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ABSTRACT BOOK

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ABSTRACTS

Keynote Presentations

Neuronal Intranuclear Inclusion Disease (NIID) Caused 2-day Loss of Consciousness

Yuko Harada

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Abstract

Neuronal Intranuclear Inclusion Disease (NIID) is a rare and slowly progressive neurodegenerative disease. NIID may affect any part of the nervous system, such as central, peripheral, or autonomic, as well as visceral organs. Signs and symptoms may begin from infancy to late adulthood. Symptoms of NIID worsen over time and may include dementia, limb weakness, cerebellar ataxia, dystonia, Parkinsonism, seizures, and autonomic dysfunction.

The features of NIID result from the presence of eosinophilic intranuclear inclusions inside neurons and glial cells. Diagnosis is made by skin biopsy and brain MRI. Recently, a genetic change in the NOTCH2NLC gene has been found to cause NIID. There is no treatment that cures or slows the progression of NIID which is ultimately fatal.

We experienced a case of NIID for a male who was found unconscious for 2 days. Since he was found lying on the floor for many hours, he had developed bedsores in his chest and thighs. Brain MRI revealed characteristic features of NIID, and skin biopsy confirmed the diagnosis. NIID should be taken into consideration in diagnosing patients with syncope.

Biography

Dr. Yuko Harada received her M.D. degree from the Keio University School of Medicine. She is currently Vice Director of Cardiology, Kawasaki Muncipal IDA Hospital. From 2014 to 2017 she was Director of the Department of Internal Medicine at Shin-yurigaoka General Hospital. Until 2013, where she also completed her residency. She received the Chairman's Award from the Japan Endocrinology Association for her life-saving work on thyroid storm. She has authored numerous research papers in the pioneering fields of Internal Medicine, Cardiology, and Radiology

AP-2 Prevents Amyloidogenesis via Regulation of BACE1 Trafficking in Neurons

Natalia L. Kononenko[1] and Sujoy Bera[1], Santiago Camblor-Perujo[1], Elena Calleja Barca[1], Albert Negrete-Hurtado[1], Julia Racho[1], Elodie De Bruyckere[1], Christoph Wittich[1], Nina Ellrich[1], Soraia Martins[2], James Adjaye[2]

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Abstract

Cleavage of amyloid precursor protein (APP) by BACE-1 (β-site APP cleaving enzyme-1) is the rate-limiting step in amyloid-β (Aβ) production and a neuropathological hallmark of Alzheimer's disease (AD). Despite decades of research, mechanisms of amyloidogenic APP processing remain highly controversial. Here, we show that in neurons Aβ generation is controlled by the endocytic adaptor protein complex-2 (AP-2). AP-2 prevents amyloidogenesis by functioning downstream of BACE1 endocytosis, regulating BACE1 endosomal trafficking and its delivery to lysosomes. AP-2 is decreased in iPSC-derived neurons from patients with late-onset AD, while conditional AP-2 knockout (KO) mice exhibit increased Aβ production, resulting from accumulation of BACE1 within late endosomes and autophagosomes. Deletion of BACE1 decreases amyloidogenesis and mitigates synapse loss in neurons lacking AP-2. Taken together, these data suggest a mechanism for BACE1 intracellular trafficking and degradation via an endocytosis-independent function of AP-2 and reveal a novel role for endocytic proteins in AD.

Biography

Dr Natalia L. Kononenko is a dedicated neuroscientist aimed to solve the enigma of selective neuronal vulnerability in neurodegeneration. Originally trained in physiology in Russia and in neuroanatomy in Norway, I received an extensive postdoctoral training in the lab of Volker Haucke in Berlin, Germany, where I used a combination of state-of-the-art imaging and genetic approaches to understand the function of endocytic adaptors in the brain. My work established a novel non-canonical function of endocytic proteins in neurons, where they mediate the survival by regulating the neurotrophin signaling. Since October 2015, I am a Group Leader at the University of Cologne.

