ASIAN-PACIFIC SOCIETY FOR NEUROCHEMISTRY

ISN International Society for Neurochemistry

17th Meeting of the Asian-Pacific Society for Neurochemistry

19th - 21st June 2023

Hibiscus & Jasmine Rooms, Level 3,
Marina Bay Sands, Singapore

Organised By:

Lee Kong Chian School of Medicine — Nanyang Technological University Singapore — Imperial College London

DukeNUS Medical School

NUS National University of Singapore — Yong Loo Lin School of Medicine

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APSN2023 Local Organising Chair's Welcome Message

Dear Friends and Colleagues,

On behalf of the Local Organizing Committee, I would like to extend our warmest welcome to all of you to the 17th Biennial Meeting of the Asian Pacific Society for Neurochemistry (APSN). This is a key international meeting for the neuroscience research community and we are privileged that Singapore has been selected for the venue of the conference this year.

In celebration of the event, the three medical schools in Singapore, i.e. Nanyang Technological University's Lee Kong Chian School of Medicine, National University of Singapore's Yong Loo Lin Medical School and Duke-NUS Medical School, have come together to organize this event with the support from APSN and the International Society for Neurochemistry.

Over the next three days, you will be treated to an exciting scientific programme that features 3 plenary speakers respectively from the United Kingdom, Japan and Singapore, an ISN special symposium with 4 eminent speakers from the United States and Switzerland, 11 symposia focusing on a variety of hot topics and finally 3 workshops/young investigator colloquia, oral communications and poster presentations that showcase young and promising neuroscientists.

The conference aims to bring together leading scientists and clinicians from the Asia-Pacific region and across the world to share latest findings and foster new regional and international collaborations. At the same time, we also hope to stimulate and invigorate greater interest in neuroscience research in Singapore and to feature Singapore as one of the centers of excellence for neuroscience research in Asia. I am pleased to note that more than 200 participants including researchers, clinicians and students from the Asia-Pacific region will attend this on-site symposium.

This conference would not be possible without the generous support from our sponsors. First, I would like to acknowledge the generous sponsorship support of International Society for Neurochemistry. I would like to acknowledge and express our sincere thanks to our Diamond Sponsors, Einst, Oxford Instruments Andor, and Wong Peng Onn and family; Our Gold sponsors Zeiss, NovogeneAIT Genomics, ICE Bioscience, and MedChem Express; and our Silver sponsors Abex and Aerobe. I encourage delegates to visit their exhibition booths at the symposium. I would also like to record my special thanks to all the hardworking members of the local organizing committee, the scientific programme committee led by Prof. Itsuki Ajioka and staff and student volunteers for their tremendous support of the conference.

As the ice of the COVID pandemic that has restricted our global mobility for so many years finally started to thaw out, I hope this conference would be an excellent platform for us to revisit old friends, as well as spawn new friendship and research collaborations. At the same time, I hope our overseas delegates would be able to afford some time to enjoy Singapore and to soak in our vibrant multiculturalism and epicurean range of gourmet treats.

Thank you and wishing all a productive and enjoyable meeting!

Kah-Leong LIM
Chair, Local Organizing Committee
17th Meeting of the Asian Pacific Society for Neurochemistry (APSN)

Pre-Conference **Day 0 Program Sunday (18 Jun 2023) Sunday**	
09:00	**Asian-Pacific Society for Neurochemistry Council Meeting** ***Only for Invited Members** **Lee Kong Chian School of Medicine,** **Headquarters Building, Boardroom, Level 3** **11 Mandalay Road, Singapore 308232**
12:00	**Lunch**
14:00	**APSN Event for Young Researchers (Hybrid) at LKCMedicine** **"The Story behind the Published Data"** **Opening Remarks** **Ying-Shing Chan (APSN President)** **Discovery of a long-hidden role of dermal macrophages in pain sensation** **-It started from serendipitous behavioral observation-** **Akio Wanaka** (Nara Medical University) **A scientist's perspective: Bridging the gap between lab work and the clinical world through researcher-clinician collaborations** **Christine Cheung** (LKCMedicine, Nanyang Technological University) **Roads to publication: Every journey is different** **Jacque Pak Kan Ip** (The Chinese University of Hong Kong) **Closing Remarks by Kah Leong Lim, Chair, Local Organising Committee** (LKCMedicine, Nanyang Technological University) **Headquarters Seminar Room, Level 2, 11 Mandalay Road,** **Singapore 308232**
17:00	**End of APSN Event** **Bus pick-up at LKCMedicine Headquarters Carpark to Sands Expo & Convention Centre**
19:00	**Welcome Reception at Sands Expo & Convention Centre** Level 4, Bay View Foyer **10 Bayfront Avenue, Singapore 018956**
End of Day 0 Program	

Day 0 Program (18 Jun 2023) Sunday	
13:00	**Registration at Sands Expo & Convention Centre** Level 4 **10 Bayfront Avenue, Singapore 018956**
19:00	**Welcome Reception at Sands Expo & Convention Centre** Level 4, Bay View Foyer **10 Bayfront Avenue, Singapore 018956**
End of Day 0 Program	

	Day 1 Program, Monday (19 Jun 2023)
08:30	**Welcome Address** **Kah Leong Lim** **Chair, Local Organising Committee** (Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore) **Opening Remarks** **Ying-Shing Chan** **APSN President** (Li Ka Shing Faculty of Medicine, The University of Hong Kong) Level 3, Hibiscus Room, 3711
09:00	**Plenary Lecture** **Mechanisms of differential genetic risk for Alzheimer's disease with TREM2 variants** **Paul M. Matthews** (Imperial College London, United Kingdom) **Introduction by: Kah Leong Lim** Level 3, Hibiscus Room, 3711
10:00	**Coffee Break**
10:30	**The International Society for Neurochemistry (ISN)** **Special Symposium** **RNA metabolism in neurodegenerative disease** **Chair:** **Aaron Gitler** (Stanford University, USA) **Expanding mechanisms and therapeutic targets for neurodegenerative disease** **Aaron Gitler** (Stanford University, USA)

	Understanding the molecular mechanisms of ALS and FTD to inspire targeted therapies **Magdalini Polymenidou** (University of Zurich, Switzerland) **Structured and disordered domains antagonize to balance neuronal Ribonucleoprotein granule dynamics** **Baskar Bakthavachalu** DBT/Wellcome Trust India Alliance Intermediate Fellow **Designer DNA drug therapy for neurodegenerative disease** **Don Cleveland** (University of California San Diego, USA) Level 3, Hibiscus Room, 3711	
13:00	**Lunch Poster** (Level 3, Jasmine Room 3812 & 3911-3)	
13:30	**Jasmine Room 3811**	**Jasmine Room 3813**
	Lunch Talk (X01) **The International Society for Neurochemistry (ISN)** **Flávia Gomes, Alessandro Prinetti & Caroline Rae** ISN Officers	**Lunch Talk (X02)** **How journal editors decide "go" or "no-go" with your paper submission** **Speaker 1:** **Recent publishing developments at the Journal of Neurochemistry** **Andrew Lawrence** The University of Melbourne / Journal of Neurochemistry **Speaker 2:** **Essentials of a Quality Manuscript: Merit and Integrity** **Ying-Shing Chan (APSN President)** The University of Hong Kong / IBRO Neuroscience Reports

14:30	**Symposium S01 – S03**		
	Hibiscus Room	**Jasmine Room 3811**	**Jasmine Room 3813**
	S01 **Mechanisms of brain development in health and disease** **Chair: Shen-Ju Chou** (Academia Sinica, Taiwan)	**S02** **Mechanisms and Role of Dendritic Organelle and Membrane Trafficking in Synaptic Plasticity** **Chair: Victor Anggono** (The University of Queensland, Australia)	**S03** **Epigenetic regulation of neurons and brain function** **Chair: Chenchen Song** (LKCMedicine, Nanyang Technological University, Singapore)
	Presentation 1 Transcription factors and cortical patterning Shen-Ju Chou (Academia Sinica, Taiwan)	Presentation 1 The endoplasmic reticulum puts a new spin on synaptic tagging Anja Konietzny (University Medical Center Hamburg-Eppendorf, Center for Molecular Neurobiology Hamburg, Germany)	Presentation 1 Epigenetic regulation of brain function within and between generations Anthony Hannan (University of Melbourne, Australia)
15:00	Presentation 2 Functional human cortical circuitry assembled in vivo for the study of neuropsychiatric diseases Vincenzo De Paola (Duke-NUS Medical School, Singapore)	WITHDRAWN ~~Presentation 2~~ ~~Homeostatic scaling alters lattice organization of nanoscale condensates at excitatory synapses~~ ~~Deepak Kumaran Nair~~	Presentation 2 Unraveling the roles of RNA modification for mRNA localization in the developing brain Ki-Jun Yoon (Korea Advanced Institute of Science and Technology, Korea)

		(Indian Institute of Science at Bangalore, India)	
15:30	Presentation 3 Early postnatal developmental period for ASD-related social behavioral circuits Goichi Miyoshi (Gunma University Graduate School of Medicine, Japan)	Presentation 3 The specific role of the motor protein KIF5B in dendritic transport, synaptic plasticity and memory Kwok On Lai (City University of Hong Kong, Hong Kong)	Presentation 3 From mice to men: Epigenetic regulation of neuroplasticity throughout lifespan and its implication Judy Sng (National University of Singapore, Singapore)
16:00	Presentation 4 Opposite effects of Wntless on the development of diencephalic habenula nuclei and choroid plexus in zebrafish larval brain Yung-Shu Kuan (National Taiwan University, Taiwan)	Presentation 4 Copine-6 is a calcium sensor that regulates AMPA receptor exocytosis during synaptic potentiation Victor Anggono (The University of Queensland, Australia)	Presentation 4 Expanding the glioblastoma universe in epigenetic regulation Derrick Ong (National University of Singapore)
16:30	**Coffee Break**		
17:00	**Oral Presentation O1 – O3**		
	Hibiscus Room 3711	**Jasmine Room 3811**	**Jasmine Room 3813**
	O1 **Chair: Kensuke Ikenaka** (Osaka University, Japan)	**O2** **Chair: Jacque Ip** (The Chinese University of Hong Kong, China)	**O3** **Chair: Kwok On Lai** (City University of Hong Kong, Hong Kong)

	Presentation 1 Neuroprotective role of chicken essence in D-galactose/AlCl3- induced mouse model of Alzheimer's disease Kitipong Promyo (School of Food Technology, Institute of Agricultural Technology, Suranaree University of Technology, Thailand)	Presentation 1 Matrix-assisted Golgi staining in whole-brain expansion imaging under near-infrared light microscopy Yi-Fen Cheng (Research center for applied science, Taiwan)	Presentation 1 Novel allosteric modulator SRI-32743 reverses HIV-1 Tat-induced increase in dopamine release and alleviates the potentiation of cocaine reward in inducible HIV-1 Tat transgenic mice Jun Zhu (University of South Carolina, USA)
17:15	Presentation 2 Establishing fluid biomarkers associated with cellular senescence in Alzheimer's disease Bryan Ng (Singapore Institute for Clinical Sciences, Singapore)	Presentation 2 Sphingosine kinase 2 is essential for remyelination Huitong Song (The University of Sydney, Australia)	Presentation 2 A dopaminergic memory circuit signals valence via a trio of transmitters in Drosophila melanogaster Yishan Mai (Duke-NUS Medical School, Singapore)
17:30	Presentation 3 TRPV2 activation by focal mechanical stimulation enhances growth cone motility Kavita Babu (Indian Institute of Science, India)	Presentation 3 APOE regulates myelin lipid turnover in healthy brains Jun Yup Lee (University of Sydney, Australia)	Presentation 3 Contrasting effects of finasteride administration on depression and anxiety-like behaviour and synaptic plasticity in male and female rats Bettadapura N Srikumar (National Institute of Mental Health and Neurosciences, India)

17:45	Presentation 4 Extrasynaptic GluN2B causes excitotoxicity and neurodegeneration through FOXO1 interaction with Txnip in YAC128 model of Huntington's Disease Sok-Hong Kho (LKCMedicine, Nanyang Technological University, Singapore)	Presentation 4 GPCR signaling-mediated actin remodeling drives quiescent neural stem cell activation Kun-Yang Lin (Duke-NUS Medical School, Singapore)	WITHDRAWN ~~Presentation 4~~ ~~Developing Liang's contextual-stress box as an advanced anxiety-related murine behavioral test apparatus~~ ~~Jian-Hui Liang~~ ~~(Peking University School of Pharmaceutical Sciences, China)~~
18:00	Presentation 5 Gut microbiome profile and intestinal permeability in patients with schizophrenia and healthy controls - a plausible non-invasive biomarker? Kuppan Gokulakrishnan (National Institute of Mental Health and Neurosciences, India)	Presentation 5 Golgi-dependent reactivation and regeneration of quiescent neural stem cells Mahekta Gujar (Duke-NUS Medical School, Singapore)	Presentation 5 Oligodendrocyte dynamics dictate individual performance outcomes of working memory training in mice Takahiro Shimizu (University College London, UK)
18:15	Presentation 6 Inhibition of connexin hemichannels alleviates neuroinflammation and hyperexcitability in temporal lobe epilepsy Geoffrey Lau (City University of Hong Kong, Hong Kong)	Presentation 6 Sciatic nerve pulsed-radiofrequency therapy improves pathophysiology in a mouse model of knee osteoarthritis via anti-inflammatory effects Tomoo Yuba (Osaka University Graduate School of Medicine, Japan)	Presentation 6 Nervous system-wide connectome of larval zebrafish based on single-excitatory/inhibitory-neuron atlas Xufei Du (Center for Excellence in Brain Science and Intelligence Technology, Chinese Academy of Sciences, China)
18:30	**End of Day 1 Program**		

Day 2 Program, Tuesday (20 Jun 2023)			
09:00	**The International Society for Neurochemistry (ISN) Lecture** **Plenary Lecture** **Modeling Neurological diseases using iPS cell technologies and Genetically Modified Non-human primates** **Hideyuki Okano** (Keio University, Japan) **Introduction by: Ying Shing Chan** Level 3, Hibiscus Room, 3711		
10:00	**Coffee Break**		
10:30	**Symposium S04 – S06**		
	Hibiscus Room 3711	**Jasmine Room 3811**	**Jasmine Room 3813**
	S04 **Neural circuits and dynamics underlying sensorimotor and cognitive functions** **Chair: Wing Ho Yung** (The Chinese University of Hong Kong)	**S05** **Drosophila systems for modelling brain development and neurological disease** **Chair: Leonie Quinn** (Australian National University, Australia)	**S06** **Brain organoids** **Chair: Alfred Sun** (Duke-NUS, Singapore)
	Presentation 1 Purkinje neuron activity during behavior Bernd Kuhn (Okinawa Institute of Science & Technology Graduate University, Japan)	Presentation 1 SETDB2 regulates sensory neuron survival and pain perception from flies to humans Greg Neely (Sydney University, Australia)	Presentation 1 Generating vascularized human brain orga¬noids to study development and disease Qian Wu (Beijing Normal University, China)

11:00	Presentation 2 Postnatal refinement of glutamategic and GABAergic transmission in the developing vestibular nucleus tunes the brain circuitry for adult navigation Ying-Shing Chan (University of Hong Kong, China)	Presentation 2 Odor-memory retrieval in Drosophila requires a state of arousal Adam Claridge-Chang (Duke-NUS Medical School, Singapore)	Presentation 2 Transcriptomic profiling of cerebral organoids reveals dysregulated genes in a subpopulation of PSEN1-mutant astrocytes in regulating mitochondria and lysosomal processes Qiu Lifeng on behalf of Li Zeng (National Neuroscience Institute, Singapore)
11:30	Presentation 3 Learning in intelligent systems Hiroshi Makino (LKCMedicine, Nanyang Technological University, Singapore)	Presentation 3 Par3 condensates in regulating asymmetric division of neural stem cells Wenyu Wen (Fudan University, China)	Presentation 3 Morphing bioelectronics for developing organoids and animals Yuxin Liu (National University of Singapore)
12:00	Presentation 4 Neural circuits contributing to cognitive flexibility Ya Ke (Chinese University of Hong Kong, China)	Presentation 4 Solving mysteries of the neural stem cell niche to understand brain cancer Leonie Quinn (Australian National University, Australia)	Presentation 4 Using human midbrain organoids to understand floor plate DA neuron development and degeneration Alfred Sun (Duke-NUS Medical School, Singapore)
12:30	**Lunch Poster** (Jasmine Room 3812 & 3911-3)		**APSN Business Meeting**

13:00		**Lunch Talk (X03)** Jasmine Room, 3811 **Overview of Neuroscience Research Singapore** **(Kah Leong Lim)** APSN 2023 Chair, Local Organising Committee	Jasmine Room, 3910 & 3810B
14:00	**Workshop / Young Investigator Colloquium**		
	Hibiscus Room 3711	**Jasmine Room 3811**	**Jasmine Room 3813**
	W1 **Cutting-Edge Technology of Stem Cell Applications** **Chair: Michael Ling** (Universiti Putra Malaysia, Malaysia)	**W2** **Frontiers in Research of Neurodegenerative Diseases** **Chair: Kensuke Ikenaka** (Osaka University, Japan)	**W3** **Energy Homeostasis** **Chair: Yu Fu** (Institute of Molecular and Cell Biology, Singapore)
14:00	Presentation 1 PAX6 controls cell fate choice in human cerebral organoids John Mason (University of Edinburgh, UK)	Presentation 1 Mechanisms of dendrite pruning of nociceptive sensory neurons in Drosophila Fengwei Yu (Temasek Life Sciences Laboratory, Singapore)	Presentation 1 Light regulates glucose metabolism Jianjun Meng (University of Science and Technology, China)
14:25	Presentation 2 REST-JAK-STAT in the neurogenic-to-gliogenic shift in Down syndrome Michael Ling (Universiti Putra Malaysia, Malaysia)	Presentation 2 Conformational state of the alpha synuclein monomer imparts the fibril polymorphisms of the synucleinopaties Kensuke Ikenaka (Osaka University, Japan)	Presentation 2 Brain-Fat interactions and how to find them? Ken Loh (Yale University, USA)

14:50	Presentation 3 Progress towards use of human bone marrow stromal cell-derived Schwann cells for treatment in PNS/CNS trauma Daisy Shum (The University of Hong Kong, HKSAR, China)	Presentation 3 The role of circRNAs in synaptic plasticity: Implications for neurodegeneration Jacque Ip (The Chinese University of Hong Kong, China)	Presentation 3 How contextual cues modulate feeding behavior Yu Fu (Institute of Molecular and Cell Biology, Singapore)
15:15	Presentation 4 Microsystem-based neural patterning in 2D and 3D culture system for the drug screening Woong Sun (Korea University College of Medicine, South Korea)	Presentation 4 Impaired synaptic vesicle recycling in Parkinson's disease Cao Mian (Duke-NUS Medical School, Singapore)	Presentation 4 Reverse translational approach to understand how genetics and context modulate feeding Ajay Mathuru (Yale-NUS College, Singapore)
15:40	Presentation 5 Defined hydrogels for spinal cord organoid derivation, maturation, and modeling of spinal cord diseases Wai Hon Chooi (Institute of Molecular and Cell Biology, Singapore)	Presentation 5 Adenosine A2A receptor signaling in astrocytes contributes to multiple sclerosis progression Chih Hung Lo (Lee Kong Chian School of Medicine, Singapore)	Presentation 5 Novel proteolytic pathway in lysosomes required for neuromuscular homeostasis Yuuki Fujiwara (Osaka University, Japan)
16:05	Q&A	Q&A	Q&A
16:20	**Break**		
18:30	**Banquet** **Sands Expo & Convention Centre** **10 Bayfront Avenue, Singapore 018956** Begonia Main Ballroom, Level 3		
20:30	**End of Day 2 Program**		

Day 3 Program, Wednesday (21 Jun 2023)			
09:00	**Plenary Lecture** **Human stem cells for neuroscience discovery and therapeutic development** **Su-Chun Zhang** (Duke-NUS Medical School, Singapore) **Introduction by: Hongyan Wang** Level 3, Hibiscus Room, 3711		
10:00	**Coffee Break**		
10:30	**Young Investigator Colloquium**		
	Hibiscus Room 3711	**Jasmine Room 3811**	**Jasmine Room 3813**
	YIC1 **Chair: ST Dheen** (National University of Singapore)	**YIC2** **Chair: Judy Sng** (National University of Singapore)	**YIC3** **Chair: Mitchell Lai** (National University of Singapore)
	Presentation 1 Investigating the role of lysosomal acidification in alpha synuclein induced Parkinson's disease models using acidic nanoparticles Jialiu Zeng (Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore)	WITHDRAWN ~~Presentation 1~~ ~~Bioluminescent reporters for noninvasive longitudinal imaging of kinase inhibitor pharmacodynamics in the brain~~ ~~Yichi Su~~ ~~(Stanford University, USA)~~	Presentation 1 Adolescent social isolation induces pathway-selective functional changes in the medial and lateral orbitofrontal- amygdala circuits. Hiroshi Kuniishi (University of Fukui, Japan)

10:50	Presentation 2 Long-distance axonal regeneration in the brain recovers memory deficits in a mouse model of Alzheimer's disease Ximeng Yang (University of Toyama, Japan)	Presentation 2 Optogenetic inhibition with kalium channelrhodopsins Stanislav Ott (Duke-NUS Medical School, Singapore)	Presentation 2 Remote hippocampal cerebrovascular dysregulation and cognitive impairment after cortical photothrombotic stroke Lin Kooi Ong (University of Southern Queensland, Australia)
11:20	Presentation 3 Analysis of the pathogenesis of vertigo associated with autoimmune diseases Yoshihisa Koyama (Osaka University, Japan)	Presentation 3 Abnormal development of cortex and behavior induced by deficit of fucosylation of glycan Asmaa Abdullah (Shiga University of Medical Science, Japan)	Presentation 3 Targeting heterogeneous nuclear ribonucleoprotein U in astrocytes to restore central nervous system impairment Lili Quan (National Center of Neurology and Psychiatry, Japan)
11:40	Presentation 4 Mitochondrial complex-I: A potential target for evaluation of mitochondrial targeted therapeutics in AD? Jia Hui Wong (LKCMedicine, Nanyang Technological University Singapore, Singapore)	Presentation 4 Function of transcription factor Meis1 in the differentiation of Bergmann glia from astroglial progenitor Toma Adachi (National Center of Neurology and Psychiatry, Japan)	Presentation 4 Subgroup specific alterations in the kynurenine pathway in the anterior cingulate cortex in major depressive disorder Samara Brown (University of Wollongong, Australia)
12:10	Presentation 5 Alteration of neural activity in the layer V pyramidal neuron of prelimbic cortex in ASD model mice	Presentation 5 Unravelling the role of BACE2 in a human cerebral organoid model of Alzheimer's disease Yee Jie Yeap	Presentation 5 Changes in the brain structure and functions in menopausal rat model and its association with the cognitive performance

	Yoshinori Otani (Shimane University, Japan)	(Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore)	Hanafi Damanhuri (The National University of Malaysia, Malaysia)
12:30	**Lunch**		
13:30	**Symposium S07 – S09**		
	Hibiscus Room 3711	**Jasmine Room 3811**	**Jasmine Room 3813**
	S07 **Primary cilia in cell signalling and neuronal function** **Chair: Xuecai Ge** (University of California, USA)	**S08** **Control of neuroinflammation and myelin health by lipid signalling molecules** **Chair: Anthony Don** (The University of Sydney, Australia)	**S09** **Pathogenic mechanisms, novel therapeutic targets and drug development in ALS** **Chair: Shuo-Chien Ling** (National University of Singapore, Singapore)
	Presentation 1 An axon-cilium synapse Sheu Shu-Hsien (Janelia Research Campus, USA)	Presentation 1 Critical roles of lysophospholipid transport in brain development David Silver (Duke-NUS Medical School, Singapore)	Presentation 1 Pathogenic mechanism and therapeutic potential for misfolded TDP-43 oligomers in ALS Yun-Ru Chen (Academia Sinica, Taiwan)
14:00	Presentation 2 Primary cilia and Hedgehog signaling in Parkinson's disease Suzanne Pfeffer (Stanford University, USA)	Presentation 2 Inhibiting S1P lyase to combat inflammatory demyelination Junhua Xiao (Swinburne University of Technology, Australia)	Presentation 2 Targeting mitochondrial respiration reverses disease phenotypes in motor neurons derived from ALS iPSCs Shi-Yan Ng (Institute of Molecular and Cell Biology, Singapore)

14:30	Presentation 3 Identifying new ciliary signaling pathways that control neuronal connectivity and viability in the mammalian brain Sarah Goetz (Duke University, USA)	Presentation 3 Harnessing sphingosine-1-phosphate transporters for treatment of neuroinflammation Nam Long Nguyen (National University of Singapore, Singapore)	Presentation 3 Adipokine is associated with worse prognosis and abnormal motor neurons in amyotrophic lateral sclerosis Yijuang Chern (Academia Sinica, Taiwan)
15:00	Presentation 4 New tricks for old proteins: Numb regulates Hedgehog signalling in the primary cilium Xuecai Ge (University of California, USA)	Presentation 4 Endogenous sphingosine 1-phosphate is essential for oligodendrocyte survival and remyelination Anthony Don (The University of Sydney, Australia)	Presentation 4 Decipher the physiological functions of TDP-43 in distinct glia Shuo-Chien Ling (National University of Singapore, Singapore)
15:30	**Coffee Break**		
16:00	**Symposium S10 – S11**		
	Jasmine Room 3811	**Hibiscus Room 3711**	
	S10 **From synapses to behaviour: How early life experiences shape plasticity, memory and behaviour in adolescence and adulthood** **Chairs: Sreedharan Sajikumar** (National University of Singapore, Singapore) **&** **Yasunori Hayashi** (Kyoto University Graduate School of Medicine, Japan)	**S11** **Endogenous regeneration and repair in the adult central nervous system** **Chair: Juan Song** (University of North Carolina, USA)	
	Presentation 1 Online and offline LTP during memory consolidation Yasunori Hayashi	Presentation 1 Activation of hypothalamic-enhanced adult-born neurons is sufficient to restore	

	(Kyoto University Graduate School of Medicine, Japan)	cognitive and affective function in Alzheimer's disease Juan Song (University of North Carolina, USA)
16:30	Presentation 2 Stressed prolonged adolescence hypothesis: early life stress sex-specifically delays maturation of conditioned fear extinction Jee Hyun Kim (Deakin University, Australia)	Presentation 2 Integration of adult-born neurons into mature neural circuits in aged hippocampus Hwai-Jong Cheng (Academia Sinica, Taiwan)
17:00	Presentation 3 Inhibitory metaplasticity in juvenile stressed rats restores associative memory in the adulthood by regulating epigenetic complex G9a/GLP Sreedharan Sajikumar (National University of Singapore, Singapore)	Presentation 3 Development of Therapeutic Strategies against Parkinson's Disease Yunlong Zhang (Westlake University, China)
17:30	Presentation 4 Small molecules that restore GABAergic function as potential therapeutics to treat autism spectrum disorder James Clement Chelliah (Jawaharlal Nehru Centre for Advanced Scientific Research, India)	Presentation 4 Inducing neurogenesis in the adult mouse spinal cord for repair Chun-Li Zhang (UT Southwestern, USA)
18:00	**Closing Remarks By Respective Chairs**	
18:30	**End of Day 3 Program**	

Day 1 (19 Jun 2023) Monday

Plenary Lecture — **Hibiscus Room 3711, Level 3**
Introduction by: Kah Leong Lim

08:30-09:00 Opening Remarks
Kah Leong Lim

09:00-10:00 Mechanisms of differential genetic risk for Alzheimer's disease with TREM2 variants
Paul M. Matthews

The ISN Special Symposium: RNA metabolism in neurodegenerative disease — **Hibiscus Room**
Chair: Aaron Gitler

10:30-11:10 Expanding mechanisms and therapeutic targets for neurodegenerative disease
Aaron Gitler

11:10-11:45 Understanding the molecular mechanisms of ALS and FTD to inspire targeted therapies
Magdalini Polymenidou

11:45-12:20 Structured and disordered domains antagonize to balance neuronal Ribonucleoprotein granule dynamics
Baskar Bakthavachalu

12:20-13:00 Designer DNA drug therapy for neurodegenerative disease
Don Cleveland

Symposium 01: Mechanisms of brain development in health and disease — **Hibiscus Room**
Chair: Shen-Ju Chou

14:30-15:00 Transcription factors and cortical patterning
Shen-Ju Chou

15:00-15:30 Functional human cortical circuitry assembled in vivo for the study of neuropsychiatric diseases
Vincenzo De Paola

15:30-16:00 Early postnatal developmental period for ASD-related social behavioral circuits
Goichi Miyoshi

16:00-16:30 Opposite effects of Wntless on the development of diencephalic habenula nuclei and choroid plexus in zebrafish larval brain
Yung-Shu Kuan

Symposium 02: Mechanisms and role of dendritic organelle and membrane trafficking in synaptic plasticity — **Jasmine Room 3811**

Chair: Victor Anggono

14:30-15:00	The endoplasmic reticulum puts a new spin on synaptic tagging **Anja Konietzny**
15:00-15:30	Homeostatic scaling alters lattice organization of nanoscale condensates at excitatory synapses **Deepak Kumaran Nair**
15:30-16:00	The specific role of the motor protein KIF5B in dendritic transport, synaptic plasticity and memory **Kwok On Lai**
16:00-16:30	Copine-6 is a calcium sensor that regulates AMPA receptor exocytosis during synaptic potentiation **Victor Anggono**

Symposium 03: Epigenetic regulation of neurons and brain function **Jasmine Room 3813**

Chair: Chenchen Song

14:30-15:00	Epigenetic regulation of brain function within and between generations **Anthony Hannan**
15:00-15:30	Unraveling the roles of RNA modification for mRNA localization in the developing brain **Ki-Jun Yoon**
15:30-16:00	From mice to men: Epigenetic regulation of neuroplasticity throughout lifespan and its implication **Judy Sng**
16:00-16:30	Expanding the glioblastoma universe in epigenetic regulation **Derrick Ong**

Oral Presentation 1 **Hibiscus Room**

Chair: Kensuke Ikenaka

17:00-17:15	Neuroprotective role of chicken essence in D-galactose/AlCl3-induced mouse model of Alzheimer's Disease **Kitipong Promyo**
17:15-17:30	Establishing fluid biomarkers associated with cellular senescence in Alzheimer’s disease **Bryan Ng**
17:30-17:45	Studying worm locomotion through the lens of neuropeptidergic signalling mechanisms **Kavita Babu**

17:45-18:00 Extrasynaptic GluN2B causes excitotoxicity and neurodegeneration through FOXO1 interaction with Txnip in YAC128 model of Huntington's Disease
Sok-Hong Kho

18:00-18:15 Gut microbiome profile and intestinal permeability in patients with schizophrenia and healthy controls - a plausible non-invasive biomarker?
Kuppan Gokulakrishnan

18:15-18:30 Inhibition of connexin hemichannels alleviates neuroinflammation and hyperexcitability in temporal lobe epilepsy
Geoffrey Lau

Oral Presentation 2
Chair: Jacque Ip

Jasmine Room 3811, Level 3

17:00-17:15 Matrix-assisted Golgi staining in whole-brain expansion imaging under near-infrared light microscopy
Yi-Fen Cheng

17:15-17:30 Sphingosine kinase 2 is essential for remyelination
Huitong Song

17:30-17:45 APOE regulates myelin lipid turnover in healthy brains
Jun Yup Lee

17:45-18:00 GPCR signaling-mediated actin remodeling drives quiescent neural stem cell activation
Kun-Yang Lin

18:00-18:15 Golgi-dependent reactivation and regeneration of quiescent neural stem cells
Mahekta Gujar

18:15-18:30 Sciatic nerve pulsed-radiofrequency therapy improves pathophysiology in a mouse model of knee osteoarthritis via anti-inflammatory effects
Tomoo Yuba

Oral Presentation 3
Chair: Kwok On Lai

Jasmine Room 3813, Level 3

17:00-17:15 Novel allosteric modulator SRI-32743 reverses HIV-1 Tat-induced increase in dopamine release and alleviates the potentiation of cocaine reward in inducible HIV-1 Tat transgenic mice
Jun Zhu

17:15-17:30 A dopaminergic memory circuit signals valence via a trio of transmitters in Drosophila melanogaster
Yishan Mai

17:30-17:45	Contrasting effects of finasteride administration on depression and anxiety-like behaviour and synaptic plasticity in male and female rats **Bettadapura N Srikumar**
17:45-18:00	~~Developing Liang's contextual-stress box as an advanced anxiety-related murine behavioral test apparatus~~ ~~**Jian-Hui Liang**~~
18:00-18:15	Oligodendrocyte dynamics dictate individual performance outcomes of working memory training in mice **Takahiro Shimizu**
18:15-18:30	Nervous system-wide connectome of larval zebrafish based on single-excitatory/inhibitory-neuron atlas **Xufei Du**

Day 2 (20 Jun 2023) Tuesday

Plenary Lecture — **Hibiscus Room 3711, Level 3**
Introduction by: Ying-Shing Chan

09:00-10:00	iPS cell-based regenerative medicine and drug development for CNS disorders **Hideyuki Okano**

Symposium 04: Neural circuits and dynamics underlying sensorimotor and cognitive functions — **Hibiscus Room**
Chair: Wing Ho Yung

10:30-11:00	Purkinje neuron activity during behavior **Bernd Kuhn**
11:00-11:30	Neural circuits contributing to cognitive flexibility **Ya Ke**
11:30-12:00	Learning in intelligent systems **Hiroshi Makino**
12:00-12:30	Postnatal refinement of glutamategic and GABAergic transmission in the developing vestibular nucleus tunes the brain circuitry for adult navigation **Ying-Shing Chan**

Symposium 05: Drosophila systems for modelling brain development and neurological disease — **Jasmine Room 3811, Level 3**
Chair: Leonie Quinn

10:30-11:00	SETDB2 regulates sensory neuron survival and pain perception from flies to humans **Greg Neely**

11:00-11:30	Odor-memory retrieval in Drosophila requires a state of arousal**Adam Claridge-Chang**
11:30-12:00	Par3 condensates in regulating asymmetric division of neural stem cells **Wenyu Wen**
12:00-12:30	Solving mysteries of the neural stem cell niche to understand brain cancer **Leonie Quinn**

Symposium 06: Brain organoids
Chair: Alfred Sun

Jasmine Room 3811, Level 3

10:30-11:00	Generating vascularized human brain orga¬noids to study development and disease **Qian Wu**
11:00-11:30	Transcriptomic profiling of cerebral organoids reveals dysregulated genes in a subpopulation of PSEN1-mutant astrocytes in regulating mitochondria and lysosomal processes **Qiu Lifeng on behalf of Li Zeng**
11:30-12:00	Morphing bioelectronics for developing organoids and animals **Yuxin Liu**
12:00-12:30	Using human midbrain organoids to understand floor plate DA neuron development and degeneration **Alfred Sun**

Workshop/YIC 1: Cutting-edge technology of stem cell applications
Chair: Michael Ling

Hibiscus Room

14:00-14:25	PAX6 controls cell fate choice in human cerebral organoids **John Mason**
14:25-14:50	REST-JAK-STAT in the neurogenic-to-gliogenic shift in Down syndrome **Michael Ling**
14:50-15:15	Progress towards use of human bone marrow stromal cell-derived Schwann cells for treatment in PNS/CNS trauma **Daisy Shum**
15:15-15:40	Microsystem-based neural patterning in 2D and 3D culture system for the drug screening **Woong Sun**
15:40-16:05	Defined hydrogels for spinal cord organoid derivation, maturation, and modeling of spinal cord diseases **Wai Hon Chooi**

16:05-16:20 Q&A

Workshop/YIC 2: Frontiers in research of neurodegenerative diseases
Chair: Kensuke Ikenaka

Jasmine Room 3811

14:00-14:25 Mechanisms of dendrite pruning of nociceptive sensory neurons in drosophila
Fengwei Yu

14:25-14:50 Conformational state of the alpha synuclein monomer imparts the fibril polymorphisms of the synucleinopaties
Kensuke Ikenaka

14:50-15:15 The role of circRNAs in synaptic plasticity: Implications for neurodegeneration
Jacque Ip

15:15-15:40 Impaired synaptic vesicle recycling in Parkinson's disease
Cao Mian

15:40-16:05 Adenosine A2A receptor signaling in astrocytes contributes to multiple sclerosis progression
Chih Hung Lo

