 9.55am	**Program Overview** **Charlie Teo**, Director, Centre for Minimally Invasive Neurosurgery
9.55 – 10.00am	**Announcement of 2015 World Brain Mapping in LA, Shouleh Nikzad**, SBMT President Elect
10.00 – 10.15am	**Conference Opening Address** **The Hon. Jillian Skinner MP**
10.15 – 10.30am	**Morning Tea Networking Break with exhibitors – *Grand Foyer***
10.30 – 11.00am	**Plenary session 1** **Neurology and neurophysiology** **Chair: Peter Schofield** **Prof Trevor Kilpatrick**, Director, Melbourne Neuroscience Institute, University of Melbourne
11.00 -11.30am	**Plenary session 2** **The central role of RNA in cognitive function** **Chair: Peter Schofield** **Prof John Mattick AO**, Executive Director, Garvan Institute of Medical Research Sydney
11.30 – 12.00pm	**Plenary session 2A** **Chair: Peter Schofield** **Prof Peter Burger**, Professor of Pathology, Oncology, and Neurosurgery, The Johns Hopkins Hospital
12.00 – 1.30pm	**Lunch Break with exhibitors – *Grand Foyer***

Information correct as of 7/3/2014

Program

1.30 – 2.45pm

Grand ballroom 1

Breakout Session 1

Pluripotent Stem Cells & Neural Lineages

Chair: Martin Pera, Kuldip Sidhu

1. **Martin Pera (Keynote)**
2. **Alice Pebay** *Role of Lysophosphatidic acid in neural stem cells and in traumatic brain injury*
3. **Henry Chung** *Whole transciptome analysis of Alzheimer's disease specific human induced pluripotent stem cells*
4. **Lezanne Ooi** *Altered Neuronal Function In Networks Derived From Induced Pluripotent Stem Cells From Alzheimer's Disease Patients*

Gallery

Supported by:

ACRO American College of RADIATION ONCOLOGY

Breakout Session 2a

CME Symposium

Neuro-oncology

Chair: Michael Back Kerrie McDonald

1. **Charlie Teo (Keynote)** *Maximising technology in the Surgical Treatment of Gliomas*
2. **Michael Back** *Radiation Therapy Dose Painting utilizing FET and FDG PET in the management of high grade glioma*
3. **Jeff Rosenfeld** *Targeting calcitonin receptor expressed by brain tumour initiating cells of gliobastoma multiforme*
4. **Kerrie McDonald**
5. **Surasak Phuphanich** *Immunotherapy for Brain Cancer: Vaccine, PD1/PDL1 Antibody*

Residential Suite

Supported By:

Medtronic

Breakout Session 2b

Functional Neurosurgery

Chair: Ray Cook,

1. **Ray Cook (Keynote)**
2. **Colleen Loo** *Non Invasive Therapeutic Brain Stimulation :ECT, TMS, tDCS*
3. **Raymond Schwartz**

The relationship between vascular risk factors, small-vessel disease and Parkinson disease: a clinico-pathological study

4. **Socrates Dokos** *Modelling Direct Brain Activation in Electroconvulsive Therapy*
5. **Takeshi Shimizu**

Functional connectivity specific to central post stroke pain and alterations after repetitive transcranial magnetic stimulation

2.45 – 4.00pm

Breakout Session 3

ACRO CME Symposium

Supported by:

Neuro-radiation oncology and stereotactic radio-surgery

ACRO American College of RADIATION ONCOLOGY

Chair: Anatoly Rosenfeld and Jim Welsh

1. **Jim Welsh (Keynote)** *Proposed New Boron Neutron Capture Therapy Program at Fermilab*
2. **Anatoly Rosenfeld** *Advanced quality assurance in Stereotactic Radiosurgery for error free treatment*
3. **Stephanie Weiss**

Information correct as of 7/3/2014

Program

2.45 – 4.00pm (Cont.)

Supported by:

Breakout Session 4

Neuro-trauma and Neuropsychiatry

Chair: Michael Roy, Skye McDonald

1. Jeffrey Chung (Keynote)

Post Traumatic Epilepsy: Present and Future

2. Skye McDonald

3. Michael Roy

Identification of Predictors of Post-Deployment PTSD and postconcussive syndrome in Combat Veterans

4. Stuart Grieve

Structural MRI and Diffusion Tensor Imaging evidence of network abnormalities in Major Depressive Disorder - data from the iSPOT-D trial

5. Michele R. Aizenberg

6. Mayuresh Korgaonkar

Functional Imaging markers of treatment prediction in depression: data from the International Study to Predict Optimized Treatment in Depression (iSPOT-D).

Supported by:

Breakout Session 5

Translational Neuroscience

Chair: Gary Housley

1. Gary Housley (Keynote)

Neurotrophin-based neural repair and protection

2. Renee Morris

Gene therapy for spinal repair

3. Matthias Klugmann

Gene therapy for leukodystrophies

4. Andrew Moorhouse

The KCC2 chloride transporter as a target for epilepsy

5. John Power

Molecular targets for addiction and memory disorders

4.00 – 4.30pm **Afternoon Tea Networking Break with exhibitors – *Grand Foyer***

4.30 – 5.45pm

Breakout Session 6

Adult Stem Cells & Personalised medicine

Chair: Bob Williamson, Mirella Dottori

1. Bob Williamson (Keynote)

Stem Cells and Personalised Medicine

2. Vicky Yamamoto

Small molecule based approaches for personalized medicine and adult stem cell therapy

3. James Bourne

Does Functional Neurogenesis Occur in the Injured Neocortex of the Nonhuman Primate?

4. Mirella Dottori

Functional characterization of Friedreich Ataxia iPS-derived neuronal progenitors and their integration in the adult brain

5. Yashar Kalani

exRNAs as biomarkers of neurological disease

Program

Keith Black Supported by: Brain Sciences UNSW	**Breakout Session 7** **Neurology and Neurophysiology** **Chair: Matthew Kiernan S** **1. Keith Black (Keynote)** **2. Mourad Tayebi** **3. Ian Hickie** *Delayed sleep offset and other markers of circadian rhythm disruption are common in young people with emerging mood disorders* **4. Steve Vucic** *Cortical dysfunction in Motor Neurone Disease* **5. Trevor Kilpatrick** *Genomics of multiple sclerosis*
	Breakout Session 8 **Molecular Imaging** **Chair: Roger Ordidge and Gary Egan** **1. Kishore Bhakoo (Keynote)** **2. David Reutens** **3. Roger Ordidge** *Sodium selenate as a therapy for traumatic brain injury: a pre-clinical MRI study*
5.35 – 6.00pm	**Plenary Session 3** **Regenerative medicine and stem cells** **Martin Pera,** Stem Cell Science, University of Melbourne
7.00 – 7.30pm	**Pre-Dinner Drinks at the IVY, 1/330 George St, Sydney**
7.30 – 10.00pm	**Gala Dinner**

2

TUESDAY 18 MARCH 2014

9.00am – 5.00pm	**Delegate Registration**
	Grand ballroom 1
10.00 – 10.30am	**Plenary Session 4** **Neurosurgery** **Prof Jeffrey Rosenfeld AM, OBE**, Monash University *Improving the outcome from severe traumatic brain injury: how much further can we go?*

Information correct as of 7/3/2014

Program

10.30 – 11.00am	**Morning Tea and Networking with Exhibitors**
11.00am – 12.15pm	***Grand ballroom 1***

Oral Poster Presentations

Chair: Kuldip Sidhu

1. Cecelia Gzell
Small increases in enhancement on MRI may predict survival post radiotherapy in patients with glioblastoma

2. Timur Gureyev
Quantitative analysis of the EEG source localization problem

3. Andrew Tosolini
The Motor End Plates (MEPs) Are A Conduit To Increase Adenoviral Transduction Of Motor Neurons, Dorsal Root Ganglia (DRG) And Myofibres

4. Terry Peters
Correlation of quantitative MRI and histology of surgical specimens in drug-resistant focal epilepsy

5. Michael Lerch
X-Tream: A Unique Realtime QA System for Submillimeter X-Ray Radiosurgery

6. Terry Peters
A pipeline for histology to in-vivo registration of surgically resected specimens in focal epilepsy

Gallery

Breakout Session 9a

NanoBioElectronics

Chair: Babak Kateb

1. Jeff Rosenfeld (Keynote)
The development of bionic vision at Monash University

2. Shouleh Nikzad
Advanced Technology for Planetary, Astrophysics, and Medical Applications

3. Justin Gooding
Nanobioelectronic Interfaces that Facilitate Efficient Electron Transfer to Biomolecules

4. Uttam Sinha

Studio

Breakout session 9c

Emerging application of synchroton radiation in Neuroscience

Chair: Pantaleo Romanelli

1. Alberto Bravin
Synchrotron-generated microbeams: overview and state of the art

2. Jeffrey Crosbie
Microbeam radiation therapy: the state of the art in cancer treatment

3. Pantaleo Romanelli
Brain modulation using synchrotron-generated microbeams

4. Paola Coan
Brain microimaging using synchrotron radiation

12.15 – 1.30pm	**Lunch and Networking with Exhibitors**

Information correct as of 7/3/2014

Program

1.30 – 2.45pm

Grand ballroom 1

Breakout Session 10

Sport and Concussion

Chair: Geoffrey Ling & Babak Kateb

1. Michael Roy (Keynote)
Linking TBI with PTSD in Combat Veterans: Lessons Learned from the Predictors Study

2. Dan Perl

3. Pantaleo Romanelli
A Fully-Integrated Externally Rechargeable Wireless System for Long-Term Electrocorticography and Cortical Stimulation

4. Daryl Kipke

5. Geoffrey Ling

6. James Ecklund
Building a Community Concussion Program

Gallery

Breakout Session 11

Stem cell technology and tissue engineering

Chair: John Whitelock & Jean Paul Allain

1. Ernst Wolvetang (Keynote)
Human induced pluripotent cells is tools to study neurological diseases

2. RA Green
Conductive hydrogel electrode coatings for optimal neural interfacing

3. John Whitelock

Studio

Breakout Session 12

Brain Networks

Chair: Perminder Sachdev

1. Michael Breakspear (Keynote)
Brain Connectomics

2. Alex Fornito
Mapping context-dependent changes in brain functional networks using event-related graph analysis

3. Michael Valenzuela
Plastic Network Responses in Aged Brains to Lifestyle-based Intervention

4. Wei Wen
Structural topological organisation of the elderly brain

5. Gilles Guillemin
Mapping of the tryptophan metabolism in physiological and pathological conditions

2.45 – 3.30pm **Afternoon Tea and Networking with Exhibitors**

Information correct as of 7/3/2014

Program

3.30 - 4.45pm	**Breakout Session 13** **Neuroimaging genetics** **Chair: Perminder Sachdev & Peter Schofield** **1. Margaret Wright** *The ENIGMA Projects: identifying genetic loci for brain structure and function* **2. Karen Mather** *Heritability and genetic correlations of cortical and subcortical structures in a cohort of community-dwelling older adults* **3. Peter Schofield** *Neuroimaging and Biomarker Changes in Dominantly Inherited Alzheimer's Disease* **4. Mayuresh Korgaonkar** *Heritability of neural structure and connectivity changes across the adult lifespan – results from the TWIN-E study.* **5. Philip Liu** *Brain Mapping and Therapy Monitored by Genetic Imaging; A Preclinical Platform*
	Breakout Session 14 **Commercial and Community Considerations in Personalised Medicines** **Chair: Megan Munsie & Caroline Gargett** **1. Ben Borson (Keynote)** *Commercialization and Protection of Intellectual Assets in Brain Disorders* **2. Alfredo Martinez-Coll** **3. Megan Munsie** **4. Glenn Cross** **5. Bob Williamson**
	Breakout Session 15 **Stem Cells & Clinical Translation** **Chair: Uli Schmidt & Michael Morris** **1. Uli Schmidt (Keynote)** *Huntington's disease-affected human embryonic stem cells as a model of mitochondrial dysfunction and metabolic disturbances* **2. Michael Morris** *Amino acids act as growth factors to stimulate embryo development up to and including early neurogenesis* **3. Mirella Dottori** *Multipotent caudal neural progenitors derived from human pluripotent stem cells that give rise to lineages of the central and peripheral nervous system* **4. Amanda Capes-Davis** *Spontaneous transformation of stem cells in vitro: Believe it or not*
4.45 – 5.45pm	**SBMT Board meeting 2014** By invite only
4.45 - 5.45pm	**Networking Drinks with Exhibitors**

Information correct as of 7/3/2014

Program

3

WEDNESDAY 19 MARCH 2014

8.00am – 5.00pm	**Delegate Registration**
	Grand ballroom 1
9.00 – 9.30am	**Plenary Session 5** **New frontiers in brain science** **Geoffrey Ling**, Neurologist, Defence Advanced Research Projects Agency (DARPA) USA
9.30 – 10.00am	**Plenary Session 6** **New structural maps of the Brain** **Jacopo Annese,** Director, The Brain Observatory, USA
10.00 – 10.30am	**Morning Tea and Networking with Exhibitors**
10.30 – 11.45am	***Grand ballroom 1***
	Breakout Session 18
	Gallery
Supported by: Medtronic	**Breakout Session 17** **Brain Neuromodulation in the Treatment of Epilepsy, Parkinson's and ALS** **Chair: Evgeny Tsimerinov** **1. Evgeny Tsimerinov (Keynote)** *Brain Neuro Modulation in Treatment of Parkinson's, Tremor and Dystonia* **2. Tony DeSalles** *Future Applications of Brain Neuro Modulation in Treatment of Parkinson's and Neurodegenerative Disorders* **3. Lilit Mnatsakanian** *Advances in Technology in the Treatment of Epilepsy* **4. Reese Terry** *The Brain-Vagus-Heart Connections: Therapeutic Investigations* **5. Ashraf Elsayegh** *Use of Diaphragmatic Pacing System in ALS and Spinal Cord Injury* **6. Evgeny Tsimerinov** *Modern Technologies of Neuro and Brain Modulations in Treatment of ALS*
	Studio
	Breakout Session 16 **Neural Stem Cells and Regeneration** **Chair: Rasul Chudary & Ann Turnley** **1. Brent A Reynolds (Keynote)** *Building Better Brains: From Theory to Reality* **2. Rasul Chaudary** *Promise of Embryonic and Adults Stem Cells for Neural Regeneration*

Information correct as of 7/3/2014

Program

10.30 – 11.45am (Cont.)	**3. Quenten Schwarz** *Understanding the origin of neurodevelopmental disorders* **4. Ann Turnley** *What will it take to make endogenous adult neural stem cells repair the adult nervous system?*
11.45 – 1.00pm	**Breakout Session 19** **Electrodes and Electrochemistry in Brain Mapping** **Chair: Justin Gooding** **1. Evgeny Tsemerinov (Keynote)** *Modern Brain NeuroModulation in Neurologic Disorders* **2. Greg Suaning** *Electrodes in the supra-choroidal space for visual prosthesis – effecting focused cortical activation* **4. Alex Harris** *A Method for the Systematic in vitro and in vivo Evaluation of Neural Recording Electrodes* **5. Justin Gooding** *Electrodes that resist protein fouling when used in biological fluids: Applications for biosensing, cell biology and implantable electrodes*
	Breakout Session 20 **Brain 'All Omics'** **Chair: Howard Federoff** **1. Howard Federoff (Keynote)** **2. Brett Stringer** *The Establishment and Characterisation of Patient-Derived Cell line and Mouse Models for Studying Glioblastoma* **3. Brandon Wainwright** *An integrative functional genomics approach to defining key gene networks in medulloblastoma* **4. Bryan Day** *EphA3 Maintain Tumour-Initiating Cells and is a Therapeutic Target in Brain Cancer* **5. Jan Fullerton** Enrichment of polygenic risk alleles in a longitudinal cohort at high-risk of bipolar disorder
Supported by: NeuroLogica A Subsidiary of Samsung Electronics Co., Ltd	**Breakout Session 20a** **Clinical Neurology and Neurointerventions** **Chair: George Paxinos & Perminder Sachdev** **1. Bryce Vissel (Keynote)** **2. Wieslaw Nowinski** *CAD systems for ischemic and hemorrhagic strokes* **3. Eric Bailey** *Ambulance based CT and its Impact on Thrombolytic Therapy for Acute Ischemic Stroke* **4. Penelope McNulty/ Christine Shiner** *Investigating neuroplasticity post-stroke: contrasting bilateral differences in magnetoencephalography, transcranial magnetic stimulation and functional motor assessments* **5. Yih Yian Sitoh** *Neuroimaging in Psychiatry* **6. Paul Fitzgerald** *Enhanced neuroimaging based targeting to improve response to rTMS treatment in depression*
1.00 – 2.00pm	**Lunch and Networking with Exhibitors**

Information correct as of 7/3/2014

Program

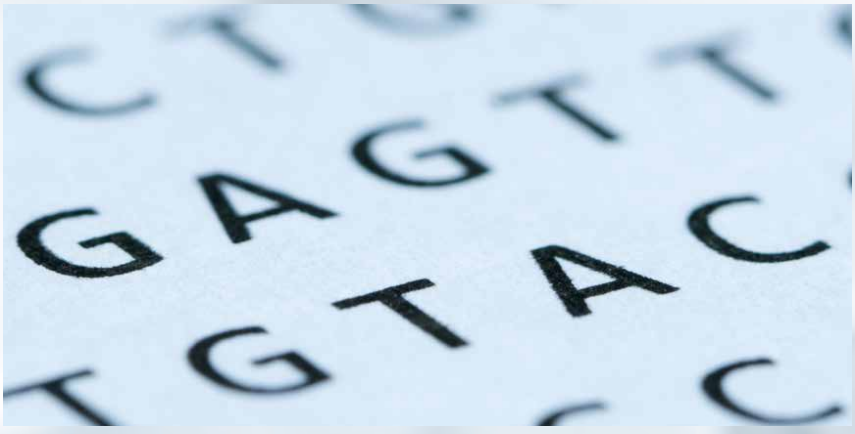
2.00 – 3.15pm	***Grand ballroom 1***
	Oral Poster Presentations **Chair: Glenn Cross** **7. Solventa Krackauskaite** *Accuracy, precision, sensitivity and specificity of non-invasive ICP absolute value measurements* **8. Jun-Young Lee** *Alzheimer disease progress and cognitive reserve* **9. Abigale Besemer** *Impact of PET and MRI Threshold-Based Tumor Volume Segmentation on Targeted Radionuclide Therapy Dosimetry using CLR1404* **10. Li Li & Yifan Zhang** *Metabolic alterations in the frontal white matter of patients with Major Depressive Disorder with treatment of SSRIs :A proton magnetic resonance spectroscopy study* **11. Avinash Waghmare** *A Novel Application of High Frequency Magnetic Stimulation: Enhancing Putative Mirror Neuron Activity* **12. NA** **13. NA** **14. Taskin Duman** *Internal Carotis Artery Thrombosis in Acute Ischemic Stroke* **15. PhuaHwee Tang** *Arterial Spin Labelling Method of assessing cerebral perfusion compared against PET imaging in children with focal epilepsy*
	Gallery
	Breakout Session 21a **Intra-operative Brain Mapping** **TBC**
	Studio
	Breakout Session 22 **New Frontiers in Brain Sciences (Nanobiotechnology, bioengineering and biomaterials)** **Chair: Babak Kateb & Jean Paul Allain** **1. Jeff Sutton (Keynote)** *Brain Alterations in Spaceflight* **2. Kuldip Sidhu** *Brain in the Petri dish – disease modelling* **3. Jean Paul Allain** *Development of magnetic bacterial nano-cellulose (MBNC) for regenerative neuroendovascular therapeutics* **4. Vicky Yamamoto** *TBC*
3.15 – 4.00pm	**Afternoon Tea and Networking with Exhibitors**
	Grand ballroom 1
4.00 - 4.30pm	**Plenary lecture 7** **Prof Warwick Anderson,** Chief Executive Officer, National Health & Medical Research Council NHMRC Funding and International Collaborations
4.30 – 5.00pm	**Conference closing remarks by organising chairman and President, Kuldip Sidhu**

Information correct as of 7/3/2014

“

Seeing the results of research translate into better patient care makes every dollar and every effort invested worthwhile”

Hon Jillian Skinner MP



NSW NOW The new state of business

NSW GOVERNMENT Health

www.health.nsw.gov.au\ohmr

Society for Brain Mapping & Therapeutics CME Disclosure Grid

March 17-19, 2014
Four Seasons Hotel Sydney, 199 George St, Sydney NSW 2000, Australia

Planning Committee and Speakers	Commercial Interest	What I received	My Role	Conflict/ Resolution
A/Prof Michael Back, MBBS, Franzcr, GradDipPsyOnc, MBA	I do not have any relevant financial relationships with any commercial interests.			None required
Valerie Brown, CPS – planning	I do not have any relevant financial relationships with any commercial interests.			None required
Babak Kateb, MD	I do not have any relevant financial relationships with any commercial interests.			None required
Dr Kerrie McDonald	I do not have any relevant financial relationships with any commercial interests.			None required
Surasak Phuphanich MD FAAN	I do not have any relevant financial relationships with any commercial interests.			None required
Major General, Professor Jeffrey V. Rosenfeld AM, OBE	I do not have any relevant financial relationships with any commercial interests.			None required
Professor Anatoly B. Rozenfeld (Rosenfeld) M.Sc., Ph.D.	I do not have any relevant financial relationships with any commercial interests.			None required
Kuldip S. Sidhu PhD	I do not have any relevant financial relationships with any commercial interests.			None required
A/Pro Charles Teo, AM, MBBS, FRACS	Aesculap	Honorarium	Consultant	Reviewed and discussed. No conflict found to exist.
Stephanie E. Weiss, MD	I do not have any relevant financial relationships with any commercial interests.			None required
James Welsh, MD	Bayer/Algeta Colossal Fossils Coqui radiopharmaceuticals Radion Global	Honorarium Nothing yet Nothing Nothing	Speaker Board member Board member (Former) co-founder and chief science officer	Reviewed and discussed. Determined no conflict exists.

Keynote and Plenary Speakers

A/Prof Kuldip Sidhu

UNSW Medicine

A/Professor Kuldip Sidhu, PhD, BSC (Medical) is a stem cell expert at the Faculty of Medicine, University of New South Wales, Australia. His post doc training is from St Louis MO USA (1979-80) in assisted reproductive technology and he also worked with Prof James Thompson, Wisconsin USA (2000) who produced the first human embryonic stem cells in 1998.

His research focus is on neural stem cells derived from both the embryonic and non-embryonic sources for developing future cell therapies for various neurodegenerative diseases, like Alzheimer's, Parkinson's and other neuronal diseases.

He has established a state-of-the-art facility to study the cell and developmental biology of stem cells. SCL has expertise to culture, propagate, differentiate, engineer and transplant in animal models the neural stem cells from various sources like human embryonic stem cells, skin-derived neuroprogenitors and human mesenchymal stem cells from bone marrow. In addition, he has expertise in the derivation of new human embryonic stem cell lines including their clonal propagation. His lab was first to produce two hESC lines, Endeavour (E) 1&2 from Australia and E2 is listed on NIH registry USA for distribution. SCL has seriously embarked on iPS Technology and produced over 100 iPSC clones from Alzheimer's patients for studying the disease processes and drug discovery.

A/Prof Sidhu has produced two books – the latest one (2012) on stem cells, thirteen book chapters, nine review chapters, two international patents, four proprietary items and one hundred and seventy original research papers including abstracts in journal of repute including one in Nature Biotechnology (2011) and all dealing with mammalian cell and developmental biology including stem cells. He shared this paper in Nature Biotechnology with Noble Laureate (2012), Prof Yamanaka. He has served on the International Society of Stem Cell Research Sub Committee and the NHMRC Cell Therapy Advisory Committee; he is a member of the editorial board of International Stem Cell Journals, the open stem cell journal and recent patent on regenerative medicine, International journal of neuropsychiatric diseases. He is on the expert panel on iPSC research for the European Union. He is president of the local chapter and vice president of the board of Society for Brain Mapping and Therapeutics, USA. He was the chair of the program committee of the 4th annual meeting of the Australasian society of stem cell research held in Sydney 2011. He has eight national and five international active research collaborations and including three with industry. He has widely travelled around the world and presented invited lectures, chaired sessions in scientific meetings, conferences.

He is recognised by many awards e.g. Medallist for outstanding research from Indian National Science Academy 1981, Best book prize, 1996, Medal for best presentation in an international conference on frontiers of reproductive biology, 1989, Best invention prize, Australia, 2007, Finalist of Eureka prize 2009, Advanced Innovation Award (Finalist), UNSW 2012. He has produced 9 PhD, 2 MSC, 4 HONS students and some of them are also recognised with Dean's list and McConaghy Prize.

His passion in science is as good as in Tennis.

Keynote and Plenary Speakers

Dr Babak Kateb

SBMT/Cedars Sinai

Babak Kateb, Neuroscientist, Chairman of the Board of SBMT and President of Brain Mapping Foundation and one of the main architects of President Obama's BRAIN initiative at the East room of the White House prior to the announcement of BRAIN initiative by President Obama (April 2ed, 2013; courtesy of BRAIN MAPPING FOUNDATION)

Dr Babak Kateb is a neuroscientist with more than 15 years of research experience. His research has been focused on peripheral neuropathy, stroke, epilepsy, fetal cell transplant into the brain, pancreatic islet xenotrasplantation, human brain computer interface and brain implants, effect of hypothermia in traumatic brain injury patients with low Glasgow Coma Score, image guided surgery using NASA's thermal and UV imaging technology, optical imaging and laser spectroscopy, microwave ablation, stem cell research, nanoneurosurgery and virtual reality neurosurgical simulation.

Babak has been serving as the founding chairman of the board of directors, CEO and Scientific director of Society for Brain Mapping and Therapeutics (SBMT) as well as President and Scientific Director of the Brain Mapping Foundation and Director of National Center for Nano-Bio-Electronics. He is a visiting scientist at NASA/JPL and Research Scientist at Department of Neurosurgery at Cedars Sinai Medical center. He is recipient of NASA Tech Brief Award for his pioneering work on sniffing cancer cells using NASA's electronic nose. He also pioneered the technique, which allowed NASA Multiwall Carbon nanotubes to be used as a nano-drug/siRNA delivery system for brain cancer therapy. He also has significant collaboration with Los Alamos National Lab on ultra-low field MRI technology and new generation of smart microscopes.

He chairs the publication committee of SBMT, as editor in chief. He has established a new publication with world's largest open access publisher: PLoSOne, which is called PLoSOne_ NeuroMapping & Therapeutics and was the force behind 3 successful IBMISPS-NeuroImage special issues with high impact factors. He is editor of "The Textbook of Nanoneuroscience and Nanoneurosurgery", which is published by one of the world's leading medical publishers, Taylor & Francis Publisher by 2012. This textbook is the first book ever published on the subject of Nanoneurosurgery.

Babak has been one of the key players in President Obama's BRAIN initiative. He has been deeply involved in global neuroscience legislation and closely collaborating with the US Congressional Neuroscience Caucus as well as members of Canadian and Australian Parliaments in order to advance neuroscience. His initiatives have impacted the way we care about the wounded warriors and created a global alliance for nanobioelectronic, a consortium that could revolutionize the way neurological disorders are diagnosed and treated.

Keynote and Plenary Speakers

Consul General Hugo Llorens

Embassy of United States of America

Hugo Llorens arrived in Sydney October 3, 2013 to become Principal Officer at the U.S. Consulate General with responsibility for the region encompassing New South Wales, Queensland and Norfolk Island.

Previously, he served as the Assistant Chief of Mission at the U.S. Embassy in Kabul, Afghanistan from May 2012 to June 2013. In that position, he served as the Chief Operating Officer of the largest Embassy in the world with a combined staff of 3,000 U.S. local and Third Country employees representing 19 U.S. government agencies. Prior to his assignment in Afghanistan, Llorens was Ambassador-in-Residence and a faculty advisor at the National War College in Fort McNair, Washington DC.

Llorens served as U.S. Ambassador to Honduras from September 2008 to July 2011. Prior to his nomination and confirmation as Ambassador, he served for two years as the Deputy Chief of Mission (DCM) at the American Embassy in Madrid, where he took up his duties September 1, 2006. Ambassador Llorens was also Deputy Chief of Mission at the American Embassy in Buenos Aires, Argentina, where he served for three years from August 2003 until July 2006.

From 2002-2003, Mr. Llorens was Director of Andean Affairs at the National Security Council (NSC), where he was the principal advisor to the President and National Security Advisor on issues pertaining to Colombia, Venezuela, Bolivia, Peru, and Ecuador. Prior to the NSC, he served for three years as Principal Officer at the Consulate General in Vancouver, Canada. In Vancouver, he created a novel multi-agency "Law Enforcement Hub" that included the opening of FBI, ATF, U.S. Customs, Secret Service, and Regional Security offices to work with Canadian counterparts on counterterrorism and international crime investigations.

From 1997-1999, Mr. Llorens was Deputy Director of the Office of Economic Policy in the Bureau of Inter-American Affairs where he helped launch Free Trade Area of the Americas negotiations in 1998. As a 32-year veteran of the U.S. Foreign Service, he has served in economic, commercial, and consular positions in Tegucigalpa, La Paz, Asunción, San Salvador, and Manila.

Mr. Llorens received his Master of Science in National Security Studies, National War College in 1997; Master of Arts in Economics, University of Kent at Canterbury, England in 1980; and Bachelor of Science in Foreign Service from Georgetown University in 1977.

Mr. Llorens has earned numerous awards for distinguished performance, including eight Superior Honor and five Meritorious Honor Awards. He is a past recipient of the Cobb Award for excellence in the promotion of U.S. business, was runner-up for the Saltzman Award for distinguished performance in advancing U.S. international economic interests, and was nominated for the James Baker Award for superior performance by a Deputy Chief of Mission. He speaks Spanish, Tagalog, and some French.

Keynote and Plenary Speakers

Kirsty Duncan

Member of Canadian Parliament

Kirsty Duncan is a Canadian medical geographer and current MP for the Liberal Party of Canada in the Toronto riding of Etobicoke North.

After graduating from Kipling Collegiate Institute in 1985 as an Ontario Scholar, Duncan studied Geography and Anthropology at the University of Toronto. She then entered graduate school at the University of Edinburgh in Scotland, and completed a Ph.D. in geography in 1992

From 1993 to 2000, Duncan taught meteorology, climatology, and climate change at the University of Windsor. In 1992, as she became increasingly aware of the increasing probability of a global flu crisis, she was led to investigate the cause of the similar 1918 Spanish flu pandemic, saying, "I was horrified we didn't know what caused [Spanish flu], and also knew that if we could find fragments of the virus, we might be able to find a better flu vaccine"

Though at the time she "knew nothing about influenza", she began what she called a "six-month crash course in virology". Eventually, she began searching for possible frozen samples of lung and brain tissue that might contain the virus. Her initial thoughts led her to think of Alaska, as it contains large areas of permafrost, which would leave the viruses intact, but the search proved fruitless.

Eventually, after several years of searching, Duncan learned of seven miners who had died from the Spanish flu and were buried in the small town of Longyearbyen, Norway, an area that would contain permafrost. She then began assembling a team of scientists to accompany her. After several more years of preparation, which involved garnering various permissions to perform the exhumations, the ground survey began in 1998. However, the samples were not viable, as the bodies were not in the permafrost, and the expedition was ultimately proved a disappointment.

In 2003, Duncan wrote a book about her expedition, entitled Hunting the 1918 Flu: One Scientist's Search for a Killer Virus. Published by the University of Toronto Press, it details Duncan's process and the expedition itself. After the book's publication, Duncan began speaking about pandemics, which led her to begin teaching corporate social responsibility at the University of Toronto's Rotman School of Management. In 2008, Duncan published a second book, Environment and Health: Protecting our Common Future.

Duncan was an adjunct professor teaching both medical geography at the University of Toronto and global environmental processes at Royal Roads University, and served on the Intergovernmental Panel on Climate Change, an organization that won the 2007 Nobel Prize with Al Gore.

Keynote and Plenary Speakers

Congressman Chaka Fattah

Senior Member of the House Appropriations Committee

Congressman Chaka Fattah is a senior member of the House Appropriations Committee. This committee is responsible for setting spending priorities for over $1 trillion in annual discretionary funds. Congressman Fattah is Ranking Member on the Subcommittee on Commerce, Justice, Science and related agencies (CJS). The Subcommittee on CJS oversees close to $51 billion in discretionary spending including the Commerce and Justice Departments, NASA. NOAA and the National Science Foundation. Fattah is also Chair of the Congressional Urban Caucus, a bipartisan group of Members representing America's metropolitan centers. These Members work collaboratively with other stakeholders to address the unique challenges facing America's urban communities.

Current Initiatives:

Fattah Neuroscience Initiative – In November 2011, President Obama signed into law the Fattah Neuroscience Initiative, the first ever federal inter-agency collaborative focused on neuroscience. Currently, the National Institutes of Health, the Department of Defense, Department of Veterans Affairs and National Science Foundation all fund research on brain development, cognition, disease and injury. While specific research or single-disease-focused projects are critical, the Congressman believes that the greatest impact from federal funding can be achieved by broad support and coordination at the highest levels of government for diverse research, addressing all areas of neuroscience. Neuroscience and brain disease affect every American family. Whether a relative is afflicted by Alzheimer's, stroke, Parkinson's, Multiple Sclerosis, depression or a traumatic brain injury, it is well understood that the incidence and national impact of these diseases is huge – and expected to grow tremendously as our population ages. It is with this knowledge, and a fascination for scientific discovery, that Congressman Fattah began this effort to highlight the role of neuroscience research, and this important area of science.