Oral Presentations

Diffusion Tensor Imaging Reveals Distinct Cerebellar Defects as a Result of Spinal Muscular Atrophy (SMA)

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Abstract

Spinal Muscular Atrophy (SMA) is an autosomal recessive disease that affects ~1/8,000 individuals at birth, making it the leading genetic cause of infant mortality. Patient response to treatment and their long-term effects remain unclear. SMA is defined by a depletion of ubiquitous survival motor neuron protein (SMN) in motor neurons, leading to neural dysfunction and degeneration in the anterior horn of the spinal cord and neuromuscular junction. However, recent studies support that SMA is a multi-system disease. The brain hasn't received much attention; especially the cerebellum, even when widespread pathology has been re-

ported in SMA patients. Due to its important role in motor function, we investigated it's development using the SMNΔ7 mouse model. Volumetric brain data was acquired via segmentation of T2-weighted images from magnetic resonance imaging (MRI). Cerebellar growth was significantly reduced in SMA-affected mice compared to wild type. Furthermore, the cerebella of late-stage SMA (P12) mice was particularly affected relative to whole-brain volume. We then observed overall cerebellar tractography using diffusion tensor imaging (DTI) to quantify white matter pathway abnormalities in SMA. Spinocerebellar tracts and intracerebellar connections were significantly diminished in late stage mice. Additionally, significant differences in DTI metrics such as fractional anisotropy, radial, medial, and axial diffusivity were observed. Immunohistochemical and electrophysiological data are still being analyzed. We conclude that cerebellar axonal development and white matter pathways connecting the cerebellum with the CNS are affected by SMA. More work on SMA in the brain may lead to more effective avenues for treatment.

Biography

He is a second year doctoral student at Delaware State University studying SMA defects in the brain. He was born and raised in Massachusetts, USA. With a dwindling interest in academics in general, He found a passion for science and decided to attend a local community college to study chemistry. He received an Associate's degree, and from there went on to receive a Bachelor's degree in Biochemistry at the University of Southern Indiana. He truly enjoy conducting research and making strong connections with my peers and colleagues.

The Role of Astrocytes in SMA Motor Neuron Synaptic Defects

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Abstract

Dynamic detection of the changes of soluble amyloid-β42 (Aβ42) monomers (Aβ42Ms) and misfolding Aβ42 oligomers (Aβ42Os) is crucial for investigating the correlation between Aβ levels and the disease progression of AD. However, the simultaneous detection of the dynamic changes of natural Aβ42Ms and Aβ42Os is challenging because of their transient and heterogeneous nature as well as due to the lack of sequence- and conformation-specific antibodies against Aβ42. Herein, we screened Aβ42-specific monoclonal antibodies 1F12 and 2C6 via the hybridoma technology and confirmed both 1F12 and 2C6 were sequence- and conformation-specific antibodies with preferential selectivity to Aβ42Ms and Aβ42Os. To specifically detect Aβ42Ms and Aβ42Os, preferred antibody pairs 1F12/2C6 and 1F12/1F12 for sandwich ELISAs were screened out. 1F12/2C6 ELISA displayed a specific detection limit of 5 pM for total Aβ42 (Aβ42Ms and Aβ42Os), while 1F12/1F12 ELISA specifically measured AβOs with the detection limit of 2.5 pM. 1F12/2C6 and 1F12/1F12 ELISAs revealed that high Aβ42Ms levels appeared in 4-month-old APP/PS1 mice, and significantly increased Aβ42Os and declined Aβ42Ms levels existed in 14-month-old APP/PS1 mice, indicating that the changes of Aβ42Ms and Aβ42Os levels in the blood and brains reflect the disease progression of AD. Furthermore, the changes of Aβ42Ms and Aβ42Os in the gastrointestinal system were also correlated with the progression of AD. Together, our finding will facilitate an early and accurate diagnosis of AD and further understanding of the pathology of AD

Dissecting the Molecular Heterogeneity of Dopaminergic Neurons in Parkinson's Disease Patients Using Induced Pluripotent Stem Cells (iPSCs) Technology