16:05-16:20 Q&A

Workshop/YIC 3: Energy homeostasis
Chair: Yu Fu

Jasmine Room 3813

14:00-14:25 Light regulates glucose metabolism
Jianjun Meng

14:25-14:50 Brain-Fat interactions and how to find them?
Ken Loh

14:50-15:15 How contextual cues modulate feeding behavior
Yu Fu

15:15-15:40 Reverse translational approach to understand how genetics and context modulate feeding
Ajay Mathuru

15:40-16:05 Novel proteolytic pathway in lysosomes required for neuromuscular homeostasis
Yuuki Fujiwara

16:05-16:20 Q&A

Day 3 (21 Jun 2023) Wednesday

Plenary Lecture — **Hibiscus Room 3711, Level 3**
Introduction by: Hongyan Wang

09:00-10:00 Human stem cells for neuroscience discovery and therapeutic development
Su-Chun Zhang

Young Investigator Colloquium 1 — **Hibiscus Room**
Chair: ST Dheen

10:30-10:50 Investigating the role of lysosomal acidification in alpha synuclein induced Parkinson's disease models using acidic nanoparticles
Jialiu Zeng

10:50-11:20 Long-distance axonal regeneration in the brain recovers memory deficits in a mouse model of Alzheimer's disease
Ximeng Yang

11:20-11:40 Analysis of the pathogenesis of vertigo associated with autoimmune diseases
Yoshihisa Koyama

11:40-12:10 Mitochondrial complex-I: A potential target for evaluation of mitochondrial targeted therapeutics in AD?
Jia Hui Wong

12:10-12:30 Alteration of neural activity in the layer V pyramidal neuron of prelimbic cortex in ASD model mice
Yoshinori Otani

Young Investigator Colloquium 2 — **Jasmine Room 3811, Level 3**
Chair: Judy Sng

10:30-10:50 Bioluminescent reporters for noninvasive longitudinal imaging of kinase inhibitor pharmacodynamics in the brain
Yichi Su

10:50-11:20 Optogenetic inhibition with kalium channelrhodopsins
Stanislav Ott

11:20-11:40 Abnormal development of cortex and behavior induced by deficit of fucosylation of glycan
Asmaa Abdullah

11:40-12:10 Function of transcription factor Meis1 in the differentiation of Bergmann glia from astroglial progenitor
Toma Adachi

12:10-12:30 Unravelling the role of BACE2 in a human cerebral organoid model of Alzheimer's Disease
Yee Jie Yeap

Young Investigator Colloquium 3 — **Jasmine Room 3813, Level 3**
Chair: Mitchell Lai

10:30-10:50	Adolescent social isolation induces pathway-selective functional changes in the medial and lateral orbitofrontal- amygdala circuits **Hiroshi Kuniishi**
10:50-11:20	Remote hippocampal cerebrovascular dysregulation and cognitive impairment after cortical photothrombotic stroke **Lin Kooi Ong**
11:20-11:40	Targeting heterogeneous nuclear ribonucleoprotein U in astrocytes to restore central nervous system impairment **Lilli Quan**
11:40-12:10	Subgroup specific alterations in the kynurenine pathway in the anterior cingulate cortex in major depressive disorder **Samara Brown**
12:10-12:30	Changes in the brain structure and functions in menopausal rat model and its association with the cognitive performance **Hanafi Damanhuri**

Symposium 07: Primary cilia in cell signalling and neuronal function — **Hibiscus Room**
Chair: Xuecai Ge

13:30-14:00	An axon-cilium synapse **Sheu Shu-Hsien**
14:00-14:30	Primary cilia and Hedgehog signaling in Parkinson's disease **Suzanne Pfeffer**
14:30-15:00	Identifying new ciliary signaling pathways that control neuronal connectivity and viability in the mammalian brain **Sarah Goetz**
15:00-15:30	New tricks for old proteins: Numb regulates Hedgehog signalling in the primary cilium **Xuecai Ge**

Symposium 08: Control of neuroinflammation and myelin health by lipid signalling molecules — **Jasmine Room 3811**
Chair: Anthony Don

13:30-14:00	Critical roles of lysophospholipid transport in brain development **David Silver**
14:00-14:30	Inhibiting S1P lyase to combat inflammatory demyelination **Junhua Xiao**
14:30-15:00	Harnessing Sphingosine-1-phosphate transporters for treatment of neuroinflammation

Nam Long Nguyen

15:00-15:30 Endogenous sphingosine 1-phosphate is essential for oligodendrocyte survival and remyelination
Anthony Don

Symposium 09: Pathogenic mechanisms, novel therapeutic targets and drug development in ALS — **Jasmine Room 3813**
Chair: Shuo-Chien Ling

13:30-14:00 Pathogenic mechanism and therapeutic potential for misfolded TDP-43 oligomers in ALS
Yun-Ru Chen

14:00-14:30 Targeting mitochondrial respiration reverses disease phenotypes in motor neurons derived from ALS iPSCs
Shi-Yan Ng

14:30-15:00 Adipokine is associated with worse prognosis and abnormal motor neurons in amyotrophic lateral sclerosis
Yijuang Chern

15:00-15:30 Decipher the physiological functions of TDP-43 in distinct glia
Shuo-Chien Ling

Symposium 10: From Synapses to behaviour: How early life experiences shape plasticity, memory and behaviour in adolescence and adulthood — **Jasmine Room 3811**
Chair: Sreedharan Sajikumar, Yasunori Hayashi

16:00-16:30 Online and offline LTP during memory consolidation
Yasunori Hayashi

16:30-17:00 Stressed prolonged adolescence hypothesis: early life stress sex-specifically delays maturation of conditioned fear extinction
Jee Hyun Kim

17:00-17:30 Inhibitory metaplasticity in juvenile stressed rats restores associative memory in the adulthood by regulating epigenetic complex G9a/GLP
Sreedharan Sajikumar

17:30-18:00 Small molecules that restore GABAergic function as potential therapeutics to treat autism spectrum disorder
James Clement Chelliah

Symposium 11: Endogenous regeneration and repair in the adult central nervous system — **Hibiscus Room**
Chair: Juan Song

16:00-16:30 Activation of hypothalamic-enhanced adult-born neurons is sufficient to restore cognitive and affective function in Alzheimer's disease

Juan Song

16:30-17:00 Integration of adult-born neurons into mature neural circuits in aged hippocampus
Hwai-Jong Cheng

17:00-17:30 Development of Therapeutic Strategies against Parkinson's Disease
Yunlong Zhang

17:30-18:00 Inducing neurogenesis in the adult mouse spinal cord for repair
Chun-Li Zhang

Poster Presentation
Day 1 (19 Jun, Monday, 13:00 - 14:00)

Day 2 (20 Jun, Tuesday, 12:30 - 13:30)

Jasmine Room 3812, Level 3
Jasmine Room 3911, Level 3

PP01	Modeling of fetal spinal cord ischemia using necrotic core-free human spinal cord organoids **Aeri Shin**
PP02	DNA methylation levels of RELN promoter region in ultra-high risk, first episode, and chronic cohorts of schizophrenia **Luke Han**
PP03	Sustained release triple drug loaded colloidosomes for management of Parkinson's Disease **Mani Bhargava**
PP04	Regulation of synaptic plasticity genes by curcumin in scopolamine-induced amnesic mice **Akash Gautam**
PP05	Mapping of brain phosphodiesterase 4D (PDE4) through 11C labelled high affinity inhibitors and their empirical quantitative structure-activity relationship **Anjani Kumar Tiwari**
PP06	Neuroprotective effect of berberine loaded mesoporous silica nanoparticles: unravelling the mitochondrial pathways and cell cascades **Anurag Singh**
PP07	Correlation of inflammatory cytokines, synaptic proteins and oxidative stress with developmental outcomes in autism spectrum disorder **Ayushi Jain**
~~PP08~~	~~Citral inhibits neuroinflammation in HFD/STZ induced diabetic rats via p38MAPK/Nrf2 signalling pathways~~ ~~**Chetna Mishra**~~
PP09	Eugenol attenuates LPS induced cognitive impairments in male rats by suppressing oxidative stress and inflammation in male rats : An in vivo and in-sillico study **Anchal Dubey**
PP10	Integration of MRS and labeled glucose analysis for mapping the dynamics of metabolism (glial/astrocytic) **Deepika Mishra**
~~PP11~~	~~Neuroprotective Effect of Citral against Transient Focal Cerebral Ischemia through the Regulation of mitochondrial function and autophagy in Type II Diabetes in Rats~~

~~**Dinesh Tripathi**~~

~~PP12~~ ~~Protective effect of neurosteroid Ganaxolone in APPswe transfected SH-SY5Y cells~~

~~**Divya Divya**~~

PP13 Lactic acid conjugated SLN for effective management of neurocysticercosis

Saurabh Bhargava

PP14 Analysis of defects in neuromuscular junction maintenance in a zebrafish model for intermediate type spinal muscular atrophy

Goh Yun Jing

PP15 An integrated single-cell transcriptome landscape of postnatal and young adult mouse hypothalamus

Su Bin Lim

PP16 Studying worm locomotion through the lens of neuropeptidergic signalling mechanisms

Kavita Babu

PP17 TRPV2 activation by focal mechanical stimulation enhances growth cone motility

Koji Shibasaki

~~PP18~~ ~~Exploring headache management and self-medication practices among health care professionals in Karachi, Pakistan~~

~~**Muhammad Liaquat Raza**~~

PP19 Investigating the relation between valence and locomotor performance using well established optogenetics in drosophila melanogaster

Nicole Lee

PP20 The D1R-specific NSFdeficient mice as a novel schizophrenic model

Min-Jue Xie

PP21 Micropattern-based axonal growth assay using human neural organoid

Kahee Ko

PP22 Particulate Matter (PM2.5) exposure contributes to glial cells activation and neurodegeneration through the olfactory-brain axis

Samir Ranjan Panda

PP23 Study of metabolites of the kynurenine pathway in a rat model of neuropathic pain

Saroj Kaler Jhajhria

~~PP24~~ ~~TBD~~

~~**Sayma Azeem**~~

PP25 Genotype-phenotype correlation of Synaptojanin 1 mutations in Parkinsonism

Serene Gwee

PP26 Minocycline inhibits lipopolysaccharide (LPS)-induced neurotoxicity
Sharumadhi Veloo

PP27 In vitro generation of brain regulatory T cells by co-culturing with astrocytes
Shinichi Yamamoto

PP28 Elucidating a novel role of Parkinson's disease-associated protein Parkin (PARK2) in synaptic membrane trafficking
Sidra Mohamed Yaqoob

PP29 The role of NAG-1 proteins in formalin-induced inflammatory pain
Sheuran Choi

PP30 Venous susceptibility to chronic cerebral hypoperfusion
Vanessa Wazny

PP31 The Parkin-SREBP2-LPL axis regulates neuronal lipid homeostasis – Implications for Parkinson's disease
Willcyn Tang

PP32 The diagnosis, mechanism and treatment of Parkinson's disease and related neurodegenerative disease
Wang Qing

PP33 Synergistic effect of mutations in two Parkinsonism related endocytic proteins: SJ1 and Auxilin
Xin Yi Ng

PP34 The role of circHomer1 in dendritic spine maintenance and hippocampus-dependent spatial learning and memory
Ying Cai

PP35 Synaptic and circuit level deficits in CDKL5 deficiency disorder
Shiyang Yuan

PP36 Characterization of a novel non-canonical mutation in Rett Syndrome
Yue Chai

PP37 The mechanism of neurostimulation modulating synaptic plasticity in protein kinase regulation
Chi-Wei Lee

PP38 Aβ-mediated nuclear pore complex dysfunction in a mouse model of Alzheimer's Disease
Vibhavari Bansal

PP39 Rynchophylline as a therapeutic agent improves functional recovery in traumatic spinal cord injury
Manjeet Chopra

PP40 Acetylcholinesterase inhibitory activity and antioxidant properties of α-Mangostin as a potential drug for the treatment of Alzheimer's disease

Suksan Changlek

PP41 Correlation of oxidative-antioxidative cascade, Inflammatory cytokines and synaptic metalloproteinase in women with epilepsy: A cross sectional study
Vinod Kumar Mehta

PP42 Visualization of accessible cholesterol using a GRAM domain-based biosensor
Dylan Koh

PP43 MAPK-dependent presynaptic potentiation in the lateral habenula induces depressive-like behaviors in rats
Hoyong Park

PP44 In vivo imaging for visualization of nerve regeneration in sciatic nerve crush animal model
Hsuan-Ju Chen

~~PP45~~ ~~Elucidating the Pharmacological Mechanisms of Aloe Vera in Alzheimer's disease using Molecular Docking and MD Simulation~~
~~**Abhishek kumar**~~

~~PP46~~ ~~Electrophysiological measures of subcortical auditory functioning in persons with Parkinson's disease~~
~~**Mohammad Shamim Ansari**~~

PP47 DNA Methylation analysis of OPRM1 and DAT1 genes in a drug-dependent population of Manipur, India
Reena Haobam

PP48 Neuroprotective effect of Valproate on pathological synaptic response during cerebral ischemia
Ming-Chia Chu

PP49 Ermin deficiency as a model for understanding early mechanisms of abnormal myelination in neurodegeneration
Sher Li Oh

PP50 Familial Alzheimer's Disease patient iPSC-Derived endothelial cells exhibit dysregulated angiogenesis and altered function
Yu-Hsin (Yvonne) Yen

PP51 Ultrasensitive fluorogenic probe for detecting ferrous ion in Parkinson's disease models with multimode imaging
Chengwu Zhang

PP52 Plasma CXCL-5 chemokine is increased in Alzheimer's Disease but not Vascular Cognitive Impairment
T.Y Amelia Yam

PP53 Brevican is reduced in pre-dementia patients with significant cerebral vascular disease: implications for treatment and biomarker utility
Rachel S.L. Chia

Plenary Lectures

P1

Mechanisms of differential genetic risk for Alzheimer's disease with TREM2 variants

Paul M. Matthews

UK Dementia Research Institute Centre and Department of Brain Sciences, Imperial College London, UK

TREM2 (triggering receptor expressed on myeloid cells 2) is a cell surface receptor expressed on myeloid cells. Coding variants increase the risk of late onset Alzheimer's disease (AD). We have used highly multiplexed immunohistology with imaging mass cytometry in combination with bulk and single nuclear RNA sequencing to broadly characterise TREM2 genotype (common allele, R47H or R62H) dependent responses to increased levels of beta-amyloid protein in human post mortem brain tissue. Increased beta-amyloid was found with impairment of its clearance for both TREM2var, while differences in plaque structure and microglial and astroglial morphologies, activation marker and spatial clustering defined distinct functional differences between TREM2 risk genotypes. For example, while the disease activated microglia (DAM) response was reduced with R47H, DAM genes were relatively enriched in R62H microglia in conjunction with up-regulation of classical and alternative activation and interferon signalling. Astrocytes also showed TREM2 genotypic differences likely contributing to neurodegeneration with markedly increased expression of the dectin-1 (CLEC7A)/NFAT pathway for R47H and downregulation of homeostatic protective kinase and growth factors signalling with R62H. Cortical neurons showed differential vulnerability to increased beta-amyloid or tau with greatest transcriptional differences found in association with the R47H genotype in excitatory neurons of L2 and L5-6. By contrast, excitatory neurons in deepest layers (EN L5-6 III) appeared most vulnerable with the R62H risk variant. Together, these results suggest distinct mechanisms of neurodegeneration with the different TREM2 risk genotypes, providing further evidence for the genotypic heterogeneity of AD pathology. They also suggest calcineuron/NFAT as a promising therapeutic target.

P2

Modeling Neurological diseases using iPS cell technologies and Genetically Modified Non-human primates

Hideyuki Okano
Dept. Physiology, Keio University School of Medicine, Japan

Investigating human neurological/psychiatric disorders is challenging due to several factors such as limited access to affected cells and pathogenic sites, unclear genotype-phenotype causal relationships, and unidentified neuronal circuits. To overcome these challenges, iPSC technology and genetically modified non-human primates, particularly common marmosets, are being used.

iPSCs offer new opportunities for disease modeling and drug development, including for ALS. Using iPSCs-MNs derived from ALS patients, we identified Ropinirole as a potential anti-ALS drug. A clinical trial (ROPALS trial) found that ropinirole was safe and tolerable, with maintenance of daily activity and muscle strength. In the open-label extension period, ropinirole significantly suppressed the decline in ALSFRS-R and extended survival without disease progression by 27.9 weeks at 12 months. iPSCs-derived motor neurons showed D2R expression and potential involvement of the SREBP2-cholesterol synthetic pathway in the therapeutic effects.
Genetically modified common marmosets have been successfully generated and used as models for neurodegenerative and neurodevelopmental disorders. The PD model marmoset showed stage-dependent progression of the disease, and the Rett syndrome model marmoset may accelerate the discovery of disease biomarkers and mechanisms.

P3

Human Stem Cells for Neuroscience Discovery and Therapeutic Development

Su-Chun Zhang
Duke-NUS Medical School, Singapore

Human pluripotent stem cells (hPSCs) can be differentiated to defined neural cell types and tissues, offering a useful model for dissecting cellular and molecular processes during development and under pathological conditions. By generating induced pluripotent stem cells (iPSCs) from patients with an undiagnosed disease and guiding them to target neural cells, we identified key cellular and molecular events that lead to the pathological changes, uncovering molecular mechanisms underlying cellular senescence and neural developmental deficits associated with the disease. The hPSC-derived neural cells also provide a platform for drug testing and a source for cell therapy. Following transplantation of neural cell types into animal models of neurological disorders, we found that the human neurons not only project axons in a long distance but also find their targets in the mature brain, thus reconstructing the functional neural circuit. Strikingly, the pathfinding and circuit reconstruction are largely dependent upon the grafted neuronal type, highlighting the therapeutic potential of hPSC-derived neural cells and the necessity for guiding hPSCs to enriched and functionally specialized subtype-specific neural cells.

The ISN Special Symposium

SS1
RNA metabolism in neurodegenerative disease
Chair: Aaron Gitler

Synopsis:

We propose a symposium to present the latest research on RNA metabolism pathways and how their dysregulation underlies the pathogenesis of several devastating neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). We have brought together a diverse group of speakers who are all internationally recognized leaders in the field and who have made field-leading contributions to neurodegenerative disease research. Dr. Gitler will chair the symposium and also be a speaker. He will present the latest research from his laboratory using genomewide functional genomics screens to define modifiers of ALS disease genes and using these as new drug targets. Dr. Polymenidou will present data from her laboratory discovering mechanisms by which RNA-binding protein TDP-43 contributes to ALS and FTD. Dr. Shorter will talk about harnessing powerful new engineered disaggregases to dismantle disease-associated aggregates formed by RNA-binding proteins TDP-43 and FUS. Dr. Clevleand will talk about the discovery cryptic splicing targets of TDP-43 and their dysregulation in ALS, leading to a new therapeutic approach for sporadic ALS and FTD. Together, the symposium speakers will present a range of experimental approaches and viewpoints and make for a very engaging and timely topic for the attendees to participate in.

SS1P1

Expanding mechanisms and therapeutic targets for neurodegenerative disease

Aaron Gitler

Stanford Medicine Basic Science Professor Stanford University, USA

Nuclear depletion and cytoplasmic aggregation of the RNA-binding protein TDP-43 is the hallmark pathology in ALS and FTD. One of the major functions of TDP-43 in the nucleus is a repressor of cryptic exon inclusion. We discovered that TDP-43 represses a cryptic exon-splicing event in UNC13A, one of the top genetic contributors to ALS/FTD. Loss of TDP-43 from the nucleus results in the inclusion of a cryptic exon in UNC13A mRNA and reduced UNC13A protein expression. The top variants associated with FTD or ALS risk in humans are in the intron harboring the cryptic exon, and we show that they increase UNC13A cryptic exon splicing in the face of TDP- 43 dysfunction. Together, our data provide a direct functional link between one of the strongest genetic risk factors for FTD and ALS (UNC13A genetic variants), and loss of TDP-43 function.

We have previously discovered ataxin-2 as a potent modifier of TDP-43 toxicity. A therapeutic strategy using antisense oligonucleotides targeting ataxin-2 has entered clinical trial in humans. Additional ways to decrease ataxin-2 levels could lead to cheaper or less invasive therapies and elucidate how ataxin-2 is normally regulated. We will present two new genomewide screens (one siRNA screen and one CRISPR screen) to identify regulators of ataxin-2 levels. We discovered components of the lysosomal vacuolar ATPase (v-ATPase) as modifiers of endogenous ataxin-2 protein levels and show that multiple FDA-approved small molecule v-ATPase inhibitors lower ataxin-2 protein levels in mouse and human neurons, and oral administration of at least one of these drugs-etidronate-is sufficient to decrease ataxin-2 in the brains of mice. We also show that targeting RTN4R (also known as the NoGo- Receptor) is sufficient to lower ataxin-2 levels in vitro and in vivo. These types of protein levels-based screens are useful for identifying genetic-and potentially druggable-modifiers of human disease proteins.

SS1P2

Understanding the molecular mechanisms of ALS and FTD to inspire targeted therapies

Magdalini Polymenidou
Department of Quantitative Biomedicine University of Zurich, Switzerland

ALS and FTD are fatal and incurable neurodegenerative diseases, characterized by accumulation of pathologic forms of RNA-binding proteins, predominantly TDP-43. The functional consequences and potential neurotoxic effects of the highly heterogeneous TDP-43 aggregates observed in postmortem brains are debated. Combining structural protein analysis with cellular systems we uncovered a novel and unexpected mechanism that counteracts pathologic aggregation of TDP-43. More recently, we described two distinct mechanisms of aggregation resulting in either nuclear of cytoplasmic TDP-43 aggregates, resembling the neuropathological heterogeneity described in FTD patients and potentially unravels the origins of heterogeneous pathological species occurring in TDP-43 proteinopathies. We also showed that FTD heterogeneity is associated with alternate pathological TDP-43 conformations, reminiscent of prion strains. We used advanced microscopy techniques to explore the differences in the physical and seeding properties between these pathological TDP-43 aggregates. We found that the subcellular environment and organization of TDP-43 aggregates differs in patient brains in a subtype- specific manner. When isolated and introduced in cells, these distinct TDP-43 assemblies triggered neoaggregate formation with seeding potencies and morphologies that mimicked human brain pathology.

To study neurodegeneration phenotypes in human neurons, we developed a new methodology for generating human neuronal networks with remarkable maturity, longevity and reproducibility. Combining high density multielectron arrays and single cell RNA sequencing, we demonstrated the potential of these cultures for modeling neurodegeneration. In this new model, we identified novel RNA targets of TDP-43, which we found abnormally accumulated in neurons with TDP-43 pathology in human brains of ALS and FTD patients. The implications of these studies for understanding

the mechanisms of neurodegeneration and inspiring therapeutic approaches will be discussed.

SS1P3

Structured and disordered domains antagonize to balance neuronal Ribonucleoprotein granule dynamics

Baskar Bakthavachalu
DBT/Wellcome Trust India Alliance Intermediate Fellow

Neurodegeneration, the progressive loss of nerve cells, is influenced by genetic mutations in RNA binding proteins (RBPs) and is conserved between fruit flies and humans. In our lab, we leverage fruit flies as a model organism to study RNA regulation in vivo. Specifically, we investigate how RBPs with IDR govern RNP assemblies. In my talk, I will discuss how structured and disordered domains in Ataxin-2 have opposing effects in RNP aggregation and cellular toxicity.

SS1P4

Designer DNA drug therapy for neurodegenerative disease

Don Cleveland

University of California San Diego, USA

Sustained gene silencing or altered pre-mRNA splicing within neurons and non-neurons throughout the nervous system has been achieved using a clinically feasible approach with “designer DNA drugs”. The approach is now a standard of care for the fatal childhood disease spinal muscular atrophy, with ongoing and planned trials in ALS, Parkinson’s, and Alzheimer’s diseases. Loss of nuclear TDP- 43 is a hallmark of ALS/FTD neurodegeneration, resulting in cryptic splicing/polyadenylation of STMN2 pre-mRNAs encoding stathmin-2 (SCG10), a protein required for axonal regeneration. Cryptic splicing is determined to be the critical step in STMN2 pre-mRNA misprocessing. TDP-43 binding to a GU-rich region within the cryptic STMN2 exon is shown to sterically repress use of the cryptic splice site. While removal of the GU domain is sufficient to activate STMN2 misprocessing, binding of the unrelated RNA binding protein MS2 restores correct pre-mRNA maturation. Blocking cryptic splicing by binding of dCasRx or antisense oligonucleotides (ASOs) rescues axonal regeneration capacity in TDP-43 deficient human motor neurons. Injection of ASOs into humanized Stmn2 mice establishes a therapeutically viable approach to rescue stathmin-2 levels in TDP-43 proteinopathies. Designer DNA drugs can also be used to produce direct conversion of glia into neurons. Transient suppression of the RNA binding protein PTB converts glia into new hippocampal neurons in the aged mouse brain or into new dopamine- synthesizing, nigral neurons that reestablish the nigrostriatal dopamine pathway, restore striatal dopamine levels, and reverse chemically-induced Parkinson’s disease in mice. Development of methods to transdifferentiate non-neurons into a wide range of neural cells has opened a new era for treating neurodegenerative diseases.

Special Events

X01

The International Society for Neurochemistry (ISN).

Flávia Gomes, Alessandro Prinetti & Caroline Rae

ISN Officers,
7, rue François-Versonnex I C.P. 6053 I 1211 Geneva I Switzerland
1250 I Street, NW, Suite 650 I DC 2005 I Washington I Unites States of America
Teleport boulevard 130 I 1043 EJ I Amsterdam I The Netherlands

The International Society for Neurochemistry (ISN) is a non-profit membership organisation and the only international society focused on neurochemistry. Established in 1965, ISN is the owner of The Journal of Neurochemistry and has affiliated sister societies, The American Society for Neurochemistry, The Asian-Pacific Society for Neurochemistry and The European Society for Neurochemistry. Members of sister societies are able to also become members of ISN at no extra cost.

ISN operates several schemes to support neurochemists and neurochemistry around the world. These schemes include Schools, Conferences, travel awards, lectureships and grants to support early and mid-career researchers as well as researchers in economically disadvantaged countries.

This ISN Forum, presented by the ISN Officers, will provide details about the advantages of being an ISN member, including information on how to apply for ISN funding, what makes a winning application as well as information on how you can get involved in ISN and contribute to the global neurochemistry community.

Symposium

S01
Mechanisms of brain development in health and disease
Chair: Shen-Ju Chou

Synopsis:

Brain development is a tightly regulated process that involves progenitor proliferation, neuronal differentiation, neuronal migration, axonal guidance, and synapse formation. The timing of molecular and cellular events that regulate brain development are important as temporally distinct perturbations may differentially impact cortical structure, activity in the brain, or behavior. Emerging studies are providing evidence that various coordinated molecular and cellular mechanisms are utilized to govern brain development. These studies are contributing greatly to our understanding of the underpinnings of neurodevelopmental disorders. This symposium will highlight the latest findings from a diverse group of neurodevelopmental researchers and state-of-the-art tools that are facilitating identification of the cellular and molecular rules and logic governing brain development.

S01P1

Transcription factors and cortical patterning

Shen-Ju Chou

Academia Sinica, Taiwan

The mammalian cerebral cortex is a remarkably complex organ responsible for the perception of sensory stimuli, the execution of motor actions, learning, cognition, and consciousness. To perform such complicated functions, it is compartmentalized into multiple functional units or cortical regions, including the newly evolved neocortex and evolutionarily older paleocortex and archicortex. Each cortical region has unique cytoarchitectures, patterns of gene expression, and distinct sets of input and output projections to perform specific functions: the neocortex, consists of six layers of neurons and processes visual, auditory, and somatosensory inputs and implements motor functions, the piriform cortex, the major component in the paleocortex, consists of three layers of neurons and processes olfaction, and the hippocampus, the major component in the archicortex, consists of three layers of neurons and is involved in spatial learning and memory formation. The research in my laboratory concerns the patterning of the cerebral cortex into different cortical regions. We focus on the functions of transcription factors (TFs) in specifying neuronal properties in different cortical regions. Our goal is to understand the mechanisms (i) controlling the number of neurons produced in different cortical regions, (ii) endowing cortical neurons with their region-specific properties, and (iii) integrating cortical neurons into functional neuronal circuits. Uncovering the mechanisms controlling cortical regional specification would allow us to understand how the brain functions, which is the first step toward understanding cortical dysfunction in disease states.entifying genetic-and potentially druggable-modifiers of human disease proteins.

S01P2

Functional human cortical circuitry assembled in vivo for the study of neuropsychiatric diseases

Vincenzo De Paola

Duke-NUS Medical School, Singapore

Proper wiring of cortical circuits is a critical step in human brain development and maturation of high-order cognitive abilities. Despite their pivotal role, we do not yet clearly understand how human cortical circuits assemble *in vivo,* nor why this process can fail, leading to cognitive disturbances in neurodevelopmental conditions. Cellular analyses in the human brain focus on post-mortem fixed tissue samples, which cannot provide direct observation of dynamic events such the formation of synaptic connections and electrical activity patterns. Our understanding of human cortical circuit formation and function, including pruning, synaptogenesis and network activity, is greatly limited by the lack of in vivo systems amenable for high-resolution longitudinal imaging. Recently, we developed a new system to study human cortical circuitry development and function *in vivo* using transplanted human induced Pluripotent Stem Cell (iPSC)-derived neurons. Importantly, transplanted cortical neuron progenitors self-assemble in large (up to 100 mm^3) vascularised territories with complex cytoarchitecture and functionality, resembling human cortical tissue. Longitudinal multiphoton imaging of human cortical circuitry assembled *in vivo* over several months reveals that neuronal arbors extensively refine via branch-specific retraction. Human synaptic networks grew by increasing dendritic spine survival, while keeping balanced rates of spine formation and elimination. Finally, we show that this system can be used to identify neural network activity and synaptic phenotypes in Down syndrome, a major cause of congenital intellectual disability triggered by a trisomy of chromosome 21. I will present recent unpublished data which build on these findings and address the molecular mechanisms underlying these phenotypes.

S01P3

Early postnatal developmental period for ASD-related social behavioral circuits

Goichi Miyoshi

Gunma University Graduate School of Medicine, Japan

While abnormalities in GABAergic inhibitory circuits have been implicated in the etiology of ASD (Autism spectrum disorders), when and how ASD-related social dysfunction emerges during development is poorly understood. Recently, we have selectively manipulated the expression of the syndromic ASD gene FOXG1 in rodent models to identify that the second postnatal week is the critical period to establish juvenile inhibitory circuits and to prevent ASD social phenotypes. We find that either increased or decreased FoxG1 levels result in social impairments but only when alterations take place in both excitatory and inhibitory populations, indicating a pre- and postsynaptic role for FoxG1 in GABAergic circuit development. While we found that a decrease in GABAergic tone exacerbates social impairments, supplementation of GABAergic interneuron precursors prior to the critical period ameliorates ASD-related circuit and behavioral phenotypes of the FOXG1 ASD model animals. Our results reveal the developmental timing and inhibitory circuit mechanisms that are promising for therapeutic intervention of ASD.

S01P4

Opposite effects of Wntless on the development of diencephalic habenula nuclei and choroid plexus in zebrafish larval brain

Yung-Shu Kuan
National Taiwan University, Taiwan

Wnt chaperon Wntless (wls) is a transmembrane protein found on ER, Golgi, and plasma membranes which mediates the intracellular transport of Wnt molecules in both vertebrate and invertebrate cells. Prior studies indicated that the expression of the proneural gene neurogenin1 (ngn1) is selectively reduced in cells immediately adjacent to the HA region of wls mutants. However, the regulatory relationship between Wls, ngn1 progenitor generation and HA neuronal specification is unclear. In addition, the impact of wls null mutation in the development of broader diencephalic region has never been carefully examined before.

Utilizing ngn1:GFP transgenic line, we found that there was no difference in GFP signals in the HA progenitor zone while ngn1 transcripts are reduced in wls mutant embroys at 48 hpf (hours post-fertilization), suggesting that the signal reduction of ngn1 antisense probe staining is not caused by loss of ngn1-positive cells. Utilizing IR-LEGO and Kaeda-mediated cell-lineage tracing, we were able to confirm that ngn1-positive cells located ventral to the HA at 48 hpf convert into the dorsal HA neurons at 72 hpf. Utilizing 3D gene expression volume analyses, we found that while ngn1 expressions are reduced as expected, her6 expressions are increased and expended into HA progenitor zone in the diencephalon of wls mutant embryos at 48 hpf. In addition, an expansion of gene expression in the ependymal cell layer of choroid plexus in the dorsal diencephalion was observed in wls mutants at 3 and 4dpf. Ectopic overexpressing her6 by endogenous ngn1 promoter resulted in a reduction of ngn1 expressions in HA progenitor zone, suggesting that Wls restricts her6 expression to promote the specification of ngn1 progenitors. Cell proliferation assays indicated that there are proliferation reductions in the mutants at 48, 72 and 84 hpf in the HA developing zone. However, no cell death has been detected in the mutants at 48, 50, 72, 78 and 84 hpf, suggesting that the reduction of HA neurons at 96 hpf is primarily caused by HA progenitor proliferation defects. All these results demonstrate that both

cell fate alterations and abnormal cell proliferation contribute to the HA neuronal generation defects and glia-lineage ependymal cells expansion in the choroid plexus in wls mutants.

S02
Mechanisms and Role of Dendritic Organelle and Membrane Trafficking in Synaptic Plasticity
Chair: Victor Anggono

Synopsis:

Activity-dependent and bidirectional changes in the weights of relevant synapses mediate the formation, reactivation, and update of memory of prior experiences. Long-term potentiation (LTP) of excitatory synapses is a form of synaptic plasticity thought to be a cellular correlate of learning and memory. It is widely accepted that the expression of LTP critically depends on the rapid increase in the numbers of AMPA-type glutamate receptors on the postsynaptic membrane, as well as the formation and maintenance of stable dendritic spines. Given the complexity of neuronal architecture and extensive arborization of dendritic branches, multiple mechanisms exist to ensure the efficient trafficking of organelles and integral membrane proteins to dendritic spines. This symposium will highlight the latest advances in synaptic neurobiology research (both technically and conceptually) that shed new insights into the molecular regulation of dendritic trafficking in mammalian central neurons. Dr. Lai (Hong Kong) will describe the unique role of kinesin KIF5B in the long-range trafficking of cargoes along the dendrite and its functional implication in dendritic morphology, synaptic plasticity, and memory formation. Dr. Anggono (Australia) will present work on the identification of copine-6, a postsynaptic calcium- and lipid-binding protein, as a novel calcium sensor that controls the exocytosis of AMPA receptors during synaptic potentiation. Dr. Nair (India) and Dr. Konietzny (Germany) will discuss the concept of liquid-liquid phase separation in regulating the nanodomain organization of transsynaptic nanocolumns (between presynaptic voltage-gated calcium channels and postsynaptic AMPA receptors) and the lattice organization of smooth endoplasmic reticulum (ER) into spine apparatus in the dendritic spine, respectively. Through this symposium, we hope to illustrate the power of applying combinatorial approaches (biochemistry and live-cell imaging) in revealing new insights into our understanding of the molecular and cellular mechanisms of synaptic plasticity in the mammalian central nervous system.

S02P1

The endoplasmic reticulum puts a new spin on synaptic tagging

Anja Konietzny

University Medical Center Hamburg-Eppendorf, Center for Molecular Neurobiology Hamburg, Germany

The heterogeneity of the endoplasmic reticulum (ER) makes it a versatile platform for a broad range of homeostatic processes ranging from calcium regulation to synthesis and trafficking of proteins and lipids. Stretching through the entire cell as a continuous, dynamic network of tubules and sheets, local specializations of the ER are a key factor in maintaining the high degree of compartmentalization observed in neurons. We address the various mechanisms how the dendritic ER fine-tunes synaptic properties and thereby provides specificity to synaptic inputs. In the focus are calcium-signalling pathways that regulate the activity-dependent recruitment of a single ER tubule into dendritic spines, as well as local formation of the spine apparatus (SA) organelle. The SA is formed by stacks of smooth ER-membrane intercalated with a dense F-actin matrix, and is continuous with the main ER network. To date, the protein synaptopodin is the only known essential component of the SA, and its presence has been suggested to function as a protective “tag” that marks stable, long-lived synapses. We have shown that the F-actin motor myosin V plays a role in determining the localization of both synaptopodin and the SA, and recent findings suggest that SA formation depends on the local translation of synaptopodin mRNA. Interestingly, bioinformatics analysis suggests a potential phase-separation of synaptopodin, and localization and expression studies point towards a clustered distribution which is typical for phase-separation proteins. We use a combination of structural methods, cell- free and cellular reconstitution assays and high-resolution fluorescence live imaging to investigate organelle dynamics and explore key triggers that govern the local formation of the SA at selected synapses, with a focus on the possibility of condensate-driven transformation of ER membranes into the SA organelle.