A/Prof Charlie Teo

Director, Centre for Minimally Invasive Neurosurgery

Prince of Wales Private Hospital, Sydney NSW

Dr Teo is an internationally acclaimed neurosurgeon and a pioneer in keyhole minimally invasive techniques. He has been invited to many distinguished universities in over 50 countries as Visiting Professor, including the Karolinska Institute, Vanderbilt, Stanford and Johns Hopkins universities. Dr Teo has published over 100 articles in peer-reviewed journals and authored 2 books on keyhole techniques in neurosurgery. He is the past President of ThinkFirst Australasia, the Director of the Centre for Minimally Invasive Neurosurgery, the Australian representative for the Tumor Section of the AANS and CNS and the Founder of the Cure for Life Foundation that has raised over $8 million for brain cancer research. Dr Teo has been recognised with awards from Rotary International, including the Paul Harris Fellowship (for contribution to World Health), the Brainlab Community Neurosurgery Award by the Congress of Neurological Surgeons and as a finalist in the NSW Australian of the Year awards in 2003 and 2009. In the 2011 Australia Day awards he was named as a Member of the Order of Australia and in 2012 was given the honour of delivering the Australia Day Address to the Nation. Charlie is a father to 4 beautiful girls and when not performing brain surgery is proud to support his 2 favourite charities, the Cambodian Children's Trust, which runs an orphanage in Battambang, and Voiceless, which funds legislative reform for the prevention of cruelty to industrial and farm animals.

Keynote and Plenary Speakers

Shouleh Nikzad

SBMT President Elect

Dr. Shouleh Nikzad is a Senior Research Scientist at JPL, a position conferred by the Director and the Office of the Chief Scientist in recognition of her achievements. She is also a Principal Member of the Staff and she leads the Advanced Detector Arrays, Systems, and Nanoscience Group at JPL.

Dr. Nikzad's interests in research span a wide range of fields, including materials, devices, astrophysics, space weather, and medicine. Dr. Nikzad's work in non-equilibrium techniques to modify surface and interface bandstructures has pioneered high performance imaging devices. She has initiated, developed and managed successful and innovative technology development programs, including the development of advanced UV and visible imagers and cameras, broadband UV-NIR detector arrays, soft x ray detectors, solid-state charged and neutral particle detectors, human-eye-inspired curved focal plane arrays, and nanostructure based devices. Her work on single photon counting UV imaging has produced world record sensitivity in UV that enables future NASA missions mapping of the intergalactic medium, studying primitive bodies as well as Europa and its moons. Her team also holds the record on low energy ion and neutral detection energy threshold after they improved that by an order of magnitude. This work enables compact and low power instruments for Space Weather and mass spectrometry instruments that can be used in a variety of fields including planetary atmospheric studies, life detection, and commercial applications.

Dr. Nikzad is the recipient of several awards including the Lew Allen Award of Excellence, NASA Space Act Awards, JPL Instrument Division Team awards for, and the TAP Team award for development of high speed UV camera. In 2012, She was elected as a Fellow of the American Physical Society. Shouleh is a Senior member of IEEE and has been recognized and featured by the IEEE's Women in Engineering (2011) and the SPIE's Women in Optics (2012) for being a pioneer and role model. She gave a keynot address at the Society for Women Engineers (SWE) last October in Cal Poly Pomona.

Dr. Nikzad is Visiting Faculty at Caltech's Physics Math, and Astronomy Division and Cedar Sinai Neurosurgery Department. She holds a PhD in Applied Physics from Caltech, a MSEE from Caltech and a BS degree in Electrical Engineering (Electrophysics) from USC. She has over 50 peer publications and holds over 10 US patents.

Dr. Nikzad has been with the SBMT since it's inception. In the first annual meeting, she organized a "New Horizon" session in which NASA scientists shared their work with nuerosurgeons and neuroscientist which spawned many collaborations. She is the president elect of SBMT and will be co organizing the 2015 SBMT World Congress.

Keynote and Plenary Speakers

The Hon, Jillian Skinner MP

Jillian Skinner is the Deputy NSW Liberal Leader, Minister for Health and Minister for Medical Research.

She was first elected as the Member for North Shore in February 1994 and has been re-elected five times.

Jillian began her career as a journalist in Melbourne, becoming the first woman journalist on the Victorian Parliamentary Press Gallery. She later worked as a journalist in Adelaide, Sydney and South East Asia before operating her own editorial, strategic planning and marketing consultancy.

Prior to her election to the NSW Parliament, Jillian was the Director of the New South Wales Office of Youth Affairs and she has served on bodies such as the New South Wales Women's Advisory Council and the New South Wales Youth Advisory Council.

Jillian has more experience in the health field than any other politician in Australia, having first been appointed Shadow Minister for Health in 1995. She has also held the Shadow portfolios of Education and Training and Youth Affairs and Arts.

Since becoming Minister for Health and Minister for Medical Research in March 2011, Jillian has:

- boosted the workforce (4000 additional nurses and 900 extra doctors)
- overseen a $4.7 billion hospital building program
- overseen record health spending to deliver tens of thousands more emergency department treatments, hospital admissions and elective surgeries.

Prof Trevor Kilpatrick

Melbourne Neuroscience Institute, University of Melbourne

Trevor Kilpatrick is a Professor of Neurology and Director of the Centre for Neuroscience Research and the Melbourne Neuroscience Institute at The University of Melbourne; he is the leader of the MS Division at the Florey Institute of Neuroscience and Mental Health and is a neurologist and Head of the MS Unit at the Royal Melbourne Hospital.

Professor Kilpatrick graduated with a Bachelor of Medicine, Bachelor of Surgery from the University of Melbourne in 1982 and then went on to specialise in neurology. He undertook graduate studies at The University of Melbourne and gained a Doctor of Philosophy in 1993. Appointments at The Salk Institute for Biological Studies (La Jolla, USA), Institute of Neurology (London, UK) and The National Hospital and Moorfields Eye Hospital (London, UK) followed. He returned to Melbourne as the Viertel Senior Medical Research Fellow at the Walter & Eliza Hall Institute for Medical Research and as the Head of the Melbourne Multiple Sclerosis Research Unit at the Royal Melbourne Hospital.

Professor Kilpatrick has been the recipient of the Sunderland Award (1994), AMRAD Postdoctoral Award (1995), inaugural Leonard Cox Award (2000), Bethlehem Griffiths Research Foundation Award for Medical Research (2004), the Australian Museum's Jamie Callachor Eureka Prize for Medical Research (2008), the Stephen C. Reingold Research Award by the US MS National Multiple Sclerosis Society (2010) and most recently, (2013), Professor Kilpatrick was awarded the Bethlehem Griffiths Research Foundation Medal for outstanding leadership in medical research.

Professor Kilpatrick has published widely including publications in Nature, Nature genetics and Nature Medicine. His research interests include the neurobiology of multiple sclerosis, neural precursor cell biology and the study of genetic and environmental factors that contribute to MS as well as the translation of basic research discoveries to the clinic.

Keynote and Plenary Speakers

Prof John Mattick

Garvan Institute of Medical Research

John Mattick is the Director of the Garvan Institute of Medical Research. He undertook his undergraduate and graduate training at the University of Sydney and Monash University in Melbourne. He subsequently worked at Baylor College of Medicine in Houston, the CSIRO Division of Molecular Biology in Sydney, and the University of Queensland, where he was the Foundation Director of the Institute for Molecular Bioscience and the Australian Genome Research Facility. He has also spent research periods at the Universities of Cambridge, Oxford, Cologne and Strasbourg.

John Mattick has published over 250 papers, which have received over 25,000 citations. His honours include the Honorary Fellowship of the Royal College of Pathologists of Australasia, the inaugural Gutenberg Professorship of the University of Strasbourg, the International Union of Biochemistry and Molecular Biology Medal, Fellowship of the Australian Academy of Science, Associate Membership of the European Molecular Biology Organization, and the Human Genome Organisation's Chen Award for Distinguished Achievement in Human Genetic and Genomic Research.

Prof Peter Burger

Lowy Cancer Centre

Dr Peter Burger MD, Professor of Pathology, Neurosurgery and Oncology, is the Director of Surgical Neuropathology at Johns Hopkins Hospital in Baltimore, USA. Over the last 35 years, he has made a wide range of contributions to the field of neuro-oncology and is one of the world's leading authorities on the classification and diagnosis of tumors of the central nervous system.

He has published over 400 original papers and review articles. Their impact is evidenced by the fact that more than 100 of these have been cited at least 50 times, and 38 were cited 100 times or more. He played a key role in generating all three editions of the WHO classification for CNS tumors, and influences countless pathologists and others in the field of neuro-oncology, through his many textbooks. An engaging speaker, he has given over 250 invited or honorary lectures around the globe.

Each year he reviews 1,500+ difficult brain tumor cases sent to him in consultation. He served as chairman of the Pediatric Oncology Group pathology review committee for brain tumors from 1981-2000, and has also been involved with numerous other brain tumor groups as an expert neuropathology consultant or medical advisor.

Dr Burger is the recipient of many awards including the Award for Dedication and Distinguished Service, American Association of Neuropathologists in 2009 and the Lifetime Achievement Award from the Society for Neuro-Oncology in 2010.

Dr Burger is the current Cure For Life Foundation Brain Cancer Research Visiting Academic at UNSW.

Keynote and Plenary Speakers

Major General, Professor Jeffrey V. Rosenfeld AM, OBE,

Monash University

Jeffrey V. Rosenfeld is Professor and Head, Division of Clinical Sciences of the Department of Surgery, Central Clinical School, Monash University, Director, Department of Neurosurgery at the Alfred Hospital, Adjunct Professor in Surgery at the F. Edward Hébert School of Medicine, Uniformed Services University of The Health Sciences (USUHS), Bethesda, MD, USA, Adjunct Professor, Centre for Military and Veterans' Health, University of Queensland and Honorary Professor in Neurosurgery, University of Papua New Guinea (PNG). His main research interests are traumatic brain injury and bionic vision. He is on of Australia's leading academic neurosurgeons and senior military surgeons and is internationally recognised for his neurotrauma research and teaching. He was the CIB on the landmark Decompressive Craniectomy Study, the first multicentre randomised controlled trial of this procedure which was published in the New England Journal of Medicine (NEJM) in 2011. He has been an invited Visiting Professor in 11 countries and an invited speaker for 12 named orations and 65 international meetings. He has published over 223 peer reviewed articles (including Lancet, Lancet Neurology and NEJM), 40 book chapters and 2 books. He has over 3000 citations and has over his career been awarded $20.516 million of competitive grant funding including $9.9 million from the ARC and $4.973 million from the NH&MRC. He is a member of 8 editorial boards and is a reviewer for 27 international journals. He is a Principal Investigator within the Monash Bionic Vision Group which aims to develop a bionic vision direct to brain implant with a first-in-human implant in 2015. He was a member of the Court of Examiners in Neurosurgery for the Royal Australasian College of Surgeons (RACS) for 8 years. He is a Major General in the Australian Defence Force (ADF) and was immediate past Surgeon General, ADF-Reserves 2009-2011. He has served on 7 ADF Operations including Rwanda, East Timor, Bougainville, Solomon Islands and Iraq. He was awarded the United States Air Force (USAF) Commendation Medal and the Michael E. DeBakey International Military Surgeons' Award for Excellence in Military Surgery from USUHS in 2009. He is an Honorary Fellow for 3 surgical colleges. He is also Pro-Vice Chancellor (Major Projects), Monash University, Chair, Victorian Neurotrauma Advisory Council, Honorary Fellow of the Bionics Institute, Victoria, Chair, ADF Human Research Ethics Committee and a member of the Neuroethics Committee, and the Neurotrauma and Education Committee of the World Federation of Neurosurgical Societies. He is President, Graduate Union of the University of Melbourne.

Dr Jacopo Annese

The Brain Observatory, USA

Jacopo Annese, Ph.D. is the director of The Brain Observatory in San Diego and Assistant Professor of Radiology, at the University of California San Diego (UCSD). Dr. Jacopo Annese graduated from the University of Rome (La Sapienza) with a Master degree in Biology and Zoology. He obtained his Masters in Neurological Science from University College London (London, UK) and a Ph.D. in Cognitive Neuroscience from Dartmouth College (NH, USA).

Keynote and Plenary Speakers

Dr Geoffrey Ling

Defence Advanced Research Projects Agency (DARPA)

Dr. Geoffrey Ling is the Deputy Director of the Defense Sciences Office at the Defense Advanced Research Projects Agency (DARPA) and attending neuro critical care physician at Johns Hopkins Hospital. He retired from the US Army in 2012 after serving as a military intensive care physician with multiple deployments to Iraq and Afghanistan. He formerly served in the Science Division at the White House Office of Science and Technology Policy.

Dr. Ling's DARPA research includes Revolutionizing Prosthetics, a program to develop a brain controlled prosthetic arm for amputees that has been featured on CBS's "60 Minutes", and Preventing Violent Explosive Neuro Trauma, an effort to develop new understanding and treatment of blast brain injury.

Dr. Ling received his BA from Washington University in Saint Louis, Ph.D. in pharmacology from Cornell University, and M.D. from Georgetown University. He completed a neurology residency at Walter Reed and a neuro-intensive care fellowship at Johns Hopkins.

Dr. Ling is board certified in Neurology and Neuro Critical Care. He has published over 150 peer-review articles, reviews, and chapters, including the TBI chapter in Cecil's Textbook of Medicine, the VA-DoD Guidelines for Managing mTBI/ concussion, and the DoD Guidelines for Prehospital Management of Combat Related Head Injury.

Prof Warwick Anderson

National Health and Medical Research Council

Professor Warwick Anderson is the Chief Executive Officer (CEO) of NHMRC, Australia's major governmental funding body for health and medical research. Previously, he was Head of School of Biomedical Sciences at Monash University and Deputy Director of the Baker Medical Research Institute, following research fellowships at the University of Sydney and Harvard Medical School.

Professor Anderson obtained his PhD from the University of Adelaide. His research has focused on renal causes of hypertension, including the roles of renal vascular remodeling, renal innervation and the renin-angiotensin system. He has published over 170 peer review articles.

Professor Anderson is a member of the Prime Minister's Science Engineering and Innovation Council, a Board member of the Global Alliance for Chronic Disease, a member of Heads of International (Biomedical) Research Organizations and of the National Lead Clinicians Group. He is an Honorary Fellow of the Royal College of Pathologists of Australasia and an International Fellow of the American Heart Foundation. He was made a Member of the Order of Australia in 2005.

Session Abstracts - Day 1

Plenary session 1

Neurology and neurophysiology

Prof Trevor Kilpatrick
Director, Melbourne Neuroscience Institute, University of Melbourne

Therapeutic challenges for neurodegenerative disease: the case of multiple sclerosis

Neurodegenerative diseases collectively account for a major percentage of the disability burden in our community and one that, if left unchecked, will inexorably increase with time. Over the last twenty years there has been a revolution in our understanding of the pathogenesis of these diseases but this has not, as yet, translated into improved treatment paradigms beyond the adoption of symptomatic approaches. In this lecture I will explore the challenges that face us in this arena and will illustrate the relevant issues with particular reference to Multiple Sclerosis (MS) the commonest neurodegenerative disease that affects young Caucasian adults. Multiple Sclerosis has been traditionally considered to be an autoimmune disease that results from an attack against myelin, the layer which surrounds axons. However, the pathophysiology of MS is complex, with both demyelination and axonal degeneration contributing to what is essentially an inflammatory neurodegenerative disease. Axonal loss is increasingly being accepted as the histopathological correlate of neurological disability. Currently, the underpinnings of neurodegeneration in MS, and how to promote neuroprotection are only partly understood. No established treatments that directly reduce nervous system damage or enhance its repair are currently available. Moreover, the ability of currently available immunomodulatory therapies used to treat MS, to prevent long-term disability is uncertain. Novel neuroprotective agents have been identified in preclinical studies but their development is being hampered by the absence of appropriate clinical platforms by which to test them. I will discuss some of the principal therapeutic candidates that could provide neuroprotection and emerging methodologies by which to test them. I will also discuss the academic and commercial interactions that will need to be brokered in order to develop effective translational paradigms in this field.

Plenary session 2

The central role of RNA in cognitive function

Prof John Mattick AO,
Executive Director, Garvan Institute of Medical Research
Sydney

It appears that the genetic programming of complex organisms has been misunderstood, primarily because of the assumption that most genetic information is transacted by proteins. Surprisingly, humans possess only about 20,000 protein-coding genes, similar in number and functional repertoire to those in simple nematodes that have only 1,000 cells, including a high proportion of those involved in the nervous system. By contrast, the extent of intergenic and intronic non-protein-coding sequences increases with increasing complexity, reaching 98.8% in human. The majority of these sequences are transcribed, to produce a plethora of short and long non-protein-coding RNAs (lncRNAs) that show specific expression patterns and subcellular locations. This is particularly evident in the brain, where the majority of lncRNAs are expressed in highly restricted patterns in the hippocampus, cortex and cerebellum, among others. Some lncRNAs are relatively highly expressed and associated with specialized subnuclear organelles, one of which appears to be involved in activity-dependent splicing changes in neurons and be linked to schizophrenia, whereas others are highly cell-specific. Recent evidence suggests that a major function of these lncRNAs is to guide chromosomal organization and chromatin-modifying complexes to their sites of action, to supervise the epigenetic processes that underpin development and cognition. The former is relatively hard-wired, but the latter appears to be enabled by the superimposition of plasticity on these regulatory networks by RNA editing and retrotransposon mobilization, which have evolved rapidly in mammals and especially primates.

Plenary session 2A

Molecular Markers in CNS Tumour Pathogenesis, Diagnosis, and Classification

Prof Peter Burger
Professor of Pathology, Oncology, and Neurosurgery,
The Johns Hopkins Hospital

Session Abstracts - Day 1

Progress in the molecular characterisation of CNS tumours is opening many doors for improved diagnosis and therapy. Correlation of such findings with classical histopathologic features helps define and sub classify known tumour types and aids in identifying new entities. Molecular features now supplement histological diagnoses in some cases, the "1p/19q" test for oligodendroglioma being the best example. Pathways of tumour origin and evolution are becoming apparent. Most importantly, efforts to find therapeutically exploitable molecular targets proceed apace. The extent to which histopathologic classification will be bypassed in favour of purely molecular approaches is unclear since pathogenic effects and responsiveness to treatments of specific genetic abnormalities are contextual; they depend in part on the tissues or cells from which the tumours arise. Thus, in the near future, it seems likely that molecular features will continue to sub classify classic entities such as glioblastoma rather than to establish a primary diagnosis independent of histopathological study. This may well change, however, especially if molecular inhibitors are identified whose effects are independent of tumour type or cell of origin. The latter two concepts may become less relevant, or irrelevant, in such a setting. Discovering markers and therapeutic targets identified by non-invasive techniques such as neuroimaging is a subject of great interest.

Breakout Session 1

Pluripotent Stem Cells & Neural Lineages

Chair: Martin Pera & Kuldip Sidhu


Martin Pera *(Keynote)*

Alice Pebay

Role of Lysophosphatidic acid in neural stem cells and in traumatic brain injury

Henry Chung

Whole transciptome analysis of Alzheimer's disease specific human induced pluripotent stem cells

Henry Chung[1], Perminder Sachdev[1], Kuldip Sidhu[1]

Alzheimer's disease is the most common form of dementia. Despite extensive research, no immediate therapy is available, which is due to our limited understanding of the disease. Animal models have provided great insight, but do not fully recapitulate the major disease hallmarks of human AD, hence alternative models need to be developed. Human pluripotent stem cells are one such candidate as they mimic the developmental processes of human growth and possibly disease onset and progression.

Following standard procedures, we generated human induced pluripotent stem cells (hiPSCs) from healthy, sporadic AD and familial AD individuals. Vigorous characterization assays were carried out and all cell lines were positive for classic pluripotent features, including: expression of OCT4, NANOG, SSEA4, TRA160; teratoma formation and in vitro differentiation into derivatives of the three germ layers.

To gain a better understanding of the possible disease onset/progression mechanisms, we performed a whole transcriptome analysis of the hiPSC lines. Differential gene expressions were performed and subsequent gene ontology and pathway enrichment analyses revealed a number of neuronal and immune system related terms, which correlates well with current literature.

The next steps are to differentiate this cohort of hiPSC lines into mature neurons and examine whether they develop AD phenotypes such as plaque and neurofibrillary tangle formation and importantly neurodegeneration.

[1]Centre for Healthy Brain Ageing, UNSW Medicine, UNSW 2052

Lezanne Ooi

Altered Neuronal Function in Networks Derived from Induced Pluripotent Stem Cells from Alzheimer's Disease Patients

School of Biological Sciences, Illawarra Health and Medical Research Institute, University of Wollongong, NSW2522, Australia.

Session Abstracts - Day 1

Induced pluripotent stem cells (iPSCs) from patients are facilitating research into neurodegenerative disease pathogenesis. The neuronal iPSC derived models exhibit phenotypes synonymous with their in vivo counterparts and provide a means to interrogate sporadic diseases, including Alzheimer's disease. Using a combination of advanced mass spectrometry, gas chromatography and imaging techniques we have identified key changes in lipids and proteins in cells from Alzheimer's disease patients. By promoting the formation of neuronal networks from patient iPSCs we have further interrogated the mechanisms by which these changes alter neuronal function in vitro. Using a variety of techniques we have tracked these changes during differentiation from pluripotent cells into neurons. These changes lead to extensive functional effects on neuronal signalling events. Our data establishes lipids as key players in differentiation and identifies major changes in specific lipid species in Alzheimer's disease patient cells.

Breakout Session 2a

CME Symposium, Neuro-oncology

Chair: Michael Back & Kerrie McDonald


Charlie Teo *(Keynote)*

Maximising technology in the Surgical Treatment of Gliomas

Michael Back

Radiation Therapy Dose Painting utilizing FET and FDG PET in the management of high grade glioma

Anaplastic oligodendroglial tumours are a favourable subsite of high grade glioma that have recently been shown to be associated with median survival beyond 15 years with management by combined modality therapy with limited surgery, radiation therapy and chemotherapy. The more durable survival in this high functioning younger population places a greater emphasis on optimizing therapy with a balance between tumour control and minimization of late morbidity. Although favourable prognosis, the tumour is often quite extensive at initial presentation with MRI demonstrating widespread T2 Flair change surrounding the initial T1 dense or enhancing mass. Radiation therapy is the key component of management but high dose therapy and large volume standard treatment has been associated with potential late neurocognitive effects that may reach clinical significance in patients with durable survival.

Technological improvements in diagnostic imaging, nuclear medicine and radiation therapy treatment can potentially deliver a more targeted dose of radiation to the tumour and spare normal brain. In these favourable anaplastic oligodendroglial tumours, there may be a less aggressive region identified within the tumour by these improved brain imaging techniques that may be managed with lower radiation dose. Patients can then be managed with a novel radiation approach utilizing improved targeting of radiation therapy (intensity modulated radiation therapy) to areas within the tumour at different dose levels (integrated boost) defined by MRI and PET techniques (dose painting).

This presentation will detail the technical aspects of treatment mapping, dosimetric benefits and clinical outcome in the initial 40 patients with anaplastic glioma managed under this protocol.

Prof Jeffrey Rosenfeld AM, OBE, Monash University

Targeting calcitonin receptor expressed by brain tumour initiating cells of gliobastoma multiforme

Jeffrey V Rosenfeld & Peter J Wookey[1]

The aggressive tumours GBM are generally resistant to conventional treatments. A number of potential treatments based on antibody regimens, stimulation of the immune system and drugs that target tumour-specific intracellular pathways have been tested, and are currently under trial. However **the necessity for new, effective targets remains a high priority** whilst the outcomes for patients remain poor.

- A new target, the **calcitonin receptor (CTR)**, has been identified by our group, found expressed by glioma cells in a high proportion of tumour tissue samples of patients with GBM (>90%, $p<0.05$)[2].
- In particular, CTR is expressed by cells with morphology and nucleus characteristic of malignant cells some of which express markers of brain tumour initiating cells (BTICs)[2].

Session Abstracts - Day 1

- 40% of high grade glioma cell lines that represent 4 subtypes of BTICs (proneural, neural, classical & mesenchymal) express CTR protein (QIMR data, unpublished) across all subtypes.
- Cell death is induced in CTR+ve BTICs in vitro with picomolar concentrations of the immunotoxin anti-CTR antibody:saporin conjugate in the presence of an enhancer of endosome release, namely saponin-1641 (unpublished data).

These recent, interesting results suggest testing the immunotoxin for efficacy in a mouse xenograft model to be undertaken by collaborators at QIMR[3], Brisbane in 2014.

1. Collaborators include David L Hare (Uni Melb), Sebastian GB Furness (Monash Uni), Andrew W Boyd (QIMR), Brett Stringer (QIMR), Bryan Day (QIMR), Peter Hwang (Monash Uni), Mayank Thakur & Alexander Weng (Charité University, Berlin).
2. Wookey PJ, McLean CA, Hwang P, Furness SGB, Nguyen S, Kourakis A, Hare DL, Rosenfeld JV. The expression of calcitonin receptor detected in malignant cells of the brain tumour glioblastoma multiforme and functional properties in the GBM cell line A172. Histopathol 60, 895-910, 2012. Listed by Global Medical Discovery: 25th July 2012.
3. Day BW, Stringer BW, Al-Ejeeh F, Ting MJ, Wilson J, Ensbey KS, Jamieson PR, Bruce ZC, Lim YC, Offenhauser C, Charmsaz S, ……, Boyd AW. 2013. EphA3 maintains tumourigenicity and is a therapeutic target in glioblastoma multiforme. Cancer Cell 23:238-248.

Kerrie McDonald

Surasak Phuphanich

Immunotherapy for Brain Cancer: Vaccine, PD1/PDL1 Antibody

Glioblastoma is the most common primary neoplasm of the central nervous system in adults. Despite rigorous therapeutic efforts, overall prognosis remains dismal. Specifically, multimodality therapy integrating surgery, radiation therapy and temozolomide chemotherapy is associated with a median progression-free survival of only 6.9 months, and a median overall survival of 14.6 months (Stupp, et al, 2005). For recurrent GBM the historical PFS-6 rate is dismal at ≤ 16% (Prados, 2006). Following progression, salvage therapies have historically been of nominal benefit with PFS-6 rates under 10% noted in recent meta-analyses. In one of the largest phase 3 trials for recurrent GBM, enzastaurin was compared to lomustine (CCNU). The overall survival (6.6 v 7.1 months) was disappointing demonstrating CCNU to represent one of the few agents with any activity at recurrence (Wick et al., 2010). The FDA Approval of Bevacizumab (Avastin) within the Neuro-Oncology field has been controversial and demonstrated limited efficacy in the upfront setting with a mediocre improvement in overall survival at recurrence(Lai et al., 2011). There is a need for novel therapeutic strategies for this uniformly fatal disease.

PD-1 signaling mediates immunosuppression in glioblastoma

Profound immunosuppression is a hallmark of many complex cancers including glioblastoma. Immunosuppression represents a critical tumor adaptation that contributes to poor outcome by fostering tumor immunotolerance rather than rejection. Emerging data implicate enhanced activity of the inhibitory immunoregulatory molecules programmed death-1 (PD-1) and its associated binding partners PD-L1 and PD-L2 as pivotal mediators of tumor immunoevasion for many cancers including GBM. Indeed, recent analyses confirm that PD-L1 is expressed by a high percentage of GBM cell lines and primary tumors. _ENREF_180 _ENREF_161In addition, PD-L1 expression correlates with glioma grade and is detected on CD133+ GBM stem cells. We recently evaluated PD-L1 expression in a formalin-fixed, paraffin-embedded tissue microarray of 83 GBM tumors and noted that 85% express PD-L1 in over 80% of the tumor cells, including approximately 25% that exhibited a membranous staining pattern (D. Reardon, personal communication). Furthermore, inactivating mutation of the phosphatase and tensin homolog (PTEN) tumor suppressor, which occurs in 40-50% of GBM tumors, leads to upregulation of PD-L1 expression and immunoresistance. Targeting PD-1 and PD-L1 has recently generated encouraging evidence of anti-tumor activity among advanced solid tumor patients.

ICT-107 is an autologous vaccine consisting of patient dendritic cells pulsed with six synthetic class I peptides from AIM-2, MAGE1, TRP-2, gp100, Her2/neu and IL-13Rα2. The rationale for combining MK3475 with ICT-107 is that an adaptive immunotherapy regimen combining PD-1 checkpoint blockade with anti-tumor vaccination may significantly enhance anti-tumor activity than either agent alone.26-30 Specifically,

Session Abstracts - Day 1

inhibition of PD-1 suppression of T-cell activation is expected to enhance tumor antigen-specific T cell responses. In a recently reported single-arm study, ICT-107 vaccination was associated with median PFS and OS of 16.9 months and 38.4 months and 5-year survival was 50%, respectively among newly diagnosed GBM patients (Phuphanich et al, 2013). In addition to these highly encouraging efficacy data, ICT-107 is the only vaccine that has completed accrual to a randomized, placebo-controlled clinical trial among GBM patients (clinicaltrials.gov NCT01280552). Preliminary results of this trial that enrolled 124 patients were reviewed after 67 events and demonstrated that ICT-107 was very well tolerated, and that PFS increased by 3 months in the ICT-107, per-protocol arm of the study (p=0.01, HR=0.53). A trend of improved OS was also noted on the ICT-107 arm, although final results are pending further data maturation (Immunocellular Therapeutics, unpublished data). Evaluation of pre-ICT-107 vaccine and post- vaccine samples demonstrated increase in PD-L1 expression in tumor in ¾ post vaccine samples and absence of PD-L1 expression in all pre-vaccine samples. There was also evidence of antigen specific cytotoxic T cells in post vaccine sample in a patient treated with ICT-107 demonstrating the development of a robust CTL response intratumorally (J Yu, personal communication). These clinical and immunologic data support the significant immune response correlated with clinical outcome using ICT-107 alone and provide a strong rationale for testing the synergy of PD-1/PD-L1 Antibody and ICT-107 in combination.

Breakout Session 2b

Functional Neurosurgery

Medtronic

Chair: Ray Cook

Ray Cook *(Keynote)*

Colleen Loo

DBS and Alzheimer's disease

Non Invasive Therapeutic Brain Stimulation

This talk will focus on three non invasive brain stimulation techniques, used in the treatment of neuropsychiatric disorders : Electroconvulsive therapy (ECT), Transcranial Magnetic Stimulation (TMS) and transcranial Direct Current Stimulation (tDCS). Studies have shown that these brain stimulation treatments can lead to lasting changes in brain structure and/or function. Changes shown after brain stimulation include induction of neurogenesis, alteration in functional connectivity and regional cerebral metabolism, and enhancement of neuroplasticity.

Raymond Schwartz

Neurological perspective on DBS for neurological conditions

Socrates Dokos

Modelling Direct Brain Activation in Electroconvulsive Therapy

The efficacy and cognitive outcomes of electroconvulsive therapy (ECT) have been shown to depend on variations in treatment technique. In order to investigate the effects of electrode montage and stimulus parameters on direct activation of the brain during ECT, we have developed a novel computational approach utilising high resolution finite element human head models generated from MRI scans, with anisotropic conductivity and excitable ionic formulations to simulate neuronal activation in the brain. Our computational approach can be used to compare the effects of electrode montage, as well as altered ECT stimulus amplitude, pulse width and frequency on the spatial extent of directly activated brain regions. Simulation results indicate that increases in stimulus frequency, as well as decreases in amplitude and pulse width, lead to overall reductions in the spatial extent of activated brain regions as expected. The model represents a powerful approach in understanding transcranial current flow and activation of the brain during ECT.

Session Abstracts - Day 1

Takeshi Shimizu

Functional connectivity specific to central post stroke pain and alterations after repetitive transcranial magnetic stimulation

Author & Co-authors

Takeshi Shimizu Department of Neurosurgery, Osaka University

Kouichi Hosomi Department of Neurosurgery, Osaka University

Tomoyuki Maruo Department of Neurosurgery, Osaka University

Hui Ming Khoo Department of Neurosurgery, Osaka University

Yoshiyuki Watanabe Department of Radiology, Osaka University

Toshiyuki Yoshimine Department of Neurosurgery, Osaka University

Youichi Saitoh Department of Neuromodulation and Neurosurgery, Osaka University

Introduction: It is popularly thought that repetitive transcranial magnetic stimulation (rTMS) of the primary motor cortex can relieve the neuropathic pain altering the activity of not only the target area of stimulation but the remote brain regions involved in pain sensation as well. In the analysis of neuroimaging series, the functional connectivity is defined as the statistical correlations between spatially remote neurophysiological events. The aim of this study is to investigate the functional connectivity specific to central post-stroke pain (CPSP) and the alteration of the functional connectivity induced by rTMS.