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Abstract

Personalized medicine is a concept very suitable for Parkinson's disease (PD), a neurodegenerative disease that includes a highly heterogeneous group of patients. Understanding the basis of the large diversity of phenotypes with appropriate clinical, imaging, and biochemical measures is an important step to guide therapy toward its greatest precision and safety. Alongside these key features, the chance to investigate with the induced pluripotent stem cell (iPSCs) technology PD patient-derived dopamine neurons (DAn) at the molecular level, can make a strong contribution not only for clarifying pathogenic mechanisms underlying neurodegeneration, but also for developing the most appropriate therapeutic approach for each PD patient and patient subgroups. On these bases, we recently investigated the characteristics of DAn derived from iPSCs obtained from two PD patients harboring the G2019S LRRK2 mutation. Our results show that, LRRK2 G2019S DA neurons were characterized by reduced dendritic arborization and reduced soma area and exhibited a spontaneous accumulation of non-fibrillary alpha-synuclein. Moreover, DAn differentiated from G2019S LRRK2-derived iPSCs are resistant to the neurotrophic effects of dopamine D2 and D3 receptor (D2R/D3R) agonists and nicotine, and the analysis of synaptic function demonstrated a remarkable dysregulation of receptor mechanisms controlling DA release, suggesting that G2019S mutation significantly impacts on the trafficking and function of key receptors controlling DAn function. Together, our results may indicate that, an abnormal expression or activity of these receptors could represent an early, pre-degenerative event in patients carrying LRKK2 mutation with various consequence that likely contribute to make DAn more vulnerable.

Biography

She is a Assistant Professor of Pharmacology at the Department of Molecular and Translational Medicine, University of Brescia. Her scientific activity started in 2009 and has been focused on the study of functional characteristics of dopamine (DA) receptors in the brain. After a period at the Harvard Stem Cell Institute, she established in my lab the technology to develop human neurons from induced pluripotent stem cells (iPSC) and she is currently involved the study of early alterations of DA neurons derived from Parkinson's Disease (PD) patients. During the last two year she also collaborate to the management of a technological platform for brain imaging in our department.

Targeted Precision Therapies for Infantile Parkinsonism

Joanne Ng[1,2+], Serena Barral[2+*], Carmen De La Fuente Barrigon[3], Gabriele Lignani[4], Fatma A. Erdem[2,5], Rebecca Wallings[6], Riccardo Privolizzi[1,2], Giada Rossignoli[2], Haya Alrashidi[3], Sonja Heasman[2], Esther Meyer[2], Adeline Ngoh[2], Simon Pope[7], Rajvinder Karda[1], Dany Perocheau[1], Julien Baruteau[1,3], Natalie Suff[1,8], Juan Antinao Diaz[1], Stephanie Schorge[4,9], Jane Vowles[10], Lucy R. Marshall[11], Sally A. Cowley[10], Sonja Sucic[5], Michael Freissmuth[5], John R. Counsell[12], Richard Wade-Martins[6], Simon J. R. Heales[3,7], Ahad A. Rahim[9], Maximilien Bencze[12,13], Simon N. Waddington[1,14#], Manju A. Kurian[2,15#]

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Abstract

Parkinsonism is widely reported across a broad spectrum of neurodegenerative conditions. For such medically intractable disorders, elucidation of the underlying disease mechanisms is crucial to accelerate development of personalized medicine strategies. Dopamine Transporter Deficiency Syndrome (DTDS) is a form of infantile parkinsonism associated with significant morbidity and high risk of mortality. DTDS is due to loss-of-function bi-allelic mutations in SLC6A3, encoding the dopamine transporter (DAT). Patients present with early infantile hyperkinesia and severe progressive childhood parkinsonism. Using human induced pluripotent stem cells (hiPSCs), we have generated a midbrain dopaminergic model of DTDS. Patient-derived dopaminergic neurons showed loss of dopamine transporter activity and dysregulated dopamine metabolism. Furthermore, patient neurons showed marked neurodegeneration, with apoptotic neuronal loss due to dopamine toxicity and TNFα-mediated inflammatory response. Loss of transporter function was partially rescued by the pharmacochaperone Pifithrin-μ. Lentiviral SLC6A3 gene transfer fully restored DAT activity and stopped the neurodegenerative progression. We then performed gene therapeutic preclinical studies in a knockout (KO) mouse model of DTDS, presenting with reduced survival and parkinsonism features, including tremor and bradykinesia, as observed in DTDS patients. Neonatal intracerebroventricular injection of human SLC6A3, using an adeno-associated virus (AAV) vector, rescued mice motor phenotype, lifespan and prevented neurodegeneration in the substantia nigra (SNc) and striatum. To progress

towards clinical translation, we performed stereotactic delivery of AAV2.SLC6A3 gene therapy targeted to the midbrain of adult DAT knockout mice, which rescued motor phenotype.