S02P2

Homeostatic scaling alters lattice organization of nanoscale condensates at excitatory synapses

Deepak Kumaran Nair

Indian Institute of Science at Bangalore, India

Miniature excitatory postsynaptic currents (mEPSCs) generated by events of spontaneous neurotransmitter release play important roles in basal synaptic transmission and maintenance of synapses. Several synaptic molecules are known to regulate spontaneous release events, however the exact mechanisms that modulate their activities remain unclear. Although spontaneous and evoked release differ in their spatial and functional properties, evidence supports that a common subset of molecules are involved in both events. This is consistent with paradigms that evoke homeostatic plasticity results in synaptic scaling induced by the absence of evoked release. We address how synaptic localization of the arrangement of voltage-gated calcium channels (VGCCs) in the presynaptic membrane and its association with glutamate receptor (AMPA receptor) nanodomain in the postsynapse may fine tune functional properties of synaptic transmission. To do this we evaluate the nanoscale lattice distribution of active zone marker Bassoon and VGCCs and postsynaptic density markers AMPA receptor subunit GluA2 and Shank2 to extract the molecular determinants that gives rise to differential effects of homeostatic scaling in young and mature neurons. Using single molecule and ensemble super resolution microscopy techniques, we examine thermodynamic signatures resulting from phase transition of nanodomain formation and evaluate how the lattice distribution of these nanoscale condensates are altered in homeostatic scaling. The molecular signatures of single-order phase transitions confirm that nanodomains are indeed a result of molecular condensation of VGCCS, and receptors. They occur independently or in association scaffolding molecules. Additionally, these results show distinct molecular fingerprints of synaptic scaling in young and older neurons. The foresaid results confirm that regulation of release events is a result of several coordinated spatial parameters resulting from nanoscale lattice arrangement of active zone and postsynaptic density. Furthermore, the presented data points towards differential nanoscale organization in

modulating the properties of mEPSC resulting from stochastic fusion of synaptic vesicles.

S02P3

The specific role of the motor protein KIF5B in dendritic transport, synaptic plasticity and memory

Kwok On Lai

City University of Hong Kong, Hong Kong

Kinesin and dynein are microtubule-dependent molecular motors that mediate long-distance transport of molecules and organelles in neuron. The kinesin superfamily is very diverse and contains 45 members in mammal. One key question that is not well-addressed is whether and how the different kinesin motors exhibit transport specificity that underlie distinct neuronal functions such as synapse development and plasticity. While there is only one kinesin I protein in the invertebrates, gene duplication and subsequent diversification give rise to three homologous kinesin I proteins (KIF5A, KIF5B and KIF5C) in the vertebrates. These homologs were initially regarded as functionally redundant because of their conserved cargo-binding domains. Here we show that conditional knockout mice which specifically lack KIF5B in excitatory neurons after birth display defects in dendritic spine morphogenesis and plasticity, which are coupled with impaired long-term potentiation and memory formation. Notably, using specific shRNAs to acutely knock down individual KIF5s, we found that KIF5B but not the closely related KIF5A has a specific function for excitatory synapse formation and dendritic transport of the RNA-binding protein FMRP. The functional specificity is conferred by their highly diverse short carboxyl-tails at the proximity of the cargo-binding domain. Furthermore, the carboxyl-tail of KIF5B might undergo post-translational modification that regulates cargo binding. We are currently investigating the potential role of KIF5B in mRNA trafficking to the sub-dendritic compartments of neurons.

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S02P4

Copine-6 is a calcium sensor that regulates AMPA receptor exocytosis during synaptic potentiation

Victor Anggono
The University of Queensland, Australia

The activity-dependent insertion of AMPA (α-amino-3-hydroxy-5-methyl-4- isoxazole propionic acid)-type glutamate receptors (AMPARs) into the postsynaptic membrane is essential for maintaining long-term potentiation (LTP), learning and memory. This process is triggered by the N-methyl-D- aspartate receptor (NMDAR)-dependent calcium (Ca2+) influx into the postsynaptic compartment. Synaptotagmin-1 and -7 have previously been shown to regulate the Ca2+-dependent exocytosis of AMPARs. However, they are mainly expressed in the presynaptic terminals and are functionally redundant. Here we show that Copine-6, a postsynaptic Ca2+-dependent membrane binding protein, forms a complex with the GluA1 subunit of AMPARs. Their interaction in the somatodendritic regions is enhanced by synaptic potentiation in a Ca2+-dependent manner. Knockdown of Copine-6 impairs activity-induced insertion of AMPARs in primary hippocampal neurons and the organotypic slice culture. These deficits can be restored by re-expressing wild-type Copine-6, but not the Copine-6 Ca2+-binding mutants. The loss of Copine-6 function does not affect the expression levels of synaptotagmin-1 and -7, steady-state levels of surface AMPARs or tetrodotoxin-induced synaptic up-scaling of AMPARs. Collectively, our results demonstrate the role of Copine-6 as a postsynaptic Ca2+-sensor in mediating the activity-dependent exocytosis of AMPA receptors during LTP.

S03
Epigenetic regulation of neurons and brain function
Chair: Chenchen Song

Synopsis:

Epigenetic modifications regulate gene expression in brain cells not only to control brain development but also to fine-tune adult state function in an experience-dependent manner. Alterations in epigenetic modifications have been associated with various neuropsychiatric traits. A comprehensive understanding of how epigenetic modifications regulate brain functions is therefore a crucial step towards understanding the brain and its disorders, and devising new diagnostic markers and therapeutic strategies.

In this symposium, we will discuss recent progress and findings on the key involvement of epigenetic mechanisms in neurological and neuropsychiatric conditions including Huntington's disease, schizophrenia and neurodegeneration, and how these mechanisms can be targeted as treatment strategies. We will also highlight the crucial roles of epigenetic regulations in corticogenesis and critical periods in neurodevelopment, which may influence brain functions and their alterations in later life. Further, we will also cover mechanisms of epigenetic inheritance, where impacts on brain functions from environmental effects and experiences are propagated across generations through epigenetic mechanisms.

S03P1

Epigenetic regulation of brain function within and between generations

Anthony Hannan

University of Melbourne, Australia

Huntington's disease (HD) is one of over 50 tandem-repeat disorders, involving psychiatric, cognitive and motor symptoms. In a mouse model of HD, expressing the CAG tandem-repeat expansion encoding a polyglutamine tract in the huntingtin protein, we have demonstrated that environmental enrichment (enhanced cognitive stimulation and physical activity) can delay onset of disease. These findings have been extended to include exercise and stress models in HD mice, and environmental manipulations in models of other disorders. Our molecular investigations have revealed key pathways implicated in HD pathogenesis, some of which involve epigenetic abnormalities. Similarly, these environmental modulators have various molecular impacts, some of which involve epigenetic modifications. These findings inform both pathogenic mechanisms and novel therapeutic targets. These approaches to gene-environment interactions may facilitate the development of 'enviromimetics' for a variety of disorders known to be modulated by environmental stimuli. We are also exploring the impact of therapeutic approaches, including subclasses of enviromimetics ('exercise mimetics' and 'epimimetics'), and the relevance of these discoveries to various brain disorders.

We have also been exploring epigenetic inheritance via the paternal lineage. We have discovered the transgenerational effects of various paternal environmental exposures. Our findings reveal significant experience-dependent effects on cognitive and affective function of offspring via intergenerational and transgenerational epigenetic inheritance. We are investigating the impact of specific environmental and pharmacological factors, including exercise, stress hormone elevation and diet, and the relevance of these discoveries in mice to human epigenetics and associated 'epigenopathy'. One of mechanisms whereby environmental exposures in fathers may epigenetically impact offspring is via non-coding RNAs in sperm. Furthermore, we are investigating the possibility that experience-dependent DNA methylation contributes to this epigenetic

inheritance. Our ongoing investigations are exploring mechanisms whereby experience can modify germ cells and associated sperm epigenetics, and how these epigenetic modifications (of mice and men) may modulate offspring phenotypes.

S03P2

Unraveling the roles of RNA modification for mRNA localization in the developing brain

Ki-Jun Yoon

Korea Advanced Institute of Science and Technology, Korea

Proper development of the nervous system is critical for its function, and deficits in neural development have been implicated in many brain disorders. Recent discoveries of widespread mRNA chemical modifications raise the question of whether this mechanism plays a post-transcriptional regulatory role in the development and function of the brain. Neurons are distinctly polarized cells where mRNA can be transported and localized in distal structures like axons and dendrites. However, how RNA modifications influence such RNA localization in developing neurons has not been understood well. N6- methyladenosine (m6A), installed by the Mettl3/Mettl14 methyltransferase complex, is the most prevalent internal mRNA modification that controls various aspects of mRNA metabolism. First, we showed that Mettl14 deletion in postmitotic neurons resulted in diminished m6A content and impaired axonal projection during corticogenesis. RNA-seq analysis and single molecule in situ hybridization experiments revealed subsets of mRNA targets were mislocalized in the neurites of postmitotic neurons with m6A loss-of-function. Further, we identified that YTHDF2 is the reader protein responsible for m6A-mediated mRNA transportation in the developing brain. Our study will enlighten the epitranscriptomic mechanism to regulate mRNA localization during mammalian neurodevelopment.

S03P3

From mice to men: Epigenetic regulation of neuroplasticity throughout lifespan and its implication

Judy Sng

National University of Singapore, Singapore

Environmental stimuli at one phase of development can shape cellular and neuronal function over our lifespan and impact our phenotypic outcome later in life. In this talk, I will take you through the link between critical period plasticity to epigenetic regulation in neurodevelopment using the mouse visual and barrel cortices, followed by perturbation of critical periods and DNA methylation to determine severity of psychosis in patients with schizophrenia and depression and lastly, losing the neuroplasticity via chromatin modifying enzymes such as HDACs in neurodegeneration using mouse models of dementia.

S03P4

Expanding the glioblastoma universe in epigenetic regulation

Derrick Ong
National University of Singapore

TBC

S04
Neural Circuits and Dynamics Underlying Sensorimotor and Cognitive Functions
Chair: Wing Ho Yung

Synopsis:

Recent advances in experimental and theoretical approaches have significantly enriched our understanding of neural dynamics at cellular and circuit levels that underlie various brain functions. This symposium will bring together experts in the field to showcase recent exciting advances in this endeavour. The focus will be on sensorimotor and cognitive functions. Prof. Bernd Kuhn (Okinawa Institute of Science & Technology) will share works on deciphering cerebellar Purkinje neuron activity during behaviours at dendritic and population levels. Prof. Ya Ke (Chinese University of Hong Kong) will present results of studies on cortical and subcortical circuits contributing to cognitive flexibility. Prof. Hiroshi Makino (Nanyang Technological University) will elaborate on recent efforts to understand representation learning in biological and artificial neural networks. Finally, Prof. Ying-Shing Chan (University of Hong Kong) will elucidate neuromodulator-directed developmental assembly of brainstem circuitry for navigational behaviour.

S04P1

Purkinje neuron activity during behavior

Bernd Kuhn

Okinawa Institute of Science & Technology Graduate University, Japan

The cerebellum receives sensory-motor input and integrates these inputs. The result of this integration contributes to coordination and timing precision of motor activity. Purkinje neurons with their fan-shaped dendritic tree and about 50000 spines (mouse) play a crucial role in this neuronal circuit as the sole output of cerebellar cortex. We use voltage and calcium imaging to study their activity during behavior in detail. I will show dendritic coincidence detection on a millisecond time scale in response to sensory input, dendritic voltage changes in Purkinje cells during eye blink conditioning, and population calcium activity of Purkinje neurons during a tongue grasping task.

S04P2

Neural circuits contributing to cognitive flexibility

Ya Ke

Chinese University of Hong Kong, Hong Kong, China

Cognitive flexibility refers to the ability to adjust one's thought and behavior in response to the changing environment, to increase the chance of survival and maximize rewards. It is regarded as a higher cognitive function that integrates different basic executive functions. The neural circuit basis of this cognitive function is not clearly known. Based on different cognitive flexibility paradigms in the mouse model, we have dissected a cortical-subcortical circuit that underlies the switch of strategy to get reward, and also neuronal activities of a prefrontal cortical area contributing to the simultaneous execution of multiple tasks. To address these questions, a variety of experimental approaches were employed, including track tracing, multi-photon imaging and optogenetics.

S04P3
Learning in intelligent systems

Hiroshi Makino
Nanyang Technological University, Singapore

Artificial intelligence (AI) and neuroscience could mutually be beneficial. While research in AI could offer new theories and hypotheses about how the brain solves computational challenges, neuroscience could provide new algorithms and network architectures to endow machines with human- or animal-like cognitive abilities. However, collaborations between the two fields have become less common and direct comparisons between the artificially and biologically intelligent systems have been rarely made. Here I will present our recent efforts to understand representation learning in the two intelligent systems. Training head-restrained mice and artificial deep reinforcement learning (RL) agents in the same tasks and extracting task representations in their respective neural networks, we discovered that the representation learning in the mouse cortex shared key features of modern deep RL algorithms. Systematic hyperparameter search by evaluating thousands of deep RL models revealed that behaviorally optimized artificial agent models better recapitulated neural representation patterns observed in the biological system. These results highlight striking similarities between the two systems in their representation and demonstrate utilities of such comparative approaches, which may define new research directions in the fields of AI and neuroscience.

S04P4

Postnatal refinement of glutamategic and GABAergic transmission in the developing vestibular nucleus tunes the brain circuitry for adult navigation

Ying-Shing Chan

University of Hong Kong, Hong Kong, China

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Vestibular input is indispensable for shaping spatial cognitive systems, but the requirements for maturation of circuits that process these inputs remains elusive. With the use of whole-cell patch clamp recording and Fos expression, we demonstrated that timely unsilencing of glutatmatergic circuits in the neonatal vestibular nucleus (VN) is critical for the recruitment of neurons into the vestibulo-cerebellar and vestibulo-thalamic circuits in rats. Delayed unsilencing of NMDAR-only synapses in the neonatal VN impacted not only on the execution of righting reflexes in postnatal rats but also effective spatial navigation in adults. Since the excitatory drive needed for activation of NMDAR in the neonatal brain is known to be provided by early depolarizing GABAergic transmission, we found that antagonizing GABAergic transmission in the VN during the first postnatal week also led to deficits in navigational behavior in adulthood. These rodents also showed permanent miswiring of GABAergic interneurons that in control animals are used to provide feedforward tuning of VN output neurons along the ascending vestibular pathway. Altogether, our results demonstrated that maturation of the nascent vestibular circuitry within a precise timeframe is the key for successful integration of vestibular signals in higher brain centres for spatial navigation in the adult.

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S05
Drosophila systems for modelling brain development and neurological disease
Chair: Leonie Quinn

Synopsis:

Invertebrates, such as Drosophila, have emerged as excellent model systems for studying mechanisms of neurodevelopment and are providing insight into major diseases, including brain cancer (glioma), neurodegenerative, and psychiatric disorders.

This symposium will comprise leading molecular geneticist that use Drosophila genetic systems to understand brain development and model a range of complex neurological disorders.

These international experts will highlight knowledge gained using the Drosophila nervous system to elucidate the basis of pain, neurodegeneration, autism spectrum disorder, Alzheimer's, psychiatric diseases, drug addiction, behaviour disorders, microcephaly, and brain cancer.

S05P1

SETDB2 regulates sensory neuron survival and pain perception from flies to humans

Greg Neely
SydneyUniversity, Australia

Chronic pain affects hundreds of millions of people world-wide and current therapies do not adequately address pain for most patients. To identify core regulators of pain perception we combine functional screening in fruit flies with human exome sequencing of extreme pain patients. From this, we identified 99 conserved genes that control sensory neuron development or function, including the new conserved pain gene SETDB2. SETDB2, as a core regulator of pain perception and a new cause of congenital insensitivity to pain (CIP). We generated SETDB2 KO mice and found they also exhibit defective acute pain perception, primarily mechanical nociception. We next generated humanized SETDB2 CIP mutant mice, and these animals also recapitulate the human CIP patients. While SETDB2 is predicted to be a histone methyltransferase, we could not observe this activity. To identify the molecular cause of CIP in SETDB2 CIP mutant mice, we performed single cell sequencing, and identified ROS and translational stress signatures specifically in mechanical sensory neurons. Moreover, both isolated primary sensory neurons and SETDB2 CIP patient iPSC-derived sensory neurons exhibit outgrowth phenotypes, and this could be rescued by the antioxidant AD4. Mechanistically, we found SETDB2 forms a complex with P53 and DAXX, and disruption of this complex may contribute to the observed pain phenotype. Overall, our conserved functional genomics approach highlights SETDB2 as a critical new pain gene, and treatment with antioxidants like AD4 may help SETDB2 CIP patients or other individuals at risk of peripheral neuropathy.

S05P2

Odor-memory retrieval in Drosophila requires a state of arousal

Adam Claridge-Chang

Duke-NUS Medical School, Singapore

A major goal of neuroscience is to decipher the mechanisms of learning and memory. Our understanding of the importance of arousal in these processes remains incomplete. We investigated how olfactory memory retrieval in Drosophila is affected by the arousal state. We found that learned odor avoidance is dependent on mechanical agitation. Without mechanical agitation, flies store the aversive memory, but do not express this aversion during testing. In the presence of agitation, inhibition of several mechanosensor classes abolished recall. Conversely in the absence of agitation, by activating peripheral mechanosensors, performance was restored to total recall. These results establish that arousal-dependent retrieval requires, and is induced by, activation of mechanosensors. A screen of CNS mechanosensory drivers identified a specific cluster of interneurons that were required and instructive for memory retrieval. In the brain, a mushroom-body dopamine cluster is required for, but cannot instruct, agitation-dependent memory retrieval. These studies highlight the relevance of arousal to memory, and new roles for dopamine, peripheral and central mechanosensors in the expression of olfactory memory.

S05P3

Par3 condensates in regulating asymmetric division of neural stem cells

Wenyu Wen

Fudan University, China

As an evolutionarily conserved mechanism to generate cell diversity, asymmetric cell division (ACD) relies on the unequal segregation of cellular components in daughter cells. During ACD of Drosophila neuroblasts and mouse radial glia cells, the conserved polarity protein Par3 and its related proteins are asymmetrically localized on the apical cortex, and then unequally segregated into the apical daughters with stem cell fate. We have discovered that via oligomerization, Par3 undergoes liquid-liquid phase separation (LLPS) in vitro and in vivo. Binding to other regulatory proteins could induce conformational change of Par3 to initiate its LLPS, or enhance Par3 phase separation via increased multivalence. Perturbation of LLPS of Par3 impairs its polarized localization and results in defects of neuronal differentiation. We propose that LLPS provides a unique local environment to bridge the polarity protein and the signaling pathway to control proliferation and differentiation of neural stem cells/progenitors, and LLPS may be a common and conserved mechanism in regulating ACD.

S05P4

Solving mysteries of the neural stem cell niche to understand brain cancer

Leonie Quinn

Australian National University, Australia

To determine the significance of brain cancer (glioma) mutations, identified by large-scale next generation sequencing (NGS) and genome wide association studies (GWAS), we require functional genetic model systems. Moreover, we must understand how mutations drive glioma stem cell expansion in context with the co-evolving microenvironment, largely comprised of glia. The Drosophila brain provides an excellent model; with the cortex glia microenvironment, or niche, providing neural stem cells (NSCs) with the structural support and secreted signals required for stemness and differentiation. Indeed, our exciting data demonstrate orthologs of major glioma drivers, transcriptional regulators (FUBP1/Psi and CIC/Cic), function in cortex glia to cell non-autonomously promote NSC differentiation i.e. their loss-of-function in the niche drives NSC overproliferation. To determine the molecular basis of our observation, direct transcriptional targets specifically in the cortex glia were identified via genome-wide binding studies (Targeted DamID). We further identified differentially expressed (DE) targets of FUBP1/Psi or CIC/Cic KD in cortex glia (RNA-seq of FACS-isolated glia). Significantly, common direct DE targets of FUBP1/Psi and CIC/Cic included signalling factors (e.g. FGF, EGF, and Notch), providing a rationale for loss-of-function in the glial niche driving NSC overproliferation cell non- autonomously. Thus, we provide the first evidence that mutations identified by NGS have potential to drive glioma stem cell tumours as a result of defective glial-stem cell interactions.

S06
Brain Organoids
Chair: Alfred Sun

Synopsis:

Brain organoids, 3D aggregates of spatially organized neural cells, are emerging powerful tools to understand how the brain develop, mature and potentially degenerate. This symposium focuses on this promising new technology, comprising of talks covering various aspects – from technology development to applications, to translation via bioengineering. Latest advances in this field will be presented and discussed.

S06P1

Generating vascularized human brain orga¬noids to study development and disease

Qian Wu
Nanjing Medical University, China.

S06P2

Transcriptomic profiling of cerebral organoids reveals dysregulated genes in a subpopulation of PSEN1-mutant astrocytes in regulating mitochondria and lysosomal processes

Li Zeng (Presented by Qiu Lifeng)
NNI, Singapore

Alzheimer's disease (AD) is the primary form of dementia with at least 50 million people suffering from it. Our understanding of AD pathophysiology is still rudimentary, due to the complexity of the brain and disease and limitations with animal models. Cerebral organoids (COs) are self-organizing and offer an unprecedented model with better structural and functional complexity resembling the human brain. Our work aims to model Presenilin1 (PS1)-L271V AD pathogenesis and study the effects of astrocytes on Aβ clearance using patient iPSCs-derived COs. COs were differentiated from patient-derived iPSCs that harbour PS1-L271V mutation and their isogenic controls were corrected via CRISPR/Cas9. Subsequently, we conducted single-cell RNA sequencing (snRNAseq) on young mutant and corrected COs and observed transcriptomic differences in a population of astrocytes. We observed typical neurodevelopment patterning and spontaneous differentiation of astrocytes in COs with accumulation AD disease hallmarks such as Aβ aggregates and p-Tau in PS1-L271V COs which recapitulates AD progression. scRNAseq revealed genes that were significantly upregulated in a population of astrocytes present in PS1-L271V COs. These genes are implicated in lysosomes, mitochondria and zinc transport processes respectively and have also been reported to be implicated in other diseases such as Parkinson's Disease.

S06P3

Morphing bioelectronics for developing organoids and animals

Yuxin Liu

NUS, Singapore

Neural interface establishes bidirectional communication between the nervous system and bioelectronics and provides unprecedented opportunities for neuroscience research and treatments of medical conditions such as Parkinson's disease and autoimmune diseases. Despite the advancement of neurotechnology, the electrical and mechanical mismatch between the soft neural tissue and existing rigid electronics causes adverse immune response, data inaccuracy, tissue constraint, and motion artifacts. This talk will feature our recent works on soft neurochemical and electrophysiological interfaces that can accommodate biomechanical motion in dynamically moving tissues and morphing electronic that is shape-shifting and self-adapting to cellular growth in growing organoid in vitro and during the adolescent developmental in vivo.

S06P4

Using human midbrain organoids to understand floor plate DA neuron development and degeneration

Alfred Sun
Duke-NUS, Singapore

How human floor plate progenitors form and give rise to midbrain DA neurons that eventually degenerate and cause Parkinson's disease remain poorly understood. We attempt to address this gap in knowledge by our newly developed 3D human midbrain organoid model. In this talk, I will present our work characterising these organoids and demonstrate that they can reveal pathogenic development in PD patients.

S07
Primary cilia in cell signalling and neuronal function
Chair: Xuecai Ge

Synopsis:

The primary cilium is a miniature cell surface organelle that occurs in almost all cells in human body, including neurons and neural progenitors. Accumulating evidence show that cilia are vital in transducing various cell signaling during a broad range of biological processes. Ciliary dysfunctions are associated with many serious human diseases. Recent groundbreaking discoveries in cilium biology have revolutionized our understanding of the pivotal roles of cilia in cell signaling, neuronal function and neurodegenerative diseases. This symposium will highlight the latest advances in cilium biology in the nervous system from a diverse group of researchers.

S07P1

An axon-cilium synapse

Sheu Shu-Hsien

Janelia Research Campus, USA

Chemical synapses between axons and dendrites mediate neuronal intercellular communication. Here, we describe a synapse between axons and primary cilia: the axo-ciliary synapse. Using enhanced focused ion beam-scanning electron microscopy on samples with optimally preserved ultrastructure, we discovered synapses between brainstem serotonergic axons and the primary cilia of hippocampal CA1 pyramidal neurons. Functionally, these cilia are enriched in a ciliary-restricted serotonin receptor, the 5-hydroxytryptamine receptor 6 (5-HTR6). Using a cilia-targeted serotonin sensor, we show that opto- and chemogenetic stimulation of serotonergic axons releases serotonin onto cilia. Ciliary 5-HTR6 stimulation activates a non-canonical Gαq/11-RhoA pathway, which modulates nuclear actin and increases histone acetylation and chromatin accessibility. Ablation of this pathway reduces chromatin accessibility in CA1 pyramidal neurons. As a signaling apparatus with proximity to the nucleus, axo-ciliary synapses short circuit neurotransmission to alter the postsynaptic neuron's epigenetic state.

S07P2

Primary cilia and Hedgehog signaling in Parkinson's disease

Suzanne Pfeffer

Stanford University, USA

Pathogenic, activating mutations in the LRRK2 kinase cause Parkinson's disease. Parkinson's disease causes death of dopaminergic neurons that rely on Hedgehog signaling for their viability. Dopaminergic neurons of the substanita nigra send Hedgehog signals to cholinergic interneurons of the dorsal striatum that send back neuroprotecitve GDNF to support dopaminergic neuron viability. We discovered that LRRK2 phosphorylaiton of Rab10 blocks cilia formaiton in the same striatal cholinergic neurons that need their cilia to sense this Hedgehog signal. In addition, astrocytes in the dorsal striatum also lose cilia. We are using single nucleus transcriptomics, proteomics, and single cell in situ hybridization to learn more about why specific cell types lose cilia in Parkinson's disease, and how that impacts Hedgehog signaling in the brains of mice and humans.

S07P3

Identifying new ciliary signaling pathways that control neuronal connectivity and viability in the mammalian brain

Sarah Goetz
Duke University, USA

Primary cilia play a vital role in the developmental patterning of the vertebrate nervous system. Recent findings have also revealed requirements for cilia in regulating the connectivity of neurons, as well as neuronal viability. Our lab previously showed that the ciliary genes Ttbk2 and Ift88 are required in the adult mouse brain to maintain excitatory synapses to cerebellar Purkinje neurons (PNs) and ultimately for PN viability. However, despite the mounting evidence for their major contributions to neural function, the ciliary signals important for maintaining neural connectivity and viability are unknown.

To address this gap in knowledge, we have undertaken an unbiased approach to identify signaling molecules that reside in neuronal cilia. Proximity-dependent biotin identification (BioID) has been used extensively to identify new components of the cilium and centrosome, but this approach has not been applied to cilia in vivo.

In this study, we targeted the proximity labeling enzyme BioID2 to the cilia of neurons by fusion to SSTR3. Following viral transduction throughout the mouse brain and injection with exogenous biotin beginning at postnatal day 30, we achieved specific biotin labeling of neuronal primary cilia. Through affinity purification and quantitative mass spectrometry, we identified several known ciliary membrane proteins, as well as many proteins not previously linked with primary cilia. These include synaptic components and proteins important for axon guidance, among others. In the latter category, we identified several proteins participating in Eph/Ephrin signaling. Our ongoing work is focused on characterizing the trafficking of these membrane proteins within cilia in response to pathway activation, as well as determining how perturbations of ciliary trafficking impact the response of neurons to these signals. Through these studies we will generate insights into the mechanisms by which cilia regulate the

establishment and maintenance of neuronal morphology, and thereby how ciliary dysfunction leads to neurological disorders.

S07P4

New tricks for old proteins: Numb regulates Hedgehog signalling in the primary cilium

Xuecai Ge
University of California, USA

The transduction of Hedgehog (Hh) signaling relies on the primary cilium, a cell surface organelle acting as a signaling hub for the cell. Using proximity labeling and quantitative proteomics, we identified Numb as a new ciliary protein that positively regulates Hh signaling. Numb localizes to the ciliary pocket and acts as an endocytic adaptor to incorporate Ptch1 into clathrin-coated vesicles, thereby promoting Ptch1 exit from the cilium, a key step in Hh signaling activation. Numb loss impaired Sonic Hedgehog-induced Ptch1 departure from the cilium, resulting in severe attenuation of Hh signaling. Genetic ablation of Numb and its homolog Numblike in the developing cerebellum impaired the proliferation of granule cell precursors, a Hh- dependent process, resulting in reduced cerebellar size. This study demonstrates a key function of Numb in controlling protein levels in the cilium, and highlights Numb's critical role in the regulation of Hh signaling.

S08
Control of Neuroinflammation and Myelin Health by Lipid Signalling Molecules
Chair: Anthony Don

Synopsis:

The brain is one of the most lipid-rich organs in the body, attributed largely to the abundance of myelin. Signalling lipids such as lysolipids, eicosanoids, cholesterol metabolites, and endocannabinoids are critically-important regulators of brain physiology and often mediate their effects through druggable G-protein coupled receptors. This symposium will focus on recent advances in our understanding of the regulation of neuroinflammation, oligodendrocyte health, and myelin synthesis by essential fatty acids and the signalling lipid sphingosine 1-phosphate (S1P). The symposium will cover new advances elucidating the nature and molecular function of transporters that regulate levels of these essential lipid mediators in the brain, and the biochemical mechanisms through which these lysolipids control neuroinflammation, oligodendrocyte survival, and remyelination. The importance of tight regulation of these essential lipid mediators for brain growth and development, and for multiple sclerosis will be discussed. Given the recent approval of a series of pharmacological S1P receptor agonists as first- line therapeutics for both relapsing and progressive multiple sclerosis, it is particularly important to understand the neuroprotective and immunomodulatory roles of the endogenous ligand for these receptors, as this will better inform the use of these drugs in the clinic. Similarly, new advances in our understanding of the mechanisms regulating essential fatty acid transport into the brain will improve management of microcephaly, demyelinating disorders, and other neurological conditions.

S08P1

Critical roles of lysophospholipid transport in brain development

David Silver

Duke-NUS Medical School, Singapore

The brain is a lipid rich organ that has a large demand for phospholipids and essential fatty acids during development and in adult life. Our lab discovered that the Major Facilitator Superfamily Domain containing 2A (Mfsd2A), part of the MFS family of transporters, is highly expressed within endothelial cells of the BBB where it facilitates Na+-dependent uptake of DHA and other mono-and polyunsaturated fatty acids in the chemical form of lysophosphatidylcholine. Our recent CryoEM structural studies of Mfsd2a identified critical sites for LPC interactions within the transporter cleft that suggested Mfsd2a functions as a phospholipid flippase, although direct biochemical evidence is lacking. Importantly, patients with loss-of-function mutations in MFSD2A present with severe microcephaly and hypomyelinated brains, a disease designated as Microcephaly 15, Autosomal Recessive, underscoring the essentiality of the Mfsd2a/LPC transport pathway in human brain development. In this seminar, I will present our recent biochemical data demonstrating that Mfsd2a indeed functions by a flippase-type mechanism. Moreover, I will present our in vivo studies using mouse models that provide mechanistic insights into the causes of microcephaly and hypomyelination due to loss-of-function of Mfsd2a.

S08P2

Inhibiting S1P lyase to combat inflammatory demyelination

Junhua Xiao

Youtian Hu, Tonghui Zhang, Willemijn M. Passtoors, XiaoYa Li, Jacqueline Orian, Nelson George, Fang Wu, Junhua Xiao*

Swinburne University of Technology, Australia

The ongoing inflammatory demyelination ultimately leads to irreversible neurodegeneration in Multiple sclerosis (MS), determining the progressive clinical disabilities. Sphingosine 1-Phosphate lyase (S1P lyase or SPL) is the terminal enzyme that controls the final exist of sphingolipid metabolites. SPL not only regulates inflammation and nerve cell survival but also the lipids required for myelin formation, making it an attractive target for treating neurodegenerative diseases such as MS. This interest is reflected in the current drug development by pharmaceutical companies. To date, however, only a limited number of SPL inhibitors have been identified and almost all of them are indirect inhibitors of SPL with poor selectivity and efficacy, resulting in none of them being moved to Phase I clinical trial. We have recently adopted a high throughput drug screen approach using the US FDA approved drug compound libraries. The talk will present our recent discoveries on new and direct inhibitors of SPL with high therapeutic potentials. This talk will also present our recent data indicating that selectively inhibiting SPL could be a new strategy to combat inflammatory demyelination in the context of MS. Outcomes of this study will represent a critical step towards determining if selectively inhibiting SPL activity is a new and preferred therapeutic strategy to stall the progress of MS, prompting pre-clinical and clinical evaluation.

S08P3

Harnessing Sphingosine-1-phosphate transporters for treatment of neuroinflammation

Nam Long Nguyen

National University of Singapore, Singapore

Sphingosine-1-phosphate (S1P) is a potent signaling molecule that plays critical roles in the vasculature and immune system. Targeting S1P receptors in the immune system has been successfully employed for the treatment of neuroinflammation such as multiple sclerosis. Mfsd2b and Spns2 were recently cloned out as the two S1P transporters which provide S1P for signaling. In this talk, I will discuss about the roles of these S1P transporters in the vasculature and highlight their roles in the immune system. Our results show that the sources of S1P from Mfsd2b and Spns2 are both required for protection from vascular damages. However, Mfsd2b is the major S1P transporter for maintenance of the vasculature, whereas Spns2 provides S1P for immune trafficking. To obtain evidence for Spns2 as a potential drug target, we characterized the mice with postnatal knockout of Spns2 (Spns2-Mx1Cre). Our results show that Spns2-Mx1Cre mice have significantly low number of lymphocytes in blood and lymphoid organs similar to Spns2-/- mice. Lymph but not plasma S1P levels are significantly reduced in both groups of knockout mice. Our lipidomic results also show that Spns2 releases different S1P species into lymph to guide lymphocyte egress. Importantly, we show that Spns2- Mx1Cre mice are resistant to multiple sclerosis in experimental autoimmune encephalomyelitis (EAE) models with significant reduction of pathogenic Th17 cells in the central nervous system (CNS). The blood vasculature of these Spns2 deficient mice is indifferent from controls under homeostasis and vascular insults. Our findings suggest that pharmacological inhibition of Spns2 may be exploited for therapeutic applications in treatment of neuroinflammation without potential damages to the vasculature that have been seen with S1P receptors' modulators.

S08P4

Endogenous sphingosine 1-phosphate is essential for oligodendrocyte survival and remyelination

Anthony Don

The University of Sydney, Australia

Therapeutics that promote oligodendrocyte survival and remyelination are needed to restore neurological function in demyelinating diseases. Sphingosine 1-phosphate (S1P) is an essential lipid metabolite that signals through a family of five G-protein coupled receptors. S1P receptor agonists Fingolimod, Siponimod, Ozanimod, Ponesimod, and others are clinical immunosuppressants used to treat multiple sclerosis. Clinical evidence suggests that these drugs may also have direct neuroprotection actions in the CNS, however experimental evidence to support this hypothesis is lacking. This talk will detail our recent research demonstrating that endogenous S1P, synthesised by the enzyme sphingosine kinase 2 (SphK2) is an essential mediator of oligodendrocyte survival and remyelination after treatment with the demyelinating agent cuprizone, or in response to amyloid beta. We demonstrate that functional SphK2 is necessary to maintain myelin integrity with normal ageing, and will present new data on the molecular mechanisms underpinning the requirement for SphK2 in oligodendrocyte differentiation to myelinating cells. The talk will also demonstrate how activation of S1P receptors on astrocytes promotes a neurotrophic signalling response that favours neuronal survival and remyelination. This work establishing the requirement for endogenous S1P in protection and maintenance of oligodendrocyte functions is fundamental to understanding the potential neuroprotective properties of clinical S1P receptor agonists, and will therefore guide clinical decision making.