Method: 9 healthy adults and 14 CPSP patients underwent the resting state fMRI scan. The mean age of CPSP patients was 61.5. All the CPSP patients had the neuropathic pain in their upper limbs. Then, 12 CPSP patients among them underwent 5Hz rTMS over primary motor cortex and resting state fMRI after the rTMS sessions. The rTMS was applied through a figure-8 coil connected to a magnetic stimulator, which provides a biphasic pulse. It was consisted of 500 pulses at 90% intensity of resting motor threshold. 7 CPSP patients experienced pain reduction more than 10% in VAS. Functional MR data were acquired with GE (Signa HDX 3T) in the Osaka University Hospital. We analyzed the difference of the functional connectivity between 9 healthy controls and 14 CPSP patients and between pre-rTMS fMRI and post-rTMS fMRI in 7 CPSP patients who were responders to rTMS. Functional connectivity maps were calculated using the statistical software package SPM and conn, which is the toolbox running on SPM. For the group analysis, the images of the patients who had the lesions in the right hemisphere were flipped by SPM. Voxel level threshold of uncorrected $p < 0.001$ and Cluster level threshold of FWE corrected $p < 0.05$ were applied.

Results: Compared with healthy adults, CPSP patients exhibit the statistically significant increase of functional connectivity between primary sensory cortex and motor cortex and premotor cortex. After the rTMS sessions to CPSP patients, the mean reduction rate of VAS was 23.6%(±17.2%) and the functional connectivity between posterior cingulate cortex (PCC) and anterior cingulate cortex (ACC) and the functional connectivity between PCC and prefrontal cortex decreased.

Conclusion: Our findings demonstrate that the functional connectivity related to primary somatosensory cortex is different in CPSP patients and healthy controls. They also suggest that rTMS sessions restore the functional connectivity specific to CPSP patients and change the functional connectivity in default mode network (DMN) involving PCC. We speculate that the increased functional connectivity related to primary somatosensory cortex in CPSP patients may result from differentiation and interhemispheric inhibitory interaction. And we also speculate that rTMS may affect the substrates of pain perception.

Keywords: Transcranial Magnetic Stimulation (primary keyword)

Functional brain mapping (fMRI, PET?)

Breakout Session 3

ACRO CME Symposium, Neuro-radiation oncology and stereotactic radio-surgery

Chair: Anatoly Rosenfeld & Jim Welsh

Jim Welsh *(Keynote)*

Proposed New Boron Neutron Capture Therapy Program at Fermilab

James S Welsh[1]

The Neutron Therapy Facility (NTF) at Fermi National Accelerator Laboratory

Session Abstracts - Day 1

treated its first patient using fast neutrons in September 1976. As a fully functional and independent clinic, the NTF could be an ideal environment to reinitiate investigations into boron neutron capture therapy and boron neutron capture enhanced fast neutron therapy in the USA.

The Fermilab p(66)Be(49) fast neutron beam has a mean neutron energy of 25 MeV. Our team has created a means of moderating the energy down to the energies appropriate for neutron capture therapy. We have been exploring the physical characteristics of this modified beam and using it for in vitro radiobiology experiments. The moderated beam energy is enriched neutrons of epithermal energy making it potentially suitable for BNCT of deep-seated tumors without intraoperative exposure.

In parallel with the physics and radiobiology advancements, our team has been developing and evaluating various novel boronated compounds (e.g. glutamine derivatives), which may offer improved biodistributions over traditional BNCT agents.

We propose addressing two primary malignancies in future clinical trials – glioblastoma multiforme in human patients and locally advanced bladder cancer in veterinary patients, if the final analysis of the modified beam proves acceptable for clinical implementation.

[1] Northern Illinois University

Anatoly Rosenfeld

Advanced quality assurance in Stereotactic Radiosurgery for error free treatment

Anatoly Rosenfeld (on behalf of CMRP) Centre for Medical Radiation Physics, University of Wollongong, Australia

Stereotactic Body Radiation Therapy (SBRT) and Stereotactic Radiosurgery (SRS) are new radiation oncology modalities which allow the delivery of a spatially conformed high dose of radiation to the target volume, i.e. the tumour. This is achieved by directing radiation beams at the tumour from multiple angles and by delivering several sub-beams or 'beam segments' through differently shaped apertures at each treatment angle, which allows an accurate 3D "dose painting" of the target volume. Both techniques involve the delivery of a single fraction of a high dose of radiation, and therefore the uncertainty of the dose placement should not exceed 1 to 2 mm. This requirement makes Quality Assurance (QA) in SBRT and SRS extremely important and challenging. A suite of detectors aimed at performing SBRT, SRS and proton therapy pretreatment QA have been developed and implemented at the Centre for Medical Radiation Physics. Dubbed Magic Plate and Dose Magnifying Glass, both systems are capable of measuring the dose deposition pattern with a very high spatial and temporal resolution (1 mm and 0.1 ms respectively). These devices are currently being evaluated in a phantom prior to their deployment in clinical in vivo application. Results of the dosimetric pre-treatment QA of static spinal SBRT and SRT for brain tumours along with the preliminary results of targeting movable small targets in motion adaptive radiotherapy will be presented.

Synchrotron microbeam radiotherapy (MRT) is a new form of spatially fractionated radiation therapy which shows great potential as an effective treatment option for certain cancers (such as paediatric glioblastoma) while causing little damage to non-cancerous tissue compared to an equivalent treatment delivered via broad beam synchrotron radiotherapy. The radiation patterns consist of periodic narrow slit beams of 50 to 600 keV X-rays with extremely high peak dose rates of the order of hundreds to tens of thousands of Gy/s, for a typical sub-second treatment time. Conventional dosimetry techniques are not suitable for synchrotron microbeam QA since they cannot accurately measure dose with the necessary micron-scale resolution due to the extreme brightness of the synchrotron source and the enormous dynamic range of the dose delivered by the microbeam pattern. Performing direct QA dosimetry on a patient in real-time is impossible; therefore, performing accurate pretreatment dose QA in a phantom and developing suitable beam quality assurance protocols using CMRP's newly developed high-resolution dosimeter, X-Tream, is of utmost importance. Our results demonstrate that X-Tream is capable of performing fast and accurate measurements of the Peak to Valley Dose Ratio (PVDR). Its "beam transparency" and fast readout time allow for real time monitoring of the intensity of the photon microbeams in both peaks and valleys and provides a count of the number of microbeams in the MRT microbeam array, and can be used to terminate the treatment within 20 us. Results from its deployment at the European Synchrotron Radiation Facility (ESRF) as an important step towards the clinical trials on MRT technology will be presented.

Stephanie Weiss

Session Abstracts - Day 1

Breakout Session 4

Neuro-trauma and Neuropsychiatry

GE Healthcare

Chair: Michael Roy & Skye McDonald


Jeffrey Chung *(Keynote)*

Post Traumatic Epilepsy: Present and Future

Traumatic brain injury (TBI) is an increasingly prevalent disorder and, according to the World Health Organization, it will surpass most diseases as the major cause for mortality and disability. About 10 million people world-wide are affected by TBI annually, and in the United States, approximately 1.7 million new cases are reported every year. One of the sequelae of TBI is the development of post traumatic epileptic, which accounts up to 20% of all epilepsy cases. The relative risk of developing post traumatic epilepsy is 2.9 in moderate cases and 17.2 in severe cases. As high as 50% of patients suffering from penetrating head injury would develop post traumatic epilepsy. While some studies have shown that the presence of acute seizure in TBI patient is associated with a higher incidence of post traumatic epilepsy, the mechanism of epileptogenesis remains elusive. Central and lateral fluid-percussion TBI models in rats, followed by continuous EEG monitoring demonstrated the timeline of seizure development. Changes on the molecular level after TBI have been postulated in animal models; however, pharmacologic interventions including anti-inflammatory and anti-epileptic agents did not appear to be promising in preventing the development of epileptic seizures. Better understanding of epileptogenesis after TBI is necessary for earlier, more targeted interventions to prevent of development of post traumatic epilepsy.

Skye McDonald

Improving emotion regulation and heart rate variability after severe traumatic brain injury: Biofeedback has potential

Skye McDonald[1]*, Jacqueline A. Rushby[1], Alana Fisher[1], Rebekah Randall[1] & Robyn Tate[2]

Severe traumatic brain injury (TBI) is known to impair emotion regulation and arousal. Heart rate variability (HRV) is an index of autonomic (dys)regulation, reflecting the balance between sympathetic and parasympathetic influences on the central nervous system. Biofeedback techniques can regulate disrupted HRV and alleviate symptoms in disorders associated with impaired arousal. The present study aimed to examine, whether adults with severe TBI show: i) HRV dysregulation at rest; ii) improved HRV regulation via a biofeedback intervention; as well as how these relate to aspects of emotion regulation. When 30 adults with severe TBI were compared to demographically matched control particpants, they were found to have more variable HRV and SCL at rest. Three TBI particpants were excluded due to excessively high HRV. The remainder were significantly lower than the control group in HRV. This normalised somewhat after biofeedback. Higher HRV during biofeedback, and higher SCLs at rest and during biofeedback, correlated negatively with trait alexithymia (i.e. emotional awareness) in both the overall sample and separate groups. These results suggest that HRV shows promise as an index of impaired autonomic regulation in severe TBI. Biofeedback training may help normalise HRV in severe TBI; improved autonomic regulation may ameliorate impairments on emotional self-awareness.

1. School of Psychology, University of New South Wales, Australia
2. Faculty of Medicine, University of Sydney, Australia

*Corresponding author email: s.mcdonald@unsw.edu.au

Michael Roy

Identification of Predictors of Post-Deployment PTSD and postconcussive syndrome in Combat Veterans

Center for Neuroscience and Regenerative Medicine, and Department of Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD, 20814

Background: PTSD and TBI are the signature wounds of recent wars in Iraq and Afghanistan. There is often a “honeymoon” period for weeks after return when service members (SMs) often underreport symptoms, yet many subsequently develop PTSD, and TBI frequently

Session Abstracts - Day 1

leads to postconcussive syndrome (PCS). However, PTSD and PCS have similar symptoms and can be difficult to distinguish. Effective methods for identifying those at high risk immediately after deployment is important to enable early intervention to reduce symptoms, promote resilience and prevent progression to full PTSD. Sorting out the two disorders from each other also may be critical to appropriately direct therapy. The objective of this prospective cohort study is to identify the best predictors of post-deployment PTSD and PCS.

Methods: This is a prospective cohort study involving 81 SMs (including 11 with mild combat TBI) representing all military services from across the U.S. We first conducted a comprehensive baseline assessment within 2 months post deployment, including fMRI, DTI, EEG, ERPs, SNPs, neuroendocrine measures and psychophysiology. We then performed serial follow-ups at 3, 6, and 12 months, and used univariate and multivariate analyses to determine the strongest predictors of the development of PTSD and PCS.

Results: In our cohort, 6 developed PTSD and 1 developed PCS. Univariate analysis identified 49 baseline measures which were associated with PTSD at a $p<0.15$ level, and two different sophisticated multivariate measures (CART and random forests approaches) each identified 3 factors that were associated with PTSD. Two were single nucleotide polymorphisms for the dopamine transporter (DAT) and S100B genes, respectively, while the final significant factor was connectivity between the parietal operculum and the amygdala, as measured on resting state fMRI. We then performed a nested case-control study comparing those with TBI with age- and sex-matched controls. We found links between reduced fractional anisotropy in the cingulum on DTI, reduced connectivity between the PCC and MFC on fMRI, and elevated reexperiencing symptoms of PTSD (e.g, flashbacks and nightmares).

Discussion: We identified 3 factors that were associated with the development of PTSD after deployment. Variation in the DAT gene has also been reported in association with PTSD and depression in other studies. Variation in S100B, a calcium binding protein, has been associated with brain injury and neurodegenerative diseases, and is thus one potential link between TBI and subsequent PTSD. The amygdala has been associated with hypervigilance and easy startling in PTSD in other studies, so the associated activity we found on fMRI fits with that. The links we found between changes on DTI and fMRI, and PTSD symptoms is suggestive of a relationship between TBI and PTSD, which warrants further assessment in future studies.

A/Prof Stuart Grieve
Sydney Medical School & Brain Dynamics Centre, University of Sydney

Structural MRI and Diffusion Tensor Imaging evidence of network abnormalities in Major Depressive Disorder - data from the iSPOT-D trial

The iSPOT-D imaging substudy is a multi-modal MRI study of major depressive disorder (MDD) and is the largest imaging treatment prediction ever performed[1]. The study aims to answer these central questions: Is there a core brain circuitry dysfunction in depression? Are there distinctive patterns that identify specific "subtypes" of depression? What pre-treatment aspects of brain circuitry predict and moderate response to anti-depressants? We have already shown that MDD is associated with multiple sites of focal grey matter volume that markedly exceed the expected rate of loss via aging_ENREF_2[2]. We have also provided evidence of sub-types in depression using DTI[3], and have used discriminant analysis of DTI data alone to accurately distinguish MDD subjects from control subjects[4]. Most recently, we have published the most comprehensive connectomic analysis of MDD, describing in detail to key networks that characterise MDD[5]. Finally we ill present predictive data that demonstrates for the first time that DTI connectivity measures can be used to predict remission and non-remission to anti-depressant medications.

1. Grieve SM, Korgaonkar MS, Etkin A, Harris A, Koslow SH, Wisniewski S, Schatzberg AF, Nemeroff CB, Gordon E, Williams LM. Brain imaging predictors and the international study to predict optimized treatment for depression: Study protocol for a randomized controlled trial. Trials. 2013;14:224

2. Grieve SM, Korgaonkar MS, Koslow SH, Gordon E, Williams LM. Widespread reductions in gray matter volume in depression. NeuroImage. Clinical. 2013;3:332-339

3. Korgaonkar MS, Grieve SM, Koslow SH, Gabrieli JD, Gordon E, Williams LM. Loss of white matter integrity in major depressive disorder: Evidence using tract-based spatial statistical analysis of diffusion tensor imaging. Hum Brain Mapp. 2011;32:2161-2171

4. Korgaonkar MS, Cooper NJ, Williams LM, Grieve SM. Mapping inter-regional connectivity of the entire cortex to characterize major depressive disorder: A whole-brain diffusion tensor imaging tractography study. Neuroreport. 2012;23:566-571

5. Korgaonkar MS, Fornito A, Williams LM, Grieve SM. Abnormal structural networks characterize major depressive disorder: A connectome analysis. Biological psychiatry. 2014; in press

Session Abstracts - Day 1

Mayuresh Korgaonkar

Functional Imaging markers of treatment prediction in depression: data from the International Study to Predict Optimized Treatment in Depression (iSPOT-D).

Major depressive disorder (MDD) is the leading cause of disability and has an economic impact in the United States of $42 billion per year. Typically, only about 50% of MDD patients respond to antidepressant treatment and even fewer achieve remission. There are currently no clinically useful means to predict response to antidepressant medications. Improved methods for objectively predicting response to medication could therefore have an important clinical impact. Brain imaging offers a means to identify treatment predictors that are grounded in the neurobiology of the treatment and the pathophysiology of MDD. The International Study to Predict Optimized Treatment in Depression (iSPOT-D) is a multi-center, parallel model, randomized clinical trial which seeks to identify factors that predict treatment response to three commonly prescribed antidepressants. This talk will present the functional imaging markers of general-medication and specific responses to antidepressant medications identified using data from the iSPOT-D study.

Breakout Session 5

Translational Neuroscience

NSW GOVERNMENT Health

Chair: Gary Housley

Gary Housley (Keynote)

Neurotrophin-based neural repair and protection

Department of Physiology & Translational Neuroscience Facility, School of Medical Sciences, University of New South Wales, Sydney, NSW 2052, Australia.

Across the breadth of brain and nervous system injury and disease, neurotrophin signalling is moving to the vanguard of neurotherapeutics. Neurotrophins are key molecular signals for the developing central, peripheral, autonomic and enteric nervous systems. As examples, brain-derived neurotrophic factor (BDNF), acting via the tyrosine kinase receptor TrkB and downstream phospholipase C signalling, promotes development of the cerebellar Purkinje cell dendritic arbor, and during cochlear in the cochlea, BDNF and NT3 are necessary for. Expression of neurotrophins and associated Trk receptors is down-regulated with maturation of the nervous system, as the physiological function of neurotrophin signalling switches from promoting brain circuit development to maintenance of circuit function and synaptic plasticity. However, potent latent capacity for neural (re) development is evident by the propensity of neuronal outgrowth when neurotrophins are delivered to the nervous system following injury. The potency of neurotrophins to stimulate neural repair following sensori-neural hearing loss exemplifies this. The establishment of the afferent innervation of the cochlea occurs via a precise spatiotemporal program, where promiscuous spiral ganglion neurite outgrowth is followed by pruning and selective neuronal apoptosis; processes inherently tied to neurotrophin signalling[1]. Sensori-neural hearing loss, for example with noise or chemical ototoxicity, causes loss of the neurotrophin source and consequent auditory nerve atrophy. Cell-based, drug or gene therapy strategies around the neurotrophin translational research platform in the cochlea promote vigorous auditory nerve regeneration, with directional guidance queues reminiscent of the developmental programming. Such control of neural repair provides an opportunity to enhance medical bionics neural prosthetic interfaces; a neurotrophin gene delivery platform we have developed has established proof of principle showing improved hearing performance with cochlear implants. More broadly, neurotrophin-induced neural regeneration and neuromodulation is establishing a translational base across the spectrum of injury and age-related neurological disorders.

1. Barclay M, Ryan AF, Housley GD (2011) Type I vs type II spiral ganglion neurons exhibit differential survival and neuritogenesis during cochlear development. Neural Development 6:33 doi:10.1186/1749-8104-6-33.

Session Abstracts - Day 1

Renee Morris

Gene therapy for spinal repair

Department of Anatomy & Translational Neuroscience Facility, School of Medical Sciences, UNSW Australia, Sydney, NSW 2052, Australia.

Spinal cord injury (SCI) is a long-term health and socio-economic burden worldwide. Although there is no cure for SCI, there is evidence that implants of cells genetically modified to secrete neurotrophic factors elicit axonal elongation and sprouting in the injured spinal cord[1]. However, axons tend to dwell in these neurotrophin-rich implants rather than to seek out for and reconnect with motor neurons caudal to the lesion, a process that is essential for the recovery of function. Our research efforts aim to overcome the limitations associated with these cell implants.

We have developed a rat model of partial SCI transection at cervical levels. While retaining the ability to reach, rats with such transection are no longer capable to rotate the paw during the grasping action, a motor sequence called the arpeggio movement[2]. This movement in the rat shares extensive similarities with human prehension (e.g. typing on a keyboard, operating a hand-controlled wheelchair joystick etc.), the return of which is most important to quadriplegics.

We have also characterized the relationship between the spinal cord motor neurons and the forelimb muscles that they supply[3-4]. This analysis revealed that motor neurons are organized into discrete columns that span across several segments of the cervical spinal cord. Neurons in the uppermost segments of the spinal cord innervate the proximal muscles of the neck and shoulder, while those located in the middle and lower cervical segments supply more distal muscles of the upper and lower forelimb, respectively.

One can take advantage of the muscle/motor neuron topography as well as the retrograde transport machinery of neurons to shuttle neurotrophin genes into motor neurons occupying specific spinal cord segments. In our rat model of SCI, we are currently performing intramuscular injections of adenoviral vectors to achieve gradients of gene expression into the cervical spinal cord. In this minimally invasive gene therapy scenario, the motor neurons per se become baits for the pre-synaptic injured axons. This innovative approach, by encouraging axons to elongate enough to possibly reconnect with motor neurons, has the potential to overcome the poor outcomes obtained so far with static implants of genetically engineered cells, therefore bringing gene therapy a step closer for human SCI.

1. Morris R. Neurotoxicity and neuroprotection in spinal cord injury. In: Handbook of Neurotoxicity (R Kostzewa ed) Springer (in press).

2. Morris R, Tosolini A P, Goldstein J D and I Q Whishaw (2011). Impaired arpeggio movement in skilled reaching by rubrospinal tract lesions in the rat: a behavioural/anatomical fractionation. J. Neurotrauma 28:2439-2451.

3. Tosolini A P and R Morris (2012). Spatial characterization of the motor neuron columns supplying the rat forelimb. Neurosci. 200:19-30.

4. Tosolini A P, Mohan R and R Morris (2013). Targeting the full length of the motor end plate region in the mouse forelimb increases the uptake of Fluoro-Gold into corresponding spinal cord motor neurons Front. Neurol. 4, 58:1-10

Matthias Klugmann

Gene therapy for leukodystrophies

Department of Physiology & Translational Neuroscience Facility, School of Medical Sciences, UNSW Australia, Sydney, NSW 2052, Australia.

Oligodendrocytes represent a highly specialized class of glia in the CNS. They provide electrical insulation of axons by sheathing them in membrane extensions (myelin) enabling fast impulse conduction of axons. Oligodendrocyte dysfunction results in demyelination and secondary axonal degeneration. Acute or chronic demyelination underlies the pathology of leukodystrophies, inherited myelin diseases typically caused by single gene mutations. These disorders are incurable and associated with substantial morbidity and mortality. This represents a strong rationale for gene therapy. In fact, the leukodystrophy Canavan Disease was the first neurological disorder ever on trial using a gene replacement approach. Gene therapy is based on the simple concept of introducing a therapeutic gene to dysfunctional cells with the aim of slowing or reversing disease progression. However, sufficient expression levels of the therapeutic protein require efficient and specific gene delivery systems. Promising results were obtained recently following lentivirus-mediated gene therapy to treat children with metachromatic leukodystrophy, a disease caused by deficiency of the secreted enzyme ARSA. The genetic treatment of this disease type can be benefited by cross-correction - the transduction of a small number of host cells followed by release of the

Session Abstracts - Day 1

therapeutic enzyme and subsequent uptake by non-transduced cells. However, leukodystrophies caused by loss of non-secreted proteins, require a gene delivery system that targets sufficient numbers of oligodendrocytes in large CNS areas, ideally through the systemic route of administration. Recent advances in the development of recombinant adeno-associated virus (AAV) vectors – the most efficient vehicles for CNS-targeted delivery – address both requirements. In summary, gene therapy for leukodystrophies, one of the most devastating group of neurological disorders, has been shown to actually work. The technologies involved might be employed to establish effective treatments for other demyelinating diseases such as multiple sclerosis.

Andrew Moorhouse

The KCC2 chloride transporter as a target for epilepsy

Department of Physiology & Cellular and Systems Physiology, School of Medical Sciences, University of New South Wales, Sydney, NSW 2052, Australia.

The correct balance of neuronal excitation and inhibition is critical for normal brain function and is disrupted in a myriad of neuronal disorders. A key determinant of the efficacy of neuronal inhibition is KCC2, a Potassium Chloride Co-transporter (SLC12A5, isoform 2) that typically extrudes Cl- and thereby maintains a low intracellular Cl- in neurons that facilitates a robust hyperpolarisation in response to activation of inhibitory GABAA receptor channels. It has become strikingly clear in recent years that KCC2 function is rapidly lost in various neuronal injuries, including axotomy, ischemia, chronic pain and epilepsy[1]. The loss of KCC2 renders GABA inhibition ineffective or even excitatory, which may exacerbate the neuronal injury and maladaptive plasticity accompanying this change. We have been investigating the mechanisms and consequences of this KCC2 down-regulation in different neuronal injury models, both in vitro[2,3] and in vivo[4], recently focussing on epilepsy. Injection of mice with the chemoconvulsant kainic acid or pilocarpine results in a severe seizure phenotype, status epilepticus, characterised by continuous stage 3-5 behavioural seizures and high amplitude bursts of spikes on electroencephalography (EEG). Using a conditional tetracycline biogenic mouse developed by our colleagues in Japan, upregulation of KCC2 in adult mice confers a marked resistance to seizure activity and completely prevents status epilepticus. Furthermore, KCC2 upregulation has no effect on a range of mouse behaviours including locomotion in the open field test and measures of exploration and anxiety in the elevated plus maze. We have now established a robust mouse model of Temporal Lobe epilepsy in which we can reproduce the symptoms of frequent focal seizures and temporal lobe necrosis, and in which changes in GABA signalling seem to contribute to the pathogenesis of seizures. In summary our results suggest that upregulating KCC2 has little effect on basal GABA signalling and transmission in the healthy, normal brain, but can markedly sustain inhibition in the hyperactive brain, thereby preventing seizures. Targeting KCC2 and Cl- homeostasis is a novel approach to maintain neuronal inhibition and potentially mitigate against neuronal diseases such as epilepsy and chronic pain.

1. Moorhouse, A.J. and Nabekura, J (2011) Cellular Mechanisms of Neuronal Cl- Homeostasis and its Modulation by Neuronal Injury. In Inhibitory Synaptic Plasticity. Contemporary Neuroscience Series. Springer. Ch. 9, pp. 123-36.
2. Wake, H., Watanabe, M., Moorhouse, A.J., et al. (2007) Early changes in KCC2 phosphorylation in response to neuronal stress results in functional downregulation. J. Neurosci., 27: 1642-1650.
3. Watanabe, M., Wake, H., Moorhouse, A.J. & Nabekura, J. (2009) Clustering of neuronal K+-Cl- cotransporters in lipid rafts by tyrosine phosphorylation. J Biol Chem., (4) Eto, K., Ishibashi, H., Yoshimura, T et al., (2012) Enhanced GABAergic activity in the mouse primary somatosensory cortex coupled with reduced potassium-chloride cotransporter function is insufficient to alleviate chronic pain behaviour. J Neurosci. Nov 21; 32(47); p 16552-16559.

John Power

Molecular targets for addiction and memory disorders

Department of Physiology & Translational Neuroscience Facility, School of Medical Sciences, University of New South Wales, Sydney, NSW 2052, Australia

Our memories and the emotions they evoke not only allow us to adapt to our environment, but also help define our sense of self. Memories are thought to be coded by the coordinated activity of small networks of neurons. New memories are formed by activity dependent changes in the synaptic connections between neurons leading to the formation of new neuronal ensembles. The cellular processes that underlie the formation of new neuronal networks involve both changes at individual synapses and changes in the neuronal response to synaptic activity. Learning-associated excitability changes include the reduced activity of a calcium-activated potassium current that limits the generation of action potentials.

Session Abstracts - Day 1

This excitability change occurs in several brain regions involved in memory formation, including the hippocampus, the amygdala, and the cortex. Interestingly, in hippocampal neurons, this current increases with age and this increase correlates with age-related memory impairments observed in humans and other animal species[1,2]. Our results have shown that this calcium-activated potassium current reduces the integration of synaptic inputs, thus limiting the neurons capacity to form enhanced neuronal connections[3]. Pharmacological agents, such as muscarinic acetylcholine receptor agonists, that reduce this specific potassium current in vitro, facilitate hippocampal-dependent learning in ageing subjects[4]. It is becoming increasingly apparent that the cellular changes that underlie addiction are strikingly similar to that of memory formation; involving changes in both synaptic connectivity and intrinsic neuronal excitability. Thus, targeting the specific ion channels and cellular mechanisms involved in intrinsic neuronal excitability is likely to have therapeutic value not only for the treatment of cognitive disorders involving impaired or inappropriate memory formation such as Alzheimer's disease and post-traumatic stress-disorder, but also for addiction.

1. Power, J.M., Wu, W.W.H., Sametsky, E., Oh, M.M., Disterhoft, J.F. (2002). Age-Related Enhancement of the sIAHP in Hippocampal CA1 Pyramidal Neurons in vitro. J. Neurosci. 22:7234-43.
2. Moyer JR, Jr., Power JM, Thompson LT, Disterhoft JF (2000) Increased excitability of aged rabbit CA1 neurons after trace eyeblink conditioning. J Neurosci 20:5476-5482.
3. Power, JM, Bocklisch, C, Curby, P and Sah, P. (2011). Location and Function of the Slow Afterhyperpolarization channels in the Basolateral Amygdala. J. Neurosci. 31:526-37.
4. Oh, M.M., Power, J.M., Thompson, L.T., Moriarty, P., Disterhoft, J.F. (1999) Metrifonate increases neuronal excitability in CA1 pyramidal neurons from both young and aging rabbit hippocampus. J. Neurosci. 19(5):1814-1823.

Breakout Session 6

Adult Stem Cells & Personalised medicine

Chair: Bob Williamson & Mirella Dottori


Bob Williamson FRS
University of Melbourne *(Keynote)*

Stem Cells and Personalised Medicine

"Personalised Medicine" infers clinically relevant information from the genotype and phenotype of an individual; it is hard to think of anything more personal than someone's stem cells. The various medical uses proposed for stem cells each raise questions of feasibility, safety and ethics. Cells prepared from a patient have obvious immunogenetic advantages over cells from another individual (whether embryo or adult), but vary from one preparation to another. In the case of the newest suggested procedure, using acid to induce pluripotency, we are not even sure it works! Risks of rejection, and of causing cancer, are real, but also apply to bone marrow transplants, the one form of stem cell therapy that has already been in common use for thirty years. Stem cell tourism is deplorable, but it does seem to tell us that most patients survive injections of poorly characterised unmatched cells without serious damage, if also without serious improvement. We should encourage, even demand, careful clinical trials of stem cell therapies in countries which are experienced in such matters, including the use of matched stem cells for cerebral palsy, for eye diseases, for tissue engineering, and for heart attacks. We should remind ethics committees that it is unethical to stop much-needed research into diseases for which, at present, we have no satisfactory treatment. We should remember that advances in clinical care are almost always incremental and not revolutionary, often individual rather than general, and we should discipline ourselves to abjure wild, sweeping claims of the coming impact of stem cell science on medicine.

Vicky Yamamoto

Small molecule based approaches for personalized medicine and adult stem cell therapy

Abstract: There is considerable interest in the development of personalized medicine for the treatment of various human diseases including neurological disorders and cancer. Adult stem cells offer enormous potential as therapies as they can replace diseased or damaged tissues. Reprogrammed adult cells are even more attractive as a therapy as they can overcome any immune rejection. While viral transfection methods and using growth factors have been commonly used to manipulate stem cell fate, the methods have some limitation, especially for clinical application. Using small molecule modulators can circumvent some of the limitation and is becoming an emerging method in stem cell biology. Here, we will describe the current progress of using small molecule modulators to control

Session Abstracts - Day 1

stem cell fate and how they can be used in clinical application. In addition, we will present how a small molecule Wnt/beta-catenin inhibitor was used for cancer therapy.

James Bourne

Does Functional Neurogenesis Occur in the Injured Neocortex of the Nonhuman Primate?

Research over the last 15-20 years has overturned the dogma that the generation of neurones in the mammalian central nervous system (CNS) is restricted to development. It is now firmly established that new neurones are generated in the hippocampus and the olfactory bulbs throughout adult life. Whether neurogenesis can be induced in other areas of the adult CNS following injury and in particular whether these neurones can functionally integrate into existing neural circuits remains controversial. Most keenly debated is the idea that new neurones could be generated in the adult neocortex and contribute to neural repair, an area normally refractory to adult neurogenesis. Fuelling this debate is the finding that that new neurones are generated in the adult neocortex of the rodent following specific types of cortical injury. Moreover, significant synaptic plasticity and neurogenesis occurs following CNS injury in higher-order mammals, including monkeys.

The significant finding that neurogenesis in the monkey can be induced following injury of the neocortex, an area that is often damaged as a result of traumatic brain injury and stroke, raises the exciting possibility that similar mechanisms could operate in the human. A rigorous understanding of endogenous regenerative mechanisms in the monkey neocortex could have a transformational influence on our attempts to potentiate CNS regeneration in the human. We are now undertaking to address the fundamental question as to whether quiescent NPCs exhibit the capacity to generate neurones that functionally integrate and survive long term in the visual cortex of the marmoset monkey following an ischemic injury.

Mirella Dottori

Functional characterization of Friedreich Ataxia

iPS-derived neuronal progenitors and their integration in the adult brain.

Matthew J. Bird[1, 2], Karina Needham[3], Ann E. Frazier[1,2], Jorien van Rooijen[4], Jessie Leung[4], Shelley Hough[4], Mark Denham[4], Matthew E. Thornton[5], Clare L. Parish[6], Bryony Nayagam [3], Martin Pera[4, 6, 7], David R. Thorburn[1,2,8], Lachlan H. Thompson [6] and Mirella Dottori [4, 9].

Friedreich ataxia (FRDA) is an autosomal recessive disease characterised by neurodegeneration and cardiomyopathy that is caused by an insufficiency of the mitochondrial protein, frataxin. Our previous studies described the generation of FRDA iPS cell lines that retained genetic characteristics of this disease. Here we extend these studies, showing that neural derivatives of FRDA iPS cells are able to differentiate into functional neurons, which don't show altered susceptibility to cell death, and have normal mitochondrial function. Furthermore, FRDA iPS-derived neural progenitors are able to differentiate into functional neurons and integrate in the nervous system when transplanted into the cerebellar regions of host adult rodent brain. These findings are highly significant for developing FRDA therapies using patient-derived stem cells.