Biography

Dr. Serena Barral is Lecturer in Neurosciences at University College London, Great Ormond Street Institute of Child Health (GOS-ICH). Her interest is to elucidate disease mechanisms and develop novel therapies for inherited childhood-onset neurodegenerative diseases affecting the basal ganglia. During her first post-doctoral position, she gained expertise in clinically translatable therapeutic approaches for Parkinson's disease. She was then appointed as a Wellcome-funded Senior Research Associate at the UCL GOS-ICH, where she further pursued clinically relevant research modelling infantile-onset neurological disorders using patient-derived neuronal models to understand underlying disease mechanisms and develop novel precision therapeutic approaches.

Uncovering the Pathological Role of Astrocytes in SMA

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Abstract

Spinal muscular atrophy (SMA) is the most common genetic cause of infant mortality and is caused by mutations of the survival motor neuron 1 gene (SMN1) leading to motor neuron loss and early death. It is unclear why motor neurons are particularly impacted, but emerging data indicate that astrocytes contribute to motor neuron vulnerability.

We previously found that SMA astrocytes undergo morphological and functional changes very early in disease and are capable of inducing motor neuron pathology. Others showed that SMA microglia exhibit activation later in the disease process and are involved in synapse engulfment. However, the mechanisms of glia-mediated neuron dysfunction and the temporal contributions of astrocyte-microglia crosstalk to SMA pathology have not been elucidated.

We hypothesize that early SMA astrocyte malfunction induces motor neuron pathology and simultaneously activates microglia. We found that induced pluripotent stem cell (iPSC)-derived astrocytes exhibit aberrant expression of the transcription factor GATA6, increased NFκB nuclear localization, and increased complement factor C3 release, and astrocyte conditioned medium (ACM) is sufficient to induce motor neuron death. Separately, we found that SMA iPSC-derived microglia exhibit a reactive morphology, increased phagocytosis, and increased expression of complement C1q compared to control microglia. Exposure of SMA iPSC-derived microglia to SMA ACM significantly increased their phagocytic activity compared to untreated microglia. Together, these data are consistent with a pathological role of astrocyte-microglial crosstalk in SMA. Better understanding the non-cell autonomous processes involved in SMA will help elucidate the mechanisms of motor neuron loss and may help identify additional therapeutic targets.

Biography

Dr. Allison Ebert received undergraduate degrees in chemistry and psychology from Indiana University and a Ph.D. in neuroscience from Northwestern University. She then completed post-doctoral training in stem cell biology at the University of Wisconsin-Madison. She is currently an Associate Professor at the Medical College of Wisconsin in Milwaukee, WI, in the Department of Cell Biology, Neurobiology, and Anatomy. Her current research focuses on characterizing glial-neuron interactions contributing to neuronal loss in

SMA and ALS as well as studying the impact of congenital viral infections on early neural development and function.

Mutant TMEM230 Induced Neural Transport Impairment

Xiaobo Wang[1,2], Gongbo Guo[1], Jinru Zhang[1], Nicolas Aebez[1], Zhaohui Liu[2], Chun-Feng Liu[2], Christopher A. Ross[1] and Wanli W. Smith[1*]

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Abstract

Parkinson's disease (PD) is a neurodegenerative disease with movement disorders including resting tremor, rigidity, bradykinesia, and postural instability. Recent studies have identified a new PD associated gene, TMEM230 (transmembrane protein 230). However, the pathological roles of TMEM230 and its variants are not fully understood. TMEM230 gene encodes two protein isoforms. Isoform2 is the major protein form (~95%) in human. In this study, we overexpress isoform2 TMEM230 variants (WT or PD-linked *184Wext*5 mutant) or knockdown endogenous protein in cultured SH-5Y5Y cells and mouse primary hippocampus neurons to study their pathological roles. We found that overexpression of WT and mutant TMEM230 or knockdown of endogenous TMEM230 induced neurodegeneration and impaired mitochondria transport at the retrograde direction in axons. Mutant TMEM230 caused more severe neurotoxicity and mitochondrial transport impairment than WT-TMEM230 did. Our results demonstrate that maintaining TMEM230 protein levels is critical for neuron survival and axon transport. These findings suggest that mutant-TMEM230-induced mitochondrial transport impairment could be the early event leading to neurite injury and neurodegeneration in PD development.