S09
Pathogenic mechanisms, novel therapeutic targets and drug development in ALS
Chair: Shuo-Chien Ling

Synopsis:

Amyotrophic lateral sclerosis (ALS), the most common adult-onset motor neuron disease, is universally fatal with expected survival rate less than 5 years after diagnosis. Currently, ALS has no disease-modifying therapies with 3 FDA-approved drugs that extend survival for a few months. ALS is heterogenous and caused by an array of complex genetic, metabolic and environmental factors. Nevertheless, TDP-43 aggregates in neuron and glia represents the pathological hallmark for most ALS patients, indicating a converging end point of pathogenesis.

In this symposium, we will start with how misfolded oligomeric TDP-43 may cause motor neuron degeneration, and the therapeutic potential by TDP-43 oligomer- based immunotherapy (Yun-Ru Chen, Academia Sinica, Taiwan). This will be followed by discussing how deficits in mitochondrial respiration is a hallmark for human ALS motor neurons, and conversely, targeting the underlying molecular machinery, including NAD+, could reverse the metabolic deficit and extend the survival of ALS motor neurons (Shi Yan Ng, IMCB, Singapore). Extending the metabolic angle in ALS, Prof Yijuang Chern (Academia Sinica, Taiwan) will discuss using patient-derived material to identify an adipokine, known as adiponectin, as a potential biomarker in ALS. Furthermore, adiponectin triggers TDP-43 mislocalizaiton that mimics TDP-43 proteinopathies observed in ALS patients likely via AMPK, a key kinase in regulating cellular energy homeostasis. We will end by exploring the potential non-cell-autonomous mechanisms, i.e., how glial TDP-43 dysfunction contribute to motor neuron toxicity, is caused by disruption of TDP-43 functions in distinct glia, including astrocytes, oligodendrocytes and Schwann cells (Shuo-Chien Ling, NUS, Singapore).

This symposium is unique and comprehensive. The speakers use a wide range of methods, including protein chemistry, immunotherapy, iPSC technology, and mouse genetics, as well as patient-derived materials and various model systems to address the underlying pathogenic mechanisms and conversely, probe the translational

potential of the discoveries, including biomarker discovery and therapeutic interventions.

S09P1

Pathogenic mechanism and therapeutic potential for misfolded TDP-43 oligomers in ALS

Yun-Ru Chen
Academia Sinica, Taiwan

TDP-43 proteinopathies were found in several neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and Alzheimer's disease (AD). In ALS, over 95% patients have TDP-43 cytoplasmic aggregation in the disease lesions, where hyperphosphorylated TDP-43 were found. The pathogenic role of TDP-43 hyperphosphorylation and aggregation are still not fully revealed. In this talk, I will present the conformational changes and toxicity of human full-length TDP-43 and the hyperphosphorylated mimetics. We employed a hyperphosphorylated mimetics with five serine residues at the C-terminus, i.e. serine 379, 403, 404, 409, and 410, to aspartate (S5D) and alanine (S5A). The conformational changes, liquid-liquid phase separation, oligomerization, and fibrillization of TDP-43 variants were characterized. The results showed the recombinant TDP-43 variants readily formed structurally similar spherical oligomers, but only the hyperphosphor-mimic TDP-43 formed amyloid fibrils after incubation. The oligomers of TDP-43 variants were neurotoxic but not the aggregated ones. Meanwhile, we generated 11 monoclonal TDP-43 oligomer-specific (TDP-O) antibodies and systematically characterized their specificity and sensitivity. TDP-43 oligomers were detected in the upper and lower motor neurons of ALS patients. We found that ALS patients have elevated TDP-43 oligomer ratio in plasma. Weekly intravenous delivery of a TDP-O antibody significantly ameliorated motor impairment, increased motor neuron survival, and reduced TDP-43 level in two ALS mouse models. Overall, these studies provide molecular mechanism for toxic and misfolded TDP-43 oligomers and facilitate the therapeutic development in ALS.

S09P2

Targeting mitochondrial respiration reverses disease phenotypes in motor neurons derived from ALS iPSCs

Shi-Yan Ng
IMCB, Singapore

Mitochondria act as powerhouses within the cells, providing energy in the form of ATP via oxidative phosphorylation. Motor neurons (MNs), in particular, are highly metabolically active cell types and rely heavily on oxidative phosphorylation to fuel their metabolic needs. In our recent publication, we found that ALS MNs are characterized by reduced mitochondrial respiration with a concomitant increase in glycolysis. This metabolic hallmark is common to both sporadic and familial forms of ALS, suggesting that this is a convergent pathological pathway. Insights into the mechanisms of mitochondrial dysfunction revealed that mitochondrial proteins were hyperphosphorylated in ALS MNs. Phosphorylation of mitochondrial proteins is governed by the activity of the NAD+-dependent deacetylase Sirtuin-3 (SIRT3) as well as GCN5L1, a small mitochondrial-enriched protein that promotes mitochondrial protein acetylation. We have demonstrated that NAD+ and other SIRT3 activators improve ALS phenotypes in iPSC-derived MNs. As GCN5L1 catalyzes the enzymatic reaction opposite to SIRT3, we investigate the therapeutic potential of GCN5L1 depletion in ALS MNs. Overall, our results suggest that correcting mitochondrial defects in ALS restore MN function and survival and may slow disease progression.

S09P3

Adipokine is associated with worse prognosis and abnormal motor neurons in amyotrophic lateral sclerosis

Yijuang Chern
Academia Sinica, Taiwan

Hypermetabolism is a common feature of ALS patients. Consistent with abnormal energy homeostasis and hypermetabolism, decreased body weight is observed in ALS patients. The body weight loss is associated with a reduction of body mass index (BMI) in ALS patients. Adiponectin is an adipokine that regulates several metabolic processes and is negatively associated with BMI. More importantly, adiponectin is also an upstream regulator of AMPK, which is known to cause mislocalization of TDP-43 in motor neurons (an early event of ALS). In this study, we found that the plasma adiponectin level of ALS patients (ALSFRS- R score < 38) was higher than that of control subjects, and was inversely correlated with ALSFRS-R. We next tested the hypothesis that adiponectin may activate the AMPK-TDP43 axis by treating a motor neuron-like cell line (NSC34) and human iPSC-derived motor neurons with adiponectin, and demonstrated that adiponectin induced the cytosolic mislocalization of TDP43 in both experimental models. Besides neurons, we also assessed the activation status of AMPK and TDP43 mislocalization in human peripheral blood mononuclear cells (PBMCs) harvested from ALS patients and control subjects. Immuno- fluorescence staining revealed that AMPK activation is associated with lower ALSFRS-R of ALS patients. Similarly, the mislocalization of TDP-43 in PBMCs of ALS patients was also observed and was negatively associated with ALSFRS-R. Given that adiponectin can be transported to the spinal cord to activate AMPK in motor neurons, these findings collectively suggest a potentially important role of the Adiponectin-AMPK-TDP43 axis in ALS pathogenesis. Furthermore, the plasma level of adiponectin might serve as a progressive biomarker for ALS.

S09P4

Decipher the physiological functions of TDP-43 in distinct glia

Shuo-Chien Ling

National University of Singapore, Singapore

Common genetic loci and pathological signatures have unified two seemingly different adult-onset neurodegenerative diseases, amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), which affect predominantly the motor system and cognition, respectively. In particular, mutations in TDP-43 are causal for both diseases coupled with the pathological TDP-43 inclusions present in the neurons and glia indicate that TDP-43 dysfunctions in these cells trigger ALS and FTD pathogenesis. Furthermore, TDP-43 aggregates, collectively known as TDP-43 proteinopathies, are common in aging human brains and in other neurodegenerative diseases, such as Alzheimer's disease (AD), underscoring the critical role of TDP-43 in brain health and diseases.

TDP-43 is ubiquitously expressed. Curiously, pathological TDP-43 also can be found in neurons, glia and other peripheral systems. Two key questions: the physiological functions of TDP-43 in different cell types, and whether the loss of TDP-43 in distinct glia contribute to ALS/FTD pathogenesis, remain unresolved. To this end, we systematically analyzed mice with TDP-43 deleted in distinct glia, including oligodendrocytes, Schwann cells and astrocytes. We uncovered that (1) TDP-43 is indispensable for oligodendrocyte survival and myelination by regulating cholesterol metabolism, (2) TDP-43 is required for maximize conduction velocity by maintaining paranodal assembly in Schwann cells, and (3) TDP-43 maintains the protective status of astrocytes. Loss of TDP-43 function in each of the distinct glia results in motor deficits without apparent damage to motor neurons. These results highlight that TDP-43 participate in different physiological role in distinct glia, and TDP-43 dysfunction in different glia may be an integral part of ALS pathogenesis.

S10

From Synapses to Behaviour: How early life experiences shape plasticity, memory and behaviour in adolescence and adulthood

Chair: Sreedharan Sajikumar

Yasunori Hayashi

Synopsis:

Synaptic plasticity mechanisms are fundamental to the memory formation resulting in various behaviours. Balance in synaptic and cellular mechanisms in relation to epigenetic factors such as lifestyle is critical for the regulation of homeostatic fine tuning of plasticity and behaviour. The symposium aims to cover the latest development in the field covering cellular, molecular and behavioural changes occurring due to epigenetic factors that leads to changes in plasticity and behaviour. Prof. Yasunori Hayashi, a world leader in the cellular and molecular mechanisms of learning and memory from Japan will start the symposium by providing the physiological aspects of cellular and molecular factors essential for formation of structural and functional plasticity that leads to long-term plasticity and memory. In the second talk, Dr. Jee Hyun Kim, will present research proposing a hypothesis that early life stress exposure causes a ‘prolonged adolescence’ of stress-responsive structures leading to impairments in extinction of conditioned fear. In the third talk, Dr. Sajikumar, an expert in synaptic plasticity will cover how juvenile stress affects learning and memory formation in adult hood. The symposium will conclude with the talk from Dr. James Clement Chelliah, an expert in cellular and molecular neurophysiology from India, by providing insights from an autism mouse model.

S10P1

Online and offline LTP during memory consolidation

Yasunori Hayashi

Kyoto University Graduate School of Medicine, Japan

Memories are initially formed in the hippocampus but subsequently transferred to the rest of brain for a long-term storage in a process called "memory consolidation". The cellular mechanism responsible for it has not been fully elucidated. LTP of synaptic transmission is known as a cellular phenomenon of memory. We developed a technique to detect when and where LTP is occurring by employing SuperNova, a fluorescent protein. Upon illumination, SuperNova releases reactive oxygen, which inactivates the surrounding proteins. We fused SuperNova with cofilin, an actin binding protein which specifically accumulates at the synapse after LTP induction. Illumination of cofilin- SuperNova within 20 min, but not beyond, after the induction erased LTP in vitro. Illumination of the hippocampus immediately after learning as well as during sleep after the learning erased the memories, indicating that two waves of LTP occurred in the hippocampus. In contrast, in the anterior cingulate cortex, a cortical region implicated in the recall of old memories, LTP was induced during sleep the day after learning but not on the same day. This technology will elucidate brain functions involved in memory at the cellular level.

S10P2

Stressed prolonged adolescence hypothesis: early life stress sex- specifically delays maturation of conditioned fear extinction

Jee Hyun Kim
Deakin University, Australia

The popular theory “Stress acceleration hypothesis” asserts that early life stress such as maternal separation speeds up the developmental process in the brain to result in adult-like learning processes, including conditioned fear extinction, which may cause some premature vulnerability to express fear early in life. However, the molecular evidence supporting this has been scarce, with any evidence largely limited to the amygdala. In addition, sex-specific impact of chronic stress on the hypothalamic-pituitary-adrenal (HPA) axis response following fear conditioning in juvenile and adolescent rats is poorly understood. We have exciting new data on sex-specific extinction of conditioned fear, neurogenesis, and the hypothalamic-pituitary-adrenal (HPA) axis that challenge the dogma on how early life stress changes the speed of brain development. New data on HPA axis also suggest that females’ resistance against stress effects on conditioned fear extinction early in life. We propose a new “Stress prolonged adolescence hypothesis” that theorises early life stress accelerates amygdala development while delaying prefrontal cortex and hippocampal development to result in extinction-resistant fear expression. This new hypothesis brings together accumulating evidence in rodents and humans to provide an innovative framework to understand the role of early life stress in health and disease.

S10P3

Inhibitory metaplasticity in juvenile stressed rats restores associative memory in the adulthood by regulating epigenetic complex G9a/GLP

Sreedharan Sajikumar
National University of Singapore, Singapore

Exposure to juvenile stress was found to have long-term effects on plasticity and the quality of associative memory in adulthood, but the underlying mechanisms are still poorly understood. We demonstrate that even long after the elimination of actual stressors, an inhibitory metaplastic state is evident, which promotes synaptic competition over synaptic co-operation and a decline in the latency of associative memory in the behavioural paradigm despite the exposure to novelty. Mechanistically, juvenile stress led to a heightened expression of the epigenetic marker G9a/GLP complex which is thus far ascribed to transcriptional silencing and goal directed behaviour. The blockade of the G9a/GLP complex was found to alleviate deficits in long-term plasticity and associative memory during the adulthood of animals that were exposed to juvenile stress. Our data provides insights on the long-term effects of juvenile stress that involve epigenetic mechanisms, which directly impact long-term plasticity, synaptic tagging and capture and associative memory.

S10P4

Small molecules that restore GABAergic function as potential therapeutics to treat autism spectrum disorder

James Clement Chelliah

Jawaharlal Nehru Centre for Advanced Scientific Research, India

A cardinal feature of human brain development is that sensory, cognitive, and emotional experiences shape synapses and neural-circuit development. Neuronal activity triggers changes at the synapse, altering the composition, shape and strength of the synapse. These neuronal activity-dependent modifications are necessary for learning and memory and various behavioural responses, particularly during development. These features are altered in Intellectual Disability (ID) and Autism Spectrum Disorder (ASD), which affects ~1% of the world's population. Heterozygous mutations in SYNGAP1 are one of the primary causes of Intellectual Disability (ID) and Autism Spectrum Disorder (ASD). Thereby, aberrant maturation of dendritic spines leads to an anomalous Excitation-Inhibition (E/I) balance at the critical period of development. In part, such changes are linked with altered chloride co- transporters, NKCC1 and KCC2, in animal models of Fragile-X and Rett syndrome but unknown in Syngap1+/- during different developmental stages. We show that the expression, and function of chloride co-transporters NKCC1 and KCC2 in P14-15 heterozygous mice is altered. In addition, we discovered that administration of a novel GSK-3β inhibitor, 6BIO, during a critical period of development and in the young adolescent rescued E/I balance and the deficits of synaptic transmission and behavioral performance like social novelty, anxiety and spatial memory in Syngap1+/- mice. Here, we demonstrated that the GABAergic circuit was disrupted during development and modulating this circuit restored cognitive, emotional, and social symptoms that result from hard-wired neuronal circuit damage during development by late pharmacological intervention in adulthood.

S11
Endogenous regeneration and repair in the adult central nervous system
Chair: Juan Song

Synopsis:

Traumatic injury, stroke, or age-related degeneration of the adult mammalian brain is often associated with persistent functional deficits as the potential for regeneration and capacity to rebuild lost neural structures in adult central nervous system is limited. Regenerating the injured or degenerated brain to allow for functional recovery remains an unmet challenge. Cell transplantation is a strategy of choice to deliver new neuronal cells, but this approach is inefficient and cumbersome due to limited cell survival and poor integration into the functional neural networks following transplantation. Therefore, harnessing endogenous repair capacity of the adult brain is critically important. The main approaches using endogenous cellular sources to improve functional regeneration of the injured or degenerated brain are based on 1) mobilization of endogenous neural stem cells (NSCs) in the discrete neurogenic regions of adult brain to promote production of neurons for functional recovery, and 2) reprogramming of injury-induced glial cells that can be directly converted into neurogenic NSCs so that de novo-generated neurons will repopulate damaged brain regions. In this symposium, our talks will focus on these two novel strategies for endogenous regeneration and repair in the adult brain. Dr. Song and Dr. Cheng will focus on strategies that promote endogenous neuroregeneration from endogenous adult neural stem cells in the context of aging and Alzheimer's disease. Dr. Fu and Dr. Zhang will focus on strategies that reprogram injury-induced glial cells for neural circuit and functional recovery.

S11P1

Activation of hypothalamic-enhanced adult-born neurons is sufficient to restore cognitive and affective function in Alzheimer's disease

Juan Song
University of North Carolina, USA

Patients with Alzheimer’s disease (AD) exhibit progressive memory loss, depression, and anxiety, accompanied by impaired adult hippocampal neurogenesis (AHN). Whether modulating AHN is sufficient to improve these cognitive and noncognitive symptoms in AD remains elusive. Here we report that chronic stimulation of hypothalamic supramammillary nucleus (SuM) during early AD restores AHN. Strikingly, activation of a small number of SuM-enhanced adult-born neurons (ABNs) is sufficient to restore memory and emotion deficits in AD mice. To probe ABN-activity-dependent signaling mechanisms, we performed quantitative phosphoproteomics in the hippocampus and showed stimulating SuM-enhanced ABNs promotes activation of the canonical pathways related to neuronal activity, synaptic plasticity, and microglia phagocytosis. Functional assays further confirmed increased hippocampal activity, long-term potentiation, and microglia phagocytosis of amyloid plaques along with reduced neuroinflammation upon activation of SuM- enhanced ABNs. Our findings reveal a robust AHN-promoting strategy sufficient to restore behavioral deficits and highlight ABN-activity-dependent mechanisms underlying functional improvement in AD.

S11P2

Integration of adult-born neurons into mature neural circuits in aged hippocampus

Hwai-Jong Cheng
Academia Sinica, Taiwan

Adult hippocampal neurogenesis (AHN) is critical for learning and memory. Disruption of this process during aging is implicated in neuropsychiatric diseases that undermine cognition in the aged brain. Most of our knowledge about AHN relates to the survival and differentiation of newborn neurons in the young adult brain. Much less is known about how these neurons integrate into existing neural circuits in the aged hippocampus. Using a reporter mouse, we investigated the development and synaptic integration of newborn granule cells in the aged hippocampus. We found that the potential for newborn granule cells to form de novo synapses with existing mature CA3 pyramidal cells in aged brain is significantly reduced, and existing mature boutons are replaced when these newborn neurons form synapses. These results reveal previously unknown changes in newborn neurons and their progenitors in the aged brain. We are currently using several approaches to address why the newborn granular cells in the aged brain lose their ability to form de novo synapses during synaptic integration. The answers to these questions will help us understand the specific functional role of AHN in the aged brain.

S11P3

Development of Therapeutic Strategies against Parkinson's Disease

Yunlong Zhang

Westlake University, China

Yunlong Zhang, Xiang-Dong Fu.

Parkinson's disease (PD) is a common and progressive neurodegenerative disorder, characterized by dopamine neuron (DA) death and the existence of Lewy body formed by α-synuclein. Although L-DOPA is a gold standard medication for PD, however, its long-term treatment is limited by detrimental consequences, such as dyskinesia. Thus, development of therapeutic strategies against PD is urgent. Recently, several approaches have been developed, such as intervention of PD risk genes, and cell replacement, including stem cell therapy and cell reprograming. This talk will introduce two topics. One is about the therapeutic strategies for clearing α-synuclein based on the evidence from a natural product, 4,4'-Dimethoxychalcone, and its structural analog in treating the mouse model of synucleinopathies. The other is about the neuronal reprogramming, which involves the discoveries, controversies and insights about our previous findings about conversion of astrocytes to DA neuron by knockdown of Ptbp1. Taken together, this talk will provide insight into several issues regarding therapeutic interventions against PD.

S11P4

Inducing neurogenesis in the adult mouse spinal cord for repair

Chun-Li Zhang

UT Southwestern, USA

Neural injury or neurodegeneration frequently leads to irreversible loss of neurons; however, the adult mammalian central nervous system (CNS) has largely lost the ability to produce new neurons. A key question in the regeneration field is how to generate new neurons for functional reconstruction. Our lab has taken an in vivo reprogramming approach, which is to engineer the fate of resident glial cells to let them become neurogenic. In this talk, I will focus on the adult mouse spinal cord, a CNS region without any ongoing neurogenesis. Our results show that resident NG2 glia can be in vivo reprogrammed to produce new neurons. Importantly, these glia-generated new neurons can become mature, make synaptic connections, and contribute to functional recovery in a mouse model of spinal cord injury. Further development of this reprogramming approach may lead to a regeneration-based therapeutic strategy for many of the neurological diseases.

Workshop
Young Investigator Colloquium

W1P1

PAX6 controls cell fate choice in human cerebral organoids

John Mason

University of Edinburgh, United Kingdom

The transcription factor PAX6 is a high level regulator of brain and eye development in many species, including humans and mice. Mutations in PAX6 have been associated with Autism Spectrum Disorders, suggesting that PAX6 exerts control over developmental processes in the human embryo that are required for normal brain function. Mouse Pax6 has been studied for many years and we have a good understanding of many of its roles, however we know much less about the activities of human PAX6. To address this, we generated multiple clonal lines of human induced pluripotent stem cells (iPSCs) that harbour a null mutation in PAX6 and used these to grow cerebral organoids. Comparison to control lines shows that neural differentiation overall is slightly less efficient in the absence of PAX6, but nonetheless, well-formed organoids containing extensive neural tissue can be grown. Single cell RNAseq analysis reveals that PAX6 mutant organoids contain a large number of GABAergic inhibitory neurons, in contrast to controls, indicating that PAX6 plays an important role in determining numbers of excitatory and inhibitory cell types in the cerebral cortex, analogous to one of its key activities in mice.

W1P2

REST-JAK-STAT in the neurogenic-to-gliogenic shift in Down syndrome

Michael Ling

Universiti Putra Malaysia, Malaysia

Over the decade, our research group has identified various dysregulated pathways involved in various stages of neurodevelopment in the Down syndrome (DS) model. Interferon and its downstream pathway, such as the JAK-STAT signalling pathway, were identified as responsible for the neurogenic-to-gliogenic shift phenomenon in all DS models and human samples. Increased interferon and JAK-STAT signalling pathways have led to increased astrogenesis and subject the DS brain to a greater basal level of neuroinflammation, a potential basis for accelerated ageing and early onset Alzheimer's disease among DS individuals. Our group targeted the JAK-STAT signalling pathway in early neurodevelopment with the hope of reverting the neurogenic-to-gliogenic shift. This will allow neurogenesis to take place and potentially restore the neuron-to-glia cell ratio among DS individuals in the future. The proof-of-concept evidence on how suppressing JAK/STAT signalling using transient ruxolitinib (an FDA-approved drug for myelofibrosis) treatment may improve spatial learning, and long-term memory consolidation in rodents will be discussed. The study will also demonstrate the transplacental effects of ruxolitinib on astrogenesis. Hence, repurposing ruxolitinib treatment can potentially revert pathological conditions caused by gliogenic-shift in early brain development. Finally, we will also present our recent discovery of a new candidate known as REST, which serves as a regulator of interferon and JAK-STAT signalling, stress resilience and neuronal differentiation.

W1P3

Progress towards use of human bone marrow stromal cell-derived Schwann cells for treatment in PNS/CNS trauma

Daisy Shum

The University of Hong Kong, HKSAR, China

Daisy Kwok-Yan Shum and Kin-Wai Tam

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Donor nerve-derived Schwann cells transplanted to the injured nerve/tract in the PNS/CNS improves prospects of post-traumatic recovery in rat models. Clinical translation however requires sufficient immuno-compatible and fate-committed human Schwann cells (hSCs). To this end, the neuroprogenitor subpopulation among human bone marrow (hBM) stromal cells were enriched in culture which, with glia-inducing supplements, yielded Schwann cell-like cells (SCLCs). Co-culture with embryonic rat/hiPSC-derived sensory neurons provided contact-mediated signalling that committed the SCLCs to the SC fate. Such derived hSCs were cryopreserved and thawed on demand for tests in rat models of (1) sciatic nerve injury or (2) thoracic cord injury. By 12-week post-treatment, significant improvement in hindlimb motor function, evoked signals on the treated side, and axons myelinated by hBM-derived SCs were evident in (1). Similar results were not observed in (2), unless the treatment with hBM-derived SCs was paired with chondroitinase ABC to address the glial scar. However, hurdles remain in the use of rat BM stromal cell-derived oligodendrocyte precursor cells for re-myelination therapy in rat spinal cord injury model. Results prime translational research towards use of hBM-derived SCs as therapeutic agents in both PNS and CNS trauma.

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W1P4

Microsystem-based neural patterning in 2D and 3D culture system for the drug screening

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Development of nervous system from early neural induction to the later axonal outgrowth and circuit formation is controlled by multiple factors which include cell autonomous genetic or non-genetic factors, and non-cell autonomous environmental factors. Comparing to the great advancement of methodologies to control genetic and humoral factors, controlling the environmental factors are yet limited. In this talk, I will briefly summary the use of microsystems to control the physical/mechanical factors affecting the nervous system development in neural cell culture. For instance, human pluripotent stem cells (hPSCs) grow as colonies with epithelial-like features of cell polarity characterized by apical and basolateral membrane domains and topological features determined by adhesive neighboring cells. When hPSCs were grown on the micropatterns, they exhibited strong topology-dependent differences in the apical structures and functions, which eventually affected the cell neural induction program. Functions of neuronal circuit are fundamentally modulated by its quality and quantity of connections, and the establishment of neuronal circuit can also be precisely controlled by micropattern technology. Improvement of the microsystems will allow us designing

W1P5

Defined Hydrogels for Spinal Cord Organoid Derivation, Maturation, and Modeling of Spinal Cord Diseases

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In the process of generating organoids, basement membrane extracts or Matrigel are often used to encapsulate cells but they are poorly defined and contribute to reproducibility issues. While defined hydrogels are increasingly used for organoid culture, the effects of replacing Matrigel with defined hydrogel on neural progenitor growth, neural differentiation and maturation within neural organoids are not well-explored. In this study, we explore the use of alginate hydrogels as a Matrigel substitute in spinal cord organoid generation. The effect of alginate encapsulation is investigated over a period of 120 days. We found that alginate encapsulation reduces organoid size variability by preventing organoid aggregation. Importantly, alginate supports neurogenesis and gliogenesis of the spinal cord organoids at a similar efficiency to Matrigel, with mature myelinated and electrophysiological active neurons observed by day 120. Furthermore, the use of alginate leads to lower expression of non- spinal markers such as FOXA2, suggesting better control over neural fate specification. To demonstrate the feasibility of using alginate- based organoid cultures as disease models, an isogenic pair of induced pluripotent stem cells discordant for the ALS-causing mutation TDP43G298S was used, where we observed increased TDP43 mislocalization in the mutant organoids. This study shows that alginate is an ideal substitute for Matrigel for spinal cord organoid derivation, especially when a xeno-free and fully defined three- dimensional culture condition is desired.

W2P1

Mechanisms of Dendrite Pruning of Nociceptive Sensory Neurons in *Drosophila*

Fengwei Yu
TLL, Singapore

Selective removal of unnecessary or exuberant neuronal processes without loss of parent neurons, referred to as neurite pruning, is a crucial step of neurite remodeling during animal development. Developmental dendrite pruning shares a number of histological features with pathological neurite degeneration occuring in age-dependent neurological disorders and therefore also serves as an important model for understanding molecular and cellular mechanisms of neurodegeneration.

Drosophila nociceptive sensory neuron, ddaC, is an excellent model to study dendrite-specific pruning, as ddaC neurons selectively prune their larval dendrites in response to a late-larval pulse of the molting steroid hormone ecdysone. We have identified a genetic pathway composed of the transcription factor Sox14 and the important cytoskeletal regulator Mical that act downstream of the ecdysone signaling to regulate neurite pruning (Kirilly D., et al., *Nat Neurosci.* 2009). We also identified two epigenetic factor, namely a Brahma (Brm)-containing chromatin remodeler, a histone acetyltransferase CREB-binding protein (CBP) that binds to the *sox14* locus in an ecdysone-dependent manner to induce Sox14 expression (Kirilly D. et al., *Neuron* 2011). This RNAi screen also revealed a conserved E3 ligase that inactivates the insulin signaling pathway to regulate dendrite pruning (Wong JJL. et al., *PLoS Biol.* 2013). Moreover, we also identified Rab5/ESCRT-dependent endocytic pathways which play crucial roles in dendrite pruning of ddaC neurons. Disruption of *Rab5* or *ESCRT* function causes formation of enlarged endosomes and aberrant ubiquitinated protein deposits in mutant ddaC neurons. We identified a highly conserved L1-type cell adhesion molecule (CAM) Neuroglian (Nrg), which is degraded by the endolysosomal pathway prior to dendrite pruning (Zhang H., et al., *Dev Cell* 2014; Wang Y., et al., *Development* 2017; Zong W., et al., *PloS Biology* 2018). More recently, we have identified several microtubule -binding protein, for their crucial roles in dendrite pruning of ddaC neurons. Our study demonstrates that minus-end-out MT

arrays is requried for dendrite-specific pruning (Wang, et al., *Elife* 2019; Tang et al., *EMBO J* 2000; Bu et la., *EMBO Rep.* 2021; *Cell Rep.* 2022). We have also reported the stress respone pathways Nrf2-Keap1 pathway/AMPK which are activated by ecdysone signaling to promote proteasomal degradation during pruning (Chew, et al., *Cell Rep.* 2021; *Development* 2022). In our other projects, our lab is establishing fruit fly as a model to understand the pharmacological effects of cannabinoids in nociception, ethanol addiction and epilepsy.

W2P2

Conformational state of the alpha synuclein monomer imparts the fibril polymorphisms of the synucleinopaties

Kensuke Ikenaka
Osaka University, Japan

-Synuclein inclusion bodies are a pathological hallmark of several neurodegenerative diseases. Although it has been hypothesized a relationship between fibril polymorphism and different pathologies, the molecular origins of polymorphism are not understood. Here, employing biophysical approaches, we demonstrate that the conformational state of the monomeric αSyn is responsible for fibril polymorphism: αSyn can exist as a compact monomer that produces rod fibrils, and as extended monomers that generate twisted fibrils. Using NMR, we found that the compaction relies on a polar interaction between the initial part of the NAC region and a wide section of the C-terminus domain. The compaction can be commonly affected by changes in the chemical environment, like NaCl, the presence of Ca2+ or cellular components, like endotoxins, that alter the interaction NAC/C- terminus domain. Our compaction model also provides mechanistic insights that explain how the behavior of the C-terminus domain imparts the polymorphism during the fibril formation. Furthermore, we explored the factors that interacts with αSyn monomer and affects the aggregation and final polymophisms by the in vitro aggregation assay. It revealed that phosphatidylinositol-3,4,5-trisphosphate (PIP3) not only accelerates the aggregation of αSyn, but also induces the formation of fibrils sharing conformational and biochemical characteristics similar to the fibrils amplified from the brain of PD patients. Treatment of cultured cells with PIP3 itself or with PIP3 phosphatase inhibitor, induced intracellular formation of αSyn inclusions. Our results provide insights into the molecular origins of the variety of synucleinopathies, as well as the required molecular events at the monomeric level that triggers each disease.

W2P3

The Role of circRNAs in Synaptic Plasticity: Implications for Neurodegeneration

Jacque Ip

Jacque Pak*, Kan IP

The Chinese University of Hong Kong, China

Neuronal circuits in our brain are known to be plastic and are subject to experience-driven changes causing neurons to modify their structure, and functional connectivity and responses. We aim to identify novel regulatory mechanisms of plasticity. Circular RNAs (circRNAs) are regulatory noncoding RNAs abundantly found in brain tissue. Their synaptically-enriched, activity-inducible, and developmentally-regulated properties suggest a role in experience-dependent synaptic plasticity. However, functional investigation of circRNAs in neurons is still in its infancy. Relatively little is known about their role in experience-dependent plasticity. Here, we identified unique activity-dependent circRNAs upon plasticity induction. We found that circRNAs were robustly and differentially regulated. We demonstrated the changes of circRNAs in cortical and hippocampal synaptic plasticity. Our study provides evidence of an experience-dependent circRNA that is a crucial regulator of synaptic development and plasticity as well as learning and memory. Importantly, alterations of circRNAs expression is observed in neurodegeneration.

W2P4

Impaired synaptic vesicle recycling in Parkinson's disease

Cao Mian

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Parkinson's disease (PD) is a neurodegenerative disorder characterized by defective dopaminergic (DAergic) input to the striatum. Mutations in two genes encoding synaptically-enriched clathrin-uncoating factors, synaptojanin 1 (SJ1) and auxilin, have been implicated in atypical Parkinsonism. SJ1 knock-in (SJ1-KIRQ) mice carrying a disease-linked mutation display neurological manifestations reminiscent of Parkinsonism. Here we report that auxilin knockout (Aux-KO) mice display dystrophic changes of a subset of nigrostriatal DAergic terminals similar to those of SJ1-KIRQ mice. Furthermore, Aux-KO/SJ1-KIRQ double mutant mice have shorter lifespan and more severe synaptic defects than single mutant mice. These include increase in dystrophic striatal nerve terminals positive for DAergic markers and for the PD risk protein SV2C, as well as adaptive changes in striatal interneurons. The synergistic effect of the two mutations demonstrates a special lability of DAergic neurons to defects in clathrin uncoating, with implications for PD pathogenesis in at least some forms of this condition.

W2P5

Adenosine A2A receptor signaling in astrocytes contributes to multiple sclerosis progression

Chih Hung Lo

Lee Kong Chian School of Medicine, Singapore

Introduction: A key pathological feature of multiple sclerosis (MS) progression is the diffuse activation of microglia and astrocytes at the rim of chronic active lesions and the perilesional normal appearing white matter (pNAWM). The molecular mechanisms that promote chronic inflammation are poorly understood. Using PET imaging, we have previously observed that adenosine A2A receptor (A2AR) expression was upregulated in pNAWM of patients with secondary progressive MS (SPMS), suggesting that A2AR signaling is implicated in disease progression.

Objectives and Aims: To determine the role of A2AR signaling in perilesional NAWM.

Methods: We employed highly multiplexed immunofluorescence imaging using a panel of 17 antibodies and performed single cell and spatial analysis to characterize A2AR+ cells in MS lesion tissue. In human astrocyte cultures, we examined the downstream effects of A2AR signaling by performing whole transcriptomic analysis and functional assays (lymphocyte transmigration assays, calcium imaging and glutamate quantification) in A2AR agonist treated and untreated astrocytes. We corroborated our in vitro findings by correlating A2AR expression in MS lesion tissue with expression of proteins that were differentially regulated in astrocyte culture.

Results: In MS lesion tissue, A2AR was expressed in two distinct astrocyte populations and localized predominantly to pNAWM. A2AR signaling in human astrocyte culture downregulated multiple adhesion molecules, resulting in reduced astrocyte connectivity, and enhanced trans-astroglial migration of lymphocytes. In addition, A2AR signaling upregulated IL23 and induced aberrant Ca2+ waves, which increased glutamate release. The correlation between A2AR expression, low expression of cell adhesion molecules, reduced astrocyte connectivity, enhanced lymphocytic infiltration and increased IL23 expression was confirmed in MS lesion tissue.

Conclusions: Our findings suggest that A2AR signaling contributes to damage in pNAWM by impairing the ability of astrocytes to contain lesional inflammation and by release of intracellular glutamate, which predisposes to oligodendroglial and axonal excitotoxicity. Because A2AR expression is increased in pNAWM of patients with SPMS, A2AR signaling may provide a therapeutic target for MS progression.

W3P1

Light regulates glucose metabolism

Jianjun Meng

USTC, China

Public health studies have revealed that artificial light is a high-risk factor for metabolic disorders, including diabetes and obesity. However, the neural mechanism underlying light modulation of glucose metabolism remains largely unknown. We serendipitously found that light can acutely decrease glucose tolerance (GT) in mice, and most importantly, also in humans. We further discovered that light blocks adaptive thermogenesis in brown adipose tissue (BAT) via retina-hypothalamus-BAT axis, leading to decreased GT. Interestingly, human GT is also modulated by light in a thermogenesis- dependent fashion. Our work unveils a previously unknown neural circuit that mediates the effect of light on glucose metabolism. This discovery may reveal a potential prevention and treatment strategy for glucometabolic disorders.

W3P2

Brain-Fat interactions and how to find them?