1. Murdoch Childrens Research Institute, Royal Children's Hospital, Australia
2. Department of Paediatrics, The University of Melbourne, Australia.
3. Department of Otolaryngology, The University of Melbourne, Australia
4. Department of Anatomy and Neuroscience, The University of Melbourne, Australia
5. Broad Center for Stem Cell and Regenerative Medicine, University of Southern California, USA
6. Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Australia
7. Walter and Eliza Hall Institute, Australia
8. Victorian Clinical Genetics Services, Royal Children's Hospital, Australia.
9. Centre for Neural Engineering, Department of Electrical and Electronic Engineering, The University of Melbourne, Australia

Yashar Kalani

exRNAs as biomarkers of neurological disease

Breakout Session 7

Neurology and Neurophysiology

Brain Sciences UNSW

Chair: Matthew Kiernan

Session Abstracts - Day 1

Keith Black *(Keynote)*

Mourad Tayebi

Ian Hickie

Delayed sleep offset and other markers of circadian rhythm disruption are common in young people with emerging mood disorders

Background: Episodic bipolar and unipolar mood disorders are characterized by disruptions in sleep-wake cycle, patterns of physical activity and circadian rhythms. These phenomena are most evident in those who experience recurrent mania or 'atypical' depressive episodes. As 75% of major mental disorders emerge before age 25 years, the focus on recording the earliest features of these disorders in teenagers and young adults

Methods: We have investigated sleep-wake cycle, physical activity and circadian features in young persons with emerging mood disorders in two large clinical samples (n=307, 30% bipolar-type, mean age = 19 years; n=1797, 16% bipolar-type, mean age = 18 years). Additionally, we are investigating phenotypic and circadian features in a longitudinal study of adolescent twins (n=2459, mean age=16 years). Measures include objective and prolonged actigraphic-derived assessments of 24-hour sleep-wake cycles and daytime physical activity, early evening melatonin secretion patterns and relevant metabolic function parameters in selected sub-groups.

Results: In clinical samples, there is evidence of delayed onset and offset of sleep-wake cycles, reduced day-time physical activity and disrupted onset of night-time melatonin release in up to half of young persons with emerging mood disorders. These features are more pronounced in those with more severe conditions and those with a history of mania or hypomania episodes. In twins, sleep-wake cycle phenotypes are predicted by shared genetic characteristics and appear to have their own longitudinal associations with the 'atypical' as distinct from more classical 'anxious depression' illness-type. Additionally, hypomanic-type features are extremely common in young people, with about one-in-five reporting at least one episode of sleep disturbance and activitation prior to age 25 years.

Conclusion: Delayed sleep offset and disrupted circadian function are characteristics of a major subgroup of young people with emerging mood disorders. While under strong genetic control, these features are exacerbated by other environmental and illness-related factors. These studies provide unique data concerning relationships between circadian factors and the onset and course of depression, and other comorbidities, in young persons during the early phases of illness. Circadian systems may represent a key target for behavioural or pharmacological treatments of depression independent of other illness characteristics.

1. Hickie IB, Rogers NL. (2011) Novel melatonin-based therapies: Potential advances in the treatment of major depression. The Lancet, 378(9791): 621-631.
2. Naismith SL, Hermens DF, Ip TKC, Bolitho S, Scott E, Rogers NL, Hickie IB (2012) Circadian profiles in young people during the early stages of affective disorder, Translational Psychiatry, e123.
3. Scott EM, Hermens DF, Naismith SL, Guastella AJ, De Regt T, White D, Lagopoulos J Hickie IB. (2013) Distinguishing young people with emerging bipolar disorders from those with unipolar depression. Journal of Affective Disorder, 144, 208–215.
4. Robillard R, Naismith SL, Rogers NL, Ip TKC, Hermens DF, Scott EM, Hickie IB (2013) Delayed sleep phase and sleep disturbances in young people with unipolar or bipolar affective disorders, Journal of Affective Disorders, 145: 260-263.
5. Hickie IB, Scott J, Hermens DF, Scott EM, Naismith SL, Guastella AJ, Glozier N, McGorry P. (2013) Clinical classification in mental health at the cross-roads: which direction next? BMC Medicine, 11:125
6. Hickie IB , Naismith1 SL , Robillard R, Scott EM, Hermens DF. Manipulating the sleep-wake cycle and circadian rhythms to improve clinical management of major depression. (2013) BMC Medicine, 11:79, doi:10.1186/1741-7015

Steve Vucic

Cortical dysfunction in Motor Neurone Disease

Trevor Kilpatrick

Genomics of multiple sclerosis

T.J. Kilpatrick[1,2], J. Field[2], M. Binder[2], A. Fox[2], H. Butzkueven[3] in collaboration with ANZgene and the IMSGC

Multiple sclerosis (MS) is the quintessential complex human disease, with its pathogenesis reflecting a breakdown in homeostatic interactions between the immune and nervous systems; its effective interrogation therefore requires a

Session Abstracts - Day 1

systems biology approach. It is clear that there is an inherited component influencing the susceptibility to MS, given that the risk for sibs of people with MS is approximately 30 fold that of the general population and given that the concordance rate for monozygotic twins is estimated at up to 30%. It has been known for over 30 years that the MHC class II complex contains susceptibility gene(s) for MS but until recently the field has failed to identify additional loci because of insufficiently powered studies, inadequate coverage of the genome and lack of standardisation to enable replication. To identify additional multiple sclerosis (MS) susceptibility loci, we and others have been taking advantage of recently developed technology that enables genome-wide association scans (GWAS). Utilising this approach, more than 100 genetic loci, identified on the basis of variable frequencies of commonly inherited polymorphisms, have now been found to contribute to the susceptibility of MS. However, the specific genes involved, the degrees to which rare genetic variants contribute to disease susceptibility and how the relevant genes interact all remain uncertain. We are currently unravelling these complexities by adopting a number of approaches, including the fine mapping of individual loci, as well as focusing on epigenetics and expression quantitative trait locus (eQTL) analyses. We are also involved in understanding how the environment and genetic variation interact to transform predisposition into active disease and in the identification of the genetic determinants of disease severity as a preamble to enabling a pharmacogenomic approach to therapeutic intervention.

1. Melbourne Neuroscience Institute, University of Melbourne
2. The Florey Institute of Neuroscience and Mental Health
3. Department of Medicine, Royal Melbourne Hospital

Breakout Session 8

Molecular Imaging

Chair: Roger Ordidge & Gary Egan


Kishore Bhakoo *(Keynote)*

David Reutens

Roger Ordidge

Study of sodium selenate as a treatment in traumatic brain injury using MRI.

Ordidge, R., Shultz, S.R., Wright, D., Zheng, P., Johnston, L., Hovens, C., O'Brien, T.

The University of Melbourne and Royal Melbourne Hospital

Hyperphosphorylated tau protein has been implicated in cerebral damage in a variety of neurodegenerative disorders, including traumatic brain injury (TBI). In this study, we used magnetic resonance imaging (MRI) to assess whether treatment with sodium selenate, a compound that reduces the pathological hyperphosphorylation of tau by increasing the activity of PP2A, would reduce neurodegeneration in a rat fluid percussion model of TBI. Animals were given either a severe lateral fluid percussion injury (LFPI), or sham-injury and treated with either a continuous administration of sodium selenate (1 mg/kg/day) or saline (sham group), via a subcutaneous osmotic mini-pump for a period of three months. Anatomical T2-weighted and high angular resolution and high b-value diffusion images were acquired at baseline and one week, one month and three months post-injury using a 4.7T Bruker MR scanner. Volumetric and axonal integrity measures including fractional anisotropy, mean diffusivity and tractography were investigated. Results demonstrated that continuous sodium selenate treatment reduced neurodegeneration after a severe LFPI. These findings were supported by behavioural and histological assessments which taken together, suggest that sodium selenate has a neuroprotective effect. Therefore, such an approach has potential value as a novel treatment following TBI.

Session Abstracts - Day 2

Plenary Session 3

Regenerative medicine and stem cells

Plenary Session 4

Neurosurgery

Prof Jeffrey Rosenfeld AM, OBE, Monash University

Improving the outcome from severe traumatic brain injury: how much further can we go?

There have been many recent advances in the management of severe traumatic brain injury (TBI) including improved trauma systems, prehospital care, and intensive care with multimodality monitoring. Despite this, on average 39% of patients with severe TBI die and 60% have an unfavourable outcome. The lowest mortality rates for severe TBI are around 10 to 20%. The efficacy of therapeutic hypothermia is uncertain. Prehospital induction of hypothermia is currently under trial. Decompressive craniectomy requires further research to determine when it is likely to be most beneficial.

Disappointingly few discoveries in the laboratory have translated into treatment for severe traumatic brain injury (TBI) in humans. There are many reasons including the heterogeneity and complexity of TBI, misleading extrapolation of animal data to humans and flawed trial design. There are also a number of confounding intrinsic host factors including genomics of mitochondrial DNA, cytokine response, and APO-E alleles which may have a deleterious effect on patient outcome. Neuro-inflammation may also have long lasting adverse effects.

On the positive side, there are some promising therapies such as erythropoietin, progesterone, cyclosporine and statins which are currently being trialled. CENTER-TBI and TRACK-TBI are large European and American TBI patient data bases which will better characterize TBI. Comparative effectiveness research from these datasets will provide an enhanced evidence base for the efficacy of various treatments in severe TBI. Enhanced neuroplasticity, reduction of neuronal cell death, and the inhibition of inflammation and gliosis will be important therapeutic strategies at a cellular level. Improved techniques in physical and mental rehabilitation will likely improve outcome further. PTSD and depression post injury are increasingly recognized. More attention will need to be focused on the quality of patient outcome as well as mortality. Further improvements in outcome following severe TBI are likely to be imminent.

Breakout Session 9a

NanoBioElectronics

Chair: Babak Kateb

Prof Jeffrey Rosenfeld AM, OBE, Monash University *(Keynote)*

The development of bionic vision at Monash University

Jeffrey V Rosenfeld
Professor and Head, Division of Clinical Sciences and Department of Surgery, Central Clinical School, Monash University.
Director, Department of Neurosurgery, The Alfred Hospital, Melbourne, Victoria, Australia 3004

Co-authors: Professor Arthur Lowery, Dr Li WH and Dr Jeanette Pritchard (Department of Electrical Engineering, Monash University), Professor Marcello Rosa and Professor Ramesh Rajan (Department of Physiology, Monash University), E Harvey (miniFAB™), Harcourt J (Grey Innovation) and the Bionic Vision Group at Monash University.

Aims: The Monash University Bionic Vision Program commenced in April 2010 and aims to develop and implant a human bionic vision device by end 2014. Electrical stimulation of human visual cortex produces light percepts (phosphenes) and we believe that with a high enough density of electrodes spread over the primary occipital cortex (V1) that there would be sufficient resolution of vision via a digital camera/computer interface, that blind individuals would be able to navigate the environment and read large print. Cortical stimulation is an alternative to retinal stimulation where the retina is unsuitable due to injury or disease.

Methods: This is a collaborative project between the Departments of Electrical and Computer Systems Engineering, Physiology, Surgery

Session Abstracts - Day 2

and Ophthalmology at Monash University and the Alfred Hospital. Commercial partners are miniFAB™ and Grey Innovation. A multi-tiled wireless electrode array has been developed and is being tested in animals. Each tile has 45 insulated titanium micro-electrodes which will penetrate the visual (VI) cortex. There will be > 400 electrodes implanted unilaterally. A small unilateral occipital craniotomy will be performed for access. Robotic vision algorithms have been incorporated into the 'pocket' computer which will enhance the visual percepts. A psychophysics program is being developed for clinical evaluation of the recipients.

Results: The progress to date in computer vision algorithms, system component design and experimental results will be presented. The challenges of producing a safe effective commercial device which is approved by the regulators will be discussed.

Conclusions: The development of a cortical implant for bionic vision is achievable. This Monash University/private industry commercial partnership is a strong model for translational research.

Shouleh Nikzad

Advanced Technology for Planetary, Astrophysics, and Medical Applications

Shouleh Nikzad
Jet Propulsion Laboratory
Pasadena, California 91109

In recent years, NASA's trend toward less costly and potentially more frequent missions has created a need for smaller and more capable instruments for astronomy, in situ planetary applications, as well as, atmospheric analysis and other remote sensing applications. With applications in many fields including astronomy, biology, planetary science, and Earth obsrevation, ultraviolet and visible imaging and detection technologies are crucial for in situ and remote sensing. neurosciences and criminology. Because many of the features and phenomena under study produce faint signals, the importance of detectors is common in many fields including neuroscience, neurosurgery, pathology, oncology, criminology, and semiconductor fabrication industry.

There is special synergy between in NASA instruments and medical instruments. We use this synergy and leverage from the technology developed for space missions for use in medical fields. In this talk, we discuss the general overlap of technological requirements in the medical field and space sciecne. We will discuss an overview of our UV/visible/near infrared detector program at JPL as well as our nanotechnology-based technologies, and their applications. We will discuss the recent results and plans of our clinical trial of imaging technology.

Keywords: UV Imaging, Nanotechnology, Neurosurgery

Justin Gooding

Nanobioelectronic Interfaces that Facilitate Efficient Electron Transfer to Biomolecules

J. Justin Gooding, Simone Ciampi, Guozhen Liu, Abbas Barfidokht

Australian Centre for NanoMedicine and School of Chemistry, UNSW Australia, Sydney, NSW 2052

The heart of the bioelectronics device is electron transfer between biomolecules and electrodes. This talk will cover two studies from our laboratory that focus on achieving efficient electron transfer at biointerfaces for sensing applications that have broader applicability in bioelectronics.

The first concept is to combine the material of electronics, silicon, with bioelectronics but modifying oxide free silicon with self-assembled monolayers that can facilitate electron transfer to biomolecules. Recently, we have shown that the modification of silicon with 1,8-nonadiyne produces silicon surfaces that are both more resistant to oxidation both during modification and afterwards. Upon hydrosilylation of 1,9-nonadiyne the surface is rendered with a distal alkyne such that the surface can be further modified via 'click' chemistry with an azide. Here we show how this interface can be used to achieve direct electron transfer to proteins in aqueous solution for the very first time. We also show how this same chemistry could be used to fabricate switchable surfaces for the capture and release of cells or proteins.

The second concept is to use molecular wires to allow efficient electron transfer through a protein resistant layer on an electrode to a surface bound protein. This technology is then applied to making immunosensors that can operate in whole blood. An example is given for the detection of glycosylated haemoglobin but this generic technology could be applied to the detection of numerous protein or small molecule biomarkers.

Session Abstracts - Day 2

Uttam Sinha

Breakout session 9c

Emerging application of synchroton radiation in Neuroscience

Chair: Pantaleo Romanelli

Pantaleo Romanelli

Brain Modulation using synchrotron-generated microbeams

Dr Pantaleo Romanelli, Brain Radiosurgery,Cyberknife Center, CDI, Milan; European Synchrotron Radiation Facility (ESRF), Grenoble,France.

Multiple subpial transections (MST) and stereotactic radiosurgery (SRS) are emerging techniques to treat seizure foci involving eloquent cortex (Romanelli et al 2012). MST is a microsurgical procedure placing vertical incisions through the epileptic cortex in order to cut the horizontal axons responsible of the propagation of seizures while preserving the vertical columns acting as the basic unit of cortical function. Seizure spread is arrested by the parcellization and disconnection of the ictal focus. The cortical columns subserving eloquent and non-eloquent neurological functions are not injured by MST, allowing the treatment of epileptic foci located over sensorimotor or language cortex not amenable to surgical resection.

Focal irradiation of an epilepsy focus through SRS provides an attractive non invasive approach, mainly limited by the delay of efficacy (several months are required to obtain seizure relief) and by side effects such as radio-induced edema and radionecrosis. Current LINAC- or cobalt-based technologies do not allow to deliver high doses to cortical slices of millimetric size, thus replicating the exquisite cortical incisions generated by MST.

A novel exciting approach combining the advantages of SRS and MST has been investigated at the ESRF, where arrays of microplanar beams(microbeams) have been used to generate cortical transections equivalent to MST in a non invasive, bloodless way. Microscopic arrays of X-ray beams (microbeams) originating from a synchrotron source have been used to generate neocortical or hippocampal transections by delivering very high doses of radiation to tissue slices of microscopic thickness. Neurons,glia and axons along the penetration path are ablated, leaving a path equivalent to that of a microsurgical incision. The adjacent tissue is exposed to much lower valley doses (less than 5 Gy) unable to induce histologically evident tissue damage (Romanelli et al. 2011). In essence, synchrotron-generated cortical transections provide a microradiosurgical equivalent of MST.Compared to MST, which require an invasive procedure involving all the risks related to open surgery, microbeam transections are performed in a non invasive way and the size and spacing of the transections can be modified by the surgeon according to the needs. Microbeam transection placed over a highly challenging target, the primary motor cortex, are well tolerated. No sign of motor deficit was found after prolonged observation and periodic rotarod testing. Convulsive seizures originating from this region disappeared almost immediately after microbeam transections(Romanelli et al. 2013). Unilateral and bilateral hippocampal transection are also well tolerated: no memory damage was detected and hippocampal neurogenesis was preserved.

The development of new devices delivering submillimetric beams able to generate cortical transections might add a powerful new tool to the clinical treatment of epilepsy and, more in general, to modulate cortical functions in a wide variety of neuropsychiatric disorders.

References:

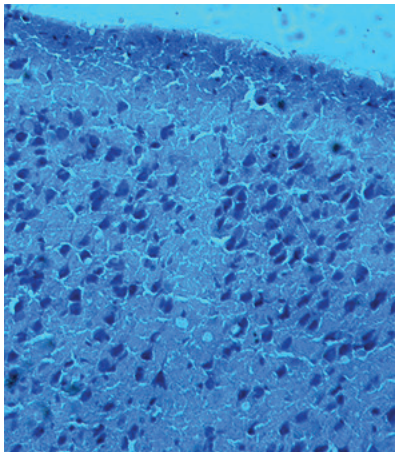
Romanelli P, Bravin A. Synchrotron-generated microbeam radiosurgery: a novel experimental approach to modulate brain function. Neurol Res. 2011 Oct;33(8):825-31.

Romanelli P, Striano P, Barbarisi M, Coppola G, Anschel DJ. Non-resective surgery and radiosurgery for treatment of drug-resistant epilepsy. Epilepsy Res. 2012 May;99(3):193-201

Romanelli P, Fardone E, Battaglia G, Bräuer-Krisch E, Prezado Y, Requardt H, Le Duc G, Nemoz C, Anschel DJ, Spiga J, Bravin A. Synchrotron-generated microbeam sensorimotor cortex transections induce seizure control without disruption of neurological functions. PLoS One. 2013;8(1):e53549.

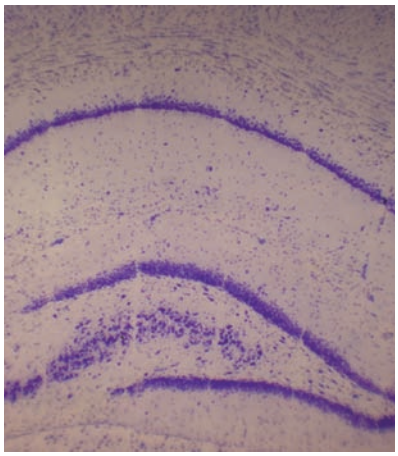
Session Abstracts - Day 2

Figure 1



Synchrotron-generated sensorimotor cortex transection

Figure 2



Synchrotron-generated hippocampal transections

Paola Coan

Brain microimaging using synchrotron radiation

Prof. Paola Coan, PhD

Department of Clinical Radiology, Ludwig Maximilians University, 15 D Marchioninistr., Munich, 81377 Germany; Department of Physics, Ludwig Maximilians University, 1 Am Coulombwall, Garching, 85748, Germany

paola.coan@physik.uni-muenchen.de

The advent of modern neuroimaging with computed tomography (CT) and magnetic resonance (MR) imaging has allowed for a better diagnosis and characterization of brain abnormalities and diseases. Despite the deep insights offered by these imaging methods, their sensitivity and/or spatial resolution are insufficient to study at the cell level the structures of this very complex tissue. Synchrotron radiation (SR) may provide the opportunity to overcome many of the limitations affecting current diagnostic methods. Pre-clinical imaging on the micro- and nano-scale with multidimensional resolution (spatial, temporal and chemical) is made possible by the high intensity, energy selectivity and collimation of the SR beam. Advanced X-ray based imaging techniques have been developed and used for investigating excised rat and human cerebella without the application of any stain or contrast agent. Images clearly depict the hippocampus and cerebellum regions (with white and gray matter) and the substantia nigra structure. Normal and tumor tissues are also effectively discriminated. Proof of principle studies in “phase contrast” micro-CT were performed on irradiated rat brains, demonstrating the ability of the method in visualizing the not only the fine architecture of the organ but also the effects of the treatment.

This presentation will give a concise introduction to the principle imaging methods used at SR facilities for neuroimaging investigations and a short overview of the recent results produced in pre-clinical research.

Keywords: Synchrotron radiation, high spatial resolution, high sensitive imaging

Educational Objectives:

1. Introducing the audience to synchrotron radiation based imaging as a powerful pre-clinical concept for high resolution and high sensitive investigation methods in neuroimaging at cell level.
2. Providing an overview of the main results of synchrotron radiation based neuroimaging.
3. Enable the audience to ask questions on the possibilities offered by the novel synchrotron radiation based imaging techniques.

Jeffrey Crosbie

Microbeam radiation therapy: the state of the art in cancer treatment

Alberto Bravin

Synchrotron radiation generated microbeams: overview and state of the art

Alberto Bravin[1], P. Romanelli[2], Gabriele Biella[3], Elke Bräuer-Krisch[1] on behalf of the Microbeam Radiation Therapy community

Synchrotron radiation facilities are large scale laboratories where extremely intense and highly collimated X-ray beams are made available to researchers for a wide range of applications, among which biology and medicine are constantly increasing of imporance.

Session Abstracts - Day 2

These applications are particularly advanced at the European Synchrotron Radiation Facility (ESRF, Grenoble, France) where intense nanometric or homogeneous broad beams are also used to study, analyze and treat pathologies of the central nervous system (CNS).

Microbeam Radiation Therapy (MRT) uses polychromatic arrays of microscopic beams (from 25 to 600 microns) delivered with submillimetric precision to the CNS. Doses up to hundreds of Grays, delivered in a fraction of a second, can be very well tolerated by the CNS in mammals as shown in several preclinical trials. The potential application of MRT in the treatment of cancers of the CNS is presently under evaluation in veterinarial trials.

MRT has also been applied to obtain the radiosurgical equivalent of multiple subpial transections. Cortical columns are the basic functional units of brain computation. Synchrotron microbeams can generate cortical transections disconnecting adjacent columns and modulating abnormal columnar processing. The hypothesis was verified in epilectic rats. Microradiosurgical transections induced seizure control while motor function was not affected. Also the ability of microbeams to generate hippocampal transections has been recently investigated. This original approach offers an interesting new way to study the hippocampal function and to develop novel treatment avenues for mesiotemporal epilepsy.

More recently, X-ray microbeams have been used to explore the electrophysiological behaviour of neurons contained inside the microbeam-transected primary sensory cortex in experimental models of chronic pain, a widespread invalidating neurological disorder currently orphan of effective medical and surgical treatments. Selected pioneering results of these new research avenues will be presented.

1. European Synchrotron Radiation Facility, Grenoble, France
2. CDI Brain Radiosurgery and ABI Medica, Milano
3. Institute of Molecular Bioimaging and Physiology, National Research Council, Segrate, Milano

Breakout Session 10

Sport and Concussion

Chair: Geoffrey Ling and Babak Kateb


Michael Roy *(Keynote)*

Linking TBI with PTSD in Combat Veterans: Lessons Learned from the Predictors Study

Michael J. Roy, MD, MPH; Michelle Costanzo, PhD; Suzanne Leaman, PhD; Jessica Gill, PhD; Dave Keyser, PhD; Mary Coughlin; Yi-Yu Chou; Dzung Pham, PhD.

Center for Neuroscience and Regenerative Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD, 20814

Background: TBI and PTSD have both been identified in large numbers of military service members (SMs) after deployment to Iraq or Afghanistan. PTSD and persistent symptoms related to TBI, which may be characterized as postconcussive syndrome (PCS), can be difficult to distinguish. Moreover, TBI is by its very nature almost invariably a life-threatening event, so it can be hard to determine to what extent the symptoms are related to the direct physical impact on the brain versus the psychological trauma, yet sorting out the relative contributions may be critical to appropriately direct therapy. We utilized novel imaging techniques to try to elucidate this issue.

Methods: We performed a nested case-control analysis within a prospective cohort study involving 81 SMs, in which we compared 11 SMs with mild combat TBI and 11 controls matched for age and sex. We compared the results of resting state functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), and PTSD symptoms on the Clinician-Administered PTSD Scale (CAPS).

Results: Those SMs with a history of mild TBI had reduced fractional anisotropy (FA) on DTI compared to controls in the white matter adjacent to the left precuneus. We then demonstrated a significant correlation between the degree of functional connectivity between the left posterior cingulate cortex (PCC/ precuneus and the left medial frontal cortex (MFC) on fMRI and the left cingulum FA on DTI (the white matter that connects these regions), such that 31% of the variance in connectivity was explained by the FA. In addition, we found a significant relationship in turn between resting state connectivity and the re-experiencing category of PTSD symptoms (e.g, flashbacks and nightmares), which explained 20% of the variance seen in such symptoms in those with combat TBI. We also identified that in our overall cohort, 2 of 11 (18%) with combat TBI compared with 3 of 70 (4%) without combat TBI developed PTSD on serial follow-up within 12 months after return from deployment.

Discussion: The links we report

Session Abstracts - Day 2

between evidence of structural impairment on DTI, functional connectivity on fMRI, and PTSD symptoms is suggestive of a relationship between TBI and PTSD. This relationship is further supported by our identification of a link between a single nucleotide polymorphism (SNP) for the calcium binding protein S100B and the development of PTSD in our cohort, as SNPs for this protein have previously been reported in association with brain injury. Links between TBI and PTSD warrant further assessment in future studies.

Dan Perl

Pantaleo Romanelli

DR Pantaleo Romanelli, Scientific Director,AB Medica,Milano,Italy

A Fully-Integrated Externally Rechargeable Wireless System for Long-Term Electrocorticography and Cortical Stimulation

Introduction: Current techniques of cortical recording for seizure focus localization and Brain Computer Interface(BCI) are limited by the need to transfer the signal through connecting wires. We have developed a fully implantable,externally rechargeable wireless system (ECOGIW-16E). This device provides a highly innovative medium for the localization and treatment of focal drug-refractory epilepsy but can also be used for BCI (e.g. to drive prosthetic limbs or an exoscheleton).

Materials and methods: ECOGIW-16E is a compact low-profile device integrating an RF antenna and a flexible thin-film custom-made Neuronexus grid with 16 platinum electrodes.The device has a square size of 30 mm with a 11.7 mm height. The grid size is 16 by 11,5 mm with a thickness of 50 µm.Electrode diameter is 1,09 mm. Spacing across electrodes is 3 mm. The device includes a microcontroller and the transceiver module for implantable medical applications within MICS band, a triaxial accelerometer, a stimulus generator, a sensor of temperature/load current and a Li-Ion battery (3,6V 350mA/h ISO 13485). The interface consumes 58mA (16CH @ 500SPS + TX_RF), 30mA (16CH @ 500SPS) and 7mA in standby.A dedicated cage equipped with RF coils was developed to allow seamless recharging.

ECOGIW-16E was implanted in a male macaque monkey (Macaca fascicularis, 6.95 kg). Experimental protocol was approved by the regional committee (Cometh Grenoble number 12/136_ Clinatec-NTM-01). The animal was anesthesized and secured to a stereotaxic frame. Craniotomy was performed , placing the 16 contacts grid over the left sensori-motor cortex.Intraoperative stimulation and motor cortex mapping was performed to confirm the correct grid placement. Dura was overlaid over the grid and craniotomy was closed. The case was fixed above the skull immediately behing the craniotomy opening using titanium plates and screws.The wound was washed and closed.

Results: The device placement was not externally visible due to low-profile design. ECoG was daily recorded for 6 months, maintaining excellent signal quality. Impedance was recorded daily for each electrode and remained consistently at very low levels(below 20 KOhm). Somatosensory evoked potentials and direct cortical stimulation have been performed monthly , showing preserved ability to map the sensorimotor cortex and to remotely evoke movements.

Remote cortical stimulation was performed by the delivery of trains of 5 pulses of rectangular shapes at 1 Hz, with an interstimulus interval of 100 ms. Stimulus intensity was gradually increased in increments of 0.5 mA, starting at 1 mA, up to a maximum of 3 mA. During cortical stimulation of the motor cortex, movements of distinct portions of the right arm and hand were consistently observed with a stimulation intensity of 2 mA. The device was explanted after 6 months. The grid was encased within a dural layer and was easily removed from the cortex. No adherence was found between the grid and the cortex.

Conclusions: ECOGIW-16E is a fully implantable, externally rechargeable device providing wireless real time ECoG recording and brain mapping through direct cortical stimulation. ECOGIW-16E provides much longer recording times as compared to those offered by current technology. Research and clinical applications include BCI and invasive monitoring of epilepsy. This fully-integrated system can evolve into a closed-loop system to abort promptly detected seizure activity in epilepsy patients.

Daryl Kipke

Session Abstracts - Day 2

Geoffrey Ling

Diagnosis and Treatment of Mild TBI/ Concussion

Geoffrey Ling, MD, PhD

Mild traumatic brain injury (TBI) or concussion is finally being recognized as a serious medical condition. As a result, organized medicine is actively developing evidence based clinical practice guidelines (CPG) to help medical providers meet patient needs. This effort is based largely on the highly successful "Guidelines for the Management of Severe Traumatic Brain Injury" created by the Joint Committee of the American Association of Neurological Surgeons (AANS) and the Congress of Neurosurgery (CNS) in 1996. It is now in its 3rd iteration which was published in 2007. Just recently, in 2013, the American Academy of Neurology published the "Summary of evidence-based guideline update: Evaluation and management of concussion in sports: Report of the Guideline Development Subcommittee of the American Academy of Neurology." In 2009, the US's Veterans Administration and Dept of Defense together published their "Clinical practice guidelines: Management of Concussion/mild Traumatic Brain Injury." This was followed soon after in 2012 with the Canadian "Guidelines for mild TBI and persistent symptoms." All of these have similar approaches which are removing victims from further risk, allowing opportunities for recovery and treating symptoms. Return to work or play should be assessed using provocative evaluation clinical tools. In the US, 49 states and the DC have adopted concussion laws that require removal of players from the game and assessment by appropriately trained advanced medical providers who must provide written authorization before a player can return to play.

James Ecklund

Building a Community Concussion Program

Concussion has received a significant amount of attention over the last 5-10 years. This increased awareness both by the medical community and the public has had a profound effect on many sports. NFL football in America has changed the rules to ban certain hits and limit the exposure of athletes to plays that pose higher risks for concussion. During the 2013 season, the NFL mandated that neurological trauma experts, predominantly neurosurgeons, be present on each sideline for every NFL game. The US military has also recognized the risk for concussion and mild head injury during combat operations and as a result of blast exposure. They have developed a robust program firmly embedded in regulation to identify, monitor, and treat soldiers with potential concussion. Fortunately, this increased vigilance at the very visible national level trickles down to youth sports where a public awareness and demand for expert concussion care in local communities has emerged. Developing a program to meets the needs of a community requires a multidisciplinary effort that recognizes the many interested parties and stakeholders. This includes multiple medical and social disciplines, school systems, youth sports leagues, and sports trainers. Confounding the development of an appropriate concussion program is the weak evidence for many practices which are often surrounded by strongly held opinions regarding their effectiveness. A desire to do something, even if ineffective, at least makes all concerned "feel" like they are positively impacting the problem. We will describe our development of a community concussion program across Northern Virginia, spanning 5 hospitals and several counties. The organization, process of development and care, lessons learned, educational efforts, and research opportunities will be addressed.

Breakout Session 11

Stem cell technology and tissue engineering

Chair: John Whitelock & Jean Paul Allain

Ernst Wolvetang (Keynote)

Human induced pluripotent cells is tools to study neurological diseases.

Ernst Wolvetang, Assoc. Prof Stem Cell Biology, Group leader Stem Cell Engineering Group

Australian Institute for Bioengineering and Nanotechnology, University of Queensland, Brisbane, St Lucia, QLD, 4072, Australia.

Investigations into the of etiology neurodegenerative diseases have been frustrated by a lack of access

Session Abstracts - Day 2

to developing human tissues, and the limited ability of mouse models to recapitulate complex human nervous system diseases, creating a need for new human cellular model systems. We have adopted human induced pluripotent stem cells (hIPSC) as our model system of choice. To reveal pathogenic mechanisms hIPSC from neurological diseases such as Down syndrome (DS) and Ataxia-Telangiectasia (A-T) we differentiate integration-free iPSC into cell types relevant to the disease, such as cortical neurons, astrocytes and cerebellar granule cells. We employ CRISPR and TALEN based genome editing tools to probe the gene regulatory networks underlying pathogenesis (such as in DS) as well as for generating disease models in isogenic backgrounds (such as Prader-Willi syndrome). In each case our approach is to combine cell phenotypic analyses, including calcium reporters, with transcriptome analysis to identify the molecular processes underlying pathogenic phenotypes that can be identified in vitro. Using this strategy we have identified early developmental phenotypes and Alzheimers disease-like changes in DS neurons, mitochondrial and calcium handling changes in A-T neurons, developmental changes in A-T cerebellar granule cells and a neuronal activity dependent LncRNA potentially involved in schizophrenia. Collectively our research provides evidence that iPSCs are useful tools for dissecting the mechanisms of complex human neurological diseases and, potentially, for testing of novel therapeutics.