Biography

Wanli W. Smith is an Associate Professor in the Department of Psychiatry at Johns Hopkins University School of Medicine. She received her M.D. in clinical medicine and her Ph.D. in biochemistry and molecular biology in China. She pursued post-doctoral work in the National Institute on Aging at the National Institutes of Health and in the Department of Psychiatry, Division of Neurobiology, at Johns Hopkins University. Currently, she is the Director of the Cellular Neurobiology Laboratory in Division of Neurobiology. Her lab is currently directed towards understanding the molecular pathogenesis of neurodegenerative diseases and other disorders such as obesity. Her research goals are to elucidate the molecular signaling pathways of these disorders, to identify potential therapeutic targets and to develop novel therapeutics. Her research goals are to elucidate the molecular signaling pathways of these disorders, to identify biomarkers for disease process and treatment evaluation, to identify drug targets and to develop new approaches for treatment and prevention. She has served as a reviewer for grant panels (e.g. NIH study section) and as an editor for several journals such as PLos One, etc. She has received funding from NIH, private foundations and pharmaceutical companies through the years. She has mentored many postdoctoral fellows and students.

Human-Based Neuromuscular System for Personalized ALS Modeling and Drug Testing

Xiufang Guo[1,*], Agnes Badu-Mensah[1,2], Virginia Smith[1], Max Jackson[1], My Tran[1], Michael Thomas[1], Yunqing Cai[1], Christopher W. McAleer[1], Ying Wang[1,2], Christopher J. Long[1], James J. Hickman[1]

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Abstract

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by progressive muscle paralysis and motoneuron (MN) degradation. An early critical hallmark shared by all ALS cases is the deterioration of the neuromuscular junction (NMJ). Our aim was to develop a human-based functional NMJ model for ALS by utilizing patient-derived induced pluripotent stem cells (iPSCs) (ALS-iPSCs). We developed a human-based functional NMJ system by integration of the ALS-iPSCs with BioMEMs technology, in which NMJ functionality can be interrogated quantitatively and drug effects can be evaluated in a dose-dependent manner. The NMJ systems were derived from the same iPSC source in this functional platform which enables the generation of patient-specific NMJ models. MNs differentiated from the ALS-iPSCs (ALS-MNs) were characterized and integrated into this functional NMJ model. Functional analysis of these NMJs demonstrated significant deficits as characterized by a set of clinically relevant parameters including NMJ quantity, fidelity and fatigue index, where the deficits were recovered by treatment with the Deana protocol. Skeletal muscle cells (SKM) were also differentiated from ALS-iPSCs. SOD1 myoblasts demonstrated delayed and reduced fusion efficiency. SOD1 myotubes demonstrated severe structural atrophy, reduced acetylcholine receptor expression, decreased contraction force and fidelity, as well as impaired mitochondrial function and altered cell metabolism mechanisms. These ALS-SKM have been integrated into the NMJ system and the NMJ system containing both ALS-MNs and ALS-SKM are currently under investigation. These functional ALS NMJ models recapitulate clinically relevant pathological phenotypes thus provide a platform for ALS etiological investigation and patient stratification for drug testing.

Biography

Dr Xiufang Guo is a Research Professor in the NanoScience Technology Center at University of Central Florida. She obtained her Ph.D. in Neuroscience from the University of Pennsylvania. Dr Guo has extensive experience in human stem cell differentiation, developing in vitro functional neural systems for disease modeling and designing functional/cellular/molecular assays for analyzing these systems. She has published 25 research papers in reputed journals. She was elected as a Member of National Academy of Inventers in 2018. She has been leading multiple research projects and has been serving as a grant reviewer for different funding agencies.