Ken Loh

Yale University, USA

Sympathetic nerve activation of adrenergic receptors on fat is the major pathway the brain uses to drive non-shivering thermogenesis in brown adipose tissue and lipolysis in white fat. There is accumulating evidence that the peripheral nerve architecture inside of organs is plastic (can be remodeled) but the factors and conditions that regulate or result in remodeling are largely unknown. Particularly for fat, it remains unclear if nerves in fat can be remodeled in step with hyperplasia/trophy of adipose tissue as result of a prolonged energy surfeit. We will discuss our work identifying the sympathetic nerve architecture in adipose tissue as highly remodeled in response to the adipose hormone leptin, the hypothalamic brain circuitry leptin acts on to regulate this and the physiological effects remodeling of innervation has on fat tissue function. Additionally, we will highlight ongoing efforts to develop new chemo-proteomic technologies that could enable the discovery of new brain body interactions.

W3P3

How contextual cues modulate feeding behavior

Yu Fu

IMCB, Singapore

Despite notable genetic influences, obesity mainly results from the overconsumption of food, which arises from the interplay of physiological, cognitive and environmental factors. In patients with obesity, eating is determined more by external cues than by internal physiological needs. However, how environmental context drives non-homeostatic feeding is elusive. Here, we identify a population of somatostatin (TNSST) neurons in the mouse hypothalamic tuberal nucleus that are preferentially activated by palatable food. Activation of TNSST neurons enabled a context to drive non-homeostatic feeding in sated mice and required inputs from the subiculum. Pairing a context with palatable food greatly potentiated synaptic transmission between the subiculum and TNSST neurons and drove non-homeostatic feeding that could be selectively suppressed by inhibiting TNSST neurons or the subiculum but not other major orexigenic neurons. These results reveal how palatable food, through a specific hypothalamic circuit, empowers environmental context to drive non-homeostatic feeding.

W3P4

Reverse translational approach to understand how genetics and context modulate feeding

Ajay Mathuru
Yale-NUS, Singapore

A number of human studies propose intranasal oxytocin as a potential intervention for appetite regulation. However, the effect sizes and the direction of change in these studies is not always consistent. We took a reverse translational approach to evaluate if there is any merit in considering oxytocin in interventional strategies. First, we performed random effects meta-analyses on the effects of oxytocin on appetite and weight regulation on 11 human controlled trials in healthy normal or overweight adults comparing intranasal oxytocin administration to placebo that included a measure of caloric intake, hunger or appetite ratings, or change in BMI. The results showed a small difference in fasted as well as snacking caloric intake such that participants in the oxytocin group had a reduced caloric intake but a high degree of variability. Next. we examined food consumption in 7-day old zebrafish. Zebrafish have two functional isoforms of the oxytocin receptor, the oxtr, and oxtrl genes. We examined feeding properties of homozygous null mutants of each gene and the double mutant. A random effects meta-analysis of these experiments showed that only one isoform oxtr-/- has detectable differences, where mutants consumed more food than the wildtype animals. This suggests that oxytocin receptor functions are likely distributed between the two isoforms making zebrafish an attractive system to untangle the complex functions of oxytocin. Together the cross-species results also suggest that oxytocin does reduce appetite but the interaction of oxytocin signaling with appetite may itself be variable. To take this further, we are now examining if the social context of food consumption, when solitary or when in a group, is also changed in the oxtr-/- mutants.

W3P5

Novel proteolytic pathway in lysosomes required for neuromuscular homeostasis

Yuuki Fujiwara
Osaka University, Japan

Regulated degradation of cellular components plays an essential role in biological homeostasis. Lysosomes are largest sites for degradation of virtually all kinds of intracellular macromolecules. Accumulating evidences point out the importance of lysosomal degradation of cellular proteins: Dysfunctions in multiple pathways to deliver cytosolic substrates into lysosomes are related to various diseases such as neurodegenerative diseases and myopathies. Accumulation of various aggregative proteins are reported as a hallmark for such diseases, suggesting that aberrancy in intracellular degradation systems is related to pathogenesis of the diseases. However, much of the effort at understanding such degradative pathways in cells has been devoted to studies on a single pathway, "macro- autophagy", which entails vast and dynamic rearrangement of membrane structure called “autophagosomes”, and knowledge on other delivery systems and functions of lysosomes per se remains scant.

Here, we show that cytosolic proteins are directly imported into lysosomes in an ATP-dependent manner by a mechanism distinct from any known pathways and degraded. We term this novel pathway as "direct-uptake- via/through-membrane-protein (DUMP)". We found that a lysosomal membrane protein, SIDT2, which was previously reported as a putative nucleic acid transporter, is involved in the translocation of substrate proteins in this system. Gain- and loss-of-function analyses revealed that SIDT2 contributes conspicuously to the lysosomal degradation of a wide range of cytosolic proteins in cells at the constitutive level.

Furthermore, we identified a patient of familial neuropathy and myopathy with rimmed vacuoles, harboring a dominant-negative mutation in SIDT2. Sidt2 knockout mice recapitulated typical features of rimmed vacuolar myopathy/neuropathy, which closely resembles observations seen in the patient, including accumulation of cytoplasmic inclusions.

These results reveal a previously unknown pathway of proteolysis in lysosomes and highlight the importance of noncanonical types of degradative pathways in physiology and pathophysiology of human.

Young Investigator Colloquium

YIC1P1

Investigating the role of lysosomal acidification in alpha synuclein induced Parkinson's disease models using acidic nanoparticles

Jialiu Zeng

Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

Parkinson disease (PD) is the second most common neurodegenerative disease in the world today. PD results mainly from the death of dopaminergic neurons in the substantia nigra (SNc) with accumulation of toxic alpha synuclein (α-syn) aggregates within Lewy bodies (LBs) that are unable to be degraded. Recent studies in both cellular and mouse models of α-syn induced PD have indicated that dysfunctions in the endolysosomal autophagy pathway contribute to α-syn accumulation and play a role in PD pathogenesis. While most studies have focused on promoting lysosomal enzyme activity to restore lysosome function and reduce α-syn pathology, direct activation of lysosomal acidification by lowering its pH has not been shown. In this study, we used a novel pH-activable acidic nanoparticles (acNPs) as an agent to induce lysosome acidification in cellular models of a-syn. We showed that the restoration of lysosomal acidification led to a rescue of autophagic function in SH-SY5Y and N2a cells, thereby leading to decreased accumulation of α-syn in cells and restoration of cellular viability. We also showed that acNPs reduce α-syn secretion by measuring the content of α-syn in the cell culture media. In a a-syn pre-formed fibrils induced rodent PD model, treatment with acNPs decreased α-syn accumulation and spreading. Hence, acNPs can serve as a tool to study the mechanism of lysosomal acidification in α-syn induced PD models and can serve as a potential therapeutic for PD.

YIC1P2

Long-distance axonal regeneration in the brain recovers memory deficits in a mouse model of Alzheimer's disease

Ximeng Yang

Section of Neuromedical Science, Institute of Natural Medicine, University of Toyama, Japan

Alzheimer's disease (AD) is a progressing neurodegenerative disorder characterized by deposition of Aβ and disruption of neural networks in the brain. We consider that it is important to regenerate neural circuits for recovering memory function in AD. We previously found that diosgenin, a constituent of Dioscorea Rhizoma, restored Aβ-induced axonal atrophy in cultured neurons and improved memory deficits in a mouse model of AD, 5XFAD. In the present study, we investigated whether diosgenin promoted long-distance axonal regeneration toward their intrinsic target area in 5XFAD brains, and clarified molecular mechanisms for accurate pathfinding of injured axons.

To investigate axonal regeneration effect of diosgenin, we focused on a long-distance neural circuit for memory formation; the hippocampus (HPC) to the prefrontal cortex (PFC). Retrograde tracing revealed that 14-day administration of diosgenin promoted axonal regeneration from the HPC to the PFC in 5XFAD mice. Subsequently, naïve neurons and axon-regenerated neurons in the brain slices were individually captured by laser microdissection to serve DNA microarray. The gene (the name is closed; gene A), whose expression level was the most elevated in axon-regenerated neurons, was overexpressed via AAV9 vector delivery in HPC neurons of 5XFAD mice. As results, overexpression of protein A significantly promoted axonal regeneration from the HPC to the PFC and recovered memory deficits in 5XFAD mice. Furthermore, when the neural activity of axon-regenerated neurons from the HPC to the PFC induced by protein A overexpression were specifically inhibited by DREADDs (Designer receptors exclusively activated by designer drugs) experiments, protein A overexpression-induced memory recovery was completely diminished.

Our study showed that axons in AD brains have capacities to regenerate toward long distance away target area by diosgenin administration. In addition, protein A overexpression-driven axonal regeneration from HPC to the PFC directly contributed to memory recovery. These findings propose a novel therapeutic strategy to promote axonal regeneration for the treatment of AD and other neurodegenerative diseases.

YIC1P3

Analysis of the pathogenesis of vertigo associated with autoimmune diseases

Yoshihisa Koyama

Osaka University, Japan

Autoimmune inner ear disease (AIED) is an organ-specific autoimmune disease characterized by irreversible, long-lasting, progressive equilibrium and hearing functional impairment. Particularly, 50% of patients develop vertigo, accompanied by symptoms such as sensorineural hearing loss, buzzing and ear fullness. Although immunosuppressive drug and steroids is treated as palliative therapy for AIED, there is an urgent need to reveal the vertigo pathogenesis and develop a curative drug from the

Since vertigo symptom associated with AIED resemble that of Meniere's disease, it is difficult to distinguish between the two diseases. Reportedly, high levels of type II collagen antibody are detected in about half of patients with Meniere's disease, whereas the prevalence rate of Meniere's disease is increased in patients with rheumatoid arthritis. Therefore, there is a possibility that rheumatoid arthritis, which is an autoimmune disease of type II collagen antibody, is involved in AIED as well as Meniere's disease.

In this study, we investigated the etiology of vertigo associated with autoimmune diseases using type II collagen-induced rheumatoid arthritis model mice. Our vestibular function test was successful in grasping vertigo symptoms in rheumatoid arthritis model mice because it can accurately evaluate the vestibulo-ocular reflex. The findings will be useful for uncovering the mechanism of vertigo symptom associated with AIED, and for developing novel therapy. We would like to discuss the achievements and prospects.

YIC1P4

Mitochondrial complex-I: A potential target for evaluation of mitochondrial targeted therapeutics in AD?

Jia Hui Wong

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In Alzheimer's disease (AD), synaptic dysfunction typically appears early in prodromal or mild cognitive impairment stages of the disease, with bioenergetic failure possibly being one of the earliest manifestations of the disease whereby hypometabolism has been observed in prodromal stages, and elevated mitochondrial reactive oxygen species (ROS) production and oxidative damage occurring prior to the development of the hallmark proteinopathies. Increasing evidence suggests close correlation of mitochondrial dysfunction with synaptic degeneration, for example, defective glucose utilization and energy metabolism, and changes in mitochondrial size and number in neurons, thus serving as a potent target for early-stage therapeutic intervention to slow AD progression. Decreased expression and activity of the respiratory chain enzyme complexes are observed in vulnerable regions of the AD brain, including specific impairments in mitochondrial complex-I (MC-I). MC-I mediates the first and limiting step in oxidative phosphorylation and is a key site of ROS production. Using positron emission tomographic (PET) imaging tracer targeting MC-I as a non-invasive in vivo functional marker of mitochondrial dysfunction, our previous study showed reduced MC-I-PET signals measured using 18F-BCPP-EF in transgenic mouse model of tauopathy (rTg4510 or TauTg) even at early stages of tauopathy. Suppression of mutant tau via tetracycline controlled transactivator (tet-off, tTA) in rTg4510 mice fed with doxycycline (DOX) diet from 6.5 – 8 months old did not rescue deficits in MC-I signals measured by PET. To evaluate the potential mechanistic role of MC-I in tauopathy, we pharmacologically inhibited MC-I activity using mitochondrial division inhibitor 1 (Mdivi-1), an MC-I inhibitor and mitochondrial fission inhibitor shown by others to improve mitochondrial function and elicit neuroprotective effects in mouse models of Aβ pathogenesis. In vivo MC-I-PET signals were lower in Mdivi-1 treated mice in brain regions measured. Analysis of brain tissue from scanned mice indicated

this reduction in in vivo MC-I signals reflected a decrease in mitochondrial and MC-I content coupled with worsening inflammation. In contrast to protective effects of Mdivi-1 in models of Aβ pathology, we observe differential outcomes in tauopathy. In vitro study of mouse neuroblastoma (N2a) showed that mutant human Tau P301L-transfected N2a have reduced oxidative phosphorylation (OXPHOS) compared to non-mutant Tau- transfected N2a and treatment with Mdivi-1 revealed dose-dependent effects on OXPHOS. These findings highlight the mediating effects of MC-I function in AD and potential target for evaluation of mitochondrial targeted therapeutics.

YIC1P5

Alteration of neural activity in the layer V pyramidal neuron of prelimbic cortex in ASD model mice

Yoshinori Otani
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Autism spectrum disorder (ASD) is a developmental disorder involving impairments in communication, reciprocal social interaction and restricted repetitive behaviors or interests. Duplication of the human chromosome 15q11-13 region is the highly frequently seen chromosomal abnormality and a risk factor for the development of ASD.

The axon initial segment (AIS) is located at the proximal axon and has a high density of ion channels, which occurs action potential initiation. In addition, the AIS regulates the excitability of neurons by changing the structures which include length and position. In addition, many studies reported abnormalities in AIS are risk factors that cause various neurological diseases.

Previously we found abnormal neural circuit between dorsal raphe nucleolus and prelimbic cortex (PrL) by using AIS length. This study we focused medial prefrontal cortex including PrL and infralimbic (IL) cortex as known important for social behaviors and anxiety. we measured the length of AIS in layer V pyramidal neuron in PrL and IL cortex. As our preliminary data, there were differences in the length of AIS of layer V pyramidal neuron in PrL but not IL cortex between 15q11-13 duplication ASD model and wild type mouse. In addition, we demonstrated there were decrease of frequency of action potential in layer V pyramidal neuron in PrL but not IL cortex by electrophysiological analysis in 15q11-13 duplication ASD model mouse.

Therefore, we suggested alteration of neural activity in layer V pyramidal neuron of PrL cortex was important in 15q11-13 duplication ASD model mouse.

YIC2P1

Bioluminescent reporters for noninvasive longitudinal imaging of kinase inhibitor pharmacodynamics in the brain

Yichi Su

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Aberrant kinase activity contributes to the pathogenesis of brain cancers, neurodegeneration, and neuropsychiatric diseases, but identifying kinase inhibitors that function in the brain is challenging. Drug levels in blood do not predict efficacy in the brain because the blood-brain barrier prevents entry of most compounds. Rather, assessing kinase inhibition in the brain requires tissue dissection and biochemical analysis, a time- consuming and resource-intensive process. Bioluminescent kinase reporters have been proposed for evaluating drug efficacy in vivo, but have not been shown to function in the brain. Here, we report kinase-modulated bioluminescent indicators (KiMBIs) based on a recently optimized luciferase- luciferin system to achieve non-invasive longitudinal imaging of drug activity in the brain. We discover a general KiMBI design applicable to multiple kinase pathways, including the Ras-MEK-ERK pathway for which no bioluminescent indicators previously existed. We find that ERK KiMBI discriminates between brain-penetrant and non-penetrant MEK inhibitors, reveals BBB compromise in xenograft models, and reports intracranial MEK inhibitor pharmacodynamics in a cell type- specific manner. Finally, we use ERK KiMBI to screen ERK inhibitors for brain efficacy, obtaining empirical results not well predicted from chemical characteristics alone and identifying temuterkib as a promising brain-active ERK inhibitor. Thus, KiMBIs enable the rapid identification and pharmacodynamic characterization of kinase inhibitors suitable for treating brain diseases.

YIC2P2

Optogenetic inhibition with kalium channelrhodopsins

Stanislav Ott

Duke-NUS Medical School, Singapore

Optogenetic manipulation of neuronal activity via light-gated channelrhodopsins transformed our understanding of neural circuits and opened novel avenues for the treatment of diseases. The identification of anion channelrhodopsins (ACRs) provided the field with potent inhibitory tools that are widely used across model systems. However, despite the inherent strengths of some ACRs, their application remains limited due to the physiological constrains of chloride-mediated hyperpolarization.

In this presentation I will introduce the recently discovered kalium channelrhodopsins (HcKCRs) and evaluate their potential as inhibitory tools in Drosophila and other model organisms. I will compare the efficacy of behavioural inhibition between GtACR1 and HcKCR1 constructs and probe the utility of HcKCRs in inhibiting chloride-conducting cells. Overall, this work will showcase the first application of HcKCRs in vivo and establish it as a potent inhibitory tool for optogenetic applications.

YIC2P3

Abnormal development of cortex and behavior induced by deficit of fucosylation of glycan

Asmaa Abdullah

Shiga University of Medical Science, Japan

Two α1,3-Fucosyltransferase, Fut9 and Fut10 are expressed in the mouse brain during embryogenesis. Using in situ hybridization we clarified spatiotemporal expression of Fut9 and Fut10. Fut9 is expressed in the dorsomedial portion of ventricular zone/subventricular zone (VZ/SVZ) and upper cortical layer of cortex in embryonic day (E) 15.5 but can be detected only in the lowest layer of the cortex in E19.5. Meanwhile, across embryogenesis, Fut10 is detected in VZ/SVZ. Fut9-expressing cells co-localized with Ctip2 and TLE4, markers of deep layer neurons residing in layer VI of the cortex while Fut10-expressing cells is colocalized with Sox2, a marker for neural stem/progenitor cells (NSCs). These findings show that Fut9 and Fut10 may have opposing roles in regulating NSCs where Fut9 regulates the differentiation and migration of dorsal NSCs and Fut10 regulates maintenance of NSCs population. We then further analyzed Fut9 function by using a knockout mouse. To examine association of Fut9 with deep layer neurons production, we performed a birthdating analysis labeling the neuron born at E11.5 or E12.5 and revealed a reduction in the percentage of neurons produced at E11.5 in layer VI/subplate of the cortex in Fut9–/– mice. Furthermore, this reduction in layer VI/subplate neurons persisted into adulthood, leading to a reduction in the number of Ctip2strong/Satb2– excitatory neurons in layer VI. To investigate if this neuronal reduction led to any behavioral abnormalities in Fut9–/– mice, we performed open field and social interaction test. Those results showed Fut9–/– mice has tendency for hyperactivity and impairment of social memory. We are still continuing the investigation for the function of Fut10 in knockout mice. Our data suggest that Fut9 plays significant roles in the cortical formation in the developing brain and its loss of function induces behavioral abnormalities and based on characterization analysis, Fut10 is associated with maintenance of NSCs population in the developing brain.

YIC2P4

Function of transcription factor Meis1 in the differentiation of Bergmann glia from astroglial progenitor

Toma Adachi

National Center of Neurology and Psychiatry, Japan

Astroglia are glial cells that generally have numerous short projections, which stabilize synapses and supply nutrients from the vasculature to the nervous system. Bergmann glia (BG) are cells with cell bodies in the Purkinje cell layer (PCL) of the cerebellum and are known to stabilize synapses between excitatory neurons and Purkinje cells. BG are considered a type of astroglia based on their gene expression patterns and functions, but they differ from normal astrocyte in having two to three long unidirectional projections. BG function as lining structures in the mature cerebellum, and during development, like radial glia in the cerebral cortex, they function as scaffolds for migration of granule neurons. Thus, BG are astroglia with specialized morphology and function, but the detailed molecular mechanism by which they acquire this specialization has not yet been elucidated.

In addition to BG in PCL, the normal forms of astrocytes (protoplasmic and fibrous astrocyte) localize to the internal granule cell layer (IGL) and white matter (WM) of the cerebellum. Interestingly, experiments labeling astroglial progenitors at embryonic mice suggest that BGs and astrocytes are produced from a common progenitor cell (Cerrato et al., 2018. PLOS Biology). However, the detailed molecular mechanisms at which developmental stages BGs and astrocytes acquire different properties and how they are differentially generated from a common progenitor are not clear.

The transcription factor Myeloid ectopic viral integration site 1 (Meis1) is a gene encoding a homeobox protein known to have various functions in nervous system development. We previously reported that Meis1 directly regulates Pax6 transcription in cerebellar granule cell progenitors (GCPs) and controls the differentiation state of GCPs via BMP signaling (Owa et al., Journal of Neuroscience. 2018). However, in developing cerebellar cells, Meis1 is expressed not only in GCPs but also in the astroglial cell lineage, and the details of its function in astroglial cells are unknown.

In this study, we found that knockout of Meis1 in cerebellar astroglial cells (astroglial progenitor cells, BGs, and astrocytes) caused ectopic localization of BGs and morphological changes to astrocyte-like structures. Furthermore, we performed single cell RNA-seq (scRNA- seq) using cerebellar specific Meis1 knockout mouse brains to examine the gene expression patterns of these atypical BGs. Interestingly, we found that the expression of known BG-specific genes (Zeb2, Vim, Glia1, Tnc, Gdf10, Sept4, Gpr126) were markedly decreased in these atypical BGs, while the expression of genes commonly expressed between astrocytes and BGs (Aqp4, Gfap, Mlc1) were increased. These results indicate that loss of Meis1 causes atypical BGs to resemble astrocytes not only in morphology but also in their properties.

Previous studies have shown that mitotic Nestin-positive astroglial progenitors are present in the PCL of the 1-week-old mouse cerebellum in addition to BG (Li et al., 2013. Nature Neuroscience). Furthermore, it has been suggested that these Nestin-positive astroglial progenitor cells may give rise to both BGs and astrocytes (Joyner et al., 2022. Development). We also confirmed that knockout of Meis1 expression not in astroglial progenitors but in BGs did not induce ectopic or dysmorphic BGs. Based on these results, we hypothesize that Meis1 expressed in astroglial progenitors localized in the PCL of postnatal week 1 mice is the key for BG production and that loss of Meis1 in astroglial progenitors induces the production of astrocytes rather than BGs.

YIC2P5

Unravelling the role of BACE2 in a human cerebral organoid model of Alzheimer's Disease

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Despite intensive research over several decades, controversies still surround the etiology of Alzheimer's Disease (AD), which remains incurable. Meanwhile, new molecular players of the central amyloid cascade hypothesis have emerged, and among these is a protease known as β-site APP cleavage enzyme 2 (BACE2).

The purpose of this study is to understand the contribution of BACE2 to the pathogenesis of AD by using a cerebral organoid model to compare the extent of amyloid and tau pathology between an individual with Early Onset Alzheimer's Disease (EOAD) harbouring a de novo 12kb deletion in intron 1 of BACE2 with his asymptomatic parental control. There is no AD history in his first-and second-degree relatives.

Induced pluripotent stem cells (iPSCs) were generated from fibroblasts derived from an EOAD individual with a BACE2 intronic mutation and his parental control using non-integrational Sendai reprogramming. Cerebral organoids were generated from these iPSCs and maintained beyond 200 days in culture. Subsequently, these organoids underwent immunohistochemical staining for the quantification of phosphorylated tau, amyloid plaques, and neuronal death – the three hallmarks synonymous with AD.

Amyloid plaques were observed in both patient and control organoids by day 70. An age-related increase in the number of amyloid plaques was observed at day 100, where the patient demonstrated a significant exacerbation in amyloid plaque deposition as compared to the control. Phosphorylated tau started to appear in the patient by day 150, and by day 200, a significant increase in phosphorylated tau accompanied by cell death was observed in the patient as compared to the control. More importantly, in our model, the appearance of amyloid plaques preceded that of

phosphorylated tau, which aligns with the order of pathology proposed by the amyloid cascade hypothesis.

We hypothesize that a deficiency in BACE2 promotes AD-related pathologies, suggesting that BACE2 normally functions as a neuroprotective factor. We propose that targeting BACE2 for therapeutic purposes in AD presents a viable alternative strategy that merits consideration.

YIC3P1

Adolescent social isolation induces pathway-selective functional changes in the medial and lateral orbitofrontal- amygdala circuits

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Because early-life period is critical window for formation and rearrangement of neural circuits, early-life experiences have great impact on brain functions. Especially, early-life social experience is important for social and emotional development and deprivation of early social experience is associated with a risk for psychiatric disorders with social and emotional problems. However, neural mechanisms underlying how social deprivation disrupts social and emotional development are poorly understood.

Recently, the orbitofrontal cortex (OFC) and basolateral amygdala (BLA) have been highlighted as key brain regions for social and emotional processing. Hence, we hypothesize that early social deprivation disrupts the information processing in the OFC-BLA pathway and leads to social and emotional abnormalities. In the present study, we examined the effects of adolescent social isolation on the OFC-BLA synaptic transmission by optogenetic and whole-cell patch-clamp methods in mice. The adolescent social isolation decreased prosocial behavior and increased passive stress-coping behavior in adulthood mice. Then, we examined the effect of adolescent social isolation on excitatory synaptic transmissions in the OFC-BLA pathway. Notably, the OFC is divided into medial or lateral subregions (mOFC or lOFC), we separately examined the mOFC-BLA and lOFC-BLA synaptic functions. The adolescent social isolation decreased the AMPA/NMDA ratio in the mOFC-BLA synapse, while the ratio was increased in the lOFC-BLA synapse. Furthermore, we optogenetically manipulated the mOFC-BLA or lOFC-BLA transmission in behaving mice and examined the effects on prosocial and stress-coping behaviors. Optogenetic manipulations of the mOFC-BLA and lOFC-BLA transmissions altered prosocial and passive stress-coping behaviors, respectively.

Our results suggest that adolescent social isolation induces distinct functional changes in the mOFC-BLA and lOFC-BLA synapses, and these changes separately contribute to abnormalities in social and emotional behaviors.

YIC3P2

Remote hippocampal cerebrovascular dysregulation and cognitive impairment after cortical photothrombotic stroke

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Accumulating evidence has shown that stroke triggers a wave of secondary damage that causes the progressive and inexorable loss of brain tissue at sites connected to the area damaged by the initial infarction, a phenomenon known as secondary neurodegeneration. Stroke induced secondary neurodegeneration is associated with late phase functional disturbances such as cognitive impairment. We recently demonstrated that a unilateral cortical photothrombotic stroke at the motor and somatosensory cortices causes persistent neuronal loss, neuroinflammation and accumulation of neurotoxic proteins in the CA1 sub-region of the ipsilateral hippocampus. In the current study, cerebrovascular morphology, BBB integrity and proteins associated with endothelial cells were investigated at time- points 7, 28 and 84 days after stroke. We found a significant increase in the density and area coverage of cerebrovascular between 7 to 84 days post-stroke. Interestingly, we observed a significant decrease in average vessel diameter in the hippocampus at 84 days post-stroke. Further analysis indicated that vessel with amyloid-beta deposited in their walls were narrower that those with no amyloid-beta deposition. We also observed persistent loss of BBB integrity together with changes in tight junction protein and matrix metallopeptidase. These cerebrovascular pathologies are associated with progressive impairment in various cognitive domains. Our findings indicated that cortical stroke induces remote hippocampal cerebrovascular dysregulation, and potentially contributes to the progression of post-stroke cognitive impairment.

YIC3P3

Targeting heterogeneous nuclear ribonucleoprotein U in astrocytes to restore central nervous system impairment

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Spinal cord injury (SCI) is one of the representative central nervous system (CNS) injuries that causes severe disability and irreversible motor and sensory dysfunction, for which effective treatments have not been fully developed. Following SCI, astrocytes are the predominant cellular component that proliferates around the lesion core, contributing to glial scar formation, which has long been considered a major cause of neuronal regeneration failure. However, the molecular mechanisms by which astrocytes proliferate in response to CNS injury remain unclear. In this study, we found that heterogeneous ribonucleoprotein U (Hnrnpu), a DNA/RNA binding protein, regulates astrocyte proliferation after SCI. siRNA-mediated Hnrnpu inhibition suppresses astrocyte proliferation as well as cell migration. Intraspinal treatment of mice with AAV2/5-Hnrnpu shRNA under the control of the astrocytic glial fibrillary acidic protein (GFAP) promoter inhibited astrocyte proliferation in vivo. Moreover, Hnrnpu knockdown in astrocytes also impaired glial scar formation and motor function recovery in injured mice. Taken together, Hnrnpu is a promising therapeutic target in astrocytes that contribute to the glial scar formation and neural regeneration after CNS injury.

YIC3P4

Subgroup specific alterations in the kynurenine pathway in the anterior cingulate cortex in major depressive disorder

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Major depressive disorder (MDD) is a serious psychiatric disorder that in extreme cases can lead to suicide. Understanding the neurobiological changes fundamental to MDD is hindered by high levels of heterogeneity in the population, suggesting a need for characterization of specific subgroups. Evidence suggests that alterations in the kynurenine pathway contribute to the etiology of MDD. Activation of the kynurenine pathway leads to the formation of neuroactive metabolites, including kynurenic acid and quinolinic acid. These metabolites modulate glutamatergic transmission, which contributes to MDD pathology. Currently, the status of the kynurenine pathway in the brain of MDD subjects is largely unknown.

The kynurenine pathway was investigated in the anterior cingulate cortex (ACC) from two independent MDD cohorts. RNA isolated from the ACC from MDD subjects with psychosis (n=12) and without psychosis (n=12), and non-psychiatric controls (n=12) was provided by the Stanley Medical Research Institute. Postmortem ACC was obtained from the National Institute of Health (NIH) NeuroBioBank, consisting of tissue samples from individuals with MDD (n=44) that died by suicide or other causes, and matched non-psychiatric controls (n=36). Gene expression levels of kynurenine pathway enzymes (kynurenic acid arm: KYAT1, KYAT2, KYAT3, KYAT4; quinolinic acid arm: KMO, KYNU, HAAO, QPRT) were investigated via RT- qPCR. In the ACC of the Stanley cohort, KYAT1 and KYAT2 mRNA were significantly increased in MDD, when combining those with and without psychosis. We were able to replicate this finding in the larger cohort from the NIH, where we report an increase in KYAT2 mRNA in the ACC in MDD. Interestingly, this increase appeared to be specific to those that did not die by suicide ($p=0.016$). In the NIH cohort, we also measured kynurenine pathway metabolite levels (tryptophan, kynurenine, kynurenic acid, 3-hydroxykynurenine, 3-hydroxyanthranilic acid and quinolinic acid) using liquid chromatography-mass spectrometry. MDD subjects that died by suicide had significantly decreased kynurenic

acid and 3- hydroxykynurenine in comparison to controls (p=0.004; p=0.040) and MDD subjects that did not die by suicide (p=0.016; p=0.034). Furthermore, female MDD subjects had significantly decreased kynurenic acid in comparison to female controls (p=0.036) and a trend decrease in the kynurenic acid to quinolinic acid ratio compared to female controls (p=0.056). Interestingly, there were no diagnostic changes specifically in males. Overall, we found sex and suicide specific alterations in the kynurenine pathway in the ACC in MDD, however, no specific psychosis related changes. This is the first molecular evidence in the brain of subgroup specific changes in the kynurenine pathway in MDD, which not only suggests that treatments aimed at upregulation of the kynurenic acid arm in the brain may be favourable for females experiencing MDD but also might assist managing suicidal behaviour. As the kynurenine pathway directly regulates glutamatergic receptor activity, these findings also highlight the possible differences in glutamatergic regulation in these subgroups and therefore their potential suitability for glutamatergic based therapeutics.

YIC3P5

CHANGES IN THE BRAIN STRUCTURE AND FUNCTIONS IN MENOPAUSAL RAT MODEL AND ITS ASSOCIATION WITH THE COGNITIVE PERFORMANCE

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During the menopause transition, women experience various neurological symptoms including cognitive decline. Among the cognitive domains affected include learning, executive functions, working, and verbal memory. Previous works suggest that alterations in the hormonal milieu during menopause modulate the brain structure and function associated with cognitive function. Administration of 4-vinylcyclohexene diepoxide (VCD) in rats induces a progressive transition to menopause by selectively destroying the ovarian follicles comparable to physiological menopause in women. However, brain changes associated with cognitive impairment in VCD-induced menopause rodents have yet to be explored. Therefore, our study aimed to identify changes in the brain region of interest (ROI) using MRI and PET scans in VCD-induced rats. Female Wistar rats aged 3 months were injected with VCD (160 mg/kg) or vehicle (sesame oil), i.p., for 15 days and underwent cognitive tests at 3 months post-injection. Subsequently, MRI and PET imaging of the brain ROI was done for volumetric and glucose uptake measurements respectively. Loss of ovarian follicles (primordial, primary, secondary, and Graafian) and corpora lutea in VCD-induced rats, was accompanied by lower estradiol levels. During the cognitive tests, VCD-induced rats exhibited impaired spatial learning and memory. While the cognitive performance of VCD-induced rats corresponds to diminished glucose uptake in the hippocampus region, the hippocampal volume showed a trend toward smaller volume. These findings were similar in neurodegenerative disorders where dysfunction in the glucose uptake occurred long before the neuronal loss. Overall, our result indicates that the hippocampus is vulnerable to the impacts of menopause.

These results reveal a previously unknown pathway of proteolysis in lysosomes and highlight the importance of noncanonical types of degradative pathways in physiology and pathophysiology of human.

Oral Presentations

O1P1

Neuroprotective Role of Chicken essence in D-galactose/AlCl3- Induced Mouse Model of Alzheimer's Disease

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by amyloid-? (A?) and neurofibrillary tangle accumulation in the brain, resulting in cognitive decline and memory impairment. Chicken essence (CE) is a liquid extract made from chicken meat. It contains a lot of nutrients like amino acids, peptides, and minerals. Many previous studies have shown that CE has anti-stress, anti-fatigue, and anti-oxidant properties, as well as the ability to improve memory and cognitive function. This experimental investigated the neuroprotective effect of CE on the development of AD in a mouse model induced by D-galactose/aluminium chloride (D-gal/AlCl3). Forty male BALB/c mice were randomly assigned to one of five groups (n=8): control, D-gal/AlCl3, and D-gal/AlCl3plus chicken essence at doses of 14, 28, and 42 ml/kg (p.o.). The mice received CE once daily for 12 weeks along with D-gal (150 mg/kg, s.c.) and AlCl3 (20 mg/kg, p.o.) treatments. The Morris water maze test revealed that CE greatly restored learning and memory deficits brought on by D-gal/AlCl3. In comparison to the D-gal/AlCl3 group, rats given with chicken essence at doses of 14 and 28 ml/kg displayed a shorter escape latency and a longer duration spent in the target quadrant. The levels of A? (1-42) in the brain were dramatically reduced by the CE at doses of 14, 28, and 28 ml/kg. Furthermore, CE decreased the expression of the proteins beta-secretase 1 (BACE1), amyloid precursor protein (APP), lipid peroxidation and inflammation in the brain. These findings suggest that CE has neuroprotective effects in D-gal/AlCl3-induce mouse model of AD.

Keywords: Chicken essence, Alzheimer’s disease, Neuroprotective, D-galactose/aluminium chloride

O1P2

Establishing fluid biomarkers associated with cellular senescence in Alzheimer's disease

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Chronological age is the biggest non-genetic risk factor of Alzheimer's disease (AD). However, there is a wide range in age at onset such that chronological age itself is a poor predictor of risk. Biological age may offer a more precise molecular measure of ageing, but it is currently unclear how biological ageing is associated with AD. We set out to test fluid biomarkers of biological ageing specifically linked to cellular senescence in AD and explore their utility in the clinical setting.

Using cerebrospinal fluid (CSF) samples from the Dementia Research Centre at UCL, we quantified the levels of seven candidate biomarkers associated with ageing and cellular senescence with various immunoassays. The levels of biological ageing markers were then analysed with clinical and pathological data from the sample donors.

We found that a subset of candidate biomarkers exhibit higher levels in AD patients, as well as significant associations with total tau and phosphorylated tau at serine 181 (p-Tau181) after correcting for age. Receiver operating characteristics (ROC) analysis showed that MMP-10 and NfL performed best in differentiating AD from non-neurodegenerative control individuals with area under curve (AUC) of more than 0.9. Subsequently combination ROC analysis indicated that NfL, Osteopontin (SPP1) and MMP-10 together produced excellent differentiating capability with AUC of 0.97. Our data support the relevance of biological ageing markers in the context of AD.

Our data support the relevance of biological ageing, specifically MMP-10 and Osteopontin which have been separately linked to AD pathology, in the context of AD and the need for further investigation.