Rylie Green

Living electrodes: Tissue engineering the neural interface

Conductive hydrogel electrode coatings for optimal neural interfacing

Dr Rylie Green
Graduate School of Biomedical Engineering, University of New South Wales, Sydney, 2052, Australia

Conducting polymers (CPs) offer advantages over conventional metal electrodes by providing a lower strain mismatch with tissue, and greater capacity for charge injection, while presenting options for modification with biological molecules. However, most CPs used in biomedical applications tend to be brittle and friable, which has limited their applicability in implant electrodes. Conducting hydrogel (CH) coatings provide an interesting new approach to tailoring the neural interface by further decreasing the strain mismatch while encapsulating the CP within a soft, deformable hydrogel matrix. In addition, the use of a hydrogel component provides the potential for delivery of therapeutic agents to promote regeneration of diseased neurons. A typical CH consists of a biosynthetic hydrogel integrated with a CP, such as poly(ethylene dioxythiophene) (PEDOT). The hydrogel is a co-polymer of poly(vinyl alcohol) (PVA) and a modified biological molecule. Varying the type of biomolecule has allowed the properties of the CH to be tailored such that specific cells will interact with the electrode coating. Studies have been conducted to establish CH efficacy as an electrode coating and explore in vivo tissue responses. Furthermore, the ability to present and deliver biomolecules, including gene constructs has been investigated. Finally, this concept has been advanced such that neural cells can be embedded in the CH coating, thereby creating a “living electrode”, to directly contact excitable tissue. These studies provide further evidence that conducting polymer hybrids with hydrophilic polymers can provide soft, bioactive interface with neural tissue for applications such as the cochlear implants, bionic eye devices and deep brain stimulators.

John Whitelock *(Keynote)*

Mapping the Neural Extracellular Matrix: Potential Biomarkers of Neurodegenerative Disorders.

Mast cells are derived from haematopoietic progenitors that are known to migrate to and reside within connective and mucosal tissues where they differentiate and respond to various stimuli by releasing pro-inflammatory mediators including histamine, growth factors and proteases. This study demonstrated that primary human mast cells as well as the rat and human mast cell lines, RBL-2H3 and HMC-1, produce the heparan sulfate proteoglycan, perlecan, with a Mr of 640kDa as well as smaller molecular weight species of 300 and 130kDa. Utilizing domain-specific antibodies coupled with N-terminal sequencing it was confirmed that both forms contained the C-terminal module of the protein core known as endorepellin, which were generated by mast cell-derived proteases. Domain specific RT-PCR experiments demonstrated that transcripts corresponding to domains I and V, including endorepellin, were present however mRNA transcripts corresponding to regions of domain III were not present suggesting that these cells were capable of producing spliced forms of the protein core. Fractions from mast cell cultures that

Session Abstracts - Day 2

were enriched for these fragments were shown to bind endothelial cells via the a2b1 integrin and stimulate the migration of cells in "scratch assays", both activities of which were inhibited by incubation with either anti-endorepellin or anti-perlecan antibodies. This study shows for the first time that mast cells secrete and process the extracellular proteoglycan perlecan into fragments containing the endorepellin C-terminal region that regulate angiogenesis and matrix turnover, which are both key events in wound healing.

Breakout Session 12

Brain Networks

Chair: Perminder Sachdev

Michael Breakspear *(Keynote)*

Brain Connectomics

Recent technical and methodological advances now make a complete description of the "wiring diagram" of the brain a distinct possibility. However summary statistics are required in order to achieve a meaningful description of these connectomic data. To address this problem, imaging and systems neuroscientists are turning to complex network theory. In this talk I will highlight the major challenges and breakthroughs in this exciting field.

Alex Fornito

Mapping context-dependent changes in brain functional networks using event-related graph analysis

Monash Clinical and Imaging Neuroscience, School of Psychological Sciences and Monash Biomedical Imaging, Monash University

Cognition emerges from complex and dynamic patterns of coordinated activity in spatially distributed neuronal ensembles. These patterns can be studied by analyzing statistical dependencies—also called functional connectivity—between activity recordings measured in distinct brain regions. Functional magnetic resonance imaging (fMRI) has emerged as a popular and powerful tool for studying the functional connectivity of large-scale brain networks, though most published literature to date has focused on examining so-called resting-states in which subjects lie quietly in the scanner without performing any explicit task. This work has led to important new insights into brain functional organization, although its applicability to understanding cognition is limited because it does not consider neural activity during active task performance. In this talk, I will describe recently developed methods that allow quantification of task-related modulations of functional connectivity that are scalable to the analysis of whole-brain networks. I will demonstrate how these techniques can be leveraged to map dynamic reconfigurations of large-scale neural systems in response to changing task conditions, and to understand how these changes relate to individual differences in cognitive performance.

Michael Valenzuela

Plastic Network Responses in Aged Brains to Lifestyle-based Intervention

Associate Professor Michael Valenzuela
Leader, Regenerative Neuroscience Group, Brain and Mind Research Institute, University of Sydney

Aged brains exhibit network and connectivity degradation that is more pronounced in dementia. Importantly, a large part of this is likely to be environmentally determined. In other words, by enriching the brain's environment we may be able to attenuate, normalise or even reverse many of these network changes. In this presentation, Associate Professor Michael Valenzuela will provide direct evidence from his group's animal research as well as human neuroimaging studies that show that physical exercise as well as intense mental exercise can have powerful network restorative properties. Moreover, these positive network effects are linked to improvement in overall memory and cognition, suggesting these may be key mechanisms by which lifestyle-based interventions can help preserve and enhance brain function.

Wei Wen

Structural topological organisation of the elderly brain

Alistair Perry[1], Perminder Sachdev[1], Anbupalam Thalamuthu[1], Michael

Session Abstracts - Day 2

Breakspear[2], Wei Wen[1]

Prior investigations of human brain structural networks have primarily focused on healthy young adults and clinical samples. We aimed to examine age-related changes in structural topological organisation using diffusion-weighted imaging (DWI) scans. To do so, the present study investigated a cognitively healthy sample drawn from the Sydney Memory and Ageing Study, which is a longitudinal study of community-dwelling, non-demented individuals aged 70 and above. We also sought to investigate whether both hemispheric asymmetry and sex differences in structural networks are present in this older population.

To investigate structural organisation, we derived edge-wise calculations, and also connectivity measures at the nodal, regional, lobar, core-network and global levels. Recent investigations of human structural networks have primarily focused on network hubs and more recently, rich-club organisation. Regions that have been found to bi-hemispherically participate in rich-clubs of traditional parcellation methods include the precuneus, thalamus, putamen, hippocampus and superior parts of frontal and parietal cortices. Rich clubs of high-resolution networks additionally include the limbic, frontal, temporal, parietal and occipital regions. However, our study revealed that structural connectivity was primarily distributed along ventral visual pathways, especially within the right hemisphere. Notably, there was a marked absence of highly connected sub-cortical and frontal regions in our older sample, suggesting a shift in topological organisation with age. Lobar level analysis provided further support for a topological shift, as the presence of left frontal regions in core networks was found to significantly decrease with age. In an additional analysis, we were able to demonstrate the continuation of traditional hemispheric lateralization in older age, as well as sex differences in asymmetry in line with previous literature.

In a separate study using the same sample, we examined the correlational relationship between cognition and brain connectivity. The cognitive domains included processing speed, memory, language, visuospatial, and executive functions. We examined the association of these cognitive assessments with both the connectivity of the whole brain network and individual cortical regions. We found that the efficiency of the whole brain network of cortical fibre connections had an influence on processing speed and visuospatial and executive functions. Correlations between connectivity of specific regions and cognitive assessments were also observed, e.g., stronger connectivity in regions such as superior frontal gyrus and posterior cingulate cortex were associated with better executive function. Similar to the relationship between regional connectivity efficiency and age, greater processing speed was significantly correlated with better connectivity of nearly all the cortical regions.

We conclude from our data that age has an impact on the organisation of the structural brain connectome. The presence of hemispheric asymmetry and sex differences in the older connectome are consistent with the topological organisation reported in the previous literature. Our data provides further evidence on the relationship beween organization of the brain network and cognition.

1. University of New South Wales, Sydney, Australia
2. QIMR Berghofer Medical Research Institute, Brisbane, Australia

Gilles Guillemin

Mapping of the tryptophan metabolism in physiological and pathological conditions

Breakout Session 13

Neuroimaging genetics

Chair: Perminder Sachdev & Peter Schofield

Margaret Wright

The ENIGMA Projects: identifying genetic loci for brain structure and function

Margaret J. Wright[1], Paul M. Thompson[2], Nicholas G. Martin[1], Barbara Franke[3], Gunter Schumann[4], Derrek P Hibar[2], Sarah E Medland[1], Jason L Stein[5], Alejandro Arias Vasquez[3], Miguel E. Renteria[1], and The ENIGMA Consortium[6]

Introduction: Findings from twin and family studies show that a substantial amount of the variance in the human brain, as measured by imaging, is due to genetic factors. In order to have sufficient power to identify these genetic variants, and to take advantage of the scale that consortium approaches can bring, in December 2009 we founded the Enhancing Neuro Imaging through

Session Abstracts - Day 2

Meta-Analysis (ENIGMA; http://enigma.loni.ucla.edu/) Consortium. While the primary aim of ENIGMA is to conduct large-scale GWAS meta-analyses of imaging phenotypes, this effort has expanded to include prospective meta-analyses of imaging phenotypes to identify how mental illnesses affect the brain.

Methods: The ENIGMA Consortium includes 28 groups from 5 continents with the majority of these groups contributing both MRI and GWAS data from either case-control or population studies. Currently, data are available for a total of 29,000 individuals from 46 cohorts. Each of the groups in ENIGMA analyse their own data using standardized protocols to harmonise the extraction of the imaging phenotypes, as well as quality assessment, genetic imputation, and genetic association. Association analyses control for age, age2, sex, 4 MDS components, intracranial volume (ICV), and disease status (if applicable). Data are then combined across sites using the inverse variance-weighted meta-analysis framework implemented in METAL.

ENIGMA's first project (ENIGMA1) was a genome-wide association study identifying common variants associated with hippocampal volume or intracranial volume. Continuing work is exploring genetic associations with subcortical volumes (ENIGMA2) and white matter microstructure (ENIGMA-DTI).

Results: Our GWASMA of seven subcortical volumes and intracranial volume, has identified SNPs at five loci that surpass the cutoff for genome-wide significance ($p<5\times10(-8)$) in the primary analysis. The strongest effects are found for the putamen and the hippocampus. Another five loci show suggestive associations ($p<1\times10(-7)$). We are currently attempting replication of these SNPs.

Discussion: Our findings show that with large sample sizes specific SNPs are associated with imaging phenotypes for brain structure. Similar efforts may soon begin to reveal loci for white matter structure as well as functional connectivity.

1. QIMR Berghofer Medical Research Institute, Brisbane, Australia
2. University of Southern California, Los Angeles, US
3. Radboud University Medical Centre, Nijmegen, The Netherlands
4. King's College London, UK
5. University of California Los Angeles, US
6. Full author list is at http://enigma.ini.usc.edu/the-enigma-consortium

Karen Mather

Heritability and genetic correlations of cortical and subcortical structures in a cohort of community-dwelling older adults

Wei Wen[1], Anbupalam Thalamuthu[1], Karen A. Mather[1], Wanlin Zhu[2], Jiyang Jiang[1], Margaret J. Wright[3], David Ames[4], Perminder S. Sachdev[1],OATS Research Team

Introduction: As the population is ageing, a greater understanding of the genetic contributions to human brain structure at older ages will assist in the elucidation of the pathways associated with normal and pathological brain ageing. Prior research suggests brain structures have moderate to strong heritability. However, few studies have examined the heritability of the shape of subcortical structures. Nor have the genetic correlations between bilateral hemispheric structures been considered.

Methods: The Older Australian Twins Study recruited twins from the eastern states of Australia who were aged 65 years and over. A subsample with neuroimaging data available (N=414) was used for these analyses. T1-MRI scans were used for computation of cortical and subcortical structure measures using either FreeSurfer or FSL. Cortical thickness was calculated for (i) each voxel and (ii) for 34 different gyral regions of interest (ROI). Vertex-wise (surface deformation-shape) and ROI data was collected for seven subcortical structures: thalamus, caudate, putamen, pallidum, hippocampus, amygdala, nuclear accumbens. Heritability estimates were obtained using variance components models for cortical thickness (voxel-wise, ROI) and vertex-wise (shape) for the subcortical surfaces of the 7 brain structures. Genetic correlations between bilateral subcortical structures and cortical thickness ROIs were assessed using bivariate variance components model as implemented in the package SOLAR.

Results: The mean heritability of the voxel-wise analysis for cortical thickness was ~0.5. Cortical thickness ROI heritability estimates varied with low to high values observed. Mean heritability for the shape of subcortical structures ranged from 0.23 for the right amygdala to the 0.72 for the left thalamus. To examine lateralisation of genetic influence on the cortex and subcortical structures, ROIs were used. Genetic correlation analysis suggested strong bilateral genetic symmetry in the brain for these measures.

Conclusions: In this study we report a comprehensive examination of heritability for both cortex voxel-wise and subcortical surface deformation. To our knowledge, it is one of the first to estimate heritability for subcortical shape measures. We also demonstrated strong bilateral genetic symmetry across the right and left hemispheres for cortical and subcortical ROIs. The information

Session Abstracts - Day 2

from this study will be used to inform further studies aiming to identify the genetic correlates of brain structure in older adults.

1. University of New South Wales, Sydney, Australia
2. Beijing Normal University, Beijing, China
3. QIMR Berghofer Medical Research Institute, Brisbane, Australia, 4National Ageing Research Institute, Royal Melbourne Hospital, Victoria, Australia

Peter Schofield

Neuroimaging and Biomarker Changes in Dominantly Inherited Alzheimer's Disease

Peter R Schofield[1], John C Morris[2], Randall J Bateman[2], Tammie LS Benzinger[2], Anne M Fagan[2], Chengjie Xiong[2], Alison Goate[2], Nick C Fox[3], Daniel S Marcus[2], Nigel J Cairns2, Xianyun Xie[2], Tyler M Blazey[2], David M Holtzman[2], Anna Santacruz[2], Virginia Buckles[2], Angela Oliver[2], Krista Moulder[2], Paul S Aisen[4], Bernardino Ghetti[5], William E Klunk[6], Eric McDade[6], Ralph N Martins[7], Colin L Masters[8], Richard Mayeux[9], John M Ringman[10], Martin N Rossor[3], Reisa A Sperling[11], Stephen Salloway[12], Clifford R Jack Jr[13], Robert A Koeppe[14], Yi Su[2], Marcus E Raichle[2], Abraham Z Snyder[2], Beau M Ances[2], Jon J Christensen[2], Lindsay Ercole[2], Russ C Hornbeck[2], Angela M Farrar[2], Patricia Aldea[2], Mateusz S Jasielec[2], Christopher J Owen[2], Xianyun Xie[2], Adam Brinkman9, Chester A Mathis[6], Paul M Thompson[10], Andrew J Saykin[5], Keith A Johnson[11], Stephen Correia[12], Christopher Rowe[15], Victor L Villemagne[15], Sebastien Ourselin[3], David M Cash[3], Michael W Weiner[16], for the Dominantly Inherited Alzheimer Network (DIAN).

The order and magnitude of pathologic processes in Alzheimer's disease (AD) are not well understood, partly because the disease develops over many years. Autosomal dominant AD has a predictable age at onset and provides an opportunity to determine the sequence and magnitude of pathologic changes that culminate in symptomatic disease.

In this prospective, longitudinal study, we analyzed data from 128 participants who underwent baseline clinical and cognitive assessments, brain imaging, and cerebrospinal fluid (CSF) and blood tests. We used the participant's age at baseline assessment and the parent's age at the onset of symptoms of AD to calculate the estimated years from expected symptom onset (age of the participant minus parent's age at symptom onset). We conducted cross-sectional analyses of baseline data in relation to estimated years from expected symptom onset in order to determine the relative order and magnitude of patho-physiological changes.

Concentrations of amyloid beta (Aβ42 in the CSF appeared to decline 25 years before expected symptom onset. Aαdeposition, as measured by positron emission tomography with the use of Pittsburgh compound B, was detected in nearly every cortical region 15 years before expected symptom onset. Reduced cortical glucose metabolism and cortical thinning in the medial and lateral parietal lobe appeared 10 and 5 y, respectively, before estimated age of onset. Importantly, however, a divergent pattern was observed subcortically. All subcortical gray-matter regions exhibited elevated PiB uptake, but despite this, only the hippocampus showed reduced glucose metabolism. Similarly, atrophy was not observed in the caudate and pallidum despite marked amyloid accumulation. Finally, before hypometabolism, a hypermetabolic phase was identified for some cortical regions, including the precuneus and posterior cingulate. Additional analyses of individuals in which longitudinal data were available suggested that an accelerated appearance of volumetric declines approximately coincides with the onset of the symptomatic phase of the disease.

Increased concentrations of tau protein in the CSF and an increase in brain atrophy were detected 15 years before expected symptom onset. Cerebral hypometabolism and impaired episodic memory were observed 10 years before expected symptom onset. Global cognitive impairment, as measured by the Mini–Mental State Examination and the Clinical Dementia Rating scale, was detected 5 years before expected symptom onset, and patients met diagnostic criteria for dementia at an average of 3 years after expected symptom onset.

We found that autosomal dominant AD was associated with a series of patho-physiological changes over decades in CSF biochemical markers of AD, brain amyloid deposition, and brain metabolism as well as progressive cognitive impairment. Our results require confirmation with the use of longitudinal data and may not apply to patients with sporadic AD.

References:

Bateman et al. New England Journal Medicine 2012, 367α795-804.

Benzinger et al. Proceedings of the National Academy of Sciences USA 2013, 110; E4502-4509.

1. Neuroscience Research Australia, Sydney, NSW, Australia
2. Washington University, St Louis, MO, USA
3. University College London, London, UK
4. University California San Diego, San Diego, CA, USA
5. Indiana University, Indianapolis, IN, USA
6. University of Pittsburgh, Pittsburgh, PA, USA

Session Abstracts - Day 2

7. Edith Cowan University, Perth, WA, Australia
8. University of Melbourne, Melbourne, VIC, Australia
9. Columbia University, New York, NY, USA
10. University California Los Angeles, Los Angeles, CA, USA
11. Brigham and Women's Hospital, Harvard University, Boston, MA, USA
12. Butler Hospital, Brown University, Providence, RI, USA
13. Mayo Clinic, Rochester, MN, USA
14. University of Michigan, Ann Arbour, MI, USA
15. Austin Health, Heidelberg, VIC, Australia
16. University California San Francisco, San Francisco, CA, USA

Mayuresh Korgaonkar

Heritability of neural structure and connectivity changes across the adult lifespan – results from the TWIN-E study.

How much of the adult brain's heritable structure and connectivity can be modified by the environment is presently unknown. Previous studies have established that neural structure, quantified by grey matter indices, and neural connectivity, quantified by white matter integrity, are moderately heritable. During development into adolescence, heritability increases with maturation. However, it remains unknown if heritability remains constant over adulthood. This talk will present neuroimaging data from 252 twin pairs aged 18-60 years to evaluate the moderating effects of age on heritability of brain structure and connectivity. Here we show that both structure and connectivity have significant regionally specific changes in heritability with age. These data provide a valuable insight into the gene-environment mechanisms that may underlie the ongoing changes in brain development over the adult lifespan. The findings also provide a valuable foundation for advancing our understanding of why the brain may be sensitive to neuropathophysiological processes at different points of the adult lifespan.

Philip Liu

Brain Mapping and Therapy Monitored by Genetic Imaging; A Preclinical Platform

Philip K. Liu[1], Iris Chen[1], Howard Prentice[2] and Jang-Yen Wu[2]

Introduction: Cardiac arrest, heart failure and stroke are the number one cause of death in developed countries. Patients who survive these episodes, regardless of age, gender or race, are at high risk for developing neurological disorders, and there are few viable interventions available to monitor tissue damage in vivo before and after treatment. Granulocyte colony-stimulating factor (G-CSF) is a cytokine that stimulates growth and differentiation of myeloid precursors. In addition, G-CSF has neuroprotective properties in animal models of Parkinson disorder, stroke, Alzheimer demintia and other neurodegenerative diseases. Protein therapy using G-CSF is attractive because G-CSF is well tolerated after systemic delivery and its receptor is expressed in neurons. However, its plasma half-life is about 4 hours; moreover, there is potential for chronically elevating white blood cells during repeated protein delivery. One alternative is to administer human G-CSF (hG-CSF) encoded by a viral vector –namely a replication deficient adeno-associated virus (AAV) in conjunction with direct monitoring of delivery. Our hypotheses are that (1) the expression of G-CSF from AAV- CMV-hG-CSF by gene therapy will protect the brain from ischemia – induced brain injury in a process that is similar to what we observed recently in therapy employing exogenous hG-CSF protein, and (2) multimodal magnetic resonance imaging (MRI) quantitatively measures neuroprotection in living brains associated with gene delivery in bilateral carotid artery occlusion (BCAO) of C57black6 mice.

Methods: Brain damage was induced using bilateral carotid artery occlusion (BCAO) for 60 min in C57black6 mice. We applied longitudinal MRI to monitor brain damage and repair by gliogenesis, microglia activation and angiogenesis in living brains by MRI (Fig 1). We have made AS sODN for hG-CSF to monitor the delivery of hG-CSF cDNA after AAV-CMV-hG-CSF vector application (post BCAO, 4 x 10^9 fpu in 2 ul, eye drops). Our sODNs targeting matrix metalloproteinase-9 (MMP-9), glial fibrillary acidic protein (GFAP), c-Fos, FosB, Actin or Nestin mRNA was linked to superparamagnetic iron oxide nanoparticles (SPION, a T2 susceptibility agent, 4mg Fe per kg) or gadolinium (1 ug), all delivered by non-invasive intraperitoneal (i.p.) injection. Angiogenesis, gliogenesis, neurogenesis, microglia activation and BBB leakage are monitored in vivo and validated by histology using electron and optical microscopies and by RT-qPCR ex vivo.

Results: The survival rate of C57black6 mice by 60 min BCAO is 5 out of 38 mice in two experiments. Gene therapy using AAV-CMV-hG-CSF improves survival rate (2 of 3 and 3 of 3 in another two trails). Mice treated with AAV-CMV-hG-CSF after BCAO show less brain damage by genetic imaging using SPION-nestin by MRI.

Conclusion: The significance of this project is in correlating gene

Session Abstracts - Day 2

delivery and the accompanied neuroprotection. This is the first step in translating longitudinal MRI of brain repair without biopsy during therapy throughout the life time of patients afflicted with neurodegenerative disorders.

Acknowledgement: Supported by the Boston Area Diabetes Endocrinology Research Center [P30DK057521-14 (J Avruch)], DA029889 and EB013768 (PKL), B Welcome Foundation (HP). The MRI system was funded in part by NIH (S10RR025563) to the Martinos Center for Biomedical Imaging.

1.MGH/HST AA Martinos Center for Biomedical Imaging, Department of Radiology, CNY149 (2301) Thirteenth St. Charlestown, MA

2.Florida Atlantic University, Department of Biomedical Science Boca Raton, FL USA

Breakout Session 14

Commercial and Community Considerations in Personalised Medicines

Chair: Megan Munsie & Caroline Gargett


Ben Borson *(Keynote)*

Commercialization and Protection of Intellectual Assets in Brain Disorders

Bringing improvements in assessing conditions of the Brain requires substantial investment in research, development of devices, and methods for diagnostic and therapeutic interventions. Investments are unlikely to be made unless returns on those investments can be realized. Returns are made possible through licensing of patented inventions, trade secrets, and other intellectual assets (IP). Patents provide rights to their owners to exclude others from using the patented invention. Trade secrets may be taking on a more significant role. A world-wide strategy for protecting intellectual assets requires knowledge of different countries' policies, laws, and procedures. Patent laws continually evolve, and recent court decisions relating to diagnosis and treatment creates ongoing challenges to understanding how intellectual property laws are interpreted and enforced. All countries now use a form of a "first to file" patent regime that severely penalizes inventors for disclosing inventions before filing a patent application. Examples will illustrate some of the challenges and opportunities available. With properly combining business, technology, and the law, commercializing important innovations will result in improved patient care, recognition of innovators' contributions, and business success, all of which can lead to improvements in health care.

Alfredo Martinez-Coll

Megan Munsie

Glenn Cross

Bob Williamson

Breakout Session 15

Stem Cells & Clinical Translation

Chair: Uli Schmidt & Michael Morris


Uli Schmidt *(Keynote)*

Huntington's disease-affected human embryonic stem cells as a model of mitochondrial dysfunction and metabolic disturbances

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by a glutamine expansion in the huntingtin protein. Research has indicated dysfunction in a myriad of systems, including mitochondrial and ubiquitin/proteasome complexes, cytoskeletal transport, cell signalling and transcriptional regulation. We examined the earliest molecular pathway malfunctions by conducting a comparative shotgun proteomics

Session Abstracts - Day 2

study of HD-affected and unaffected human embryonic stem cells (hESC), the earliest non-genetically engineered human cell type available for in vitro research. We also showed a shift from mitochondrial dysfunction to transcriptional dysregulation and cytoskeletal abnormalities during development, by conducting a second study of HD-affected and unaffected hESC terminally differentiated to a culture of neural cells. The ability of hESC to mimic HD pathology offers insight into pathology initiation, aetiology and progression while potentially leading to novel therapeutic targets.

Michael Morris

Amino acids act as growth factors to stimulate embryo development up to and including early neurogenesis

Michael B. Morris[1,2], Rachel Shparberg[1,2], Fernando Felquer[3] Nancy Hamra3, Anna C. Lonic[3], Mariana Todorova[2], Sukran Ozsoy[1], Mark Zada[1], Matthew Zada[1], Sarah Faigenbaum[1], Margot L. Day[1]

We have shown that selected amino acids act as a novel class of small-molecule growth factor, able to cooperate with other growth factors and cytokines to promote (i) pre-implantation embryonic development and (ii) the directed differentiation of ES cells across sequential developmental stages out to early neurogenesis.

In cultured mouse embryos, selected amino acids stimulate development to the hatching blastocyst stage. The mechanism does not appear to be a simple metabolic effect nor is it an osmolyte effect. Instead, it is autocrine-like, promoting development in embryos cultured at low density but not when they are cultured at high density. Another set of amino acids antagonise these effects, while other amino acids promote early pre-implantation development before becoming toxic to development thereafter.

ES cells, which are derived from the inner cell mass cells of the pre-implantation embryo, are also responsive to development/directed differentiation by selected amino acids. Here we show that LIF, the ligand responsible for ES-cell self-renewal, together with L-proline promote neurogenesis of mouse ES cells via a series of embryologically relevant cell types including epiblast-like pluripotent primitive ectoderm, germ-layer-like multipotent definitive ectoderm and neurectoderm (the first cells of the developing neural system). Inhibitor studies and kinome array analysis show that L-proline works by (i) rapidly changing the activity of signalling pathways already stimulated by LIF and (ii) acutely activating additional signalling pathways.

These results indicate that selected amino acids have growth factor-like properties in early development up to and including early neurogenesis. They point to (i) a cheap and reliable means of improving the culture conditions of embryos to be used for assisted reproduction and (ii) the development of protocols of directed differentiation of ES cells to neural cell types suitable for use in animal models of CNS disease and injury.

1. Bosch Institute and Physiology, School of Medical Sciences, University of Sydney
2. Centre for Developmental and Regenerative Medicine, Kolling Institute of Medical Research, Royal North Shore Hospital, Sydney, Australia
3. School of Biomedical Science, University of Adelaide, Australia

Mirella Dottori

Multipotent caudal neural progenitors derived from human pluripotent stem cells that give rise to lineages of the central and peripheral nervous system

Mark Denham[1, 2], Kouichi Hasegawa[3, 4],Trevelyan Menheniott[5], Ben Rollo[5], Dongcheng Zhang[5], Shelley Hough[1], Samiramis Ighaniyan[5], Jessie Leung [1], David Elliott[5], Donald F Newgreen[5], Martin F Pera[1, 6, 7] and Mirella Dottori[1,8]

The caudal neural plate is a distinct region of the embryo that gives rise to major progenitor lineages of the developing central and peripheral nervous system, including neural crest and floor plate cells. We show that dual inhibition of the GSK3b and activin/nodal pathways by small molecules differentiate human pluripotent stem cells directly into an early OCT4-/SOX2+/PAX6- caudal neural progenitor cell (CNP), which are equivalent to progenitors of the embryonic caudal neural plate. CNPs can efficiently generate neural crest, floor plate, roof plate and caudally-specified neuroepithelial cells. Neural crest derived from CNPs differentiated to neural crest derivatives and demonstrated extensive migratory properties in vivo. Our studies define a novel progenitor derived from human pluripotent stem cells, which is the precursor to major caudal lineages of the embryonic neural tube.

1. Department of Anatomy and Neurosciences, University of Melbourne, Australia
2. Danish Research Institute of Translational Neuroscience, Aarhus University, Denmark
3. Institute for Integrated Cell-Material Sciences, Kyoto University, Japan
4. InStem, NCBS, India
5. Murdoch Children's Research Institute, Australia
6. Walter and Eliza Hall Institute, Australia
7. Florey Institute of Neuroscience and Mental Health, Australia
8. Centre for Neural Engineering, University of Melbourne, Australia

Session Abstracts - Day 3

Amanda Capes-Davis

Spontaneous transformation of stem cells in vitro: Believe it or not?

Amanda Capes-Davis[1,2]

Spontaneous transformation of human adult stem cells was first published in 2005. Two studies reported that human mesenchymal stem cells (MSCs), derived from adipose tissue and bone marrow, spontaneously overcame senescence to proliferate indefinitely in cell culture and form tumours in nude mice. The risk of tumour development was a serious concern for scientists and clinicians working towards the therapeutic use of MSCs. But subsequent publications showed that not all was as it seemed on the surface. In 2010, MSC cultures in both studies were shown to be cross-contaminated by unrelated cancer cell lines. Results were therefore artefacts of the cell culture process and irrelevant to MSC research.

Spontaneous transformation of MSCs has now been conclusively demonstrated in rodent models, where MSCs are prone to chromosomal abnormalities. MSCs from other species appear to be more stable. Spontaneous transformation of human MSCs has finally been demonstrated in vitro, following authentication testing to exclude cross-contamination. However, transformation of human MSCs appears to be a rare event that only occurs after long-term culture. Clinical trials suggest that the risk of tumour development in vivo is low, although ongoing vigilance is required.

What can we learn from this complex story? A great deal of confusion could have been avoided by testing cell cultures for obvious quality concerns. Preclinical work does not have the regulatory requirement for quality control laid down as part of Good Manufacturing Practice. However, basic quality control and characterisation is part of Good Cell Culture Practice and should be performed routinely and integrated into preclinical cell culture work.

Essential quality control includes testing for Mycoplasma contamination; and authentication testing to exclude cross-contamination. For human cell lines, short tandem repeat (STR) profiling allows comparison to commonly used cell lines worldwide. The International Cell Line Authentication Committee (ICLAC) maintains a database of cell lines that are known to be cross-contaminated, in many cases from the time the cell line was first established. It is advisable to check the database before beginning work with any new cell line.

For stem cells, in addition to quality control, it is important to perform characterisation and stability testing. New stem cell lines should be assessed for pluripotency, stability of karyotype and phenotypic characteristics. Every effort should be made to keep cells at low passage by freezing down stocks in a “master bank”, with a second “working bank” to provide stocks for day-to-day requirements.

These simple measures will help to make ongoing stem cell research more reliable, avoiding the common problems that affect many cell culture based projects.

1. CellBank Australia, Children’s Medical Research Institute, Westmead NSW 2145, www.cellbankaustralia.com.
2. International Cell Line Authentication Committee, iclac.org.

Plenary Session 5

New frontiers in brain science

Geoffrey Ling
Neurologist, Defence Advanced Research Projects Agency (DARPA) USA

This is an exciting time for neuroscience. There is an expanding appreciation for the potential that innovations developed in brain science will have profound positive implications for patients throughout the international community. In particular, in April, 2013, President Obama announced his BRAIN initiative. The acronym BRAIN stands for Brain Research Advanced through Innovative Neurotechnologies. The last word, neurotechnologies is key. It refers to the need for new tools that will enable neuroscientists to test hypotheses, open new lines of investigation and to innovate. To this end, the NIH, NSF and DARPA have been charged by the President to invest over $100M of uncommitted 2014 funds to begin his initiative. This is being matched by a number of private organizations such as the Allen Institute, Howard Hughes Medical Institutions, Kavli Foundation and the Salk Foundation. DARPA has already issued a number of requests for proposals through its Broad Agency Announcement process. Specifically, DARPA seeks to develop neurotechnologies that will enable study of neuropsyciatric disease, mesoscale neuronal activity (100K-1M neurons) and memory. Other requests will be forthcoming over the next year as well. The introduction of the brain science tools will be both enabling and transformative.