Precise Closure of Single Blood Vessels via Multiphoton Photothermolysis

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Abstract

Conventional laser therapy of pathologic vasculature has imprecise spatial selectivity and usually indiscriminately denatures all blood vessels within the irradiated tissue volume, thereby, impairing normal phys-

iologic function after the disease is healed. It also causes unwanted damage to normal tissues. We hereby introduce a precise spatially selective treatment approach utilizing multiphoton absorption-based photothermolysis to target and close single blood vessels without affecting surrounding tissues/vessels. A tightly focused near infrared femtosecond laser beam is used to achieve instantaneously super high power density at the focal point to induce multiphoton absorption. Such absorption is localized to the focal point because outside of this site the power density is low. Using a mouse ear model, we successfully demonstrated the targeting of single vessels. Reflectance confocal microscopy is used to localize a target vessel, monitor the treatment process, and confirm the selected vessel closure. Closure of single targeted vessels of varying sizes ranging from capillaries to venules was demonstrated. We also showed that deeply situated vessels could be closed precisely while preserving adjacent overlying superficial vessels. Partial vessel occlusion could also be achieved. This "see-and-treat" approach provides a novel precision medicine method for non-invasive precise microsurgery treatment of vascular diseases on a per vessel/per lesion basis. It holds particular promise for treating diseases in complex organs such as the eye and brain, where high spatial selectivity is critical for preventing collateral effects on vision or central nervous system functions. The method could also be used for building ischemic stroke models for basic biology study.

Biography

Haishan Zeng is a distinguished scientist on Cancer Imaging with BC Cancer Research Centre and a professor of Dermatology, Pathology, and Physics at University of British Columbia. Dr. Zeng's research is focused on developing novel phototherapy and optical imaging/spectroscopy techniques for early cancer detection. His research has generated 169 refereed journal papers and 28 issued patents. Three medical devices derived from his patents have passed regulatory approvals and are in clinical uses. The latest device, Verisante Aura™ using Raman spectroscopy for non-invasive skin cancer detection, was awarded the Prism Award in 2013 by the International Society for Optics and Photonics.

An Association Between Carotid Blood Flow Velocities, Intima Media Thickness and Disability in Multiple Sclerosis

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Abstract

Background: Previous studies have shown that vascular comorbidity may increase the risk of disability progression in multiple sclerosis (MS). It has not been conclusively established whether vascular ultrasound can identify vascular factors associated with disability progression in MS, the major challenge for this condition.

Objectives: 1) Establish the association between the intima media thickness and blood flow velocities of the carotid and vertebral arteries and severity of disability and 2) Investigate the effects of biochemical and lifestyle factors on carotid arteries in persons with MS (PwMS).

Methods: Extracranial arterial ultrasound was performed on 51 PwMS and 25 age-matched controls. The

major neck arteries were sonographically interrogated to determine carotid intima media thickness (cIMT) and abnormal blood flow patterns. Disability assessments (EDSS) were available for 38 PwMS. Biochemical and lifestyle data were available for 42 PwMS and 20 controls.

Results: The EDSS had a highly significant positive association with the intima media thickness of the right (r=0.63; p=0.00002) and left (r=0.49; p=0.0016) CCAs and negative associations with the peak systolic blood flow velocity of the right VA (r= -0.42; p=0.0081) as well as end-diastolic blood flow velocity of the left ICA (r= -0.47; p=0.003). These associations were significantly influenced by biochemical and lifestyle factors and use of MS medication

Conclusion: These findings indicate that PwMS with increased carotid intima media thickness and reduced carotid artery blood flow velocities are not only at increased risk of cerebrovascular and cardiovascular disease but are at risk for greater disability.

Biography

Dr Merlisa Kemp is from Cape Town, South Africa and is currently employed as Head of the Department of Medical Imaging and Therapeutic Sciences at the Cape Peninsula University of Technology (CPUT). She is also an ultrasound lecturer teaching on the BSc Diagnostic Ultrasound programme. She has worked as a sonographer in Dublin and the United Kingdom (London, Cambridge, West Midlands). In Cape Town, she worked in private practice and at a government-funded teaching hospital as a Chief Vascular Sonographer in a vascular laboratory. She is a recipient of the National Research Foundation (NRF) and University grants.