O1P3

Length-dependent RNA foci formation and Repeat Associated non-AUG dependent translation in SCA12 Patient derived Neural Stem Cells: hallmarks to pathogenesis

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Spinocerebellar ataxia type-12 (SCA12) is a neurodegenerative disease and one of the most prominent SCA-subtype in India that exhibits a unique progressive tremor/ataxia syndrome induced by triplet (CAG) repeat expansion in 5' UTR region of PPP2R2B. So far, no study has been done to investigate the pathological hallmarks using the appropriate disease model. Therefore, we aimed to establish human iPSC derived SCA12 neuronal cell lines to study the cellular pathological mechanisms induced by CAG expansion. As reported previously, we found that the expression of PPP2R2B gene increases with CAG expansion. Further, expanded CAG in PPP2R2B transcript causes formation of RNA Foci inside the nucleus of the patient-derived neural stem cells, which in turn may sequester many nuclear proteins, and inhibit their necessary functions. The ectopic expression of this expanded CAG transcript from PPP2R2B accelerates non-canonical Repeat Associated Non- Aug (RAN) translation in multiple frames and may produce aggregation-prone proteins in HEK cells, further validated in patient-derived neural stem cells using novel antibodies. Next, RNA-pull down assay in HEK cells and comparative whole RNA sequencing analysis of patient and control-derived neural stem cells followed by mass-spectrometric-based protein detection identified crucial proteins involved in protein homeostasis, vesicular trafficking, ion channels, mitochondrial fission, etc. shedding light on the mechanistic relationship between RAN translation and RNA foci, and their relative contributions to cellular dysfunction. Altogether, this study identifies the molecular signatures of SCA12 disorder using patient-derived neuronal cell lines, wherein RNA foci and RAN protein accumulation impact the functioning of crucial intracellular pathways. Furthermore, overlapping of these pathways in the same cell lines demonstrates the critical partaking of two modifiers in disease progression emphasizing the new therapeutic strategies that target both processes in repeat expansion disorders.

O1P4

Extrasynaptic GluN2B causes excitotoxicity and neurodegeneration through FOXO1 interaction with Txnip in YAC128 model of Huntington's Disease

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Striatal atrophy present in Huntington's Disease (HD) is thought to result from excitotoxicity caused by dysfunctional glutamatergic corticostriatal synapse function. Our hypothesis is that reduced glutamate reuptake at synapse leads to extrasynaptic localization of GluN2B and activation of pro-death pathway involving FOXO1-Txnip interaction. We performed the study on early stage (E, 3 months old) and symptomatic stage (S, 7 months old) WT and HD mice. We observed an increase of GluN2B/GluN2A protein ratio in HD mice compared to WT and we verified with immunohistochemistry and showed that extrasynaptic GluN2B ratio increases with age and disease genotype, with significant increase from E to S in HD mice (E: 83.83%; S: 90.27%; $p<0.01$; n=3 per genotype). The increased extrasynaptic localization of GluN2B leads to an increased FOXO1 activity that activates pro-death pathway through interaction with Txnip promoter. Confocal imaging shows that there is 26.4% more FOXO1 localization in the S HD nuclei compared to WT ($p<0.0001$; n=3 per genotype). We also observed a 10.4% increase in TXNIP protein amount in S HD cells compared to WT ($p<0.05$; n=3 per genotype), with TXNIP localizing mainly in the cytoplasm, surrounding nuclei with increased FOXO1 localization. Further investigation using chromatin immunoprecipitation on 5, 7 and 9 months old mice showed a progressively increasing binding pattern of FOXO1 to Txnip promoter in HD mice as they age. This suggests that FOXO1 increasingly upregulates Txnip expression with age, leading to more excitotoxicity from the activation of pro-death pathway. We plan to investigate the amount of striatal cell death in WT and HD mice indeed due to excitotoxicity from FOXO1-Txnip interaction causes the striatal atrophy present in HD.

O1P5

Gut microbiome profile and intestinal permeability in patients with schizophrenia and healthy controls - a plausible non-invasive biomarker?

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Human gut microbiome regulates brain function through the microbiome-gut-brain axis and is implicated in several neuropsychiatric disorders. However, the relationship between intestinal permeability, gut microbiome, and the pathogenesis of schizophrenia (SCZ) is poorly defined, and very few studies have examined the effect of antipsychotic treatment response. We aim to study the differences in the intestinal permeability biomarkers, viz., zonulin, lipopolysaccharide-binding protein (LBP), and gut microbiome profile among drug-naïve (DN SCZ) and risperidone-treated SCZ patients (RISP SCZ), compared to healthy controls (HCs). We recruited a total of 60 participants, from the clinical services of a large neuropsychiatric hospital, which included DN SCZ, RISP SCZ and HCs (n=20 each). Plasma levels of zonulin, and LBP were quantified by enzyme-linked immunosorbent assay. Fecal samples were analyzed using 16s rRNA sequencing in this cross-sectional study. Plasma levels of both LBP and zonulin were significantly increased ($P < 0.05$) in patients with SCZ compared to healthy controls and also associated with neutrophil-to-lymphocyte ratio (NLR) - a marker of systemic inflammation. No significant differences were found in taxa richness (alpha diversity) but microbial composition differed between SCZ patients (both DN and RISP) and HCs (PERMANOVA, $p=0.02$). A specific genus-level microbial panel of Ruminococcus, UCG005, Clostridium_sensu_stricto_1 and Bifidobacterium could discriminate SCZ patients from HCs, RISP SCZ vs HCs with the best sensitivity and specificity. Our study identified distinct microbial signatures that could aid in the differentiation of DN SCZ, RISP SCZ, and HCs, and also demonstrates an association of zonulin, LBP, in Asian Indian SCZ patients. Our findings contribute

to a better understanding of the role of the gut microbiome/intestinal permeability in SCZ pathophysiology and suggest potential targeted interventions.

O1P6

Inhibition of connexin hemichannels alleviates neuroinflammation and hyperexcitability in temporal lobe epilepsy

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Temporal lobe epilepsy (TLE) is one of the most common types of epilepsy, yet approximately one-third of patients are refractory to current anticonvulsive drugs, which target neurons and synapses. Astrocytic and microglial dysfunction is commonly found in epileptic foci and has been shown to contribute to neuroinflammation and hyperexcitability in chronic epilepsy. Accumulating evidence points to a key role for glial hemichannels in epilepsy, but inhibiting both connexin (Cx) gap junctions and hemichannels can lead to undesirable side effects because the former coordinate physiological functions of cell assemblies. It would be a great benefit to use an orally available small molecule to block hemichannels to alleviate epileptic symptoms. Here, we explored the effect of D4, a newly developed compound that inhibits the Cx hemichannels but not Cx gap junctions using the pilocarpine mouse model of TLE. In vitro application of D4 caused a near-complete reduction in the pilocarpine-induced cell membrane permeability associated with increased Cx hemichannel activity. Moreover, pre-administration of D4 in vivo effectively reduced neuroinflammation and altered synaptic inhibition, which then enhanced animal survival rate. Post-treatment with a single dose of D4 in vivo has prolonged effects on suppressing the activation of astrocytes and microglia and rescued the changes in neuroinflammatory and synaptic gene expression induced by pilocarpine. Collectively, these results indicate that targeting Cx hemichannels by D4 is an effective and promising strategy for treating epilepsy in which neuroinflammation plays a critical role.

O2P1

Matrix-assisted Golgi staining in whole-brain expansion imaging under near-infrared light microscopy

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We developed a novel near infrared (NIR) bright field microscopy to image the neuron system of a whole animal model. This system can resolve dendritic spines with Golgi staining and expansion microscopy, called intact matrix-assisted Golgi expansion (iMAGE). The use of metal ions for staining provided excellent penetration into large tissues and leads to potential applications in non-classical large animal models such as squids, pigs, or human brains, which often require mechanical sectioning for light microscopy. In our approach, the samples are expanded and filled with hydrogel followed by the Golgi staining, where the samples become transparent to the NIR light up to several centimeters. The prepared samples are then imaged by NIR bright field light microscopy allowing direct visualization of dendritic spines in an intact brain. This technique has also been successfully utilized to study the whole embryo and extremely large samples such as pig brains for 3D mapping of the labeled neuron system.

O2P2

Sphingosine kinase 2 is essential for remyelination

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Therapeutics that promote oligodendrocyte survival and remyelination are needed to restore neurological function in multiple sclerosis (MS). Sphingosine 1-phosphate (S1P) receptor agonists (e.g Fingolimod and Siponimod) are valuable immunosuppressants used to treat MS, and are thought to promote oligodendrocyte survival. However, the role for endogenous S1P, synthesized by the enzyme sphingosine kinase 2 (SphK2), in oligodendrocyte survival and remyelination after injury remains unknown. We hypothesised that SphK2 protects oligodendrocytes and plays an important role in remyelination after injury. SphK2 knockout (SphK2-/-) mice and wildtype (WT) C57BL/6 littermates were fed cuprizone for 6 weeks to induce demyelination, followed by 0, 2, or 4 weeks of cuprizone withdrawal to quantify spontaneous remyelination. Oligodendrocyte density did not differ between untreated WT and SphK2-/- mice, however cuprizone treatment caused significantly greater loss of mature oligodendrocytes in SphK2-/- compared to WT mice, indicating that SphK2 is protective. Spontaneous remyelination was clearly evident in the corpus callosum (CC) of WT mice 2 weeks after cuprizone withdrawal. In contrast, no remyelination was observed in SphK2-/- mice even at 4 weeks after cuprizone withdrawal. The density of mature oligodendrocytes and oligodendrocyte progenitor cells did not differ between WT and SphK2-/- mice at 2 weeks after cuprizone withdrawal, indicating that SphK2 is not necessary for proliferation and maturation of oligodendrocytes, but is essential for remyelination after a demyelinating insult. Liquid chromatography-tandem mass spectrometry was used to quantify S1P and myelin lipid markers. Levels of cytotoxic sphingosine and ceramide were higher in the CC of SphK2-/- mice, and in contrast to WT mice, did not decline during remyelination in SphK2-/- mice. This direct consequence of SphK2 deficiency may sensitize oligodendrocytes to apoptosis and block remyelination. These results provide the first evidence that S1P synthesis by

SphK2 mediates oligodendrocyte survival and is essential for remyelination following a demyelinating insult.

O2P3

APOE Regulates Myelin Lipid Turnover in Healthy Brains

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Apolipoprotein E (ApoE) is the major lipid transporter in the brain, and inheritance of the ε4 allele of the APOE gene (APOE4) is the most significant genetic risk factor for Alzheimer's disease and dementia overall. Turnover of myelin sheaths, which are comprised of 80% lipids, is crucial for the maintenance of myelin integrity. This study employed proteomic and lipidomic analyses of mouse and ageing human brain tissue samples with no significant dementia pathology to investigate how APOE genotype affects the physiological brain to modulate the risk of developing dementia. A novel stable isotope mass spectrometry approach involving administration of deuterium oxide to mice was used to probe the role of APOE in myelin lipid turnover in vivo.

Significant accumulation of the myelin-enriched sphingolipids hexosylceramides and sulfatides was observed in the hippocampus of human APOE4 carriers relative to carriers of the protective APOE2 allele and risk-neutral APOE3/3 individuals. These findings were corroborated in the hippocampus of mice bearing targeted replacement of Apoe with human APOE variants (hAPOE2/2, hAPOE3/3, hAPOE4/4). More pronounced myelin lipid accumulation was observed in the hippocampus of Apoe knockout mice, suggesting that APOE4 is a loss of function allele with regard to lipid turnover. Untargeted proteomics revealed myelin proteins MAG and MOG, and proteins in the phagocytic microglial pathway (C1qA) are increased in Apoe knockout mice, indicating defective clearance of myelin debris and microglial activation. Global

metabolic lipid labelling with deuterium oxide drinking water indicated that Apoe knockout mice have slower rates of myelin lipid turnover compared to wild-type mice.

This study provides evidence for defective clearance of myelin debris in the hippocampus of non-pathological, cognitively normal humans and mice carrying APOE4, and points to a physiological role of APOE in myelin lipid clearance. Impaired myelin debris clearance may underlie the increased susceptibility of APOE4 carriers to dementia.

O2P4

GPCR Signaling-mediated Actin Remodeling Drives Quiescent Neural Stem Cell Activation

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The transition between quiescence and proliferation of neural stem cells (NSCs) is fundamental for brain development and homeostasis. The failure of NSC reactivation is often associated with neurodevelopmental disorders and brain aging. Drosophila quiescent NSCs extend an actin-rich primary protrusion toward neuropil prior to their reactivation. However, the structure and function of actin cytoskeleton during quiescence exit of NSCs are unknown. Here, we show F-actin patches undergo a retrograde flow in the protrusion of quiescent NSCs, which is regulated by G-protein-coupled receptor (GPCR) signaling. We identified an actin polymerization regulator, Formin/Diaphanous (Dia), as a novel intrinsic factor for NSC reactivation. We show that GPCR Smog-Gaq-Rho1 signaling axis regulates Dia-mediated F-actin polymerization for NSC reactivation. We have further identified a novel role of a microcephaly-associated factor, transcription factor Mrtf, in NSC reactivation. Nuclear translocation of Mrtf in quiescent NSCs prior to reactivation is dependent on F-actin polymerization mediated by Dia, overexpression of Mrtf in NSCs suppressed reactivation defects and microcephaly-like phenotype in dia mutant larvae. In addition, we have identified a ligand of GPCR Smog that is secreted from astrocyte-like glia and required for NSC reactivation. Together, this work establishes a novel role of the GPCR Smog-Gaq-Rho1 signaling axis derived from a new NSC niche, astrocyte-like glia, regulates Dia-mediated F-actin dynamics in quiescence exit of NSCs.

O2P5

Golgi-dependent Reactivation and Regeneration of Quiescent Neural Stem Cells

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The ability of stem cells to switch between quiescent and proliferative states is crucial for maintaining tissue homeostasis and regeneration. In Drosophila, quiescent neural stem cells (qNSCs) extend a primary protrusion, which is a hallmark of qNSCs. Here, we have unravelled that qNSC protrusions can be regenerated upon injury. This regeneration relies on the Golgi apparatus which acts as the major acentrosomal microtubule-organizing centre in qNSCs. A Golgi-resident GTPase Arf1 and its guanine-nucleotide exchange factor Sec71 promote NSC reactivation and regeneration via the regulation of microtubule growth. Arf1 physically associates with its new effector Mini Spindles (Msps)/XMAP215, a microtubule polymerase. Finally, Arf1 functions upstream of Msps to target the cell-adhesion molecule E-cadherin to NSC-neuropil contact sites during NSC reactivation. Our findings have established Drosophila qNSCs as a new regeneration model and identified a novel Arf1/Sec71-Msps pathway in the regulation of microtubule growth and NSC reactivation.

O2P6

Sciatic nerve Pulsed-radiofrequency therapy improves pathophysiology in a mouse model of knee osteoarthritis via anti-inflammatory effects

Tomoo Yuba

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The number of patients with knee osteoarthritis is increasing dramatically in the aging society, and there are more over 300 million patients worldwide. Knee osteoarthritis is a disease that causes chronic knee pain due to wear of the articular cartilage. Although surgical treatment is sometimes chosen for patients with severe articular deformity, the main treatment is conservative. Conservative treatment consists mainly of treatment with NSAIDs, which are often difficult to use as treatment for the elderly due to their side effects. As rapidly aging society, there is an urgent need to develop knee osteoarthritis therapy with fewer side effects.

We have reported the effectiveness of pulsed radiofrequency therapy (PRF), a type of nerve block, in treating knee osteoarthritis patients with knee pain. This treatment has few complications and provides long-lasting analgesia for several months or longer. However, the detailed analgesic mechanism of PRF remains unclear. Based on our diagnostic results for patient with knee osteoarthritis, we hypothesized that the anti-inflammatory effect of PRF might be involved in the analgesic effect, and analyzed the anti-inflammatory effect of PRF using a mouse model of knee osteoarthritis. The results showed that the PRF improved the hindlimb load imbalance, gait deterioration, and synovitis associated with knee osteoarthritis. PRF also alleviated the increased mRNA expression of inflammatory cytokines and macrophagic invasion in the knee joint. Finally, we performed the mechanistic analysis using neural tracer for the anti-inflammatory effects of PRF. The findings showed that PRF-treated group suppressed axonal transport in a small neuron-specific manner in dorsal root ganglion of the 4th lumber spinal cord.

In this study, we demonstrated that PRF exerts its anti-inflammatory effects via inhibition of axonal transport in small neurons. PRF is a safe and effective treatment method and could be a new treatment option for knee osteoarthritis.

O3P1

Novel allosteric modulator SRI-32743 reverses HIV-1 Tat-induced increase in dopamine release and alleviates the potentiation of cocaine reward in inducible HIV-1 Tat transgenic mice

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Dopamine (DA) is essential for a variety of brain activities involved in attention, learning, memory, and motivation. Development of neurocognitive disorder in HIV infected patients has been linked to dysregulation of DA by HIV-1 transactivator of transcription (Tat) protein, a negative allosteric modulator of dopamine transporter (DAT). DA transporter (DAT)-mediated DA reuptake is a dynamic DA translocation process, which is regulated by three typical conformational states: Outward-open? Outward-occluded? Inward-open. This conformational transport process can be modulated by transporter allostatic modulator, which may represent novel drug target sites on DAT that is distinct from classic neurotransmitter uptake sites with minimal effects on basal DA transport. We have developed a novel allosteric modulator, SRI-32743, which functions as allosteric modulators of DAT and act as partial antagonists of DA uptake without the full inhibitory profile that is typical of classic competitors of DAT. In this talk, we will present our recent published work that SRI-32743 attenuated Tat protein-induced inhibition of DAT-mediated DA uptake in an allosteric modulatory manner. Induction of Tat expression in inducible Tat transgenic (iTat-tg) mice by a 14-day administration of doxycycline resulted in a 2-fold increase in phasic stimulated baseline DA release in the caudate putamen slices, a 31.7% reduction of phase 3 recognition index in novel object recognition (NOR) and a 2.7-fold potentiation of cocaine-conditioned place preference (CPP) compared to the respective vehicle-treated iTat-tg mice. Systemic administration of SRI-32743 prior to testing reversed the Tat-increased DA release and ameliorated Tat-induced impairment of NOR (at a dose of 10 mg/kg) and the Tat-induced potentiation of cocaine-CPP (at a dose of 1 or 10 mg/kg). These findings demonstrate that Tat and cocaine interactions with DAT may be regulated by compounds interacting at the DAT allosteric modulatory sites,

suggesting a potential therapeutic intervention for HIV-infected patients with concurrent cocaine abuse.

O3P2

A dopaminergic memory circuit signals valence via a trio of transmitters in Drosophila melanogaster

Yishan Mai

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Dopamine (DA) is an important neurotransmitter conserved across many species, including humans, mice, and the vinegar fly Drosophila melanogaster. The function of the DA system is also conserved across these species; some of these functions include valence, arousal, and learning. In Drosophila, the DA system has been extensively studied for its role in memory, but the mechanism by which it communicates valence is not well understood. To study this, we developed an assay for examining the self-stimulation of DA neurons in Drosophila. With this assay, we show that a population of DA neurons that mediates appetitive learning also mediates positive valence. In addition, this positive valence is communicated not only by dopamine, but also by glutamate and octopamine, the insect ortholog for noradrenaline. We further show that a subset of these neurons communicates positive valence by dopamine and glutamate, but not octopamine. Our results indicate that the DA system in Drosophila communicates positive valence by a cocktail of neurotransmitters, and that subsets of this system utilize different combinations of neurotransmitters for the same purpose.

O3P3

Contrasting Effects of Finasteride Administration on Depression and Anxiety-like Behaviour and Synaptic Plasticity in Male and Female Rats

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One of the key enzymes responsible for the neurosteroid production is 5alpha-Reductase (5alpha-R) catalyzes a rate-limiting step. We examined the effects of short--term 5alpha-R inhibition using finasteride on depression and anxiety in male and female rats. We subjected male Wistar rats to repeated finasteride administration (10, 30 or 100 mg/Kg, s.c.) over a period of 6 days. We evaluated depression and anxiety-like behaviour in several paradigms. Short-term finasteride administration at 100 mg/Kg. s.c. resulted in increased immobility in the forced swim test, decreased grooming in the splash test, decreased sucrose preference and impaired social interaction. Further decreased open arm exploration in the elevated plus maze, decreased time spent in the centre in the open field test, decreased time spent in the light chamber in the light-dark test, and increased latency to feed in the novelty suppressed feeding test were observed. Further, the antidepressant effect of fluoxetine was diminished following finasteride administration. In female rats, we observed that finasteride administration decreased total immobility duration in FST, indicating antidepressant-like effect and decreased the latency to first bite in NSFT, showing anxiolytic-like effect. Interestingly, ex-vivo field potential recordings in the Schaffer Collateral-CA1 synapses showed that hippocampal LTP is impaired in male rats while it is enhanced in female rats. These results indicate interesting but contrasting effects of finasteride on male and female rats. Further research in this area has potential for development of novel neurosteroid-based therapeutics to treat neuropsychiatric diseases.

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O3P4

Developing Liang's contextual-stress box as an advanced anxiety-related murine behavioral test apparatus

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Designing new anxiety-related animal behavioral paradigms may become an important task in psychopharmacological researches. In our laboratory, Liang's contextual-stress box (Briefly, Liang's box) was designed and invented based on the 'approach-avoidance conflict theory' to induce anxiety-like behaviors in mice. Liang's box consisted of one open circular central area (diameter: 34cm) and three closed rectangular peripheral arms (length×width×height: 30cm×10cm×25cm). In order to investigate the advantages and primarily to assess the predictive validity of Liang's box, spatiotemporal data and ethological indexes in Liang's box were measured for 15min in mice using computer system and compared with their counterparts induced by the Elevated Plus-Maze (EPM) and the Open Field (OF) tests (classical experimental paradigms). Compared with EPM and OF, Liang's box showed advantages including simple experimental procedure, widened exploration area, moderate device structural conflicts, rational design of device shape, definitive division of sub-regions, and less statistical dispersions. The duration and frequency of Liang's restless posture (LRP), which is defined as the flat-back body stretching and hindleg abducting with or without creeping movement, head dipping or sniffing in mice, induced by Liang's box were significantly longer and higher than those of EPM and OF. Diazepam (0.5, 1.0 and 2.0mg·kg-1, i.p.) and buspirone (0.5, 2.0 and 10mg·kg-1, i.p.) administrated 30min before the Liang's box test could significantly reduce the duration and frequency of LRP in mice. 0.5 and 2.0mg·kg-1 diazepam statistically increased travel distance and time spent in the central area, zone transition, global activity, head-dipping, and total travel distance in Liang's box. Collectively, Liang's contextual-stress box can be used as an advanced anxiety-related murine behavioral model and experimental procedures with its advantages and developing potential in studying the pathophysiological mechanisms underlying anxiety, and screening and assessing certain new anxiolytics (National Natural Science Foundation of China, 82173799).

O3P5

Oligodendrocyte dynamics dictate individual performance outcomes of working memory training in mice

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Myelin-forming oligodendrocytes (OLs) continue to be formed in the healthy adult brain. In this work, we asked if newly forming OLs and the myelin they produce in adults are required for cognitive skills such as learning, recognition and working memory. Magnetic resonance imaging (MRI) can detect microstructural changes in white matter tracts of people practising visuospatial or auditory tasks that tax working memory, consistent with a role for oligodendrocytes and myelin in training-induced performance improvement (learning) in such tasks. To test this, we blocked OL differentiation in young adult mice, without affecting existing OLs and myelin, by conditional knockout (cKO) of the transcription factor Myelin regulatory factor (Myrf) in OL precursors (OLPs), using Pdgfra-CreERT2::Myrf(flox/flox) mice. We administered tamoxifen to 2-month-old mice, then 3 weeks later trained and tested them in T-maze and 8-arm radial maze (RAM) tasks that rely on working memory. Maze training stimulated OL production in the medial prefrontal cortex, anterior corpus callosum (genu), hippocampus and hippocampal fimbria; myelin sheath formation was also stimulated in the genu. Genetic blockade of OL differentiation and neo-myelination in Myrf-cKO mice strongly impaired training-induced performance improvement in the maze tasks while spatial and non-spatial recognition memory, reference memory, general locomotion, anxiety, and willingness to explore were not affected. Remarkably, working memory performance of individual mice correlated closely (coefficient of determination $R^2>0.7$) with the scale of OL precursor proliferation and OL generation in the genu and medial prefrontal cortex (anterior cingulate and prelimbic/infralimbic cortex) during training, indicating a key role for adaptive OL genesis and myelination in working memory training.

O3P6

Nervous System-Wide Connectome of Larval Zebrafish Based on Single-Excitatory/Inhibitory-Neuron Atlas

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Understanding the functions of the nervous system requires a comprehensive mesoconnectome. Zebrafish, as a model vertebrate, are endowed with brain-wide structural and functional connectome mapping at a cellular resolution. Using live imaging and high-precision registration, we generated a zebrafish nervous system-wide 3D Common Physical Space (CPS) with anatomical parcellations. Using this CPS, we have built a cytoarchitecture atlas of excitatory and inhibitory (EI) neurons and a single-neuron-morphology atlas with over 11,000 EI neuron reconstructions. We classified the dendrite/axon compartments and morphological types of EI projection neurons and constructed a directed and weighted inter-brain region connectome. We characterized the EI projection design rules, network motifs and hubs, and multi-sensorimotor transformation pathways. These expandable digital atlas resources in a common coordinate framework will pave ways for integrating and mining connectivity datasets of multimodality at multiple scales to support understanding of the vertebrate nervous system.

Poster Presentations

PP01

Modeling of fetal spinal cord ischemia using necrotic core-free human spinal cord organoids

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Fetal spinal cord ischemia is a serious medical condition that can result in significant neurological damage and adverse outcomes to the fetus. However, lack of appropriate experimental model has hampered the understanding of the pathology and development of effective treatments. In our study, we showed that spinal cord organoids are useful research tool to advance our understanding of fetal spinal cord ischemia. Importantly, we produced necrotic core-free human spinal cord organoids (nf-hSCOs) by reducing the organoid size, in order to avoid potential complication of spontaneous necrosis in the core of large organoids. Exposure to nf-hSCOs to hypoxia and hypoglycemia conditions resulted in significant neuronal damage, as assessed by multiple assay batteries. By utilizing this model, we tested chemicals reported to exhibit to beneficial exhibiting effects on brain organoid-based ischemia model. Surprisingly, these chemicals did not provide enough benefit, and we discovered rapamycin to be a mild neuroprotective reagent in both axon degeneration and neuronal survival. Our current system is a superior experimental model suitable for large-scale screening of fetal neural ischemia due to the scalability, ease of ischemic induction, quantifiability of the assays and the absence of spontaneous necrosis.

PP02

DNA methylation levels of RELN promoter region in ultra-high risk, first episode, and chronic cohorts of schizophrenia

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Diagnosing schizophrenia currently depends on subjective self-reported symptoms from interview-based assessments like the Positive and Negative Syndrome Scale (PANSS). Identifying an objective biomarker for psychosis would facilitate early diagnosis, intervention, and personalized treatment regimes for individuals predisposed to schizophrenia. The reelin gene (RELN) plays an essential role during brain development which makes it a prominent candidate in epigenetic studies on schizophrenia. Previous epigenetic studies investigating the transcriptional regulation of RELN have reported DNA methylation (DNAm) in individuals with schizophrenia. However, there is a paucity of such studies in other stages of psychosis.

Therefore, this study aims to (1) compare RELN DNAm levels at different stages of psychosis, (2) analyse the effect of antipsychotics (AP) on DNAm, and (3) evaluate the effectiveness of RELN promoter DNAm as a biological-based marker for symptom severity in psychosis.

The study cohort (N=199) consisted of 56 healthy controls (HC), 87 ultra-high risk (UHR), 26 first-episode (FE) psychosis, and 30 chronic schizophrenia (CS) individuals. From these individuals, PANSS was used to assess schizophrenia severity and DNA was extracted from their peripheral blood. Pyrosequencing was performed on selected CpG sites in the promoter region of RELN gene. DNAm levels were compared amongst the four subgroups and showed differing levels of DNAm, with UHR having the lowest while the CS having the highest. In addition, significantly higher DNAm levels were found in CS subjects that were medicated on antipsychotics compared to UHR without medication (*p=0.0181). A significant association was also observed between the DNAm of FE and PANSS negative symptom factor (R2=0.237, B=-0.401,

*p = 0.033). Our results showing differing levels of DNAm for patients at different stages of psychosis is consistent with existing literature, and with future experiments, there may be potential use of RELN gene DNAm levels as a biological-based marker for symptom severity in psychosis.

PP03

Sustained release triple drug loaded Colloidosomes for management of Parkinson's Disease

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Parkinson's disease (PD) is well-known as a progressive and degenerative disease of the nervous system. The degeneration of dopaminergic neurons in the substantia nigra, and a reduction in the amount of the neurotransmitter dopamine available in the striatum relate symptoms of this disease. It is hypothesized that a drug delivery system that provides controlled and sustained release of PD drugs would afford better management of PD. Hollow microcapsules composed of PMMA(polymethyl methacrylate) and poly (caprolactone) (PCL) are prepared through a modified double-emulsion technique. They are loaded with three PD drugs, i.e., levodopa (LD), carbidopa (CD), and entacapone (ENT), at a ratio of 4:1:8.

Microcapsules were prepared through a double emulsion (W1/O/W2) solvent evaporation method with modifications to produce hollow microshpheres. Microcapsules were then spray coated along with ENT. The microcapsules were analyzed for size distribution and zeta potential using Zetasizer. Shape and surface morphology were studied using SEM. Transmission electron microscope (TEM) was used as a visualizing aid for particle morpholgy. The average particle size and polydispersity index were determined by optical microscopy using a calibrated occulometer, drug entrapment, CLSM, Buoyancy tests and in-vitro drug release was studied.

LD and CD are localized in both the hollow cavity and PMMA/PCL shell, while ENT is localized in the PMMA/PCL shell. Release kinetics of hydrophobic ENT is observed to be relatively slow as compared to the other hydrophilic drugs. It is further hypothesized that encapsulating ENT into PCL as a surface coating onto these microcapsules can aid in accelerating its release. Now, these spray-coated hollow microcapsules exhibit similar release kinetics, according to Higuchi's rate, for all three drugs.

The results suggest that multiple drug encapsulation of LD, CD, and ENT in gastric floating microcapsules could be further developed for in-vivo evaluation for the management of PD.

PP04

Regulation of synaptic plasticity genes by curcumin in scopolamine-induced amnesic mice

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Rationale: Several research studies have revealed curcumin's anticarcinogenic, chemoprophylactic, antioxidant, antiangiogenic, nootropic, and immunomodulatory properties. However, definite evidence on the molecular pathways triggered by curcumin against neurological disorders, particularly amnesia or memory loss, is unavailable.

Hypothesis: As the memory process involves an interaction of diverse synaptic plasticity genes, we hypothesize that curcumin regulates the expression of specific synaptic plasticity genes in brain areas linked with memory processing.

Methodology: To test this hypothesis, we looked at how curcumin affected behaviour and the expression of synaptic plasticity genes (Arc, FMRP, c-fos and zif-268) in scopolamine-induced amnesic male mice. The Morris Water Maze test was administered for a week to assess their behavioural changes. The mice were euthanized on the seventh day, and their hippocampus and prefrontal cortex were separated for molecular research. Real-time PCR was used to examine the mRNA levels of synaptic plasticity genes, whereas Western blotting was used to examine their protein levels.

Results: In both brain areas, we found a substantial downregulation of Arc and FMRP during scopolamine-induced amnesia, which was upregulated by pre- and post-curcumin treatment. Surprisingly, we did not observe any significant change in the levels of c-fos and zif-268.

Significance: Our research indicates a molecular pattern for how curcumin alleviates amnesia, but more research on upstream signalling pathways would support the extract's medical utility in memory issues.

PP05

Mapping of Brain Phosphodiesterase 4D (PDE4) through 11C labelled High Affinity Inhibitors and their Empirical Quantitative Structure-Activity Relationship

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In this reported work we aimed to design a specific positron emission tomography (PET) radioligands for imaging of phosphodiesterase 4D (PDE4D) in brain, one of the main target for cognition enhancing and to investigate the neuropsychiatric problems.

We have exploration various chemical skeletons to get lead having optimal lipophilicity, high PDE4D inhibitory efficacy, selectivity with substantial brain uptake. These lead molecules were labeled with carbon-11 (t1/2 = 20.4 min) for evaluation in animal models. Further these molecules were pharmacological challenge by using BPN14770 and for biomathematical analysis. These radio ligands showed specific binding in prefrontal/ temporal and hippocampus which are specifically known for cognitive function. Out of four, three compounds showed instability over time in the brain region.

In addition to in vitro/in vivo analysis, we formulated an empirical equation to demonstrate the relationship between binding affinity and physic-chemical properties (R2 = 0.978, n = 52). Finally these compounds were correlated with specific TSPO markers to better understanding for the mapping of phosphodiesterase 4D (PDE4D) in brain

PP06

Neuroprotective effect of berberine loaded mesoporous silica nanoparticles: unravelling the mitochondrial pathways and cell cascades

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Berberine (BBR) loaded Mobil Composition of Matter-41 (MCM-41) mesoporous silica nanoparticles (MSNs) were prepared using modified Stober approach. The synthesized MSNs-BBR were evaluated for of particle size, morphology, polydispersity index, zeta potential, drug loading, entrapment efficiency, and in vitro drug release. Spectral analysis of the formulation was carried out using IR spectroscopy, powder X-ray diffraction analysis, Raman spectroscopy analysis, X-ray photoelectron spectroscopy analysis, and thermogravimetric analysis. Brunauer-Emmett-Teller analysis was done to determine specific surface area. Computational models were constructed to for molecular dynamics simulation study. A small PDI value indicated good dispersion homogeneity of the nanoparticles. The size of prepared MSN-BBR was in the range of 80-100 nm. XRD and SEAD analysis indicating amorphous nature of the material. The percentage BBR loading and entrapment efficiency in MSNs-BBR were found to be 28.16±2.5% and 75.21±1.55%, respectively. The zeta potential value of MCM-41 (-36.86±1.1 mV) was attributed to the presence of silanol groups on the silica surface. AFM results suggested an increased surface roughness of MSNs-BBR due to the bumps associated with the surface drug. TGA analysis confirmed BBR loading in MSNs. The drug release was delayed release up to 72 h in the selected dissolution media and followed a simple diffusion or quasi-diffusion-controlled drug release mechanism. Molecular dynamic simulation study confirmed diffusion process of the entrapped drug molecules. A dose-dependent proliferation of SH-SY-5Y cells was recorded. Phase-contrast microscopic images revealed an increase in apoptotic cells and a decrease in viable cells. MSNs-BBR treated SH-SY-5Y cells stained with DAPI showed nuclear apoptotic bodies and fragmented cell nuclei. Flow cytometric analysis showed an increased red to green ratio depicting improved mitochondrial health and prevention of apoptotic process and restoration of cellular viability in MSNs-BBR treated SH-SY-5Y cells.

PP07

Correlation of inflammatory cytokines, synaptic proteins and oxidative stress with developmental outcomes in autism spectrum disorder

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AIM-Autism Spectrum Disorder (ASD) is a complex, multifactorial neurodevelopmental disorder underscored by its heterogeneous symptomology. Accurate identification is challenging as ASD is often enmeshed with other neurodevelopmental and medical comorbidities. To assess the immune signatures as ASD biomarkers we investigated association and correlation between cytokines and synaptic proteins, where both sensitivity and specificity are of prime interest.

METHODS-A total of 142 children suspected of having an ASD and 130 matched controls were recruited for the study. Diagnosis was conducted by medical specialists, based on the International Classification – ICD-10, DSM-5, ADOS, CARS score. Serum IL's, neuron-specific enolase (NSE), indices of Lipid Peroxides-(LPO), nitric oxide-(NO), Protein carbonyls were assessed. Behavior and cognitive assessments were done quarterly.

RESULTS-The median serum TNF-α level, LPO ($p<0.01$), NO ($p<0.01$), Protein carbonyl ($p<0.01$) were significantly higher in ASD groupas compared to controls. ASD group showed significantly higher concentration of IL-1β, IL-4, IL-6 and IL-13 as compared to the controls. Significant correlations between cytokines, IL- beta and α-synuclein were observed in ASD group as compared to controls. The serum cytokine and TNF-α level were correlated with behavior recurrence and hyperactivity, but they did not correlate with family history, behavior, and sleep pattern.