Session Abstracts - Day 3

Plenary Session 6

New structural maps of the Brain

Jacopo Annese
Director, The Brain Observatory, USA

New Structural Maps of the Brain

The study of human brain anatomy has undeniably made a comeback in neuroscience and this is due largely to the sophistication of the techniques and concepts that are applied to the study of neural architecture. At a macroscopic scale and in the clinical domain, we have seen a shift of emphasis from mapping the topography and morphology of gray matter compartments to tracing interconnections of neural parcels via white matter fibers. At the other end of the scale, digital technologies boost the scope of microscopic and nanometric models of brain tissue. We are at the exciting stage where it has become conceivable and even practical to represent and measure the anatomy of a whole human brain at the cellular level; that is, the meso-scale level. Gray still matters; cytological parameters, such as neuronal number, size, and cortical layer organization are still extremely relevant to the clinical neurosciences. This knowledge, if formalized at the system level, can also bridge Connectome-era brain maps with older but still valuable human and comparative data produced by histological quantitative methods and stereology. The combination of histology, 3-D reconstruction, and algorithms for the automated analysis of cellular-level features also show unprecedented detail within the so-called white matter substance, revealing an interwoven system of axonal fibers. The challenge, presently, is to make sense of the seemingly insurmountable complexity with white and gray matter and produce discrete templates that can, in spite of individual variability, be generalized for translational applications. In other words, neuroanatomy, in the XXI Century has become the virtualization and standardization of brain tissue.

Breakout Session 16

Neural Stem Cells and Regeneration

Chair: Rasul Chudary & Ann Turnley

Brent A Reynolds *(Keynote)*

Building Better Brains: From Theory to Reality

For the better part of the past century it was a well held belief that the adult mammalian brain did not have the capacity to repair itself. The discovery of neural stem cells in the early 1990's opened the door to the possibility of brain repair, however, this hope and potential has yet to become a reality. In the lecture we will look at the discovery of neural stem cells, explore their potential and look forward to some of the applications of neural stem cell based therapies.

Rasul Chaudary

Promise of Embryonic and Adults Stem Cells for Neural Regeneration

[1,3]Chaudhry G R, [1,3]McKee C, [1,3]Beeravolu NR, [2,3]Dinda S, [3,4]Perez-Cruet M.

It is projected that one of three individuals in the United States could benefit from regenerative medicine therapy in their lifetime. Many of these individuals suffer from damage of the central nervous system, including degeneration of the intervertebral disc (IVD) and retina upon aging as well as neurodegenerative diseases such as Parkinson's, Alzheimer's and ALS. De novo regeneration is particularly difficult due to the lack of renewing capability of neural cells and tissues. We have successfully accomplished proliferation, differentiation and integration of neuro-progenitors and chondro-progenitors in animal models of retinal and IVD degeneration, respectively, using embryonic stem cells. Because of moral and ethical controversies concerning the use of embryonic stem cells, we sought alternative sources to regenerate skeletal and neural tissues of nervous system. This has led us to isolate adult stem cells from umbilical cord tissue and blood which have shown potential to differentiate into chondrogenic and neural cells in vitro. Recently, we have derived a mouse stem cell line which can be differentiated into chondro- and neuro- progenitors. The chondro-progenitors could be further differentiated into chondrocytes and osteocytes expressing Col II and Col I, respectively. Likewise, Neuro-progenitors can be differentiated into neural cell types expressing Nef, TH and RHO. We also isolated

Session Abstracts - Day 3

mesenchymal stem cells (MSCs) from umbilical cord tissues which were successfully differentiated into chondro- and neuro-progenitors. Human MSCs derived chondro-progenitors differentiated into cells capable of producing glucosaminoglycans (GAG) and expressed Sox9, ACAN and Col II in vitro. Whereas, human neuro-progenitors differentiated into neural cell types expressing Tuj1. Future studies are focused on determining the potential of these progenitors to regenerate and restore function of damaged IVD and neural tissues in vivo.

1. Department of Biology, Oakland University
2. School of Health Sciences
3. OU-WB Institute for Stem Cell and Regenerative Medicine, Oakland University, Rochester, MI, USA,
4. Beaumont Health System, Royal Oak, MI, USA.

Quenten Schwarz

Understanding the origin of neurodevelopmental disorders

Hayley Ramshaw, Xiangjun Xu, Eiman Saleh, Zarina Greenberg, Peter McCarthy, Angel Lopez and Quenten Schwarz.

Centre for Cancer Biology, SA Pathology, Adelaide, Australia.

Neurodevelopmental disorders such as schizophrenia, autism, epilepsy and intellectual disability encompass a highly prevalent group of defects thought to arise from impaired development of the brain. Despite a limited range of antipsychotic drugs masking clinical symptoms, current medications have significant levels of chronic relapse and associated functional impairment. Biomedical advances in the past 10 years underpin the hypothesis that these disorders arise from neurodevelopmental deficiencies affecting the hippocampus and prefrontal cortex. However, the vast majority of underlying defects remain unknown. Due to this gap in knowledge diagnosis is only made on the presentation of debilitating clinical symptoms, including positive (psychosis), negative (social withdrawal) and cognitive defects (working memory).

We recently found that the regulatory protein 14-3-3αplays an essential role in neuronal migration, dendritic arborization and axonal growth. Using our unique neurodevelopmental mouse model of schizophrenia and related disorders we have demonstrated that 14-3-3αmutant mice have many of the anatomical and behavioural defects associated with the human condition. Using this mouse model we are now addressing which brain defects underpin the aetiology of schizophrenia-like symptoms. The centrosome / dynein motor complex controls many neurodevelopmental processes that are thought to be disturbed in neuropsychiatic illness. At the molecular level, we have found that 14-3-3αinteracts with and maintains phosphorylation of the core centrosome protein, Ndel1, to regulate neuronal migration. Our data also show that 14-3-3αinteracts with DISC1, a known schizophrenia risk factor, raising the possibility of distinct functions for 14-3-3α/ DISC1 interactions in neuronal migration / synapse / axonal formation. These biochemical interactions suggest that 14-3-3αinteracts with the DISC1 / Ndel1 complex to promote neurodevelopment. One of our key aims is to understand the biological relevance of these interactions. To address this question we have established several in vivo / ex vivo models and generated a suite of monoclonal antibodies specific to 14-3-3α These unique tools provide us the opportunity to unravel the molecular interactions controlling neurodevelopment. Our work provides definitive support to the neurodevelopmental origin of psychiatric illness. Using a cross-disciplinary approach we are addressing several of the outstanding issues in the field. Such findings are expected to significantly progress our understanding of neurodevelopment and neurodevelopmental disorders.

Ann Turnley

What will it take to make endogenous adult neural stem cells repair the adult nervous system?

It has been known for two decades that the adult brain contains niches of neural stem cells that normally produce new neurons in the subventricular zone of the lateral ventricles and the dentate gyrus of the hippocampus. Since their discovery a lot of effort has been spent, with limited success, to enhance the ability of these neural stem cells to promote repair after injury or disease of the nervous system. Not only does production of neural precursor cells need to be increased to generate sufficient numbers for repair, the precursor cells need to migrate to the site of damage, differentiate into the right sort of neuron or glial cell and, perhaps most importantly, survive and integrate appropriately into the local neural circuitry. Most newborn neurons that are produced die within 1 month of their generation and so do not contribute to regeneration. Factors that regulate each of these

Session Abstracts - Day 3

steps – proliferation, migration and differentiation will be discussed, with a focus on our current work aiming to promote survival and integration of newborn neurons following traumatic brain injury to improve functional outcome and neural repair.

Breakout Session 17

Brain Neuromodulation in the Treatment of Epilepsy, Parkinson's and ALS

Medtronic

Chair: Evgeny Tsimerinov

Evgeny Tsimerinov *(Keynote)*

Brain Neuro Modulation in Treatment of Parkinson's, Tremor and Dystonia

Objectives: Parkinson disease (PD) is one of the most common neurologic disorders, affecting approximately 1% of individuals older than 60 years and causing progressive disability that can be slowed, but not halted, by treatment. Essential tremor, the most common movement disorder, is a syndrome of unknown etiology characterized by a slowly progressive postural and/or kinetic tremor, usually affecting both upper extremities. Fundamental debate exists as to whether essential tremor is a neurodegenerative disease. Dystonia (from Greek, meaning altered muscle tone) refers to a syndrome of involuntary sustained or spasmodic muscle contractions involving co-contraction of the agonist and the antagonist. The movements are usually slow and sustained, and they often occur in a repetitive and patterned manner; however, they can be unpredictable and fluctuate.

Scientific approach: Medication treatment of all three disorders could slow down disease but not improve its outcome. Scientists have been looking for the brain target and its modulation to achieve better clinical result.

Basal ganglia and thalamus become the center of interest of scientist and neurologist. Hirotaro Narabayashi constructed a stereotaxic apparatus based on drawings of that constructed in the United States by Victor Horsley and Robert H. Clarke and in 1951 performed the first stereotactic pallidotomy on an athetoid child. The next year he performed a procaine oil blocking of the pallidum of a patient with Parkinson's disease, successfully abolishing the rigidity and tremor symptomatic of this disease.

The usefulness of high-frequency stimulation of the ventralintermediatenucleus (Vim) as the first neurosurgical procedure in disabling tremor was assessed in 26 patients with Parkinson's disease and 6 with essential tremor. 7 of these patients had already undergone thalamotomy contralateral to the stimulated side, and 11 others had bilateral Vim stimulation at the same time. Chronic stimulating electrodes connected to a pulse generator were implanted in the Vim. Tremor amplitude at rest, during posture holding, and during action and intention manoeuvres was assessed by means of accelerometry. Of the 43 thalami stimulated, 27 showed complete relief from tremor and 11 major improvement (88%). The improvement was maintained for up to 29 months (mean follow-up 13 [SD 9] months). Adverse effects were mild and could be eradicated by reduction or cessation of stimulation. This reversibility and adaptability, allowing control of side-effects, make thalamicstimulation preferable to thalamotomy, especially when treatment of both sides of the brain is needed.

Thalamic stimulation has been proposed to treat disabling tremor. The aims of this multicentre study were to evaluate the efficacy and the morbidity of thalamic stimulation in a large number of patients with parkinsonian or essential tremor. One hundred and eleven patients were included in the study and 110 were implanted either unilaterally or bilaterally. Patients were evaluated with clinical scales, before and up to 12 months after surgery. Upper and lower limb tremor scores were reduced in both groups. Eighty five per cent of the electrodes satisfied the arbitrary criteria of two point reduction in rest tremor reduction in the parkinsonian tremor group and 89% for postural tremor reduction in the essential tremor group. In the parkinsonian tremor group, limb akinesia and limb rigidity scores were moderately but significantly reduced. Thalamic stimulation was shown to be an effective and relatively safe treatment for disabling tremor. This procedure initially applied in a very limited number of centres has been successfully used in 13 participating centers.

Multicentre European study of thalamic stimulation in essential tremor: a six year follow up.

Sydow O, Thobois S, Alesch F, Speelman JD. SourceDepartment of Neurology, Karolinska Hospital, Stockholm, Sweden.

Session Abstracts - Day 3

Thalamic stimulation is an efficient treatment for disabling essential tremor, as previously shown, but follow up has mostly been short term. 37 patients with essential tremor had implantation of a thalamic stimulator, either unilaterally or bilaterally. The results at one year have been reported earlier. After six years, 19 patients were available for follow up. The main instrument for evaluation was the essential tremor rating scale. The patients were examined with pulse generators turned on and off. In the majority of patients, the very good results with stimulation seen at one year were maintained after a mean of 6.5 years. The reduction in tremor scores and improvement in activities of daily living were highly significant compared with baseline and with the stimulation turned off. There were few serious adverse events. Minor side effects related to stimulation were common. A few device related complications were observed and most could be resolved. Good reduction in tremor can be maintained for more than six years in the majority of these severely disabled patients. Thalamic stimulation can be recommended in essential tremor where there is insufficient response to drug treatment. Surgical procedures and follow up should be concentrated in relatively few centers, which will thereby acquire a high degree of expertise.

Neurostimulation of the subthalamic nucleus reduces levodopa-related motor complications in advanced Parkinson's disease. We compared this treatment plus medication with medical management. In this randomized-pairs trial, we enrolled 156 patients with advanced Parkinson's disease and severe motor symptoms. The primary end points were the changes from baseline to six months in the quality of life, as assessed by the Parkinson's Disease Questionnaire (PDQ-39), and the severity of symptoms without medication, according to the Unified Parkinson's Disease Rating Scale, part III (UPDRS-III). Pairwise comparisons showed that neurostimulation, as compared with medication alone, caused greater improvements from baseline to six months in the PDQ-39 (50 of 78 pairs, P=0.02) and the UPDRS-III (55 of 78, P<0.001), with mean improvements of 9.5 and 19.6 points, respectively. Neurostimulation resulted in improvements of 24 to 38 percent in the PDQ-39 subscales for mobility, activities of daily living, emotional well-being, stigma, and bodily discomfort. Serious adverse events were more common with neurostimulation than with medication alone (13 percent vs. 4 percent, P<0.04) and included a fatal intracerebral hemorrhage. The overall frequency of adverse events was higher in the medication group (64 percent vs. 50 percent, P=0.08). In this six-month study of patients under 75 years of age with severe motor complications of Parkinson's disease, neurostimulation of the subthalamic nucleus was more effective than medical management alone. (ClinicalTrials.gov number, NCT00196911 [ClinicalTrials.gov].).

Surgical intervention for advanced Parkinson's disease is an option if medical therapy fails to control symptoms adequately. We aimed to assess whether surgery and best medical therapy improved self-reported quality of life more than best medical therapy alone in patients with advanced Parkinson's disease. The PD SURG trial is an ongoing randomised, open-label trial. At 13 neurosurgical centres in the UK, between November, 2000, and December, 2006, patients with Parkinson's disease that was not adequately controlled by medical therapy were randomly assigned by use of a computerised minimisation procedure to immediate surgery (lesioning or deep brain stimulation at the discretion of the local clinician) and best medical therapy or to best medical therapy alone. Patients were analysed in the treatment group to which they were randomised, irrespective of whether they received their allocated treatment. The primary endpoint was patient self-reported quality of life on the 39-item Parkinson's disease questionnaire (PDQ-39). At 1 year, surgery and best medical therapy improved patient self-reported quality of life more than best medical therapy alone in patients with advanced Parkinson's disease. These differences are clinically meaningful, but surgery is not without risk and targeting of patients most likely to benefit might be warranted.

Bilateral globus pallidus internus (GPi) deep brain stimulation (DBS) in a patient with severe idiopathic generalized dystonia resulted in immediate improvement of all aspects of dystonia. During joystick movement, GPi DBS reduced PET activation bilaterally in the primary motor, lateral premotor, supplementary motor, anterior cingulate, and prefrontal areas and ipsilaterally in the lentiform nucleus. Altering basal ganglia function with GPi DBS reverses the overactivity of certain motor cortical areas present in Dystonia.

In 22 patients with generalized Dystonia bilateral DBS showed average 55% improvement at 12 months follow up. Significant improvement is seen in 40 patients with primary Generalized and Segmental Dystonia at 3 month follow up. In sham stimulation only 15% improvement is seen. 46% improvement average is at 6 months. Up to 80% improvement is at 3 year follow up and thereafter.

Session Abstracts - Day 3

Conclusion: Brain Neuro Modulation especially DBS is a safe procedure with predictable AEs knowing anatomy and functional topography. 1. AEs are classified and reported in the long-term mostly as hardware- and stimulation-related; 2. Bradykinesia and gait difficulties have been observed long-term bilateral pallidal DBS, completely reversible when switching off the stimulation or using more dorsally located active contacts; Three suicides have been reported in patients with dystonia after DBS, all of them had depression before DBS; Three suicides have been reported in patients with dystonia after DBS, all of them had depression before DBS.

Tony DeSalles

Future Applications of Brain Neuro Modulation in Treatment of Parkinson's and Neurodegenerative Disorders

Lilit Mnatsakanian

Advances in Technology in the Treatment of Epilepsy

One-third of people with epilepsy will fail antiepileptic drug therapy. Epilepsy surgery can offer a potential cure from disabling seizures. However up to 40 % of patients suffering a drug-resistant epilepsy, might not qualify for surgical treatment. The field of neurostimulation for epilepsy has grown dramatically since the vagus nerve stimulation became available for the treatment of epilepsy. Its use has been extended not only in different types of epilepsies, but other conditions, comorbid with epilepsy. More studies have become available offering deep brain stimulation of the anterior thalamus, responsive neurostimulation, and trigeminal nerve stimulation for treatment of refractory epilepsies. The mechanisms of action, and efficacy of new neurostimulation devices are reviewed, and the key advantages and disadvantages are discussed.

Reese Terry

The Brain-Vagus-Heart Connections: Therapeutic Investigations

Implantable vagus nerve stimulation (VNS) for the control of epilepsy began 25 years ago in November 1988. More than 70,000 epilepsy patients have been treated worldwide with VNS therapy. This therapy has opened the understanding of the brain-vagus-heart connections, which have led to investigations into potential new therapies. The heart responds to seizure activity prior to EEG changes and these changes in heart rate are being investigated in clinical studies in Europe and the US as a method of seizure detection for activation of VNS therapy. Vagus nerve stimulation is being investigated by several companies as a potential method of treating congestive heart failure and animal studies suggest the potential of VNS to acutely reduce infarct size. Vagus stimulation has been demonstrated to reduce the infarct size in rat focal ischemia and to improve functional recovery. VNS therapy is currently being clinically investigated for stroke recovery with therapy delayed 6 months from the time of the stroke. Rat studies have demonstrated the ability of VNS therapy to promote functional recovery from traumatic brain injury and a clinical study has been approved. Publicly available information on these studies will be presented.

Co-authors: R. Terry[1].

1. Medical Device Consulting, BK Consulting, Houston, USA.

Ashraf Elsayegh

Management of Respiratory Failure in ALS

I will be discussing briefly the different respiratory issues that are a challenge for ALS patients. I will discuss different treatment options including devices that are helpful in reducing day to day respiratory struggles. The crux of my talk will concentrate on a relatively new device (the diaphragm pacemaker). I will discuss indications of this device, the workup required, the actual implantation technique, and our experience with the diaphragm pacemaker here in our center.

Evgeny Tsimerinov

Modern Technologies of Neuro and Brain Modulations in Treatment of ALS

Evgeny I. Tsimerinov, MD, PhD

Objectives: Amyotrophic Lateral Sclerosis (ALS) is a uniform world-wide distributed disorder with

Session Abstracts - Day 3

incidence of 2-3 per 100,000/year. Overall 1.5 to 2; male to female ratio is 2.1 to 1.8. Time of disease onset is usually 65-74 (male±10.2; female±7.4). Prevalence 3-8 per 100,000, and risk increases with age au to 74. It affects upper (UMN) and lower (LMN) motor neurons. It affects UMN in the primary motor cortex, Brodmann's area 4 and the premotor areas, Brodmann's area 6 (secondary motor complex and premotor complex); Betz's giant pyramidal neurons are the distinct group of neurons in layer 5 and other smaller neurons; corticospinal and corticobulbar tracts and reticular formation and limbic system. LMN locates in the brainstem and spinal cord, anterior horn cell.

Scientific approach: Repetitive transcranial magnetic stimulation (rTMS) of brain can modulate cortical neurotransmission, a novel paradigm of repetitive stimulation termed continuous theta-burst stimulation (cTBS) produces a pronounced and prolonged suppression of motor cortex excitability. The aim of this preliminary study was to investigate whether cTBS of motor cortex could have any beneficial effect in patients with amyotrophic lateral sclerosis (ALS). A double-blind, placebo-controlled trial of 20 patients with definite ALS were randomly allocated to blinded active or placebo stimulation. Repetitive stimulation of the motor cortex was performed for five consecutive days every month for six consecutive months. The primary outcome was the rate of decline as evaluated with the ALS functional rating scale. The treatment was well tolerated by the patients. Fifteen patients (seven active and eight sham) completed the study and were included in the 6-months analysis. Both active and sham patients deteriorated during treatment, however, active patients showed a modest but significant slowing of the deterioration rate. Though the authors cannot be sure whether the effects observed can be attributed to cTBS, because of the restricted number of patients studied, further investigation on a larger group of ALS patients is warranted. The results of the pilot study might open up a new therapeutic perspective in ALS based on neuromodulation.

Repetitive transcranial magnetic stimulation (rTMS) of brain can modulate cortical neurotransmission, a novel paradigm of repetitive stimulation termed continuous theta-burst stimulation (cTBS) produces a pronounced and prolonged suppression of motor cortex excitability. The aim of this preliminary study was to investigate whether cTBS of motor cortex could have any beneficial effect in patients with amyotrophic lateral sclerosis (ALS). We performed a double-blind, placebo-controlled trial. Twenty patients with definite ALS were randomly allocated to blinded active or placebo stimulation. Repetitive stimulation of the motor cortex was performed for five consecutive days every month for six consecutive months.

The primary outcome was the rate of decline as evaluated with the ALS functional rating scale. The treatment was well tolerated by the patients. Fifteen patients (seven active and eight sham) completed the study and were included in the 6-months analysis. Both active and sham patients deteriorated during treatment, however, active patients showed a modest but significant slowing of the deterioration rate. Though we cannot be sure whether the effects observed can be attributed to cTBS, because of the restricted number of patients studied, further investigation on a larger group of ALS patients is warranted. The results of the pilot study might open up a new therapeutic perspective in ALS based on neuromodulation.

Preliminary data suggest that repetitive transcranial magnetic stimulation (rTMS) of the brain may produce a modest slowing of disease progression in amyotrophic lateral sclerosis (ALS). The present study was designed to test the hypothesis that rTMS given as continuous theta burst stimulation (cTBS), repeated monthly for one year, would affect ALS progression. A double blind, placebo-controlled trial of patients with ALS were randomly allocated to blinded real or placebo stimulation. cTBS of the motor cortex was performed for five consecutive days every month for one year. Primary outcome was the rate of decline as evaluated with the revised ALS functional rating scale (ALSFRS-R). Treatment was well tolerated. There was no significant difference in the ALSFRS-R score deterioration between patients treated with real or placebo stimulation. ALSFRS-R mean scores declined from 32.0 (SD 7.1) at study entry to 23.1 (SD 6.3) at 12 months in patients receiving real cTBS and from 31.3 (SD 6.9) to 21.2 (SD 6.0) in those receiving placebo stimulation. Although cTBS proved a safe procedure, on the basis of the present findings a larger randomized confirmatory trial seems unjustified in ALS patients, at least in advanced stage of the disease.

From April to July 2002, four consecutive patients affected by amyotrophic lateral sclerosis (ALS) were surgically treated with bilateral chronic cortical stimulation. The preoperative diagnostic assessment was based on the results of a neurological examination, integrated by the ALS functional rating scale, electromyography, magnetic resonance imaging, and single-photon

Session Abstracts - Day 3

emission computed tomography (SPECT). In particular, SPECT provided a remarkable contribution in terms of its ability to demonstrate specific morphological and metabolic ALS lesions of the brain. These preliminary results are surprising, because they suggest that chronic cortical stimulation can play a role against ALS and deserve confirmation in larger numbers of patients and for a longer follow-up. We present the theoretical grounds for these findings, as well as the diagnostic and surgical procedures and results.

Humanitarian Device Exemption Post-Approval Study of NeuRx Diaphragm Pacing System for Amyotrophic Lateral Sclerosis is approved on 9/28/2011.

Forty four patients treated at Cedars-Sinai Medical Center, Los Angeles, California since December of 2011.

FVC <45 was not predictive of lack of response to direct diaphragm stimulation. 72% of those with low FVC and positive direct stimulation had bulbar involvement. Both phrenic nerve conduction and fluoroscopy were predictive of intraoperative response in the majority of cases (82%). Both pre-operative studies had false positives. Discordant results on phrenic nerve conduction and fluoroscopy were not explained by duration between workup and surgery. Currently planned clinical trials using minimum phrenic amplitude of 0.1 mV should expect a nonplacement rate of ~18% due to lack of DNS in the operating room.

As ALS progresses, extensive supportive care is required, including multidisciplinary outpatient care and hospitalization. The authors studied the causes, health care utilization, and outcomes for hospitalized patients with ALS. Methods: With use of the 1996 Nationwide Inpatient Sample, an administrative database representing 20% of U.S. hospitals, 1,600 hospitalizations in patients with ALS were identified and compared with 5,364,728 non-ALS hospitalizations. The most common concurrent diagnoses in patients with ALS were dehydration and malnutrition (574 patients, 36%), pneumonia (507 patients, 32%), and respiratory failure (398 patients, 25%). Only 38% of patients with ALS were discharged to home without home health care compared with 73% of patients with non-ALS. Fifteen percent of patients with ALS died in the hospital compared with 3% of non-ALS patients. The average length of hospital stay and charges were greater for patients with ALS than for non-ALS patients (8.4 days and $19,810 for ALS patients and 5.4 days and $11,924 for non-ALS patients). Mortality was significantly associated with emergency room admission (versus nonemergency admission; OR = 1.60), increasing age (per year; OR = 1.03), respiratory failure (OR = 3.37), and pneumonia (OR = 2.02)

There is a paucity of literature concerning general anesthesia and surgery in patients with amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease). This report summarizes the largest series of surgical cases in ALS during multicenter prospective trials of the laparoscopic diaphragm pacing system (DPS) to delay respiratory failure. The overall strategy outlined includes the use of rapidly reversible short-acting analgesic and amnestic agents with no neuromuscular relaxants. Fifty-one patients were implanted from March 2005 to March 2008 at 2 sites. Age at implantation ranged from 42 to 73 years and the percent predicted forced vital capacity (FVC) ranged from 20% to 87%. On preoperative blood gases, PCO2 was as high as 60. Using this protocol, there were no failures to extubate or 30-day mortalities. The DPS system increases the respiratory system compliance by decreasing posterior lobe atelectasis and can stimulate respirations at the end of each case. Laparoscopic surgery with general anesthesia can be safely performed in patients with ALS undergoing DPS.

Conclusion: Concomitant Brain and peripheral nervous system modulations of UMN and LMN by using modern advanced technologies should significantly improve survival rate of patients suffering from ALS

Breakout Session 18

Biomaterials and The Brain Therapeutics

TBC

Breakout Session 19

Electrodes and Electrochemistry in Brain Mapping

Chair: Justin Gooding

Evgeny Tsemerinov *(Keynote)*

Modern Brain NeuroModulation in Neurologic Disorders

Evgeny I. Tsimerinov, MD, PhD

Objectives: Brain Neuromodulation with continuous or intermittent

Session Abstracts - Day 3

stimulations is considered a delivery of electrical stimulation through implanted electrodes to the specific area of the brain using an implanted pulse generator. The goal is to deliver therapeutic current that modifies a disease course and improves patient health and quality of life.

Brain and Neural stimulations are used in the following Neurologic Disorders: Epilepsy, Depression, Parkinson, Tremor, Dystonia and ALS.

Scientific basics and historical aspects:

- 1938 Bailey and Bremer: VNS in cat elicited desynchronized orbital cortex activity
- 1952 Zanchetti: intermittent VNS reduced or eliminated interictal epileptic effects chemically induced in focal cortex
- 1980 Radna and MacLean: VNS in monkey caused marked single-unit effects on basal limbic structures
- 1985 Zabara: Postulated that VNS would antagonize hypersynchronous seizure states
- First Animal Studies (J. Zabara, Temple University)
- 1987 Cyberonics founded by Reese Terry
- 1988 First Human Implant (Dr. Kiffin Penry)
- 1992 First Randomized Active Control Study

The VNS Therapy System consists of an implanted pacemaker-like generator and nerve stimulation electrodes, which deliver intermittent stimulation to the patient's left vagus nerve that sends signals to the brain. Main mechanism of action is increasing of Norepinephrine output from the locus coeruleus that causes cortical and limbic Neuromodulation.

VNS has been used in treatment of Epilepsy, Depression, and Autism.

Milestone comes 25 years after the first DBS implant for Tremor carried out in Grenoble, France, Medtronic, Inc. announced that a patient from Kempenhaeghe-Heeze (The Netherlands) is the first patient to be enrolled into the MORE (MedtrOnic Registry for Epilepsy) Registry which is designed to look at the long-term efficacy, quality of life impact and safety of deep brain stimulation (DBS) in patients with refractory epilepsy. DBS for epilepsy received CE mark for use in Europe in August 2010. Medtronic DBS Therapy is not currently approved by the U.S. Food and Drug Administration for use in the United States for the treatment of refractory epilepsy. Anterior nucleus of the Thalamus is a target for DBS.

Aggression: In the final installment to this three-part, essay-editorial on psychosurgery, we relate the history of deep brain stimulation (DBS) in humans and glimpse the phenomenal body of work conducted by Dr. Jose Delgado at Yale University from the 1950s to the 1970s. The inception of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1974-1978) is briefly discussed as it pertains to the "determination of the Secretary of Health, Education and Welfare regarding the recommendations and guidelines on psychosurgery." The controversial work — namely recording of brain activity, DBS, and amygdalotomy for intractable psychomotor seizures in patients with uncontrolled violence — conducted by Drs. Vernon H. Mark and Frank Ervin is recounted.

Neuropace: New generation of smart technology that recognizes specific pattern and deliver treatment to the target in the brain. The RNS® System is an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures who have undergone diagnostic testing that localized no more than 2 epileptogenic foci, are refractory to two or more antiepileptic medications, and currently have frequent and disabling seizures (motor partial seizures, complex partial seizures and/or secondarily generalized seizures). The RNS® System has demonstrated safety and effectiveness in patients who average 3 or more disabling seizures per month over the three most recent months (with no month with fewer than two seizures), and has not been evaluated in patients with less frequent seizures.

The effectiveness of responsive stimulation is sustained over years of follow-up. Combining data from all subjects treated with the RNS System, the responder rate, defined as the percentage of subjects with a 50% or greater reduction in seizures and shown in black, and the median percent reduction in seizures, shown stippled, increases over the first 1 two years after implant and is then maintained in the 50% or higher range even past 6 years for some. The numbers of subjects, shown on the x-axis, becomes smaller primarily because subjects hadn't reached that time point as of the data cut-off.

DBS was approved for a Parkinson's disease in 1997, but it is not an accepted treatment for epilepsy at this time. Deep brain stimulation (DBS) is an effective surgical treatment for medication-refractory hypokinetic and hyperkinetic movement disorders, and it is being explored for a variety of other neurological and psychiatric diseases. Deep brain stimulation has been Food and Drug Administration-approved for essential tremor

Session Abstracts - Day 3

and Parkinson disease and has a humanitarian device exemption for Dystonia and obsessive-compulsive disorder.

Medronic, Inc. and Boston Scientific are the leaders in this field and offer diversity of electrodes and IPGs for DBS.

Direct cortical stimulation with Medtronic device patients with ALS: From April to July 2002, four consecutive patients affected by amyotrophic lateral sclerosis (ALS) were surgically treated with bilateral chronic cortical stimulation. The preoperative diagnostic assessment was based on the results of a neurological examination, integrated by the ALS functional rating scale, electromyography, magnetic resonance imaging, and single-photon emission computed tomography (SPECT). In particular, SPECT provided a remarkable contribution in terms of its ability to demonstrate specific morphological and metabolic ALS lesions of the brain. These preliminary results are surprising, because they suggest that chronic cortical stimulation can play a role against ALS and deserve confirmation in larger numbers of patients and for a longer follow-up. We present the theoretical grounds for these findings, as well as the diagnostic and surgical procedures and results.

Humanitarian Device Exemption Post-Approval Study of NeuRx Diaphragm Pacing System for Amyotrophic Lateral Sclerosis is approved on 9/28/2011.

Forty four patients with ALS treated at Cedars-Sinai Medical Center, Los Angeles, California since December of 2011.

The Diaphragmic Pacer has been the single best decision I have made since my diagnosis. My diaphragm is the one muscle in my body that not only stays the same, but has gotten stronger. 90% of ALS patients choose not to go on a ventilator. The pacer will help extend the decision while we help find a cure." June 2008 "I am not using a vent because of your device!" October 2009 (Augie Neito's Story).

Conclusion: Brain Neurostimulation is the fruit of decades of both technical and scientific advances in the field of basic neuroscience, neurology and functional neurosurgery.

Advances in Brain NeuroModulation open New Era in Human fight against Neurodegenerative Disorders and bring us Hope and Believe in Better and Healthier Future.

Greg Suaning

Electrodes in the supra-choroidal space for visual prosthesis – effecting focused cortical activation

Professor Gregg Suaning
Graduate School of Biomedical Engineering, University of New South Wales, Sydney, Australia

Objective: To describe stimulation paradigms to achieve low-threshold activation to effect selective stimulation of retinal ganglion cells via an electrode array implanted within the supra-choroidal space.

Materials and Methods: A stimulation paradigm that we have described as 'quasi-monopolar' (QMP) divides the return-path of stimulation across a ring of guard electrodes adjacent to and surrounding the stimulating electrode, and a distant monopolar return. Through acute in vivo testing in the feline, we have determined that the effect of the of guard ring electrodes is that activation is largely contained to within the ring. However, activation thresholds using this approach alone are approximately three times higher with respect to monopolar stimulation alone owing to inefficient, lateral shunting of the electric fields. By splitting a proportion of the return current to a distant monopole, the electric field is directed towards the target neurons. The monopolar component of the return current effectively reduces the threshold of activation while the guard ring component maintains the localisation of activation. QMP further affords the possibility of delivering stimulation from multiple sites simultaneously with a significant reduction in cross-talk between stimulating sites relative to monopolar stimulation alone.