CONCLUSION-Our results provide insights into cytokine-specific differences, synaptic protein & oxidative-stress-indices alterations in ASD exposed to sleep abnormalities. The result supports the possibility of using an appropriate selection of serum cytokine for early ASD diagnosis, emphasizes the need to standardize quantitative methods for serum analysis. Our findings also contribute to the ongoing efforts toward identification of early biological markers specific to ASD and rehabilitation.

PP08

Citral inhibits neuroinflammation in HFD/STZ induced diabetic rats via p38MAPK/Nrf2 signalling pathways

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Introduction: Hyperglycemia is considered to be a major pathophysiological factor in the development of diabetic neuropathy. Therefore, this study was designed to explore the effect of Citral on cognitive dysfunction and neuroinflammation in diabetic rats via p38 MAPK/Nrf2 pathway

Method: Diabetes was induced by Streptozotocin (STZ) at a dose of 35 mg/kg/b.w injected intraperitoneally (i.p.) in high fat diet (HFD) in Sprauge Dawley (SD) rats. Streptozotocin/high-fat diet-induced diabetic rats were treated orally with Citral for six consecutive weeks. Learning and memory functions were assessed using Morris water and Y maze tests. Antioxidant capacity, and lipid peroxidation markers in hippocampus were also investigated. Proinflammatory cytokines, caspase 3 and nuclear factor kappa light chain enhancer of activated B (NF-kB) were determined by ELISA kits. In addition the expression levels of p38 MAPK and nuclear factor erythroid 2 related factor 2 (Nrf2) were determined by western blot analysis

Result: The results showed that Citral significantly reduced blood sugar level and also improved serum lipid level in SD rats. Data showed that mangiferin increased the activity of anti-oxidative enzymes in the brain tissue by reducing oxidative stress. Citral improved behaviours deficit in the Morris water maze. Citral administration also significantly suppressed p38MAPK pathway and upregulated the Nrf2 pathway.

Conclusion: Our finding suggests that Citral improved cognitive dysfunction and neuroinflammation in diabetic rats by modulating MAPK and Nrf2 pathways

Key Words: Diabetes, Ischemic Stroke, Mangiferin, Neuroprotection, Neuroinflammation

PP09

Eugenol attenuates LPS induced cognitive impairments in male rats by suppressing oxidative stress and inflammation in male rats : An in vivo and in-sillico study

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Microglia induced neuro-inflammation significantly influence the pathogenesis and progression of neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis.. The drugs used in the treatment of neurodegenerative disorders are often accompanied by several side effects. In this study, we are investigating the identification of a novel drug against neuro-inflammatory disorders by using phytochemical eugenol.

The rats were orally treated with eugenol for ten days prior to LPS injection (5mg/kg I.P.) and after the treatment, assessed for neuro-inflammatory markers, Behavioral dysfunction and oxidative end points. Molecular docking and MD simulations study of the all phytochemicals of the eugenol against pro-inflammatory enzymes (Cyclooxygenase and Lipoxygenase) and NF-kB was also assessed to understand their modes of action.

In rats exposed to LPS, there were significant decrease in the activity of membrane proteins and ion channels, such as acetylcholinesterase, Na+-K+ ATPase, and the low level of reduced glutathione, as well as an increase in the amounts of superoxide anions, hydrogen peroxides, and lipid peroxidation. The rats groups received LPS injections showed mild histopathological alterations in their brains. The rat brain after LPS injection had higher levels of NF-kB, IL-6 and TNF-α transcripts. We discovered that LPS treatment causes cognitive decline in rats along with microglia activation and neuronal cell death in the hippocampus. However, eugenol administration attenuated the LPS induced neuro-inflammation by reverting the enhanced level of level of IL-6 and TNF-α. The in sillico analysis and MD simulation study showed that the eugenol provides a low docking energies against these proteins and stability during simulation

with least RMSD and RMSF fluctuation. Our study shows the anti-neuro-inflammatory potential of eugenol; thus, eugenol may have therapeutic potential to improve cognitive and behavioral function in neuro-inflammation-related diseases. And these data may provide additional insight for researchers performing neuro-inflammation research.

PP10

Integration of MRS and labeled glucose analysis for mapping the dynamics of metabolism (glial/astrocytic)

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In last century, the concept of cellular metabolism has been revolutionized in terms of biological energy production. Recently in last two decades with invention of non-invasive biomedical modalities like PET and MRS, the capabilities of getting intense inputs has been increased with reference to biochemical and physiological processes.

In this reported work, we have utilised 18F-fluorodeoxyglucose [18F]FDG along with qMRS having CSI, generating dynamic maps. This helps us to monitor dynamic metabolism in quantified manner for selected brain regions. Sprague-Dawley rats were imaged with [18F]FDG positron emission tomography (PET) on two local points.PET acquisition on both time point was performed for 20 minutes at 45 minutes after tracer injection.

In PET analysis significantly alteration was found in [18F]FDG accumulation in amygdala, hypothalamus and hippocampus regions. In our MRS studies quantified glutamate was higher in gray matter rather than white matter. In addition turnover value from glucose to glutamate was also high in gray matter in comparison to white matter.

In conclusion we identified the decrease in glutamate and the increase in small fragments (metabolites) in 1H spectrum. Given the value of glucose-to-glutamate turnover and neural glucose metabolism we may use this in different pathological conditions.

PP11

Neuroprotective Effect of Citral against Transient Focal Cerebral Ischemia through the Regulation of mitochondrial function and autophagy in Type II Diabetes in Rats

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Introduction: Emerging evidence suggests a strong correlation between apoptosis, autophagy and their pathological processes in cerebral ischemic injury particularly in diabetes. Oxidative stress and blood brain barrier dysfunction are one of the important factors causing disability and mortality in stroke patients, which have a significant impact on diabetic induced stroke progression. Citral have been reported to antioxidant and anti-inflammatory activity.

The aim of this study was to investigate the therapeutic effects of citral against ischemic stroke in diabetic rats and its role in modulating autophagy.

Methods: Diabetes was induced by intraperitoneal (i.p) injection of streptozotocin (35 mg/kg) in male Sprague Dawley (SD) rats and rats were subjected to middle cerebral artery occlusion (MCAO) for 1 hour. Citral was administered at 3 hours after the induction of MCAO. Lipid profile, blood glucose, Neurological deficit, oxidative stress makers (MDA & GSH), blood brain barrier (BBB) permeability and brain edema, were measured. Mitochondrial complexes, mitochondrial bioenergetics were also be measured to evaluate the mitochondrial dysfunction. Additionally, RT-PCR and western blot analysis of Bcl-2, Beclin-1 and LC3 were examined.

Result: Citral significantly reduced brain edema, BBB integrity, oxidative damage and ameliorated neurologic outcome in rats. Citral treatment significantly decreased serum glucose level, serum TG, TC and serum LDL. Meanwhile, treatment with citral modulates mitochondrial complexes after MCAO and also significantly restored the mitochondrial bioenergetics. Citral decreased apoptosis and autophagy via down-regulation of the LC3 and Beclin-1 expression.

~~Conclusion: Our finding suggests that citral attenuates cerebral ischemic injury in diabetic rats and promotes functional recovery via its antioxidant, anti-apoptosis, and anti-autophagy properties, may have a therapeutic potential for stroke prevention in diabetic settings.~~

PP12

Protective effect of neurosteroid Ganaxolone in APPswe transfected SH-SY5Y cells

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Background: Alzheimer's disease (AD) is a neurological disease characterised pathologically by loss of synapses and neurones, accumulation of amyloid-beta (Aβ) deposits and the formation of neurofibrillary tangles. This results in progressive cognitive impairment as people age. Ganaxolone, a synthetic analogue of allopregnanolone, has shown a protective effect on gliosis associated with demyelination. However, its effect on amyloid-beta (Aβ) deposits and neuronal loss associated with AD is still unknown. Additionally, its effect on liver x receptors (LXR) has not been reported yet. In this study, we investigated the effect of Ganaxolone on Aβ toxicity in receptor-dependent manner, and studied the downstream processes involved. Methods: The APPswe plasmid was transfected into the SH-SY5Y neuroblastoma cell line to establish a cell model of AD. Cells were treated with graded concentration of Ganaxolone for 24 h followed by ThT binding assay and Congo red staining to monitor the effect of Ganaxolone on in vitro amyloid formation. Aβ 40 and 42 levels were assessed by ELISA, immunofluorescence and Western blot. After treatment, changes in LXR gene expression and associated downstream signaling molecules were confirmed by RT-PCR and Western blot. Results: Treatment with Ganaxolone upregulated the expression of LXR and associated downstream target reducing the reactive oxygen species and amyloid-beta 40/42 expression. The results indicate that the cytoprotection conferred by Ganaxolone on APPswe transfected SH-SY5Y cells is mediated by its ability to upregulate the expression of LXR and downstream signalling pathway. Hereby, we propose that Ganaxolone may be a tractable drug for the treatment of AD.

PP13

Lactic Acid Conjugated SLN for Effective Management of Neurocysticercosis

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Neurocysticercosis(NCC) is a primary infection of brain, spinal cord or peri-meningeal structures with the larval forms of Taenia solium and associated inflammation, which is aggravated by debris of parasites by anthelminthics. The study aimed to develop Lactic acid(LA)-conjugated solid lipid nanoparticles(SLN-LA) bearing albendazole(ALB) and prednisolone(PRD) for effective management of NCC.

SLN were prepared using modified solvent injection method with slight modifications. LA was coupled to SLN by post-insertion technique. SLNs were characterized for particle size and size distribution, shape, and percent drug entrapment efficiency. In-vitro drug release kinetics, and in-vitro transendothelial transport studies were carried out to predict the fullest drug delivery potential. In-Vivo studies included fluorescence study and hematological toxicity studies.

The SLNs were found to be Spherical with high drug entrapments. In-vitro release showed initial quick release, followed by sustained release for more than 48 h. Fluorescence study and in-vitro transendothelial transport depicted selective brain uptake of SLN-LA compared to SLN attributed to carrier mediated transport via monocarboxylic acid transporters. Pharmacokinetic parameters such as AUC0-t and AUMC0-t and Cllast showed good drugs withholding capacity of SLNs. Organ distribution studies reflected high accumulation of drugs in the brain after 24 h in case of SLN-LA as compared to plain drugs solution. SLN-LA in hematological studies revealed insignificant toxicity to blood cells.

On basis of above findings, developed lactic acid conjugated SLN could be a promising tool to treat NCC effectively by dual drug delivery to brain. Since, NCC being chronic in nature requires long term therapy, SLN-LA not only targeted brain but also offered sustained and prolonged release of these synergistic drugs in which

albendazole kills the parasites and prednisolone alleviates inflammation due to deceased parasites in the brain. Hence, this targeted brain delivery was found to be safe and efficacious for the management of NCC.

PP14

Analysis of Defects in Neuromuscular Junction Maintenance in a Zebrafish Model for Intermediate Type Spinal Muscular Atrophy

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Spinal Muscular Atrophy (SMA) is a neurodegenerative disease caused by low levels of ubiquitously expressed Survival Motor Neuron (SMN) protein, leading to motor neuron (MN) degeneration. It remains unclear how a global deficiency of SMN, a chaperone essential for small nuclear ribonucleoprotein (snRNP) assembly, leads to selective MN vulnerability and defective neuromuscular junctions (NMJs). Previous studies in mouse SMA models reported alterations in the cytoskeletal network and mitochondria dynamics as possible consequences of axonal transport defects. In this study, we used a zebrafish smnA6Tindel27 mutant model for intermediate Type SMA to examine SMN's role in NMJ maintenance and to assess whether axonal transport defects represent a plausible explanation for impaired maintenance of NMJs and SMA symptoms. Preliminary transcriptome analysis of mutant zebrafish MNs at pre-symptomatic stages revealed splicing defects in crucial MN transcripts despite the lack of any observable phenotypes. This suggests that Smn is required for splicing control during early NMJ maintenance. At symptomatic stages, a significant number of genes was upregulated, which might account for a possible compensation to make MNs more resilient to Smn reduction. This approach thus opens the possibility to identify genes that are capable of promoting MN survival under Smn-deficient conditions. Next, to perform live imaging of axonal transport and synapse maintenance in zebrafish smn mutants in vivo, we established several novel transgenic reporter lines to visualise different components of the axonal transport machinery in MNs and synapse maintenance at NMJs. Our preliminary results suggest that mitochondrial dynamics is impaired in axons of Smn-deficient motor neurons. Together, these tools promise unique insights into how aberrant splicing of MN genes due to SMN deficiency results in axonal transport and NMJ maintenance defects in intermediate types of SMA.

PP15

An integrated single-cell transcriptome landscape of postnatal and young adult mouse hypothalamus

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The neural stem cells (NSCs) in the hypothalamus are relatively more narrowly defined than in other neurogenic regions of the postnatal brain. By leveraging single-cell RNA sequencing (scRNA-seq) data, we generated an integrated reference dataset comprising 296,282 cells from postnatal hypothalamic regions and the adjacent region, bed nucleus of the stria terminalis (BNST), and identified 30 hypothalamic neuronal and non-neuronal cell populations. The analyses of their gene expression pattern, and specific differentiation trajectories reveal the presence of NSCs and intermediate progenitor cells (IPCs) that show a continuum of activation and differentiation processes in the hypothalamus after birth. Through comparative analyses of the integrated dataset with our lab-generated Connect-seq data obtained from the whole hypothalamus, we further assessed the technical validity of the dataset presented in this study. Our large-scale unified scRNA-seq dataset with harmonized cell-level metadata can serve as a valuable resource for investigating cell type-specific gene expression and cellular differentiation trajectories in the postnatal mouse hypothalamus.

PP16

Studying worm locomotion through the lens of neuropeptidergic signalling mechanisms

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Foraging is an important behavior seen in most animals. In C. elegans it is an amalgam of different types of locomotory movements that include forward crawls, turns and reversals. When C. elegans are transferred from well-fed conditions to a plate without food, they explore the arena in a localised manner with a combination of reorientations. Defects in reorientations and/or the body wave parameters like the amplitude of the sinusoidal waves result in inefficient exploration of the environment. This exploration, is reported to be mediated by chemosensory and mechanosensory neurons in coordination with the metabolic status of the organism, but the mechanism is poorly understood. We hypothesise that the non-wired neuropeptidergic circuit regulates these behaviors.We screened through genetic mutants of neuropeptides for defects in local and global search behaviors. So far, from our screen, we have found that neuropeptides FLP-8, FLP-15, FLP-17, NLP-49, FLP-6, INS-3, and PDF-1 regulate the reversal frequency. Interestingly we found that FLP-15 regulates the frequency and length of reversals during both local and global search. We further observed that FLP-15, is expressed in a subset of head neurons and functions through the G-protein-coupled receptor, NPR-3, to regulate foraging behaviors. Our results show that the mutants in neuropeptide flp-15 and receptor npr-3 show significant decrease in reversal frequency during local search. In an interesting observation, we also found that FLP-15, possibly through NPR-3, also regulates amplitude of the body bends. Our experiments show that flp-15 and npr-3 mutants show a significant increase in the amplitude of the body bends during sinusoidal movements, when compared to wild-type control animals and therefore are unable to explore their surroundings effectively during foraging. Our ongoing genetic and physiological manipulation experiments will help us in elucidating the functional circuitry through with FLP-15 and NPR-3 allow for normal locomotion in C. elegans.

PP17

TRPV2 activation by focal mechanical stimulation enhances growth cone motility

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We previously reported that TRPV2 can be activated by mechanical stimulation which enhances axonal outgrowth in developing neurons (Shibasaki et al., J. Neurosci. 2010). However, the molecular mechanisms governing the contribution of TRPV2 activation to axonal outgrowth remain unclear. In this study, we examined this mechanism. Overexpression of TRPV2 enhanced axonal outgrowth in a mechanical stimulus-dependent manner. Accumulation of TRPV2 at the cell surface was 4-fold greater in the growth cone compared to the soma. In the growth cone, TRPV2 is not static, but dynamically accumulates (within ~100 msec) to the site of mechanical stimulation. The dynamic and acute clustering of TRPV2 can enhance very weak mechanical stimuli through the focal accumulation of TRPV2. Focal application of mechanical stimuli dramatically increased growth cone motility and caused actin reorganization through the activation of TRPV2. We also found that TRPV2 physically interacts with actin, and changes in the actin cytoskeleton are required for its activation. Here, we demonstrated for the first time that TRPV2 clustering is induced by mechanical stimulation generated by axonal outgrowth, and TRPV2 activation is triggered by actin rearrangements resulting from mechanical stimulation. Moreover, TRPV2 activation enhances growth cone motility and actin accumulation to promote axonal outgrowth.

PP18

Exploring headache management and self-medication practices among health care professionals in Karachi, Pakistan

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Introduction:Headache is a common neurological symptom that affects a large proportion of the population worldwide. However, there is limited research on the understanding and management of headaches in many settings, including Karachi, Pakistan. In this study, we aimed to explore the prevalence, self-medication and management of headaches among healthcare professionals and students in Karachi.

Methods:A cross-sectional survey was conducted among 140 healthcare professionals and students in Karachi. The survey consisted of questions about demographic characteristics, types of headaches experienced, self-medication and management practices for headaches.

Results:Of the 140 respondents, 55% were female and 53.6% were unmarried. In regard with the prevalence of different types of headaches. The majority of respondents reported experiencing tension-type headaches (62.8%), with 44.6% reporting migraines and 5.9% reporting other types of headaches. A large proportion of respondents reported using self-medication for their headaches, regardless of the type of headache experienced. Specifically, 38.5% of respondents reported relying on over-the-counter medications or home remedies to manage their headaches.

These findings suggest that there may be a lack of awareness or access to appropriate medical care for headaches among the population surveyed. Increased education and awareness campaigns about the importance of seeking medical care for headaches could help improve headache management and reduce reliance on self-medication. Further research is needed to explore the prevalence and impact of headaches in other settings and populations, as well as to identify effective interventions for improving headache management and reducing the burden of headaches on individuals and society.

Conclusion:Overall, the results of this study highlight the need for greater understanding and awareness of headaches among the general population in Karachi, Pakistan. Healthcare professionals and policy makers should work together to address the issues identified in this study and to improve the management of headaches in the region.

PP19

INVESTIGATING THE RELATION BETWEEN VALENCE AND LOCOMOTOR PERFORMANCE USING WELL ESTABLISHED OPTOGENETICS IN DROSOPHILA MELANOGASTER

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In affluent nations, depression is the single greatest burden on society and health care systems. Anhedonia, defined as the lack of positive affect and appetitive motivation, is the main component of depression and a symptom in many psychiatric disorders. It has been previously shown that chronic stress can induce anhedonia-like qualities, such as a lack of motivation and sleep disorders, in Drosophila melanogaster, the vinegar fly. In this commonly used genetic model, 60% of the genome is homologous to human genes and 75% of human disease-causing genes have functional homologs in flies. In the fly's brain, the mushroom body (MB) is the central region for learning, locomotion, sleep, and appetitive motivation. It is possible that there is a connection between MB circuitry and anhedonia-related processes. The MB is thought to regulate valence, the degree to which something is approachable or aversive, a function conserved between flies and mammals. MB output neurons (MBONs) have been proposed to drive both learned and innate valence-related behaviours. However, our preliminary data indicate that, in addition to affecting valence-related behavior, the activation of specific MBON populations elicits direct changes in locomotor activity. Thus, I hypothesize that specific MBONs are involved in basic locomotion and motor function. I am testing this hypothesis with a behavioural genetic screen to assess which aspects of locomotion are modified by MBON activation or silencing to generate a bias between approach and avoidance. I will also investigate if the co-activation or co-silencing of MBONs is additive or subtractive in overall motor performance. This study will advance our understanding of the MBON locomotor circuitry and the mechanisms of how MBON inputs guide approaching and avoidance behaviours, with the aim to further elucidate the link between anhedonia and MBONs.

PP20

The D1R-specific NSFdeficient mice as a novel schizophrenic model

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Dysregulated dopaminergic modulation in the striatal and prefrontal function is fundamental to many models that seek to explain the mechanisms underlying the symptoms of schizophrenia. Although binding of radioligand to the dopamine D1 receptor (D1R) was reduced in the prefrontal cortex of schizophrenics, it remains unclear whether these are causal relationship between prefrontal cortex and striatal pathology. As previous report has already shown that N-ethylmaleimide sensitive factor (NSF) expression is reduced in postmortem brain tissue of schizophrenic patients. NSF interacts with D1R and regulates the localization of D1R. In the present study, we generated the D1R-specific NSF conditional knockout mice (D1R-NSFcKO) and investigated their behavioral, neurotransmitter, and neurophysiological phenotypes in vivo. D1R-NSFcKO mice exhibited the abnormal spontaneous rotation behaviors and high locomotion activity. The dopamine D2 receptor antagonist sulpiride suppressed the hyperactive in D1R-NSFcKO mice. To investigate whether dopamine abnormalities in the striatum, we used the HPLC-ECD analysis. We found that dopamine was significantly increased in the striatum of D1R-NSFcKO mice compared with that of control mice. These findings demonstrate that NSF plays a role in motor activation via regulating the dopamine and dopamine receptor. The mice in which reduced NSF in D1R-expressing cell may be a novel schizophrenic model.

PP21

Micropattern-based axonal growth assay using human neural organoid

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Neural organoids hold great potential as a tool for modeling various brain diseases and screening effective drug candidates due to their ability to preserve the structural and cell-type complexity of the brain. However, the random growth of axons on coated culture dishes hinders the development of a rapid and sensitive method for quantifying axonal outgrowth in human neural organoids. To overcome this challenge, we have developed a micropattern-based platform that enables organoids to grow along linear patterns on the surface, allowing neurites to grow straight and facilitating easy and accurate quantification. Our platform was tested on spinal cord organoids (SCO) and revealed differences in axonal outgrowth rates depending on the developmental stage and coating materials of the organoids. We validated the robustness of the platform by using it to screen drugs that promote or prevent axonal outgrowth after nerve injury. Additionally, we demonstrated that co-cultured Schwann cells influenced the extension of the motor axons from the ventralized spinal cord organoids. Overall, our micropattern-based organoid culture system provides a highly flexible, sensitive, and easy-to-use method for evaluating the responses of outgrowing axons to various externally applied variables, including cells, coating substrates, applied chemicals, and physical/chemical damage.

PP22

Particulate Matter (PM2.5) exposure contributes to glial cells activation and neurodegeneration through the olfactory-brain axis

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Keywords: Air Pollution, Olfactory-Brain axis, Particulate Matter, neurodegeneration.

Objective: To identify the molecular mechanism that causes glial cell activation and neurodegeneration when exposed to ambient particulate matter (PM2.5).

Background: The olfactory bulb is intimately connected to environmental contaminants, inflammation brought on by exposure to PM2.5, and activation of glial cells. As the olfactory inflammation spreads, it affects cognitive and motor skills in the brain by activating glial cells and causing neurodegeneration. Our research examines how the molecular mechanism of olfactory-brain axis induced neurodegeneration.

Methods: When PM2.5 is exposed at a concentration of 60µg/ml, glial cell activation in the olfactory bulb causes neuroinflammation in the brain. To assess motor impairment and spatial memory, the Open Field Test (OFT), Novel Object Recognition Test (NORT), and Morris Water Maze were utilized (MWM). Polyaromatic hydrocarbons in PM2.5 were found to be the primary factor inducing bidirectional inflammation and neurotoxicity. Further marked imbalance was observed in the levels of neurotransmitter in hippocampus. Olfactory function test revealed critical changes in the mice indicating loss of its function and neurodegeneration in the olfactory and hippocampus tissues of C57BL/6 mice (n=10).

Results: The expression of the markers GFAP, iba-1, and CD-68 was elevated in the mouse olfactory bulb and hippocampus. Reduced neurotransmitter levels are associated with persistent bidirectional inflammation in the olfactory bulb and the brain, which results in hippocampus memory loss, as shown by the olfactory function test and neurobehavioral analysis [Open Field Test (OFT), Novel Object Recognition Test (NORT), and Morris Water Maze (MWM)].

Conclusion: According to the present research, PM2.5 exhibits neurotoxic effects at a dosage of 60μg/ml through changing the olfactory pathway's structure and operation. Chronic exposure to PM2.5 in C57BL/6 mice displayed signs of impaired motor function, increased inflammation, and worse spatial memory.

PP23

Study of metabolites of the kynurenine pathway in a rat model of neuropathic pain

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Background: Chronic pain is associated with anxiety and depression in humans. Though neuropathic pain mechanisms were extensively researched, an exact link between neuropathic pain and the kynurenine pathway (KP) is yet to be understood. In this study, we investigated the correlation between immune-mediated KP activation following peripheral nerve injury. The hippocampus was chosen for this study because it is a structure which involved in emotionality, learning, and memory. So, the aim of the study was to assess the effect of partial sciatic nerve ligation (PSNL) on the levels of kynurenine signalling pathway metabolites in the serum and brain of rats.

Methods: The experimental protocol was approved by the institutional ethics committee (IAEC no. 334/IAEC-1/2022). Sprague–Dawley rats (n=6 per group, 200-250 gms) were divided into Sham and PSNL groups. Neuropathic pain was developed by PSNL surgery under anaesthesia. The animals were sacrificed on day 14 or 28. Further, fresh brains and serum were collected, processed, and stored for LC-MS for measuring KP metabolites. All the parameters of the tandem mass spectrometer and HPLC were controlled by Analyst software, version 1.7.3 (AB Sciex, Foster City, CA, USA) and Open LAB control panel software (Agilent Technologies, 1260 Infinity, Santa Clara, CA, USA), respectively.

Results: The data of the LC-MS/MS methods were recorded as Mean ± S.E.M. (Standard error of the mean) and the graphs were plotted for intergroup comparison. In LC-MS/MS method, QUIN/TRYP ratio was founded more in the hippocampus of PSNL as compared to the Sham group and the same results were found in the concentration of tryptophan.

Conclusion: These findings provide preliminary evidence of some alteration in biochemical parameters but it is difficult to make a definition conclusion. This study provides baseline data to understand the role of KP metabolite in the development of chronic pain.

PP24

TBD

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Eukaryotic mRNA is 5'-end capped with m7 guanosine, known as cap0 (m7GpppNpNp, N: any nucleotide). Cap methyltransferase (CMTR1) further catalyzes 2'-O-ribose methylation of the first transcribed nucleotide (N1 2'-O-Me) to produce the cap1 (m7GpppNmNp) structure in all eukaryotes except yeasts. Although the cap0 structure is essential for mRNA stability and cap-dependent translation, it is not known whether cap1 modification also plays a role in regulating posttranscriptional gene expression. Our previous study found that CMTR1 deficiency affects dendritic arborization and cortical development. Because CMTR1 is highly expressed in the hippocampus, I investigated whether CMTR1 modulates synaptic plasticity and spatial memory by using conditional knockout (cKOCamk2, Cmtr1f/f, Camk2-Cre/+) mice whose Cmtr1 gene is ablated in the hippocampal CA1 and certain forebrain regions after postnatal 3-4 weeks, so dendritic development is not affected in CMTR1-cKOCamk2 mice. We found that CMTR1-cKO mice showed impaired memory consolidation in Morris water maze assay. Although one train of high-frequency stimulation (HFS) and theta-burst stimulation (TBS)-evoked long-term potentiation (LTP) was comparable between cWT and cKO mice, protein synthesis-dependent long-lasting LTP elicited by 4 trains of HFS and TBS was diminished in the cKO group. Moreover, I found that the number but not the size of dendritic spines was reduced in CMTR1-knockdown cortical neurons, suggesting the role of CMTR1 in synaptogenesis. My transcriptome study projects the possibility of that downregulated N-methyl-D-aspartate receptor (NMDAR)-related pathways may account for behavioral and electrophysiological defects. The reduction of NMDAR subunits, NR2A and NR2B, was confirmed by qRT-PCR. Intraperitoneal injection of D-cycloserine, an NMDAR coagonist, right before spatial learning seems to rescue the behavior defect. Further study is required to understand the molecular mechanism underlying impaired memory consolidation in CMTR1-cKO mice and whether the catalytic activity of CMTR1 is crucial for synaptic plasticity and memory.

PP25

Genotype-phenotype correlation of Synaptojanin 1 mutations in Parkinsonism

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Synaptojanin 1 (SJ1) is a phosphoinositide phosphatase that is essential for synaptic vesicle recycling. Previously, we identified the first homozygous mutation (i.e. R258Q or RQ in short) in the Sac phosphatase domain of SJ1, which abolished Sac domain activity, leading to partial loss-of-function of SJ1 in early-onset parkinsonism (EOP) patients. SJ1 R258Q/R258Q knock-in mice recapitulate patients' manifestations and exhibit selective axonal terminal dystrophy in nigrostriatal dopaminergic neurons. More recently, a compound heterozygous mutation (m1:W171* / m2:R258Q) was identified in a new EOP family. The patients carry an allele with SJ1 containing the R258Q mutation and an allele with a premature stop codon that rendered "knock-out" in the gene. These patients show epilepsy early in the disease progression, severe neurodegenerative symptoms and generalized dopa-responsive dystonia in their early teen years. In this study, we generated SJ1 -/RQ mice to mimic this compound heterozygous mutation and examined whether this mutation worsens Parkinson-like phenotype in a gene dosage dependent manner.

Comparing with SJ1 RQ/RQ mice, SJ1 -/RQ mice demonstrated shorter lifespan and smaller in body size and weight. They also displayed more severe motor deficits at 2 months old onwards and these deficits can be restored partially after Mao B inhibition. We also observed similar TH/DAT axon terminal clusters in both the dorsal and ventral striatum in the SJ1 -/RQ mice, suggesting that dopaminergic neurons in both SNr and VTA regions are affected. More importantly, these dystrophic terminal structures gradually disappear in the SJ1 RQ/RQ striatum, but it was maintained in SJ1 -/RQ mice at 6 months old, indicating that potential repair mechanism during development is impaired due to the further loss-of-function of SJ1 in compound heterozygous situation. Together, this study demonstrated a genotype and phenotype correlation of SJ1 mutations that further supports its important function in regulating synaptic transmission in dopaminergic neurons.

PP26

Minocycline inhibits lipopolysaccharide (LPS)-induced neurotoxicity

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Autism spectrum disorders (ASD) and mental disorders have been on the rise recently, and cerebellar degeneration is one of the pathological focal points in early ASD. In this laboratory, we have generated autism model rats treated with sodium valproate (VPA) and have confirmed folds in cerebral lobules V/VI . Whereas changes in internal immunity due to infection and antibiotics are associated with mental disorders. Lipopolysaccharide (LPS) is a proinflammatory factor via binding to Toll-like receptor 4 and may cause mental disorders. Inflammation and neurodegenerative diseases have been linked, as studies have shown that LPS levels are elevated in the brain of Alzheimer's disease, one of the most common neurodegenerative diseases. Minocycline is one of the most effective tetracycline derivatives for neuroprotection because of its antibacterial activity and inhibition of microglia activation.

We administrated 100 μg/kg of LPS to pregnant rats on gestation day 16 and observed the cerebellum of pups at 7 and 14 days after birth (P7, P14, respectively). As for minocycline post-treatment, we administrated LPS-exposed pups with 50mg/kg minocycline from P3-P9 orally. We report that LPS-administration to embryonic animals showed a similar symptom of VPA-models in the early phase and progressed neuronal cell death gradually. Rats treated with PBS were used as vehicle. In LPS-exposed rats at P7, we observed earlier and increased NeuN+ cells, similar to VPA-model. In minocycline treatment rats we observed even more NeuN+ cells in Purkinje layer. At P14, a decrease in Purkinje cells and excessive folding of lobules V/VI were observed in LPS-exposed rats. During P14, we also observed a decrease in H3K9me1 expression in LPS-exposed rats. We suggest that minocycline inhibits the neurotoxicity of LPS that would induce neurodevelopmental alteration due to immune malformation and eventually neuronal cell death. These results also suggest that LPS do not induce neurotoxicity through microglia only.

PP27

In vitro generation of brain regulatory T cells by co-culturing with astrocytes

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Regulatory T cells (Tregs) are normally born in the thymus and activated in secondary lymphoid tissues to suppress immune responses in the lymph node and at sites of inflammation. Recent studies showed that tissue Tregs are resident in various tissues or accumulate in damaged tissues and contribute to homeostasis and tissue repair by interacting with non-immune cells. We have shown that Tregs accumulate in the brain during the chronic phase in a mouse cerebral infarction model, and these Tregs acquire the characteristic properties of brain Tregs and contribute to the recovery of neurological damage by interacting with astrocytes. However, the mechanism of tissue Treg development is not fully understood. We developed a culture method that confers brain Treg characteristics in vitro. Naive Tregs from the spleen were activated and efficiently amplified by T-cell receptor (TCR) stimulation in the presence of primary astrocytes. We further found that adding IL-33 and serotonin could confer part of the properties of brain Tregs, such as ST2 and serotonin receptor 7 (Htr7) expression. Transcriptome analysis revealed that in vitro generated brain Treg-like Tregs (induced brain Tregs; iB-Tregs) showed similar gene expression patterns as those in in vivo brain Tregs. Furthermore, in Parkinson's disease models, iB-Tregs infiltrated into the brain more readily and ameliorated pathological symptoms more effectively than splenic Tregs. These data indicate that iB-Tregs contribute to our understanding of brain Treg development and could also be therapeutic for inflammatory brain diseases.

PP28

Elucidating a novel role of Parkinson's disease-associated protein Parkin (PARK2) in synaptic membrane trafficking

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Membrane trafficking defects have been implicated as one of the core components in Parkinson's Disease (PD), a progressive neurodegenerative disorder that results in severe motor deficits. Several genes associated with Clathrin-Mediated Endocytosis (CME) have been identified as PD risk genes, suggesting a putative link between trafficking defects and early dysfunction in the nigrostriatal dopaminergic fibers. Intriguingly, recent work on endocytosis-defective mutants has implicated a renowned PD protein: Parkin (or PARK2), an E3 Ubiquitin ligase conventionally involved in mitochondrial quality control. Parkin is reported to mono-ubiquitinate Synaptic Vesicle Endocytosis (SVE) proteins such as EndophilinA1, Synaptojanin1 (SJ1) and Dynamin1, indicating that it might regulate their activity. Parkinsonism linked SJ1RQ-KI as well as EndophilinA1-KO mice show increased levels of Parkin in comparison to other PD related proteins. Hence, we propose that Parkin has a novel role in modulating SVE through regulation of CME protein-protein interactions. Utilizing a SJ1RQ-KI/Parkin-KO mice model, we investigated the interaction between these proteins at a functional level. We report a decreased survival rate in the double mutant mice compared to single mutants alongside increase in epileptic seizures and behavioral defects. Aberrant clustering of SVE proteins is observed in inhibitory synapses (in vivo and in vitro), hinting at elevated synaptic dysfunction in Parkin-KO/ SJ1RQ -KI mice compared to the reported defects in SJ1RQ -KI while the Parkin-KO and WT mice exhibit no defects. Even though Parkin is reported to have a neuroprotective role, it is crucial to elucidate its exact physiological function in neurons due to its generalized expression. The present study also adds to our insight of early synaptic defects and whether they facilitate selective degeneration of Substantia Nigra (SN) dopaminergic neurons, a key mystery evading the Parkinson's field, and thereby help in the development of effective neuroprotective strategies.

PP29

The role of NAG-1 proteins in formalin-induced inflammatory pain

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Emerging evidence suggests that non-steroidal anti-inflammatory drug-activated gene-1 (NAG-1) protein inhibits cancer, obesity and diabetes in mice. However, there is limited understanding of the role of NAG-1 in nociception. The present study aimed to examine the role of NAG-1 in basal nociceptive sensitivity and formalin-induced inflammatory pain using transgenic mice overexpressing human NAG-1. Mechanical sensitivity was evaluated by using the von Frey filament test, and thermal sensitivity was assessed by the hot-plate, Hargreaves, and acetone tests. The expression of c-Fos, GFAP, and Iba-1 was examined in the lumbar spinal cord using immunohistochemistry following examination of the formalin-induced nociceptive behaviors. There was no difference in mechanical and thermal sensitivity for NAG-1 transgenic and wild-type mice. Intraplantar injection of formalin induced inflammatory nociceptive behaviors in both male and female NAG-1 transgenic and wild-type mice. The peak period in the second phase was delayed in NAG-1 transgenic female mice compared with that of wild-type female mice, while there was no difference in the cumulative time of inflammatory pain behaviors between the two groups of mice. Formalin increased spinal cord c-Fos immunoreactivity in both transgenic and wild-type female mice. Neither GFAP nor Iba-1 expression was increased in the spinal cord of WT and TG female mice. Collectively, these results demonstrate that NAG-1 transgenic mice have similar basal sensitivity against mechanical and thermal stimuli, and that female transgenic mice show delayed peak period of the second phase nociception in formalin-induced pain, but the formalin-induced neuronal activation in the spinal cord was not suppressed by NAG-1 overexpression.