Discussion: The QMP stimulation paradigm provides the dual benefits of focused activation via guard-ring localisation with reduced stimulation thresholds of monopolar stimulation.

Acknowledgement: This research was supported by the Australian Research Council (ARC) through its Special Research Initiative (SRI) in Bionic Vision Science and Technology grant to Bionic Vision Australia (BVA).

Session Abstracts - Day 3

Alex Harris

A Method for the Systematic in vitro and in vivo Evaluation of Neural Recording Electrodes

Alexander R. Harris
ARC Centre of Excellence for Electromaterials Science

New materials and designs for neural implants are typically tested separately, with a demonstration of performance but without reference to other implant characteristics. This precludes a rational selection of a particular implant as optimal for a given application and the development of new materials based on the most critical performance parameters. Different electrode designs, materials and coatings affect neural recording performance through changes to electrochemical, chemical and mechanical properties. Comparison of electrodes in vitro is relatively simple, however comparison of in vivo response is typically complicated by variations in electrode/neuron distance and between animals. This talk introduces a protocol for in vitro and in vivo testing of neural recording electrodes. This method eliminates or reduces the impact of many systematic errors present in simpler in vivo testing paradigms, especially variations in electrode/neuron distance and between animal models. The result is a strong correlation between the critical in vitro and in vivo responses, such as impedance and signal-to-noise ratio.

Justin Gooding

Electrodes that resist protein fouling when used in biological fluids: Applications for biosensing, cell biology and implantable electrodes

J. Justin Gooding, Alicia L. Gui, Guozhen Liu, Abbas Barfidokht

Australian Centre for NanoMedicine and School of Chemistry

The University of New South Wales, Sydney, 2052 Australia

Justin.gooding@unsw.edu.au

The application of electrodes in biological media is not only the basis of many electrochemical biosensors but also an imperative for in vivo stimulating electrodes. The issue all electrodes have when being used in biological media is fouling by proteins and cells. For stimulating electrodes this increases the potentials that need to be applied to an electrode to allow it to stimulate the appropriate biological response. For biosensors such fouling typically means poor analytical performance or complete failure of the device. This talk will present a number of novel strategies to developing electrodes with antifouling layers. These effectiveness of these modification layers in limiting electrode fouling will be demonstrated and their utility in biosensing and as stimulating electrodes will be shown.

Three different electrode modification strategies to allow antifouling layers to be applied to electrodes will be presented. The first type of electrode construct is where oligo(ethylene oxide) units provide antifouling and molecular wires are used to provide electrochemical communication. These interfaces are shown to be effective in the development of electrochemical biosensors based on immunoreagents. In this talk the application of these surfaces will be demonstrated for detecting antibiotics in biological samples and glycosylated haemoglobin (HbA1c). HbA1c is an important 3 month biomarker for the effectiveness of a diabetics treatment strategy. The second interface is similar to the first interface where oligo(ethylene oxides) are used to provide antifouling ability to the electrode surfaces and where nanoparticles form the conducting channels, essentially serving as molecular wires. This interface is also applied to immunosensing for the detection of HbA1c.

The final system to be described is a completely different strategy for making electrodes with antifouling layers which is well suited for implantable electrodes. The other systems described all essentially produce high impedance layers on electrodes and the molecular wire or nanoparticles are required to provide conducting channels. With the third strategy we use zwitterions to provide the resistance to non-specific protein and cell adsorption. Because other antifouling moieties are just small organic molecules this means the antifouling layer can just be a few atoms long. Hence antifouling layers can be produced which are low impedance, and hence perfect for stimulating electrodes.

Breakout Session 20

Brain 'All Omics'

Chair: Howard Federoff

Session Abstracts - Day 3

Howard Federoff *(Keynote)*

Brett Stringer

The Establishment and Characterisation of Patient-Derived Cell line and Mouse Models for Studying Glioblastoma

Brett W Stringer[1], Bryan W Day[1], Paul R Jamieson[1], Kathleen S Ensbey[1], Zara C Bruce[1], Po Inglis[2], Rosalind Jeffrey[2], Andrew W Boyd[1,3]

Glioblastoma (GBM) is the commonest form of primary brain cancer and also the most lethal. Despite surgery, radiotherapy and chemotherapy, the median survival with this disease is only 14 months and the 5-year survival rate less than 10%. Part of the reason for this is that GBM is a very heterogeneous disease. Despite this, genome-wide approaches applied to GBM have identified several unifying themes.

Part of our approach to improve the outlook for people with GBM has been to establish patient-derived cell lines and xenograft mouse models that better capture the heterogeneity of this disease, both at the intra- and inter-tumoural level. This presentation will describe the establishment of these resources, our characterisation of them and how they are being used to evaluate potential therapeutic targets and therapies for this disease.

1. QIMR Berghofer Medical Research Institute
2. Royal Brisbane and Women's Hospital
3. Department of Medicine, The University of Queensland

Brandon Wainwright

An integrative functional genomics approach to defining key gene networks in medulloblastoma.

Laura Genovesi[1], Melissa Davis[2], Ching Ging Ng[3], Nancy Copeland[4], Neil Jenkins[4] and Brandon Wainwright[1].

Medulloblastoma is the most common malignant brain tumour of childhood. Recent gene expression studies have subtyped medulloblastoma into four classes of tumor, "WNT", "SHH", "Group3" and "Group 4", each of which has a distinct clinical presentation and prognosis. Recent whole genome sequencing studies have indicated that the tumours have relatively stable genomes and one of the emergent themes is that there is a widespread deregulation of chromatin, potentially leading to genome wide gene deregulation. At this point it is difficult to conclude as to whether genomes studies have identified strong candidates for new therapeutic targets. We performed a functional screen in a mouse model for SHH medullobaltoma using the Sleeping Beauty transposon to identify genes that cooperate with SHH signalling to result in medulloblastoma. We then took these genes and constructed networks using a conservative protein=protein interaction approach. Surprisingly, we identified a number of networks that all four medulloblastoma subtypes have in common which have identified therapeutic targets that could be deployed against medulloblastoma such as CDK4/6.

1. Institute for Molecular Bioscience, The University of Queensland, Australia
2. Department of Electrical Engineering and NICTA, The University of Melbourne, Australia
3. Institute for Molecular and Cellular Biology, Singapore
4. The Methodist Hospital Research Institute, Houston, USA.

Bryan Day

EphA3 Maintain Tumour-Initiating Cells and is a Therapeutic Target in Brain Cancer

Bryan W. Day[1], Brett W. Stringer[1], Fares Al-Ejeh[1], Kathleen S. Ensbey[1], Zara C. Bruce[1], Paul R. Jamieson[1], Yi Chieh Lim[1], Po Inglis[2], Lindy Jeffree[3] and Andrew W. Boyd[1]

Significant endeavor has been applied to define markers of glioma stem cells (GSCs) and to identify functional therapeutic targets in glioblastoma (GBM) to halt the growth of this aggressive cancer. This study identifies EphA3 as a functional, targetable cell surface GSC marker in GBM.

We show that the receptor tyrosine kinase EphA3 is over expressed in GBM and in particular in the most aggressive mesenchymal stem-like subtype. Importantly, EphA3 is highly expressed on the tumor-initiating GSC population and is critically involved in maintaining tumor cells in an undifferentiated state by modulating MAPK signaling. EphA3 knock down or depletion induced differentiation and reduced the GSC pool leading to delayed orthotopic tumour formation in mice. Specific targeting of EphA3 positive GSCs in vivo using a pay loaded EphA3 mAb, reduced GBM tumour size and significantly increased survival while inducing minimal toxicity.

While debate still surrounds the cancer stem cell hypothesis in solid tumors, such as GBM,

Session Abstracts - Day 3

there is agreement that cells in an undifferentiated state exist within these highly heterogeneous tumors. These cells are thought to be responsible for tumor recurrence following treatment. Here, we demonstrate that in EphA3-expressing GBM, EphA3 is crucial in maintaining undifferentiated, tumor-initiating cells by modulation of MAPK signaling. EphA3 is lowly expressed in adult tissues and therefore represents a relatively tumor-specific therapeutic target in GBM.

We acknowledge NHMRC Australia funding (App ID: 1023695)

Jan Fullerton

Enrichment of polygenic risk alleles in a longitudinal cohort at high-risk of bipolar disorder

Fullerton JM[1,2], Koller DL[3], Edenberg HJ[4], Foroud T[3], Liu H[5], Glowinski AL[6], McInnis M[7], Wilcox HC[8], Frankland A[2,9], Roberts G[2,9], Schofield PR[1,2], Mitchell PB[2,9], Nurnberger JI[10]

Background: Bipolar disorder is a severe mood disorder with complex etiology. Recent data has indicated the highly polygenic nature of disease risk with many hundreds of risk variants of small effect, but also a small number of risk variants reproducibly associated with bipolar disorder have been identified. However the molecular, biological, and neuropsychological factors that are associated with the onset of bipolar disorder are largely unknown, and can only be dissected through longitudinal studies of high-risk individuals.

Methods: Using standardised clinical assessment protocols across five independent sites in the USA and Australia, at-risk subjects comprising adolescent and young adult (12-30 years) offspring and siblings of patients with bipolar I disorder (n=369) and controls in the same age range but without family history of mood disorder or psychosis (n=229) have been studied.

These individuals will be reviewed annually for 5-10 years with structured clinical and neuropsychological assessments, and peripheral blood samples were collected at baseline. Structural and functional brain imaging data will be collected biannually on the Australian participants. Multimodal analysis will be conducted to identify molecular, clinical and environmental risk factors which are associated with later conversion to bipolar disorder.

Results: Using a limited panel of the most robust disease-associated SNPs, we show an increased genetic loading of risk alleles in European at-risk individuals compared to European controls at a group level (additive allele-frequency-weighted model: GEE Wald χ^2=4.53, one tailed p=0.017, relative risk of score >0.30=1.28), although the distribution of scores would not clearly define future diagnostic status at an individual level. We have preliminary findings examining the impact of polygenic score on brain structure at baseline. No significant difference in methylation at any individual locus was observed at baseline between at-risk and control subjects on a group-wise basis.

Discussion: Further analysis will be conducted longitudinally, as participants who were at-risk of developing bipolar disorder at baseline convert to bipolar disorder diagnoses in subsequent years. Identification of biomarkers (genetic, epigenetic, clinical, brain structural and functional) which appear prior to conversion to bipolar disorder will be conducted as the study progresses. Incorporating information about polygenic risk, plus early changes in brain structure and function, will aid in the development of effective tools for risk prediction in the future.

1. Neuroscience Research Australia, Sydney, Australia
2. University of New South Wales, Sydney, Australia
3. Department of Medical and Molecular Genetics, Indiana University, Indianapolis
4. Departments of Biochemistry and Molecular Biology, Medical and Molecular Genetics and Center for Medical Genomics, Indiana University, Indianapolis
5. Indiana Alzheimer Disease Centre, Indiana University, Indianapolis
6. Department of Psychiatry, Washington University, St Louis, Missouri
7. Department of Psychiatry, University of Michigan, Ann Arbor, Michigan
8. Child Psychiatry & Public Health; Johns Hopkins University, Baltimore, Maryland
9. Black Dog Institute, Prince of Wales Hospital, Sydney, Australia
10. Department of Psychiatry, Institute of Psychiatric Research, Indiana University School of Medicine, Indianapolis

Breakout Session 20a

Clinical Neurology and Neurointerventions

Chair: George Paxinos & Perminder Sachdev

Bryce Vissel *(Keynote)*

Session Abstracts - Day 3

Wieslaw Nowinski

CAD systems for ischemic and hemorrhagic strokes

Wieslaw L. Nowinski
Biomedical Imaging Lab, ASTAR, Singapore

Stroke is a leading cause of death and the major cause of permanent disability. It has a great effect on public health and causes high cost for primary treatment, rehabilitation, and chronic care. Despite a critical need, there is no clinically accepted and globally used computer-aided diagnosis/detection (CAD) system for stroke yet, though there are a number of CAD systems in other fields including mammography, colonoscopy, and chest cancer.

This talk presents an overview of CAD systems for stroke: two for acute ischemic stroke (one supporting atlas-assisted analysis of the diffusion-perfusion mismatch and the other providing processing of noncontrast CT) and one for hemorrhagic stroke.

The acute ischemic stroke CAD system supports thrombolysis. The approach shifts the paradigm in stroke image processing from a 2D visual inspection of individual scans and maps to an atlas-assisted quantification and simultaneous visualization of multiple 2D and 3D images. It provides rapid, automatic, and quantitative image analysis and decision making support from anatomy, diffusion, and perfusion scans. The diffusion-perfusion mismatch and the size of the infarct versus that of the middle cerebral artery territory are calculated. For image quantification, two electronic brain atlases are employed: atlas of anatomy and atlas of blood supply territories. Atlas-assisted analysis provides the complete list of anatomical structures and blood supply territories along with their volume and percentage contributions to the infarct and penumbra[1].

The ischemic stroke CAD system for nonconstrast CT provides automatic and rapid detection, localization and volume assessment of ischemic infarcts in a single scan. It first determines the intensity ranges of cerebrospinal fluid, white matter and gray matter. Then, it separates the brain scan into the left and right hemispheres and, by analyzing the characteristics of intensity distributions in the hemispheres, it detects, localizes and assesses volume of an ischemic infarct without its actual segmentation[2].

The hemorrhagic stroke CAD system supports the evacuation of hemorrhage by thrombolytic treatment through a catheter inserted into the ventricular system. This system aims at progression and quantification of blood clot removal. The clot is automatically segmented from CT time series, its volume measured over time, and the process of clot lysis is dynamically displayed and monitored. This CAD system has been employed in the CLEAR clinical trial, phase 3.

These stroke CAD systems facilitate and speed up analysis of images, increase confidence of interpreters, and support decision making. They are potentially useful in diagnosis and research, particularly, for clinical trials.

References

1. Nowinski WL, et al Analysis of ischemic stroke MR images by means of brain atlases of anatomy and blood supply territories. Academic Radiology 2006;13(8):1025-34.

2. Nowinski WL, et al. Automatic detection, localization and volume estimation of ischemic infarcts in non-contrast CT scans: method and preliminary results. Investigative Radiology 2013;48(9):6

Eric Bailey

Ambulance based CT and its Impact on Thrombolytic Therapy for Acute Ischemic Stroke

Author: Dr. Eric M. Bailey, CEO NeuroLogica Corporation, Subsidiary of Samsung Electronics, Danvers Massachusetts, USA.

Stroke is a devastating world health issue. In most developed countries it is the 3rd leading cause of death. Even more devastating, it is the #1 cause of long term disability. Economically it is a great burden on society, but with an age increasing population, it is destined to become even worse. Most strokes (80%) are ischemic in nature and may benefit from thrombolysis, the only available acute therapy. However, thrombolysis is a time critical and potentially dangerous treatment that requires many steps. Brain imaging is necessary in order for thrombolysis to be administered safely. Because of the many time delays in transport and diagnostics, thrombolysis is generally only given to 1-3% of the total patients.

This talk is about the author's idea and ultimate creation of designing a small portable CT scanner to be installed in ambulances whereby diagnostics could be performed at the point of pickup and thrombolytic treatment could be performed in situ. Such a CT system has been designed and mobile stroke vehicles have been installed in Germany, Norway, Russia, and just recently the USA. This paper will show the different vehicles and approaches that have been developed and present some of the scientific findings that have been achieved.

Session Abstracts - Day 3

On average, the call-to-thrombolytic therapy time has decreased by 40 minutes. This also lengthens the window for available patients thus possibly extending this therapy to 30% or more of potential stroke patients. If this can be achieved on a broad scale it will have a tremendous impact on stroke treatment and ultimate cost to society.

Penelope McNulty and Christine Shiner


Investigating neuroplasticity post-stroke: contrasting bilateral differences in magnetoencephalography, transcranial magnetic stimulation and functional motor assessments

Penelope A McNulty and Christine T Shiner

Neuroscience Research Australia, Sydney, Australia
School of Medical Sciences, University of New South Wales, Sydney, Australia

Hemiparesis, or a weakness on the side of the body contralateral to the lesion is the most common cause of impaired movement ability after stroke. Other than natural recovery, rehabilitation remains the only means of improving functional movement, principally through cortical reorganisation. Many neural mechanisms contribute to cortical reorganisation but the relative contribution and sequencing of individual components is not well understood. Improvements in behaviour and cortical reorganisation cannot necessarily be inferred from each other. In this preliminary multi-modal study we examined the relationship between muscle activation, brain activation and functional movement ability.

In separate sessions 8 hemiparetic stroke patients 3-45 months post-stroke completed a magnetoencephalography scan (MEG); magnetic resonance imaging (MRI); transcranial magnetic stimulation (TMS) assessment of resting and active motor threshold; and motor-function assessments. Whole-head MEG recordings consisted of 160 coaxial first-order gradiometers with a 50 mm baseline while patients performed a unilateral finger-tapping task. Both sides were tested separately. Structural T1-weighted MRI images were acquired for co-registration of MEG data and TMS threshold motor evoked potentials were recorded bilaterally from the first dorsal interosseous muscle. Functional movement ability was assessed using the Wolf Motor Function Test timed-tasks (WMFT-tt) and stratified as low, moderate or high based on performance on the Box and Block and grooved-pegboard tests of manual dexterity.

Two patients were classified with low, three with moderate, and three with high motor-function. Time-frequency MEG analysis revealed different patterns of movement-related beta-band (13-30 Hz) activity that was associated with motor-function level. On the more-affected side there was a robust event-related desynchronisation of activity for all patients during movement execution, with no consistent pattern during movement preparation. The desynchronisation amplitude and duration was most prominent for low-functioning patients. An event-related rebound synchronisation of beta-activity followed the desynchronisation for patients with moderate motor-function, was prominent for patients with high motor-function, but absent for patients with low motor-function.

The pattern of beta-band activity was similar for each patient when tested with less-affected side movements. Motor evoked potentials could be elicited on the more-affected side at rest in 4 patients with a mean threshold of 59.0±9.7% stimulator output, and during a 10% voluntary contraction in 5 patients at 47.0±2.5% stimulator output. WMFT-tt mean times were 71.4, 12.9, and 2.4 s, for patients with low, moderate and high motor-function, respectively. In 3 patients with poor motor-function neither a resting TMS motor evoked potential nor a rebound beta-resynchronisation was evident on the more-affected side, although all had motor evoked potentials on the less-affected side. The duration of both beta-band phenomena was correlated with resting and active motor thresholds and with upper-limb motor-function. A longer desynchronisation was correlated with higher thresholds and poorer function ($p<0.001$) while a longer resynchronisation correlated with lower thresholds and higher function ($p=0.002$).

These preliminary data suggest that post-stroke movement-related MEG beta-band activity is related to both corticomotor excitability and motor-function on the more-affected side. In this study cortical beta-band activity was bilaterally affected after stroke even in patients with relatively preserved ipsilesional cortical excitability and less-affected side motor-function.

Keywords: magnetoencephalography, transcranial magnetic stimulation, functional assessment, stroke, cortical reorganisation.

Session Abstracts - Day 3

Yih Yian Sitoh

Neuroimaging in Psychiatry

The use of neuroimaging in psychiatric disorders has increased recently, with most of the work done under research protocols. In clinical practice, neuroimaging facilitates the diagnosis of psychiatric disorders and can detect structural disorders and neurodegenerative conditions causing psychosis.

The clinical use of neuroimaging in psychiatry will increase in the near future, particularly using MRI and molecular imaging techniques. It is important to appreciate the role and limitations of such techniques.

An overview of the more common clinical conditions presenting with psychosis and a summary of recent MRI based research findings in psychiatric disorders is presented.

Paul Fitzgerald

Enhanced neuroimaging based targeting to improve response to rTMS treatment in depression

Objective: Repetitive transcranial magnetic stimulation (rTMS) is an well-established new treatment modality for patients with depressive disorders. However, studies have consistently indicated that the effect sizes with standard methods of rTMS application are relatively limited. There are a number of issues which may limit the effectiveness of rTMS treatment, including methods of targeting stimulation to relevant prefrontal brain regions. The objective of this research was to enhance the application of rTMS treatment in depression by improving prefrontal stimulation target sites and localisation.

Methods: First, we conducted a functional imaging study and a quantitative meta-analysis to explore the region within the dorsal prefrontal cortex most implicated in the aetiology of depression. In addition, we conducted a randomised controlled trial evaluating the relative efficacy of neuro-navigationally targeted rTMS. Third we have developed methods using near infrared spectroscopy and EEG to optimise coil placement in prefrontal cortex.

Results: Functional imaging studies in patients with depression do not provide a clear and well defined target for rTMS treatment. However, neuro-navigationally localising treatment based on dorsolateral prefrontal cortex structure does produce a greater antidepressant response than standard methods of rTMS application. Finally, NIRS and EEG methods appear to be able to be used to improve aspects of prefrontal coil placement.

Conclusions: Improvements in the application of rTMS treatment are possible using a range of imaging tools that can enhance coil placement and localisation. Improvements in rTMS application are likely to arise from individualisation of treatment site based on individual patient brain characteristics.

Breakout Session 21a

CME Symposium, Intra-operative Brain Mapping

Chair: George Paxinos

George Paxinos

Brain, Behavior and Evolution

Standard atlases using identical nomenclature enable scientists to navigate seamlessly between the brain of humans and experimental animals to test hypotheses inspired by human considerations and relate data from experimental animals to humans.

In current atlas construction we make use of genes that are responsible for the segmentation of the brain in development (hox genes). Using evidence from transgenic mice and birds we are proposing a new plan for the organization and function of certain brain regions of mammals. The brainstem, for instance, can no longer be considered as a container of haphazardly arranged nuclei (as potatoes in a sac), but instead as regions which co-vary (start and end) with their neighbours.

The human brain features many more homologies with the brain of monkey (eg, virtually all areas of the cortex are homologous), of the rat and of the bird than previously thought. Areas which are shown to be homologous are likely to have similar function as for example are 9/46 of the prefrontal cortex which is homologous in human and monkey and is involved in executive

Session Abstracts - Day 3

processing in working memory in both species.

Using MR images in mice and non-human primates we are attempting to provide 3D volumes of canonical brains against which transgenic varieties with clinical significance can be compared.

Finally, on the issue of evolution and survival, the brain is wonderful, but it is not omniscient. Both the dazzling technological success of our species and the worrisome environmental degradation it has produced are reflections of the function of our brains. The author concludes: If the brain were smaller than what it is, it would not have been able to support language and the development of science and technology which today threatens existence; if the brain were larger than what it is, it might have been able to understand the problem and possibly even solve it. The brain is just not the right size.

Wieslaw Nowinski

Stereotactic brain atlases in intra-operative imaging

Early stereotactic human brain atlases in print form were constructed in the 1950s to support human stereotactic instruments. At the end of the 1990s, the computerized anatomical brain atlases had become prevalent in neurosurgical workstations. They are useful in pre-operative planning, intra-operative support and post-operative evaluation[1]. The intraoperative usefulness of the brain atlas is enhanced when interfaced with the micropositioning device.

Combination of various stereotactic brain atlases is advantages. Anatomical and probabilistic functional (electrophysiology- and imaging-based) atlases are complementary, as the functional atlas is of a high spatial resolution, dynamic, composed from theoretically unlimited number of brain specimens, and consistent in 3D, whereas the anatomical atlas is deterministic, sparse, static, based on a few brain specimens and inconsistent in 3D. Conversely, a low parcellated functional atlas is enhanced by a highly parcellated anatomical atlas[2].

There are various ways of integration of the brain atlas with the surgical workstation. The atlas module may contain a single or multiple atlases. The atlases may be available in 2D, in a single or all three orthogonal orientations, or in 3D. The atlas may be present in various representations (image, contour, polygonal, volumetric). The key operation is atlas to scan registration and the resulting labeling and delineation of patient's specific scans. These featured will be illustrated with the existing surgical workstations, such as StealthStation (Medtronic), and iPlan (BrainLAB).

The insertion of devices into the brain during microrecording and stimulation may potentially cause microbleeds not discernible on standard scans. A small change in location of the DBS (deep brain stimulation) electrode may result in a major change to the patient. To address this issue, a stereotactic and functional neurosurgery-aided system composed of three stereotactic brain atlases: anatomical, functional, and vascular, will be presented. This system provides simulation and assessment of cerebrovascular damage in DBS[3]. It analyzes the track-brain spatial relationship and allows the DBS electrode to be placed more effectively, potentially reducing the invasiveness of the DBS procedure to the patient.

References:

1. Nowinski WL. Computerized brain atlases for surgery of movement disorders. Seminars in Neurosurgery 2001;12(2):183-194.
2. Nowinski WL. Anatomical and probabilistic functional atlases in stereotactic and functional neurosurgery. In: Textbook of Stereotactic and Functional Neurosurgery (eds. Lozano A, Gildenberg P, Tasker R), 2ed edition. Springer, Berlin 2009:395-441.
3. Nowinski WL, et al. Simulation and assessment of cerebrovascular damage in deep brain stimulation using a stereotactic atlas of vasculature and structure derived from multiple 3T and 7T scans. Journal of Neurosurgery 2010;113(6):1234-41.

Breakout Session 22

New Frontiers in Brain Sciences *(Nanobiotechnology, bioengineering and biomaterials)*

Chair: Babak Kateb & Jean Paul Allain

Jeff Sutton *(Keynote)*

Brain Alterations in Spaceflight

Kuldip Sidhu

Brain in the Petri dish – disease modelling

K. S. Sidhu, H. Chung and P.S. Sachdev
Centre for Healthy Brain Ageing,

Session Abstracts - Day 3

Faculty of Medicine, UNSW Sydney, Australia

The number of patients with neurodegenerative diseases is escalating significantly worldwide and that accounts for disease burden of over 13%. Therefore the current focus of research in this area is to understand the underlying mechanism of disease development in an effort to identify molecular targets for therapeutic intervention. With the advent of induced pluripotent stem cell (iPSC) technology it is now possible to recapitulate the disease process in the Petri dish with cells derived from patients. These humanised disease models thus can turn the clock back on diseases such as in Alzheimer's from number of years in patient to few weeks in the Petri dish. The generation iPS cells offer a unique opportunity to develop disease-relevant neurons in large numbers and assemble them as mini brain to study the disease process from the donating patient. Here, we provide an overview of human stem cell models of neurodegeneration using iPS cells from patients with Alzheimer's disease. We report the first generation of feeder-free iPS cells from Alzheimer's patient with an early onset of disease using a polycistronic lentiviral vector containing four pluripotent genes, Oct4, Sox2, Klf4 and cMyc. These iPS cells have been analyzed by using the microarray chip and the computation of data is assisting in developing the in vitro models for this disease and future regenerative medicine. These iPSC are also differentiated to relevant neurons and our phenotype data in these neurons demonstrate disease affects that could be analysed and hence in vitro disease modelling possible.

Jean Paul Allain

Development of magnetic bacterial nano-cellulose (MBNC) for regenerative neuroendovascular therapeutics

Prof. Jean Paul Allain[1,2], Lisa M. Reece[3], Mónica Echeverry-Rendón[1,2], Sandra E. Arias[1,2], Juan Jose Pavón[1,4]

University of Antioquia, Colombia

Current treatments for brain aneurysms involve clipping and neuroendovascular coil embolization, including stent-assisted coiling in an attempt to occlude the aneurysmal defect from the parent artery. Such treatments are invasive and traumatic, not suitable in most patients with increased risks. An alternative method was developed to use scaffold stents with their inherent thrombogenicity coupled to stem cell derivatives from the arterial wall and the need to create a local, focal attraction force of cells to the abluminal side of the stent scaffold for an in situ reconstruction of the tunica media by Tigno and Armonda[1]. In 2009, Drs. Allain and Tigno introduced for the first time, a multi-functional nanostructured bioactive coating designed to render an assymetric region of the stent scaffold magnetic and biomimetic. The bioactive coating utilizes bacterial nanocellulose (BNC) as a platform for both magnetic attraction and cell attraction and proliferation. Bacterial Nanocellulose was obtained from a culture of A. xylinum bacteria. The magnetization of the BNC was realized through the reaction of Iron III and Iron II and heating up to 84°C. Ammonium hydroxide was added to the mixture in order to precipitate out super paramagnetic iron oxide nanoparticles (SPION). Subsequently, magnetic bacterial nanocelullose (MBNC) was coated with PEG to improve its biocompatibility. All samples were characterized before and after magnetization using scanning electron microscopy (SEM). Cytotoxicity and biocompability were evaluated using Porcine aortic smooth muscle cells (PASMC). Preliminary cellular migration assays demonstrated the behavior between MBNC and cells labeled with paramagnetic nanoparticles. Human aortic smooth muscle cells (HASMCs) were magnetized through passive uptake, in which cells were incubated with the 6 µg/mL SPION solution. Thick pellicles of BNC were grown as a translucent and sticky material composed of micro fibrils that bundle together to form long intertwined ribbon-shaped fibrils. After completion of the magnetization procedure, the samples exhibited a paramagnetic behavior. An effective magnetic attractive force was observed using a magnet of 6 Gauss. Internalization of SPIONs by HASMCs and their distribution was revealed using Prussian blue staining for iron oxide content. Novel nanobiomechanical in-situ testing of the BNC and MBNC membranes were conducted in a wet environments to mimic the pulsating hemodynamic conditions near the cerebral aneurysm. Results show that the MBNC and BNC hydrogels behave as viscoelastic solids with Young's moduli near 40 MPa.

1. Department of Nuclear, Plasma and, Radiological Engineering
2. Department of Bioengineering, University of Illinois at Urbana-Champaign, Urbana, IL USA
3. Birck Nanotechnology Center, Purdue University, IN, USA
4. Group of Advanced Biomaterials and Regenerative Medicine, Bioengineering Program

References:

1. J.P. Allain, J. Tigno and R. Armonda in ed. Kateb and Heiss, The Textbook of Nanoneurosurgery, Taylor & Francis, 2013.

Session Abstracts - Day 3

Vicky Yamamoto

Plenary lecture 7

Prof Warwick Anderson, Chief Executive Officer, National Health & Medical Research Council

Research into Complex Diseases – Challenges for Researchers and Funders.

The most pressing and expensive health problems faced by countries like Australia in the 21st Century are complex and multi-factorial. As the population ages, chronic ill-health becomes more common and many Australians will have more than one chronic disease. There is also a socioeconomic overlay to the prevalence of chronic disease and of access to health care. Even when knowledge is gained from research, effective implementation often does not occur; indeed it requires its own forms of research and the involvement of policy and decision makers. Addressing complex, chronic diseases represents a major challenge for researchers to put together the right teams, make use of new methodologies, and work with policy and decision makers. It's a challenge too for research funding organisations. How is peer review best performed for multidisciplinary teams tackling complex issues? What are the best funding vehicles for this type of research? How are the community's views and priorities taken into account?

Tackling dementia is a good example to consider. It already costs the community economically and socially and this is predicted to worsen during the coming decades. Most of people living with dementia will also be living with other chronic diseases such as cardiovascular disease and arthritis. Research in dementia may be a case *par excellence* in which researchers and funders will learn how to conduct and support the research needed.

The breadth of approaches and topics presented at this meeting indicates the future research approaches needed. Using dementia as an example health challenge, this talk will explore the complexities of funding the best research across the spectrum from basic to translation to implementation as the National Health and Medical Research Council seeks to deliver on its responsibility to "raise the standard of individual and public health throughout Australia".

Oral Poster Presentations

Chair: Kuldip Sidhu

1. Cecelia Gzell

Small increases in enhancement on MRI may predict survival post radiotherapy in patients with glioblastoma

Introduction: To determine the rate of pseudoprogression (PsP) in glioblastoma patients (GBM) receiving chemoradiotherapy (CRT) using both modified RANO and novel volumetric analysis techniques.

Methods: Patients >17 years diagnosed with WHO grade IV glioma managed with CRT between June 2008 and November 2011 were included. Patients who had incomplete set of MRI images for all study time points were excluded. Modified RANO and two different volumetric calculations (volumetric versus rim analyses) were performed on post-operative MRI, and MRIs at 1 month (M+1), 3 months (M+3), 5 months (M+5), 7 months (M+7), and 12 months (M+12) post completion of RT. Overall survival was calculated in months post definitive surgery. All patients were treated with intensity modulated radiotherapy (IMRT) to 60 Gray and had concurrent and adjuvant temozolomide chemotherapy (EORTC protocol).

Modified RANO technique involved measurement of the surgical cavity with surrounding enhancement on T1 gadolinium enhanced MRI and compared subsequent scans with the baseline post-operative scan to determine response. Two novel volumetric techniques used the ARIA Eclipse radiotherapy planning software to calculate the volume (cm3) of cavity plus surrounding enhancement (volumetric) versus the enhancement only (rim). RANO definitions of response were implemented for all three techniques.

Results: 52 patients were included in the analysis, with median age at diagnosis of 50 years. Seven patients were still alive at time of analysis and the median survival was 18 months (95% CI 15-23). Concordance between the three measurement techniques was an average of 62% agreement for RANO and volumetric analysis, 55% for RANO and rim analysis, and 86% for volumetric and rim analysis.