PP30

Venous susceptibility to chronic cerebral hypoperfusion

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The vascular endothelium develops organotypically to meet the oxygen and metabolic needs of distinct organs. Within the brain, the endothelium maintains tightly sealed blood-brain barrier that serves as a key homeostatic site, regulating transport between the blood and brain. Advances in single-cell RNA-sequencing have further shed light on brain endothelial heterogeneity by deconvoluting the molecular basis of zonation along the arteriovenous axis. Diseases arising from vascular malformations often manifest in organ- and vessel-type specific manner. Therefore, it is intriguing to postulate that intracranial endothelial subtype differences can impact on the zonated pattern of cerebrovascular lesions. For example, in the aged brains, most vascular segments have altered cytokine signaling, while metabolic disturbance affects specifically the capillary endothelial cells. Cerebral ischemia stimulates robust vascular remodeling and angiogenesis which could induce ageing-associated cerebrovascular pathology. When mice were exposed to chronic mild hypoxia, endothelial proliferation and vascular leakiness occurred predominately in post-capillary venules, but vascular permeability was not detected in arterioles. Leukocytes also preferentially infiltrate the central nervous system through post-capillary venules. In cerebral cavernous malformations, loss-of function mutations in one of the CCM genes lead to vascular malformations primarily of venous origin. We hypothesize that cerebral ischemia disrupts endothelial mechanisms at specific regions along the arteriovenous axis, in part contributing to cerebrovascular malformations. Vessel normalization or anti-angiogenic strategy targeted at specific regions of the vascular axis may moderate susceptibility to brain ischemia, preserve cerebrovascular integrity, and ultimately slow down progression of cognitive impairment due to vessel abnormalities.

PP31

The Parkin-SREBP2-LPL axis regulates neuronal lipid homeostasis – Implications for Parkinson's disease

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Emerging evidence implicates aberrant lipid regulation in the pathological events leading to neurodegeneration seen in Parkinson's disease (PD). Recent studies reported that lipids are enriched in the Lewy Bodies – a pathological hallmark found in PD brain tissues. Further, several PD risk genes (for example, SNCA, PLA2G6, GBA, and SREBF1) are known to regulate lipid dynamics and metabolism, suggesting a potential involvement of lipid dyshomeostasis in PD pathogenesis. However, the molecular basis of lipid dysregulation and its involvement in the sequence of neurotoxic events in PD remains to be elucidated. Notably, the PD-associated protein Parkin has been reported to functionally interact with lipid modulators, such as the fatty acid translocase CD36 and the Sterol Regulatory Element Binding Proteins (SREBPs). Here, we demonstrate a functional interaction between Parkin and Lipoprotein Lipase (LPL), a triglyceride lipase that is ubiquitously expressed in the brain. We show that Parkin expression level positively correlates with neuronal LPL protein level and activity in human neuroblastoma cell line and a Parkin knockout mouse model. Further, we show that CRISPR-mediated genetic ablation of SREBP2, a major regulator of sterol and fatty acid synthesis, negated Parkin effect on LPL expression. We then demonstrate that Parkin-SREBP2-LPL pathway regulates intracellular deposition of lipid droplets (LDs), organelles that have been proposed to play a protective mechanism against cellular stress. Importantly, this pathway is upregulated upon cellular exposure to mitochondrial oxidative stress induced by rotenone, a PD-linked environmental toxin. Finally, we show that inhibition of either LPL or SREBP2 aggravates neuronal deaths caused by rotenone. In summary, our findings identify a novel pathway linking Parkin, SREBP2, and LPL in neuronal lipid

homeostasis and LD formation in a PD-relevant context. This pathway represents a potential molecular target for disease-modifying therapy of PD.

PP32

The diagnosis, mechanism and treatment of Parkinson's disease and related neurodegenerative disease

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The speaker has long been committed to the study of diagnosis, mechanism and treatment in Parkinson's disease, Multiple system atrophy and other neurodegenerative disease. At present, the speaker has discovered the imaging features of PD and related diseases such as multiple system atrophy through neuromolecular imaging technique which indirectly indicate the changes of neurovascular units and neuroinflammation in neurodegenerative diseases. The applicant's research group also found that the level of hypoglycemia in the brain through molecular imaging 18F-FDG was related to the severity of aging-related diseases vascular Parkinson's syndrome (VP) and primary PD, suggesting that aging-related neuronal degeneration is closely related to local cerebral microvascular circulation and metabolic disorders. There is a two-way expression relationship between SOD, HDL-C, LDL-C and high sensitivity C-reactive protein (hsCRP) in serum of PD patients which is related to the severity of Parkinson's disease. Recently, an observational study found that Quantitative electroencephalography (QEEG) indices correlated with inflammation and lipid metabolism markers in PD, which suggested that QEEG indices, HDL-C and Hs-CRP are potentially useful for the evaluation of PDD.

The speaker reviewed the role of gut dysbiosis in Parkinson's disease, focusing on treatment strategies for the pathogenesis. In addition, the speaker also found that NBP can rescue dopaminergic neurons by reducing NLRP3 inflammasome activation and ameliorating mitochondrial impairments and increases in p-α-syn levels. This research elucidated the molecular mechanism of receptor regulation affecting disease progression in PD models, and discovered the effect of statins on receptor regulation in PD, laying a good theoretical foundation for drug research and development in PD.

PP33

Synergistic effect of mutations in two Parkinsonism related endocytic proteins: SJ1 and Auxilin

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Parkinson's disease (PD) is a neurodegenerative disorder characterized by defective dopaminergic (DAergic) input to the striatum. Mutations in two genes encoding synaptically enriched clathrin-uncoating factors, synaptojanin 1 (SJ1) and auxilin, have been implicated in atypical Parkinsonism. SJ1 knock-in (SJ1-KIRQ) mice carrying a disease-linked mutation display neurological manifestations reminiscent of Parkinsonism. Here we report that auxilin knockout (Aux-KO) mice display dystrophic changes of a subset of nigrostriatal DAergic terminals similar to those of SJ1-KIRQ mice. Furthermore, Aux-KO/SJ1-KIRQ double mutant mice have shorter lifespan and more severe synaptic defects than single mutant mice. These include increase in dystrophic striatal nerve terminals positive for DAergic markers and for the PD risk protein SV2C, as well as adaptive changes in striatal interneurons. The synergistic effect of the two mutations demonstrates a special lability of DAergic neurons to defects in clathrin uncoating, with implications for PD pathogenesis in at least some forms of this condition.

PP34

The Role of circHomer1 in Dendritic Spine Maintenance and Hippocampus-dependent Spatial Learning and Memory

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Circular RNAs (circRNAs), a class of long-noncoding RNA with ring-structure, are abundantly expressed in brain, and the expression profile alters with neural development and activity, but little is known about how circRNAs are involved in these process. circHomer1, a circRNA derived from Homer1 gene, is enriched in synapse, and its expression is related to neurological diseases. But the role of circHomer1 in spine maintenance and neural function remains unclear. Here we propose that circHomer1 regulates neural activity of hippocampus. We first specifically knockdown circHomer1 in hippocampus and performed behavioral tests to evaluate the spatial learning and memory of mice. We found that compared to control group, mice showed an impairment of spatial learning and memory after circHomer1 knockdown. To investigate the underlying mechanism, we knockdown circHomer1 in primary hippocampal neurons and examined the spine density and morphology. Spine density altered in circHomer1 knockdown neurons and the number of mature spines decreased. Overexpression of circHomer1 resulted in an increase of mature spines in primary hippocampal neurons. To further validate these findings, we examined the dendritic spines in hippocampus CA1 region of mouse after circHomer1 knockdown. Consistent with results in vitro, in vivo knockdown of circHomer1 led to an increase of spine density. Using 3D reconstruction analysis, we found that the spine volume decreased in circHomer1 knockdown group. Taken together, these results indicate that circHomer1 regulates hippocampus-dependent spatial learning and memory by modulating dendritic spine morphology. In next step we are exploring the potential candidates interacting with circHomer1 that are crucial to dendritic spine maintenance.

PP35

Synaptic and Circuit Level Deficits in CDKL5 Deficiency Disorder

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X-linked mutation in cyclin-dependent kinase-like 5 (CDKL5) gene causes Cdkl5 deficiency disorder (CDD), a severe neurodevelopmental disorder. A range of neuropsychiatric symptoms are observed in patients with CDD, including global developmental delay, motor dysfunction, early-onset epilepsy, cortical visual impairment, learning disabilities, and autistic features. A distinct clinical feature of CDD is cortical visual impairment, which occurs in at least 75% of CDD patients. CDKL5 is a serine/threonine kinase, and several substrates have been identified. Yet the genetic deficits in the Cdkl5 gene lead to neuron circuit-specific sensory processing impairment remain unelucidated. Here we employed a mouse model of CDD and applied in vivo two-photon calcium imaging to study how impaired neuronal activity in various cortical regions. Using a super-resolution protein imaging method, Magnified Analysis of Proteome (MAP), to visualize synaptic spines and synaptic proteins from layer II/III and layer V pyramidal neurons in V1. We observed altered density of mature spine (mushroom-shaped) in layer II/III neurons and layer V basal dendrites. Mechanistically, phopshoproteomics screen disclosed several bona fide substrates of CDKL5, which contains the Cdkl5 phosphorylation consensus motif and has been validated by a custom-made site-specific antibody. In conclusion, our findings showed circuits level impairment and spine deficits in CDD, and unraveled a novel downstream mechanism of CDKL5.

PP36

Characterization of a novel non-canonical mutation in Rett Syndrome

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Rett Syndrome (RTT) is a neurodevelopmental disorder caused by pathogenic variants in the MECP2 gene. While the majority of RTT-causing variants are clustered in the methyl-CpG binding domain and NCoR/SMRT interaction domain, we report a female patient with an unverified novel MECP2 variant in the C-terminal domain, c.1030C>T, p.R344W. We functionally characterized MECP2-R344W in terms of protein stability, NCoR/SMRT complex interaction, and protein nuclear localization in vitro. MECP2-R344W cells showed an increased protein degradation rate without significant change in NCoR/SMRT complex interaction and nuclear localization pattern, suggesting that enhanced MECP2 degradation is sufficient to cause a Rett Syndrome-like phenotype. This study highlights the pathogenicity of the C-terminal domain in Rett Syndrome, and demonstrates the potential of targeting MECP2 protein stability as a therapeutic approach.

PP37

The mechanism of neurostimulation modulating synaptic plasticity in protein kinase regulation

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Synaptic plasticity, such as long-term potentiation (LTP), plays a vital role in learning and memory. Direct current stimulation (DCS) is a non-invasive therapy reported to improve several neuronal disorders though regulation of synaptic plasticity. DCS is often treated by two directions, anodal and cathodal, which exhibit excitatory and inhibitory effects by depolarization and hyperpolarization of membrane potentiation, respectively. Previous study has showed that protein kinase M zeta (PKMζ), synthesized by an internal promoter within the protein kinase C zeta (PKCζ) gene that only transcribes the catalytic C-terminus, is necessary and sufficient for the maintenance of LTP. Moreover, PKMζ thought to maintain LTP by prevents endocytosis of α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA) receptor subunit GluA2. However, whether PKMζ is involved in DCS modulating synaptic plasticity still unclear. In present study, we applied the anodal DCS in brain slice to investigate the role of PKMζ in DCS modulated-synaptic plasticity. First, the potentiation of synaptic response was induced by anodal DCS application. The expression of PKMζ was increased after anodal DCS application; whereas the expression of PKCζ was not change after anodal DCS application. Enhanced expression of AMPA receptor subunit GluA2 was found after anodal DCS application, while the N-methyl-D-aspartate receptor subunit including GluN2A and GluN2B were not change after anodal DCS application. Lastly, the anodal DCS induced synaptic potentiation was blocked by zeta inhibitory peptide. Taken together, the anodal DCS modulated synaptic potentiation was through PKMζ.

PP38

Aβ-mediated nuclear pore complex dysfunction in a mouse model of Alzheimer's Disease

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The nuclear pore complex (NPC) is a vital component of the nuclear membrane that regulates multiple processes such as protein movement through the nuclear membrane, chromosome organisation, and transcriptional regulation. While a gradual loss of NPC function in neurons occurs during normal ageing, further NPC dysfunctions have been reported in multiple neurodegenerative disease. Surprisingly, there are few reports on NPC dysfunction in Alzheimer's disease (AD) despite it being the most prevalent form of dementia. One of the key hallmarks of AD is amyloid beta (Aβ) pathology, but the mechanisms and impact of Aβ in progression of the disease is unclear. Here, we show evidence that Aβ expression is sufficient to trigger the loss of select nucleoporins, and an overall reduction in number and distribution of NPCs on the nuclear envelope of AD neurons. This Aβ-mediated NPC dysfunction degrades the nuclear permeability barrier which results in the disruption of the subcellular compartmentalization of nucleocytoplasmic proteins, and an impairment of active import of proteins via the classical nuclear import pathway. As a result of the nuclear dysfunction, AD neurons are more vulnerable to inflammation-induced necroptosis – a programmed cell death pathway in which core proteins are activated via phosphorylation through nucleocytoplasmic shutting.

PP39

Rynchophylline as a therapeutic agent improves functional recovery in traumatic spinal cord injury

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Spinal cord injury (SCI) is a very catastrophic condition which results functional neurological deficit. It not only affects the life of the patient, but also affect the patient economically. Initial traumatic insult causes primary injury, which further activates the secondary injury events like neuroinflammation, excitotoxicity, ROS generation, astrogliosis, and fibrotic scar. Despite of the extensive research, to date no treatment is available, which completely cure this condition. Rynchophylline (Ryn) is a small molecule which has shown potential in neurodegenerative diseases. Hence, in the present study, we have explored the role of Ryn as a treatment in SCI. In-vitro experiments findings suggested that Ryn has not any cytotoxic potential and promotes neurite outgrowth under neuroinhibitory environment. Further, animal study data suggested that Ryn has effective in decreasing the immune response in acute phase of SCI. In chronic phase, it shows the potential in decreasing the astrocytic overactivity and promotes the myelination. Also, it decreases the level of neuroinhibitory ECM protein that is not permissive for neuroregeneration. Open field locomotor functional assessment has shown a promising improvement in the functional recovery following treatment with Ryn. Thus, the finding of the present study is demonstrating a promising role of Ryn in traumatic SCI.

PP40

Acetylcholinesterase inhibitory activity and antioxidant properties of α-Mangostin as a potential drug for the treatment of Alzheimer's disease

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive impairment and memory loss. The effective therapeutic options for AD are limited and thus there is a demand for research into more-effective drugs. For many years, recent modern scientific research has been conducted on the mangosteen (Garcinia mangostana Linn.) and the therapeutic properties of its pericarp (rind) as a traditionally medicinal treatment for diarrhea, skin infection and wounds in throughout South Asia. This fruit rind is an abundant source of polyphenolic xanthone derivatives. Among the xanthones, α-mangostin is the major prenylated derivatives and is also one of the most studied xanthones due to its potential beneficial properties. The present study aims to investigate in vitro acetylcholinesterase inhibitory activity of α-mangostin, and to point out the role of mangosteen as a significant source for development of newly potent and safe natural therapeutic agents of Alzheimer's disease. We investigated the antioxidant and acetylcholinesterase inhibitory activities of α-mangostin. Antioxidant capacities were evaluated by the following methods: scavenging 2, 2′azinobis-(3-ethylbenz-thiazoline-6-sulfonic acid (ABTS•+), scavenging O2 •−, 2,2-diphenyl-1-picrylhydrazyl (DPPH), and Ferric reducing antioxidant power (FRAP). The effects on inhibition of lipid peroxidation were determined by measuring the formation of thiobarbituric acid reactive substrates (TBARS).

Acetylcholinesterase inhibitory activity was measured using the β-naphthyl acetate and fast blue B salt (NA-FB) and Ellman's enzyme assays. Interestingly, α-mangostin displayed markedly acetylcholinesterase inhibitory activity and antioxidant properties. In addition, α-mangostin showed high inhibition of brain lipid peroxidation. These findings could shed new lights on searching new drugs from plant sources in hope that

α-mangostin may be potential for the treatment of memory disorders as Alzheimer's disease.

PP41

Correlation of oxidative-antioxidative cascade, Inflammatory cytokines and synaptic metalloproteinase in women with epilepsy: A cross sectional study

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AIM: Oxidative-antioxidative cascade, metalloproteinase (MMPs), and inflammatory cytokines play a pivotal role in the pathogenesis of epilepsy. The study explored the underlying mechanism of epilepsy in relation to the role of interleukin-1β (IL-1β), IL-6, α-synuclein, MMPs, neuron-specific enolase (NSE), C-reactive protein (CRP) and free radicals. The aim of study was two-fold, first to investigate the interplay between oxidative-antioxidative parameters in epilepsy and severity of its symptoms, second to investigate depression and sleep abnormalities in this dyad.

Methods:The indices of Lipid Peroxides-(LPO), nitric oxide-(NO) and Protein carbonyl in plasma, antioxidative parameters catalase, Glutathione peroxidase-(GPx) & Glutathione Reductase-(GR) in 134 female patients and 112 healthy females were recorded. Clinical parameters, Personal Impact of epilepsy scale –PIES, Demographics, sleep disturbance-visual analog scale, depression-beck's depression inventory-(BDI) were assessed.

Results:LPO ($p<0.01$), NO ($p<0.01$) and Protein carbonyl ($p<0.01$) were significantly higher in epilepsy patients as compared to controls. Catalase ($p<0.01$), GR ($p<0.01$) and GPx ($p<0.01$) were significantly lower in epilepsy-group when compared to controls. Positive correlation was found between LPO, NO, Protein-carbonyl and clinical symptoms of epilepsy group. epilepsy group scored significantly worse than the controls with respect to physical role, social functioning and pain. All subscales of SF-36 were negatively correlated with BDI scores in epilepsy group.

Conclusion:The presence of oxidative stress in women with epilepsy, are exposed to depression and sleep abnormalities, playing an important role in the etiopathogenesis of the disease. Moreover, our results show that increased oxidative stress parameters are more strongly replicated to epilepsy severity score. We also hypothesize to show

an established link between oxidative stress, inflammation, seizures, and neuropsychiatric outcomes.

PP42

Visualization of accessible cholesterol using a GRAM domain-based biosensor

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Cholesterol is important for membrane integrity and cell signaling, and dysregulation of the distribution of cellular cholesterol is associated with numerous diseases, including neurodegenerative disorders. While regulated transport of a specific pool of cholesterol, known as “accessible cholesterol”, contributes to the maintenance of cellular cholesterol distribution and homeostasis, tools to monitor accessible cholesterol in live cells remain limited. Here, we engineered a highly sensitive genetically encoded accessible cholesterol biosensor by taking advantage of the cholesterol sensing element (namely the GRAM domain) of an evolutionarily conserved lipid transfer protein, GRAMD1b. Using this novel cholesterol biosensor, which we call GRAM-W, we successfully visualized in real time the distribution of accessible cholesterol in many different cell types, including iPSC-derived neurons. Further, we combined GRAM-W with a dimerization-dependent fluorescent protein (ddFP) and established a novel strategy for the ultrasensitive detection of accessible plasma membrane cholesterol. These new tools will allow us to obtain important insights into the molecular mechanisms by which the distribution of cellular cholesterol is regulated.

PP43

MAPK-dependent presynaptic potentiation in the lateral habenula induces depressive-like behaviors in rats

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Emerging evidence suggests that the lateral habenula (LHb) is involved in depressive disorders. Excitatory synapses onto LHb neurons projecting to the ventral tegmental area (VTA) are potentiated in animal models of depression. The abnormal potentiation of LHb neurons is mainly due to presynaptic alterations; however, the mechanisms of this presynaptic enhancement are yet to be elucidated. The LHb is associated with circadian rhythms in the brain. Recently, we reported that presynaptic transmission in the LHb is temporally variable. Disrupted circadian patterns are a commonly observed symptom in patients with depression. Based on these studies, presynaptic alteration of LHb neurons should be investigated by considering circadian rhythm. Here, we used a well-established rodent model of depression to show that exposure to a stressor or incubation with stress hormone, corticosterone, abolished the presynaptic temporal variation in the LHb. In addition, selective inhibition of mitogen-activated protein kinase (MAPK) kinase (MAPKK, MEK) activity in the LHb restored the presynaptic alteration even after stress exposure. Moreover, we observed that slight increase in phosphorylated synapsin I after stress exposure. It may be induced by the activation of MAPK-dependent signaling and may promote presynaptic transmission. Finally, we found that a blockade of MAPK signaling before stress exposure successfully prevented the depressive symptoms, including behavioral despair and helplessness, in an acute learned helpless animal model of depression. Our study delineates the cellular and molecular mechanisms responsible for abnormal presynaptic enhancement of LHb neurons in a rat model of depression, which may mediate depressive behaviors.

PP44

In vivo imaging for visualization of nerve regeneration in sciatic nerve crush animal model

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Nerve damage can occur due to accidents, leading to paralysis and motor impairment. Diseases like Amyotrophic Lateral Sclerosis can cause muscle weakness, leading to the degeneration of motor neurons. As this can significantly affect both physical and mental well-being, research related to nerve regeneration is actively being pursued.

In this experiment, a sciatic nerve crush model with controlled injury to the nerve was created using the Thy1-YFP-16 strain, especially displaying fluorescence in nerves to study nerve regeneration and repair processes. Nerve regeneration was then visualized over time using a two-photon intravital microscope after injecting drugs that promote nerve cell regeneration.

To create the sciatic nerve crush model, we exposed the sciatic nerve in the right thigh of the Thy1-YFP-16 mouse and then crushed it with mosquito forceps for 15 seconds to induce injury. The drugs were intramuscularly injected right before imaging. Results showed YFP-positive nerve cell signals appearing from the third day after surgery in both the control and test groups that received the regeneration drugs. Subsequently, long nerve branches were observed. Moreover, nerve cells were observed on the 37th day in the control group and on the 21st day in the test group, indicating that nerve regeneration occurred more rapidly with nerve cell regeneration drugs.

This experiment successfully visualized nerve regeneration over time using an intravital microscope, which can repeatedly visualize images within one individual and reduce the artifacts caused by differences between several individuals. Therefore, owing to these various advantages, using an intravital microscopy is expected to be a crucial technique in the field of nerve regeneration research.

PP45

Elucidating the Pharmacological Mechanisms of Aloe Vera in Alzheimer's disease using Molecular Docking and MD Simulation

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Alzheimer's disease (AD) is a neurodegenerative disorder that affects millions of people worldwide. There is currently no cure for AD, and existing treatments are limited in their efficacy. Therefore, there is a critical need to develop new therapeutic strategies for the management of AD. One promising avenue for the development of AD therapies is the use of natural compounds derived from plants. Aloe Vera is a common herb that has been used traditionally for medicinal purposes. Recent studies have shown that Aloe Vera extracts may have neuroprotective effects and could potentially be used for the treatment of AD. However, the underlying pharmacological mechanisms of these effects remain poorly understood. In this study, we used molecular docking and molecular dynamics (MD) simulations to investigate the potential pharmacological mechanisms of Aloe Vera metabolites in the treatment of AD. We first identified the active phytochemicals present in Aloe Vera using data obtained from HPLC/GCMS and confirmed their chemical structures. We then used molecular docking to study the binding interactions between these phytochemicals and key proteins involved in AD, including acetylcholinesterase (AChE), β-secretase and β-amyloid (Aβ) peptide. Our results showed that several of the identified phytochemicals had strong binding affinities for these proteins, suggesting that they may be effective inhibitors of these proteins. We further performed MD simulations to study the stability and dynamics of the protein-ligand complexes. Our results showed that the identified phytochemicals were able to form stable complexes with AChE, β-secretase and Aβ peptide and that these complexes exhibited distinct dynamic behaviours compared to the unbound proteins. Overall, our study provides important insights into the potential pharmacological mechanisms of Aloe Vera extracts in the treatment of AD. These findings suggest that Aloe Vera phytochemicals may have therapeutic potential for AD and could be further developed as natural AD therapies.

PP46

Electrophysiological measures of subcortical auditory functioning in persons with Parkinson's disease

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Background & Objectives: Parkinson's disease (PD) is motor disorder but may additionally suffer from auditory perceptual disturbances of acoustic signals to impaired speech processing which can have cascading effect on communication and quality of life in PD. The negative consequences are amenable to auditory habilitation. Therefore, evaluation of auditory perceptual disorders to provide auditory habilitation and to monitor effects of treatment is important in this population. Hence, we intend to assess the auditory processing abilities at subcortical level of auditory pathways by comparing the behavioral and electrophysiological measures in persons with and without PD.

Methods:Simple purposive sampling technique was used to select 70 subjects in the age range of 55 to 65 years (35 persons without Parkinson's disease and 35 persons with Parkinson's disease). Behavioral Audiometry and Click evoked Auditory Brainstem Responses (ABR) at 50 dBSL at stimulus rate of 21.1/sec were measured & compared between both the groups.

Results:ABR latency and amplitude analysis showed no significant difference of wave III absolute latency and amplitude and wave III-V interpeak latencies at 50 dBSL. However, there was reduced amplitude and delayed latencies of peak I and V, and interpeak latencies of peak I-V and I-III at 50 dBSL in PD.

Conclusions:The delayed latency and reduced amplitude of ABR waves probably suggest compromised speed of neuronal transmission and magnitude which may be due to altered subcortical structures of auditory pathways in persons with PD. Thus, ABR can be used as a tool to assess and to monitor the treatment effects at peripheral level in PD.

PP47

DNA Methylation analysis of OPRM1 and DAT1 genes in a drug-dependent population of Manipur, India

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The μ-opioid receptor (OPRM1) is the site of action of many endogenous opioids as well as opiates and plays an important role in drug dependency. The dopaminergic system also plays a significant role in the development of drug dependency. Regulation of the extracellular dopamine concentration is driven by the dopamine transporter (DAT). Both the expression and function of DAT are influenced by chronic opioid intake. The OPRM1 gene and DAT1 gene promoters show differential methylation patterns in opioid-dependent populations. The aim of the present study is to examine whether there are differences in methylation patterns in the OPRM1 and DAT1 gene promoter regions between opioid-dependent individuals and control groups. Genomic DNA was isolated from the peripheral blood of 230 individuals with opioid use disorder and 108 healthy individuals as the control group. Genomic DNAs were treated with sodium bisulfite and subjected to Methylation Specific PCR (MSP) to analyze the DNA methylation patterns in the OPRM1 and DAT1 promoter regions. Whole genome sequencing of 4 random samples (2 cases and 2 controls) was also conducted. Methylation was found in 6.08% of cases and in 26.85% of controls for the OPRM1 gene, and in 2% of the cases and in 8% of controls for the DAT1 gene. Chi-square analysis has shown a significant difference in DNA methylation pattern in the OPRM1 and DAT1 gene promoter region between the cases and control subjects ($P<0.05$, $OR<1$). Sequencing results also showed a significant difference in the methylation patterns among the study groups ($P=0.046$) where the promoter region is hypomethylated in the cases group. Hence, opioid exposure may not influence DNA methylation in the promoter region of the OPRM1 and DAT1 gene in the Manipur population.

PP48

Neuroprotective effect of Valproate on pathological synaptic response during cerebral ischemia

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The pathological form of synaptic plasticity, ischemic long-term potentiation (iLTP), induced by oxygen and glucose deprivation (OGD), is implicated in the acute phase of stroke with the potentiation of N-methyl-D-aspartate receptor (NMDAR). While there has been widespread attention on the excitatory system, a recent study reported that γ-aminobutyric acid (GABA)ergic system is also involved in iLTP. Valproic acid (VPA), a histone deacetylase inhibitor, protects against ischemic damage. However, whether VPA regulates early phase plasticity in ischemic stroke remains unknown. A brief exposure of OGD on the hippocampal slices and the induction of photothrombotic ischemia (PTI) were used as ex vivo and in vivo models of ischemic stroke, respectively. Using extracellular recordings, iLTP was induced in the hippocampal Schaffer collateral pathway following OGD exposure. VPA treatment abolished hippocampal iLTP via GABAA receptor enhancement and extracellular signal-regulated kinase (ERK) phosphorylation. Administration of VPA reduced brain infarct volume and motor dysfunction in mice with PTI. Moreover, VPA protected against ischemic injury by upregulating the GABAergic system and ERK phosphorylation, as well as by reducing of matrix metalloproteinase in a PTI-induced ischemic stroke model. Together, this study revealed the protection of VPA in ex vivo OGD-induced pathological form of neuroplasticity and in vivo PTI-induced brain damage and motor dysfunction through rescuing GABAergic deficiency and the pathological hallmarks of ischemia.

PP49

Ermin deficiency as a model for understanding early mechanisms of abnormal myelination in neurodegeneration

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Despite often being considered characteristic of multiple sclerosis, abnormal myelination occurs in and has been hypothesised to be a key driver of pathophysiology in several neurodegenerative conditions, including Alzheimer's disease, Parkinson's disease, and Huntington's disease. The Ermin protein, which is localised to mature oligodendrocytes, is associated with myelin sheath formation and maintenance in the central nervous system. Changes in Ermin expression have also been observed in epilepsy, schizophrenia, and autism, and myelin defects have been observed in Ermin-deficient mice. Therefore, we aim to investigate the early molecular mechanisms of abnormal myelination in neurodegeneration using Ermin deficiency as a genetic model. We conducted a bulk RNA sequencing analysis to assess transcriptional differences between Ermin-deficient and wild-type male and female mice at either one month or three months of age. Across Ermin genotypes from all samples, we observed differences in transcriptional regulation and protein processing. Furthermore, age- and sex-dependent gene expression changes were observed, indicating that unique molecular mechanisms are altered in Ermin deficiency for male and female subjects over time. These findings may provide insight into the early mechanisms of abnormal myelination in neurodegeneration, as well as inform on age- and sex-dependent effects observed in conditions such as in multiple sclerosis.

PP50

Familial Alzheimer's Disease Patient iPSC-Derived Endothelial Cells Exhibit Dysregulated Angiogenesis and Altered Function

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Alzheimer's disease (AD) is a neurodegenerative disease characterized by an insidious onset of neurocognitive decline and hallmark histopathology of extracellular beta-amyloid (Aβ) plaques and intracellular tau tangles. Recently, a number of studies highlighted the presence of microvascular alterations and transcriptomic changes in endothelial cells (ECs) in both post-mortem AD patient brains and AD transgenic mouse models. In the AD mouse model, microvascular alterations can even be observed at postnatal day seven, suggesting early microvascular involvement in AD. However, how exactly do ECs contribute to AD in humans and whether these changes are a result of AD or a factor that contributes to AD development remain to be elucidated. We hypothesize that dysregulated EC function results in microvasculature deficits in the brain, contributing to AD pathogenesis. Deriving ECs from induced pluripotent stem cells (iPSCs) of familial Alzheimer's Disease patients with Presenilin-1 mutations and their isogenic pairs, we showed that ECs display increased proliferation, migration, and tube formation capabilities and reduced barrier integrity. Furthermore, our bulk RNA-seq data showed that PS1 FAD-iPSC ECs are transcriptionally more similar to those of AD patients than healthy controls. Interestingly, some altered genes in PS1 FAD-iPSC ECs are related to astrocyte-EC interactions, prompting further investigation of the involvement of blood-brain barrier in AD. Together, our results suggest that PS1 FAD-iPSC ECs are innately altered and may contribute to vasculature deficits seen in AD via pathological angiogenesis.

PP51

Ultrasensitive fluorogenic probe for detecting ferrous ion in Parkinson's disease models with multimode imaging

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Parkinson's disease (PD) is one neurodegenerative disorder that threatens life of people worldwide. Accumulating evidence show that the aberrance of ferrous ion (Fe2+) with redox activity is closely related to the occurrence/development of PD. Herein, we developed an ultrasensitive red emission two-photon fluorogenic probe (FJ1) for the detection of Fe2+. The limit of Fe2+ detection for FJ1 was 40 pM, which was several orders of magnitude better than most reported Fe2+ probes. Meanwhile, FJ1 was adopted to fabricate a simple and convenient paper-based sensor to visualize Fe2+ from PD models with naked eye. Importantly, FJ1 was successfully applied to detect Fe2+ in living cell, zebrafish, Drosophila and mouse PD models, in which tissue penetration depth was approximately 400 μm, indicating that FJ1 was an effective small molecular tool for in-depth investigating Fe2+ related diseases such as PD.

PP52

Plasma CXCL-5 chemokine is increased in Alzheimer's Disease but not Vascular Cognitive Impairment

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Neuroinflammation is characterised by the release of pro-inflammatory cytokines and chemokines by microglial cells in response to brain tissue injury or pathogens. Chronic neuroinflammation can damage neurons as well as contribute to the progression of small vessel disease (SVD), potentially leading to neurodegenerative dementias like Alzheimer's disease (AD) and vascular cognitive impairment.

CXCL-5 is a pro-inflammatory chemokine that amplifies the inflammatory response and abnormal levels have been linked to several inflammatory conditions, such as rheumatoid arthritis. However, CXCL-5 has not been extensively studied in relation to cognitive impairment, including the pre-dementia stage of cognitive impairment no dementia (CIND), as well as AD and vascular dementia (VaD). In this study, we aim to measure CXCL-5 levels in a Singapore-based longitudinal cohort with cognitive impairment.

Subjects from a Singapore-based memory clinic cohort were included in this cross-sectional study, with comprehensive clinical, neuropsychological and brain neuroimaging assessments, as well as clinical diagnoses based on established criteria. Plasma samples were then collected from this cohort of 25 subjects with no cognitive impairment (NCI), 90 CIND, 70 AD and 15 VaD, and CXCL-5 was measured using Luminex immunoassays.

Significantly higher CXCL5 levels was observed in AD compared to CIND, suggesting that an increase in CXCL-5 could indicate the progression from the pre-dementia stage to dementia and might be worth further investigation. In contrast, there is a lack of association with CeVD markers, such as atrophy and white matter changes, as well as unchanged CXCL-5 levels reported in VaD patients.

In conclusion, CXCL-5 may be differentially altered in AD versus VCI and should be further assessed as a potential therapeutic target in the clinical setting.

PP53

Brevican is reduced in pre-dementia patients with significant cerebral vascular disease: implications for treatment and biomarker utility.

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The neural extracellular matrix (ECM) is a structural macromolecular network composed of proteins and polysaccharides that occupies the space between neurons and glia. Its composition shapes the neuronal microenvironment and can undergo substantial changes upon development or in diseases with cerebral pathologies. Brevican is a CNS-specific chondroitin sulfate proteoglycan (CSPG), expressed primarily in astrocytes and neurons, integral to forming the highly organised structure perineuronal nets (PNNs).

Decreased brevican levels have been found in vascular dementia (VaD) patients but not subjects with Alzheimer's disease (AD), compared to subjects with no cognitive impairment (NCI). However, its involvement in pre-dementia stages, namely cognitive impairment no dementia (CIND), as well as in AD patients with concomitant cerebrovascular disease (CeVD), has yet to be explored.

This cross-sectional study included 32 NCI, 97 CIND, 46 AD and 23 VaD subjects in a study on a Singapore-based memory clinic cohort. All subjects underwent comprehensive clinical, neuropsychological and brain neuroimaging assessments and clinical diagnoses based on established criteria. Blood samples were collected, and serum brevican levels were measured using immunoassays.

After controlling for covariates, lower concentrations of brevican were associated with subjects with CeVD (odds ratios [ORs] 2.28; 95% confidence interval [CI] 1.3-4.0). Further analysis revealed that decreased brevican is associated with CIND subjects only in the presence of significant CeVD (CIND with CeVD: OR 0.4; 95% CI 0.2-0.8). Subsequent multivariate analyses showed that among the types of CeVD assessed, only WMH was associated with lower brevican levels. Our findings suggest that brevican may play a role in VCI, especially in the pre-dementia stages where early vascular damage occurs. Further longitudinal analyses are needed to assess the prognostic utility of brevican in disease prediction and monitoring.