Pseudoprogression was defined as progressive disease (>25% from baseline value or new lesions) at M+1, M+3, or M+5, with subsequent stable disease or partial response (>50% decrease from baseline) by M+12. Using RANO technique we identified four patients (8%) with pseudoprogression. There were four patients with volumetric analysis (only one in common with RANO technique), and two patients (4%) with rim analysis (both in common with the volumetric group although none in common with RANO).

Using the volumetric analysis we examined the difference in overall survival for patients that had a >5% increase in enhancement versus <5% at the time points M+1, M+3, and M+5. There were 17 patients (33%) at M+1 with >5%, 28 (54%) at M+3, and 26 patients (50%) at M+5. There was no significant difference at M+1 (19 v 18 months, p=0.548) but at M+3 and M+5 there was a significant improvement in survival for those with <5% increased volume: M+3 23 v 15 months (p=0.005), and M+5 26 v 15 months (p=0.004).

Conclusion: This series of 52 patients demonstrated low rates of pseudoprogression (4-8%). An increase in the volume of the surgical cavity and enhancement of >5% at M+3 and M+5 post completion of RT was associated with reduced survival compared with patients who had <5% increase. This suggests that increase in radiological abnormality of <25% may predict survival. Further studies are required with larger sample sizes to confirm these results.

2. Timur Gureyev

Quantitative analysis of the EEG source localization problem

Introduction: With the proliferation of computers, in addition to the spectral frequency analysis of electroencephalography (EEG) recordings, the problem of 3D spatial localization of the sources of electrical activity inside the brain from surface EEG data has attracted increased interest due to its potential importance for diagnosis and monitoring of abnormal brain activity in epilepsy, stroke, traumatic brain injury, etc. Source localization in EEG represents an example of a mathematical "inverse problem" which is severely underdetermined and, hence, requires additional constraints in order to provide an accurate solution. In this study we carry out a systematic evaluation of the localization accuracy of a popular source localization method, sLORETA (http://www.uzh.ch/keyinst/loreta.htm), applied specifically to the cases of low-density EEG headsets. We also compare these results with the performance of a new sparsity prior based EEG source localization technique utilising Brodmann map (http://en.wikipedia.org/wiki/Brodmann_area), for different number of simultaneously active sources and different noise levels. We present a detailed analysis of the corresponding lead-field matrices which not only sets an upper limit on the maximum number of simultaneous active sources that could be reliably localized in principle, but also provides a basis for an optimal application of sparsity constraints for a given

Oral Poster Presentations

electrode configuration and brain segmentation.

Methods: Experiments are performed on a realistic model obtained by segmenting the MRI images of a head into five usual components, namely scalp, skull, Cerebrospinal fluid (CSF), white matter and gray matter. sLORETA method is evaluated in the cases of a one or two simultaneously active dipoles, at different levels of noise in the EEG data. For the sparsity-prior-based source reconstruction, multiple virtual dipoles are clustered according to the Brodmann map into 84 active areas, and the Sparse Bayesian Learning method (http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=1315936) is used to perform the reconstruction. The study is carried out considering up to six completely or partially active areas and with different levels of superimposed noise, for different types of low-density electrode setups with 19, 33 and 71 electrodes.

Results: We evaluate the width of the reconstructed source distributions produced by sLORETA, which is around 83mm and 113mm for the two considered cases of low-density EEG setups with 14 and 19 electrodes, respectively. We also quantify the very large localization error produced by sLORETA in the cases involving multiple simultaneously active dipoles. We provide a systematic quantitative analysis of the accuracy of localization of multiple sources by the new Brodmann map based source reconstruction method for different low-density electrode setups.

Conclusions: Given the severely underdetermined nature of the EEG inverse problem, the state-of-the-art EEG source localization methods have certain limits for their application. sLORETA is very accurate when applied to localization of a single source of electric activity in the brain, but performs poorly in the presence of multiple simultaneously active sources. In the latter cases the proposed sparsity prior source reconstruction method based on the Brodmann map produces considerably more accurate results.

The above results related to sLORETA method have been included into a paper submitted to Medical Physics journal; other results have not been a part of any previous publication.

Educational objectives: Quantify the performance of the EEG source localization methods, including sLORETA and a new method based on Brodmann map, for different low-density electrode configurations. The results are intended as a guide for practical applications of these methods for diagnosis and monitoring of various brain disorders.

3. Andrew Tosolini

The Motor End Plates (MEPs) Are A Conduit To Increase Adenoviral Transduction Of Motor Neurons, Dorsal Root Ganglia (DRG) And Myofibres

Contact:
andrew.tosolini @unsw.edu.au

Introduction: Somatic viral-mediated gene therapy has been utilised to deliver therapeutic genes into spinal cord motor neurons. Indeed, intramuscular injections and the subsequent retrograde transport of the viral vector is a minimally invasive way to transduce the corresponding motor neurons. We have previously shown that targeting the entire length of muscles' MEP region significantly increases the uptake of a retrograde tracer into motor neurons (Tosolini et al., 2013). The aim of this study was to determine if targeting the MEP region with adenovirus would produce significant expression of the transgene in the innervating spinal cord motor neurons.

Methods: Recombinant adenovirus serotype 5 driven by the CMV promoter and encoding the reporter tag-GFP (Ad-GFP) was obtained through the UPenn vector core. Using our recently published MEP map of the mouse forelimb as a guide (Tosolini et al., 2013), Ad-GFP (5.3x1012 pfu/ml) was injected along the entire MEP region of triceps brachii muscle. Mice were subsequently intra-cardially perfused and the spinal cord, DRG, ventral and dorsal roots as well as targeted myofibres were dissected, sectioned and the tissue was analysed under epifluorescence.

Results: This analysis showed that targeting the MEPs with Ad-GFP produced significant expression of GFP within spinal cord motor neurons. Moreover, GFP expression was also present within ventral roots, dorsal roots, DRG and triceps brachii myofibres.

Discussion: This study shows that targeting muscles' MEP regions with an adenovirus is an effective and minimally invasive way to deliver therapeutic genes into the central and peripheral component of the neuromuscular junction. These data have implications for gene therapies aiming to overcome lower motor neuron dysfunctions such as spinal cord injury and motor neuron disease.
Ref: 1) Tosolini et al., (2013) Front. Neurol. 4:58.

4. Terry Peters

Correlation of quantitative MRI and histology of surgical specimens in drug-resistant focal epilepsy

Maged Goubran[1], Robert R. Hammond[2], Sandrine de Ribaupierre[3], Terry M. Peters[1], and Ali R. Khan[1]

Oral Poster Presentations

Current clinical MRI protocols used for pre-operative assessment of focal epilepsy lack sensitivity, with greater than 30% of patients diagnosed as MR negative. The histology evaluation of the surgical tissue, nevertheless, often reveals gliosis or malformations of cortical development undetected pre-operatively. Such data have motivated the need for MRI-histology correlation, to validate improved pre-operative imaging for localizing epileptogenic foci. Our objective here is to correlate quantitative MRI and histology metrics of surgical specimens from temporal lobe epilepsy (TLE) patients. 10 TLE patients who were candidates for epilepsy surgery were recruited for this study. All patients underwent pre-operative imaging (relaxation mapping and diffusion-tensor imaging) on a 3T scanner. Field maps of NeuN (representing neuronal density) and GFAP (representing gliosis) immunohistochemistry stains of surgically resected tissue were automatically computed. Regions of interest (ROIs) were subsequently delineated on 100 µm downsampled histology slices in both brain tissues (GM & WM). Using our previously reported histology to MRI registration protocol, the histology ROIs were warped to match corresponding regions on in-vivo quantitative maps (T1, T2, FA, MD). Spearman's rank correlation was employed to test for correlation between the MRI metrics: T1, T2, FA & MD, and field fractions of NeuN & GFAP. A negative correlation between NeuN field fraction and the T1 value in gray matter was found using both tests ($r = -0.617$, $p=0.001$). A negative correlation was also found between T1 and FA in white matter, as well as a positive correlation between WM T1 and MD. This study is the first to relate in-vivo T1 values to the proportion of neurons in the grey matter for focal epilepsy. These preliminary findings suggest that T1 in gray matter may act as a predictor of neuronal density and thus in-vivo T1 mapping may provide a non-invasive tool for estimating neuronal loss in neurological disorders.

1. Imaging Laboratories, Robarts Research Institute, London, Ontario, Canada,
2. Department of Pathology, Western university, London, Ontario, Canada,
3. Department of Clinical Neurological Sciences, Western university, London, Ontario, Canada

5. Michael Lerch

X-Tream: A Unique Realtime QA System for Submillimeter X-Ray Radiosurgery

Contact: mlerch@uow.edu.au

Introduction: Microbeam radiation therapy (MRT), a submillimeter X-ray radiosurgery technique, utilises the dose volume sparing effect by using highly collimated, parallel X-ray microbeams (with width 0.05 mm and pitch 0.4 mm) to deliver a uniform radiation dose to a target. A microbeam peak dose of 400 Gy, delivered in <1 sec minimises any cardiosynchronous related blurring of the microbeam X-ray paths.

MRT quality assurance (QA) is very challenging due to the high dose rates (~20,000 Gy/sec) and highly striated X-ray radiation field. X-Tream is a high speed readout system with high resolution (micron-scale) silicon detectors for real-time beam monitoring, developed at the Centre for Medical Radiation Physics (CMRP). The System has the ability to measure the instantaneous dose rate associated at any point with micron spatial resolution and hence is able to deduce the peak dose and valley dose between microbeams as well as the MRT peak-to-valley dose ratio (PVDR).

Methods: The performance of X-Tream was tested at the biomedical beamline (ID17) at the European Synchrotron Radiation Facility (ESRF), Grenoble, France. All aspects of the experimental set-up at ESRF (filters etc) were as for full MRT irradiation conditions. A tungsten multislit collimator striates the broad X-ray beam of height 0.5 mm and width 20 mm into 49 microbeams. Additionally, depth dose measurements under broad beam conditions for comparison with an ionisation chamber (IC) were carried out at the Illawarra Cancer Care Centre, Wollongong. The X-Tream and IC depth dose profiles of a 6 MV LINAC photon field in a 30cm x 30cm solid water phantom were compared.

Results: The linearity of the response of the system over five orders of magnitude is excellent with a conversion factor of 2.51 counts/nA. The measured profile of the 0.5 mm x 20 mm MRT field by the X-Tream System at 20 mm depth in perspex clearly demonstartes this excellent (<0.01 mm) spatial resolution and large operating dynamic range. The deduced PVDR and other important parameters will be presented. The response with incident photon energy, PVDR with depth in a PMMA phantom and factors that influence the measured PVDR will be discussed in the presentation. Comparison with equivalent Monte Carlo radiation transport simulations will also be made.

The depth dose profiles along the central axis of the 6 MV LINAC radiation field agree to within 1% giving confidence to our dosimetry methodology. The instantaneous peak radiation dose rate using the LINAC is ~6000 Gy/sec which is comprable to that used in MRT. The LINAC photon energy spectrum however is significantly higher than that used in MRT.

Oral Poster Presentations

Conclusions: The new X-Tream Dosimetry System has been developed and demonstrates excellent performance characteristics. X-Tream is the first, and currently only realtime QA system in the world for MRT. We have succesfully benchmarked the realtime X-ray beam monitoring capabilities of X-Tream, and the feasibility of the on line dosimetry method. It is envisaged that the X-Tream system will be used for real-time, on-line dosimetry and immediately prior to patient treatment.

6. Terry Peters

A pipeline for histology to in-vivo registration of surgically resected specimens in focal epilepsy

Maged Goubrana[3], Catherine Curriea, Sandrine de Ribaupierre[2,3], Robert R. Hammondd, Jorge J.Burneo[2], Andrew G. Parrent[2], Terry M. Peters[1,3,5], Ali R. Khana[5]

Histopathological validation of existing and emerging MRI image modalities and analysis techniques is a pressing need in the neuroimaging field and has significant implications on clinical diagnostics. Accurate registration, or alignment, between MRI and histology is required for effective quantitative comparison at a spatially-local scale. Here we present one stage of a novel pipeline for registering in-vivo MRI and histology of hippocampal and temporal lobe neocortical sections from epilepsy surgery, namely the registration of in-vivo to ex-vivo MRI, and assess the accuracy and reliability. 10 temporal lobe epilepsy patients who were candidates for anterior temporal lobectomy (ATL) surgery were recruited for this study. All patients underwent pre-operative imaging (relaxation mapping and diffusion-tensor imaging) on a 3T MRI scanner. Following surgery the excised neocortical specimens were scanned *ex-vivo* on a 9.4T small bore magnet, and then processed for histological assessment. We divide this process into two distinct steps through the use of an intermediate 3D ex-vivo MRI of the specimen, I_{ex}. The registration detailed in this work relates to finding the transformations between I_{in} and I_{ex}, thus connecting images obtained in-vivo with histological slides. These transformations are obtained in a hierarchical fashion, beginning with an initial translation, $T^{trans}_{ex,in}$, a landmark-based similarity transformation, $T^{sim}_{ex,in}$, and finally a non-rigid deformation, $\Phi_{ex,in}$. To assess significant differences between the rigid and deformable registrations, we computed a Wilcoxon matched-pairs signed-rank test between the mean TRE values of both registrations. Our mean TRE for rigid and non-rigid registrations was (1.46±0.30 mm & 1.35 ±0.11 mm) and (1.71±0.36 mm & 1.41±0.33 mm) for neocortical and hippocampal specimens respectively. Our statistical analysis confirmed that the deformable registration significantly improved the registration accuracy for the neocortex (Pneo = 0.0019) and the hippocampus. (Php = 0.0011). Our in-vivo MRI to histology registration pipeline allows for a quantitative spatially-local assessment of pathological correlates of MRI by fusing information from both modalities using dense correspondences. The reported registration accuracy is within an acceptable range and demonstrates the potential of this pipeline to enable prediction of pathology from in-vivo MRI through correlation studies.

1. Imaging Research Laboratories, Robarts Research Institute,
2. Department of Clinical Neurological Sciences,
3. Biomedical Engineering,
4. Department of Pathology,
5. Department of Medical Biophysics, Western University, London, Ontario, Canada

Chair: Glenn Cross

7.Solventa Krackauskaite

Accuracy, precision, sensitivity and specificity of non-invasive ICP absolute value measurements

Accuracy, precision, sensitivity and specificity of non-invasive ICP absolute value measurements. Solventa Krakauskaite[1], Rolandas Zakelis[1], Vytautas Petkus[1], Laimonas Bartusis[1], Romanas Chomskis[1], Aidanas Preiksaitis2, Arminas Ragauskas1.

Contact information: Studentu St. 48-446, LT-51367, Kaunas, Lithuania, solventa@mail.com, telematics@ktu.lt.

Keywords: non-invasive ICP absolute value method; two depth transcranial Doppler meter; Bland & Altman, regression and ROC analysis.

Introduction: Intracranial arteries are the natural pressure sensors. The ophthalmic artery (OA) is an unique vessel with almost the same anatomy of intracranial and extracranial segments. Because of that we proposed to use the OA as a natural „scales“ for aICP measurement and to use a two depth transcranial Doppler meter (TCD) as a balance indicator of such ”scales“. This is „re-invention“ of non – invasive ABP measurement method for aICP value measurement application.

Objectives:

1. To validate accuracy, precision, sensitivity and specificity of proposed non-invasive aICP measurement method by multicenter comparative clinical studies (Bland & Altman, regression and ROC analysis) on wide groups of neurological and ICU patients:
   - Turku Hospital: TBI patients, invasive “gold standard” ventricular or parenchymal

Oral Poster Presentations

pressure sensors prospective study.

- Republic Vilnius University Hospital: TBI patients, ventricular "gold standard" invasive ICP sensors prospective study.
- Lithuanian Life Science University: prospective neurological patient Phase III study: non – invasive ICP comparing with "gold standard" CSF pressure measured via lumbar puncture.
- Umea Hospital: dynamic infusion tests on elderly neurological patient group (age 65-85) prospective double blinded study.

2. To validate linearity study (HUT/HDT, regression analysis) at Kaunas University of Technology.

Methods: Prospective randomized comparative clinical studies of simultaneous non-invasive aICP and "gold standard" invasive ICP measurements. Data collected from 110 patients from clinical centers in Lithuania (Vilnius, Kaunas), Sweden (Umeå), Finland (Turku).

Healthy volunteers' study was performed with 217 snapshots by aICP non-invasive measurements in 6 body positions.

Results: Bland & Altman plot of 171 paired non-invasive and invasive ICP data points showed that mean systematic error (accuracy) of non-invasive aICP value measurement was equal to 0.03 mmHg and standard deviation of the random error (precision) SD = 2.65 mmHg (CL = 0.965) or SD = 2.2 mmHg (CL = 0.95).

Healthy volunteers' study confirms linearity (R=0.995) of non-invasive aICP value measurement method in the clinically important aICP range [6.3 - 37.8 mmHg] which is below and above of critical ICP thresholds 14.7 mmHg (neurology) and 20.0 mmHg (neurosurgical intensive care).

Conclusions:

1. ROC analysis confirms high sensitivity (88%), specificity (93%) and area under ROC curve (0.96) of non-invasive ICP measurement method.
2. Negligible mean systematic error (0.03 mmHg) is a statistically significant evidence of two – depth TCD based non-invasive aICP value measurement method and shows that is the only which does not need a patient specific calibration.

Clinical studies and technology development were funded by EU FP7 projects:

- Brainsafe II – Development of a Novel Autonomous Non-Invasive Absolute Intracranial Pressure Measurement Device Based on Ultrasound Doppler Technology.
- TBICare – Evidence based Diagnostic and Treatment Planning Solution for Traumatic Brain Injuries.
- BrainCare – Scientific research and development of innovative evidence based non-invasive brain diagnostic and monitoring solutions for neurological and TBI patients.

US projects:

- Randomized prospective non-invasive ICP measurement study of patients with idiopathic hypertension syndrome. Study partially supported by NASA.
- NSBRI (NASA) - Research and Technology Development to Support Crew Health and Performance in Space Exploration Missions.

1. Kaunas University of Technology, Telematics Science Centre, Kaunas, Lithuania. 2Vilnius University, Faculty of Medicine, Clinics of Neurology and Neurosugery, Centre of Neuroangiosurgery, Vilnius, Lithuania.

8. Jun-Young Lee

Alzheimer disease progress and cognitive reserve

Hyeun Ju Park
SMG-SNU Boramae Medical Center
In Hye Kim
SMG-SNU Boramae Medical Center
Hee Jung Kim
SMG-SNU Boramae Medical Center
Yu Kyeong Kim
SMG-SNU Boramae Medical Center
Dae Jong Oh
SMG-SNU Boramae Medical Center
Jun-Young Lee
SMG-SNU Boramae Medical Center

Abstract: Introduction Education is the surrogate marker for cognitive reserve. Larger cognitive reserve is related to slower cogntive change in normal elders, but, whether cognitive reserve has biological influence on Alzheimer disease (AD) progress is not well investigated. We thus aimed to investigate the effect of education on longitudinal change of AD brain.

Methods: Twelve AD patients who were educated lower than 3 years and 10 AD patients who were educated higher than 9 years were followed up for 3 years with repeated measures of magnetic resonance imaging and cognitive tests. Repeated ANOVA were used to assess whether rates of brain and cognitive change were modified by education levels.

Results: The decline of cognition was slower in AD participants with higher education. Atrophy of This effect is remarkable in left prefrontal and temporal area.

Conclusions: After buffering effect against amyloid deposition by cognitive reserve is failed, the rate of brain atrophy and cognitive change may be fast in the course of AD progression.

Oral Poster Presentations

9. Abigale Besemer

Impact of PET and MRI Threshold-Based Tumor Volume Segmentation on Targeted Radionuclide Therapy Dosimetry using CLR1404

Introduction: The treatment of malignant brain tumors, especially gliomas, with conventional external beam radiation therapy (EBRT) is unsuccessful in many cases due to the inability to deliver curative doses to the tumor while limiting the toxicity to normal brain tissues. Targeted Radionuclide Therapy (TRT) is emerging as an attractive adjuvant treatment in these cases because the selective uptake and retention of the radioactive agent within the tumor has the potential to treat the microscopic tumor extent. CLR1404, a small-molecule, phospholipid ether analog can serve as a "diapeutic" (diagnostic and therapeutic) agent for the detection and treatment of multiple cancers. Isosteric iodine substitution in CLR1404 creates a molecular imaging agent when labeled with I-124 or a targeted radiotherapeutic agent when labeled with I-131. Phase I and II trials evaluating the effectiveness of CLR1404 in patients with brain tumors are currently underway. This work investigates the impact of PET and MRI threshold-based tumor segmentation on TRT dosimetry in patients with primary and metastatic tumors.

Methods: In this study, PET/CT images of five high grade glioma patients were acquired at 4.5, 24, and 48 hours post injection of 74 to 185 MBq of 124I-CLR1404. The initial MRI and the PET/CT images at each time point were fused and used to segment tumor volumes using different thresholding techniques. Standardized Uptake Values (SUVs) and Tumor-to-Background Ratios (TBRs) were calculated from the 48 hour PET. The tumor volume was segmented using two SUV threshold levels (1.0 and 1.2) and two TBR threshold levels (1.6 and 2.0). Additionally, the tumor was also segmented based on a T1 contrast-enhanced MRI threshold. The 124I-CLR1404 activity was converted to the 131I-CLR1404 activity by accounting for the difference in decay rates. The 131I-CLR1404 cumulated activity distribution was calculated by numerically integrating the activity at each scan time point, on a voxel-by-voxel basis, over the whole patient volume. This was then used to estimate the therapeutic 131I-CLR1404 absorbed dose deposition for each patient using the Monte Carlo code Geant4.9.4.

Results: Significant differences in the shape of the MRI, SUV, and TBR tumor dose volume histograms (DVHs) were observed for each patient. Mean 131I-CLR1404 tumor doses ranged from 0.23 to 0.74 mGy/MBq and had a standard deviation between 0.05 and 0.13 mGy/MBq. In general, TBR tumor volumes were larger (2.3 – 63.9 cc) than the SUV (0.1 – 34.7 cc) and MRI (0.4 – 11.8 cc) volumes which resulted in lower mean tumor doses in most patients. One patient had notably high discordance between the gadolinium enhancement and the 124I-CLR1404 avid areas which resulted in a lower dose in the MRI tumor volume compared to the SUV and TBR volumes.

Conclusions: The tumor volume and interpretation of the 131I-CLR1404 tumor dose is highly sensitive to the imaging modality and threshold level used for tumor volume segmentation. The large variations in tumor doses clearly demonstrate the need for standard protocols for multimodality tumor volume segmentation in TRT dosimetry. The results gathered from this investigation may help guide combined TRT and EBRT of brain tumors.

10. Li Li & Yifan Zhang

Metabolic alterations in the frontal white matter of patients with Major Depressive Disorder with treatment of SSRIs: A proton magnetic resonance spectroscopy study

Introduction: Proton magnetic resonance spectroscopy (1H-MRS), provides a non-invasively detecting Metabolite levels in vivo, which can be used to measure biochemical or metabolite concentrations in circumscribed brain regions. Current research has highlighted the role of glial cells in white matters(Schipke C G, et al., 2011). It is assumed that antidepressant treatment of SSRIs not only affects neurons, but also activates glial cells(Czéh B, Di Benedetto B.,2013). Seldom article had focus on prefrontal white matter to observe a true drug response with SSRIs. The purpose of this study was aims to observe whether there was any effect of antidepressant treatment on the metabolite levels in the ventral prefrontal white matter in the depressed patients.

Methods: Forty-five patients (mean age 44 ± 13 years) diagnosed as MDD according to DSM-IV with scores of 18 or greater on the 24-item Hamilton Depression Rating Scale (HDRS). MRS studies were performed on a 3.0T MR system (General Electric, Excite Signa HD 3.0T). single voxel PRESS (spin-echo point resolved) spectroscopy with chemical-shift selective saturation (CHESS) water suppression.The volume of interest (VOI)was localized at the bilateral ventral prefrontal white matter regionsαvoxel size: 2×2×2 mm3 αThe analysis of the spectral dataset was performed with the manufacturer-supplied software package program of the MR system (GE Advantage Workstation: AW4.2).

Results: The comparison at baseline revealed significantly lower CHO/

Oral Poster Presentations

Cr (t=2.36; p=0.02) in right ventral prefrontal white matter. We also found a reduced CHO/Cr (t=1.81,p=0.07) in left ventral prefrontal white matter, however this difference was not statistically significant. After 12 wk treatment, the HDRS had significantly decreased in the patients (paired t tests. t =11, p <0.001), indicating positive treatment response.Bilateral CHO/Cr values of patients increased significantly compared to pretreatment values[left:t =3.17 p =0.006;right:t =2.35 p =0.03].

Conclusion: Our results suggest that alterations in ventral prefrontal white matter metabolite levels are likely involved in MDD pathophysiology and may help improve our understanding of this pathophysiology and the crucial role of white matter in MDD.

12.Avinash Waghmare

A Novel Application of High Frequency Magnetic Stimulation: Enhancing Putative Mirror Neuron Activity

Introduction: Social cognition deficits in schizophrenia lead to substantial socio-occupational dysfunction and respond poorly to conventional medications. Dysfunctional mirror neuron activity (MNA) has been associated with these deficits. We examined if a single session of high frequency repetitive transcranial magnetic stimulation (HF-rTMS) would enhance TMS-measured MNA compared to sham-rTMS in healthy individuals, using a randomized controlled study design.

Methods: 31 consenting, right-handed, healthy individuals were randomized to receive true (n= 15) or sham (n= 16) HF-rTMS administered over the left inferior frontal gyrus. Putative MNA before and after HF-rTMS, was assessed using investigational-TMS. We recorded 10 motor evoked potentials (MEP) in the right first dorsal interosseous (FDI) muscle with three stimulus paradigms: (a) 120% of resting motor threshold (RMT), (b) stimulus intensity set to evoke MEP of 1-millivolt amplitude (MT1) and (c) a short latency paired pulse paradigm, administered in random sequence. This was done while the subjects observed videos of (a) inanimate motion of two bouncing balls (control condition), (b) two videos depicting goal-directed action of the FDI (action-observation condition). The MEP difference between control and action-observation conditions formed the measure of putative MNA.

Results: On two-way RMANOVA, there was a significant group (true versus sham) X occasion (pre- and post-HF-rTMS MNA) interaction effect for MT1 [F (df) = 12.143 (1,29), p= 0.002] and 120% RMT stimulus [F (df)= 7.326 (1,29), p= 0.01] indicating greater enhancement of MNA in the true HF-rTMS group than the sham group. This effect was not noticed in the paired pulse stimulus paradigm [F (df) = 1.815 (1,29), p= 0.18].

Conclusions: HF-rTMS delivered at the left inferior frontal gyrus resulted in significantly greater MNA enhancement than sham-rTMS. These findings suggest the potential role of HF-rTMS as a novel therapeutic application to enhance MNA and thus improve social cognition and disability in patients with major psychiatric disorders.

13. NA

14.NA

15. Taskin Duman

Internal Carotis Artery Thrombosis In Acute Ischemic Stroke

Contact: taskinduman@yahoo.com

Mustafa Kemal University Medical Faculty Department of Neurology, HATAY Taskin Duman, Ozcan Demetgul, Esra Okuyucu, Fidan Surgun, Ismet Melek

Introduction: Cerebrovascular accidents due to carotid artery disease are amongst the most common causes for death and disability. [1] According to the results obtained by Framingham Heart Study, the frequency of carotid artery narrowing above %50 is %7 in women between 66-93 years of age, and %9 in men between the same ages [2]. According to the data from the NASCET (North American Symptomatic Carotid Endarterectomy Trial) study, the risk for ischemic SVO in the first year is %11 in carotid artery narrowing between %70-79. This risk reaches %35 when narrowing is %90 or above [3,4]. In cases of acute ischemic stroke, imaging methods used in the right time and under the right conditions with the guidence of clinical tables carries critical importance for the results.

Case: A 62 year old, right handed male patient applied with sudden weakness of the left side and unconsciousness. In his neurologic examination; somnolance, left central facial asymmetry, motor loss of 2/5 at the left upper and lower extremities and Babinski positive on the left were detected. In the DWI of the patient whose brain tomography was found to be normal; hyperintensity in the diffusion weighted imaging done on the right frontotemporoparietal area and hypointensity in the ADC mapping. In the Carotid Doppler USG performed on the patient for etiology images compatible with

Oral Poster Presentations

hypoechoic thrombus filling the lumen originating from the right ICA completely were detected and no vascular flow coding was seen in the doppler examination done for distal thrombus. For this reason CT Angiography was performed on the patient and a hypodense, soft, non ulcerated plaque formation with a lenght of 1 cm and 3.5 mm causing %90 narrowing at the right ICA origin level attracted our attention. No contrast material passage to the ICA in the distal was observed. After consultation it was agreed that right carotid endarterectomy and patch plasty operations would be done on the patient. The patient who got better neurologically shortly after the operation was discharged. No reasons besides the excessive use of cigarettes were found in the investigation done regarding the etiology. CONCLUSION This case emphasises the critical importance of the earliest possible use of appropriate imaging techniques in determining the treatment in the emergency evaluation of acute ischemic stroke.

16. PhuaHwee Tang

Arterial Spin Labelling Method of assessing cerebral perfusion compared against PET imaging in children with focal epilepsy

Contact: phuahwee@yahoo.com

Introduction: Epilepsy can result in significant childhood morbidity. MRI structural scans show abnormality in only about 50% of cases. Current ways to determine the epileptic foci rely on FDG-PET and EEG. Arterial spin labelling (ASL) perfusion MRI is a non-invasive technique for measuring regional cerebral blood flow (CBF) and may be able to improve the diagnosis of epilepsy on MRI. The purpose of this study was to investigate the use of ASL in detecting brain lesions in children with focal epilepsy, and to compare against FDG-PET.

Methods: This study was approved by the institutional review board and written consent was obtained. Four paediatric patients (ages: 13-15) with focal epilepsy were scanned on a whole-body 3T MR scanner (Siemens MAGNETOM Skyra) with a 32-channel phased-array receive-only head coil. High-resolution anatomical images were acquired using T1-weighted 3D MPRAGE and T2 –weighted 3D SPACE. FAIR-ASL was acquired using TI=1700ms with background suppression and 3D GRASE acquisition. M0 image was acquired with the same sequence but long TI and TR. All four paediatric patients had focal epilepsy localized unilaterally determined by both PET and EEG.

ASL images were pre-processed by FSL (Oxford, UK) and MIPAV (NIH, USA) for motion and inhomogeneity correction. Perfusion Weighted Imaging (PWI), calculated from the perfusion difference images divided by the M0, is proportional to CBF. PWI was registered to the standard space (MNI152 template) through linear and non-linear registration of the M0 image to MPRAGE and SPACE images using FSL. ASL CBF maps were visually compared with PET images.

Results: All except 1 had normal structural MRI scans. In 3 of the 4 patients, areas of hypoperfusion on ASL match the areas of hypoperfusion seen on PET. In one patient, the ASL CBF map was normal although PET was abnormal. In 2 patients, there were artefacts present in the parietal lobes (unilateral in one and bilateral in the other).

Conclusion: Areas of hypoperfusion on ASL CBF maps match the areas of hypoperfusion seen on PET imaging in most cases in our small cohort of patients. However, artefacts are present in the ASL CBF maps and refinement of technique is required before it can be used routinely.

We know event planning,
We know industry,
and we can help you in planning your events.

AusEvents™
LIFE SCIENCE & TECHNOLOGY EVENTS

Let us be your professional conference organiser for your upcoming life science or technology event.

The AusEvents™ team has the experience and relationships to deliver conferences, conventions, trade exhibitions, investment meetings and professional development courses.

Our connections and engagement with key stakeholders in the life sciences and technology industries make us an ideal organisation to manage your event.

Our range of services includes full management of:

- Budget and finance
- Sponsor procurement and liaison
- Registrations
- Venue negotiation and liaison
- Exhibition
- Accommodation and travel
- Supplier booking and coordination
- Website design
- Conference program and speakers (including abstract management)
- Social events/ partner program (including conference dinner)
- On site management
- Plus any other services as requested

Past conferences organised by AusEvents:

- Alternate Fuels Summit 2011
- Australasian Wireless Health Conference 2011
- Research Australia Philanthropy Conference: 2012, 2013
- Technology Transfer Summit Australia 2013

Currently organising:

- 11th Annual World Congress of the Society for Brain Mapping and Therapeutics
- Science meets Parliament 2014
- Research Australia Philanthropy Conference 2014
- Technology Transfer Summit Australia 2014
- Agricultural Biotechnology International Conference (ABIC) 2015
- International Biotechnology Symposium 2016

"AusEvents™ really gave me as CEO a lot of confidence that the event would be handled well, without cutting too deeply into 'business as usual'. It was a really constructive relationship, where AusEvents™ would advise and challenge some of our ideas on how best to run things. They handled venue selection and negotiations and helped as keep to a strict project plan, budget and timetable. The conference ran very smoothly, and was very successful. All I can say is that we didn't hesitate to use them again this year!"

Elizabeth Foley
Chief Executive Officer, Research Australia

For more information or an obligation-free discussion, please contact:

Glenn Cross
Chief Operating Officer, AusBiotech Ltd
E: ausevents@ausbiotech.org
P: 03 9828 1400
W: www.ausbiotech.org/ausevents