A Novel Insight into The Pathogenesis of Coronavirus Disease-19-Associated Ischemic Stroke: Putting Neutrophil Extracellular Traps into The Spotlight

Tjokorda Istri Pramitasuri[1]*, Anak Agung Ayu Putri Laksmidewi[2], Ida Bagus Kusuma Putra[2], Felix Adrian Dalimartha[3], Ni Made Susilawathi[4], Anak Agung Raka Sudewi[4]

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Abstract

Ischemic stroke has known as a catastrophic neurological events and is increasingly recognized among patients with Coronavirus Disease (COVID)-19. Recent studies have shown that SARS-CoV-2 may induce ischemic strokes in human brains, but the underlying mechanisms are still unclear. Recent studies have placed the potential role of excessive formation of Neutrophil Extracellular Traps (NETs), which are networks of DNA, histones, and proteolytic enzymes produced by activated neutrophils under the spotlight. This study uses the latest relevant literatures to establish the insight into the vascular and neuroinflammatory effects of NETs in the pathogenesis of COVID-19-associated ischemic stroke along with the possible future directions. Vasculopathy and neuroinflammation are the pathological mechanisms of NETs that suggested to link COVID-19 and its deteriorating complication, the ischemic stroke. Based on the newly discovered possible mechanisms, the potential clinical implications that can be applied include inhibition of NET formation and modifying the inflammatory pathways. A great deal of scientific works and collaborations are needed in order to complete the current understanding the pathogenesis of ischemic stroke as one of potential deteriorating events among COVID-19 patients. These novel findings are a worthwhile contribution in defining future experimental and clinical studies along with the appropriate frameworks.

Key Words: Neutrophil, Extracellular Traps, Coronavirus, Vasculopathy, Neuroinflammation

Biography

Tjokorda Istri Pramitasuri is a 25-year-old Ph.D Candidate in Medical Sciences of Udayana University, Bali, Indonesia, who completed her medical education at the Faculty of Medicine, Udayana University (2016) and Master of Biomedical Sciences from Udayana University (2019). She is a recipient of the PMDSU Scholarship from Ministry of Education and Culture, Republic of Indonesia (2019-2023). She has received the Best Abstract Award, Indonesia International Medical Student's Congress (2015), First Winner of Scientific Poster Presentation, Bali Neurology Update (2019), and invited to present her works in The 5th Science of Nutrition in Medicine and Healthcare Conference - Melbourne, Australia (2015).

The Challenging Clinical Management of Patients with Cranial Dural Arteriovenous Fistula and Secondary Parkinson's Syndrome: Pathophysiology and Treatment Options

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Abstract

Cranial dural arteriovenous fistula (cDAVF) may rarely lead to parkinsonism and rapid cognitive decline. Dysfunction of the extrapyramidal system and the thalamus, due to venous congestion of the Galenic system with subsequent parenchymal edema, is likely to represent an important pathophysiological mechanism. Here, we report a case of a 57-year-old man with a cDAVF of the straight sinus (Borden type III; DES-Zurich bridging vein shunt [BVS] type with direct, exclusive, and strained leptomeningeal venous drainage [LVD]) and subsequent edema of both thalami, the internal capsule, the hippocampi, the pallidum, and the mesencephalon. Several attempts at venous embolization were unsuccessful, and the neurological condition of the patient further deteriorated with progressive parkinsonism and intermittent episodes of loss of consciousness (KPS 30). A suboccipital mini-craniotomy was performed and the culminal vein was disconnected from the medial tentorial sinus, achieving an immediate fistula occlusion. Three-month follow-up MRI revealed complete regression of the edema. Clinically, parkinsonism remitted completely, allowing for tapering of dopaminergic medication. His cognition markedly improved in further course. The purpose of this report is to highlight the importance of rapid and complete cDAVF occlusion to reverse venous hypertension and prevent progressive clinical impairment. The review of the literature underlines the high morbidity and mortality of these patients. Microsurgical disconnection of the fistula plays an important role in the management of these patients and, surprisingly, has not been reported so far.

Biography

Julia Works as a Senior physician at the department of Neurosurgery. Her interests are Paediatric Neurosurgery, Epilepsy surgery and microsurgery of brain tumour's.

DOCA-Treated Sabra Hypertensive Rats: A Novel Model for Cerebral Small Vessel Disease with White Matter Hyperintensities and Peripheral Oxidative Stress

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Abstract

Background and aims: Cerebral small vessel disease (CSVD) is the second most common cause of stroke and a major contributor to dementia. CSVD manifests in a variety of pathological mechanisms including cerebral microbleeds, intracerebral hemorrhages (ICH), lacunar infarcts, white matter hyperintensities (WMH) and enlarged perivascular spaces. Chronic hypertensive models were found to resemble most key features of the disease. Nevertheless, no animal models have been identified to reflect all different aspects of the human disease. We designed experiments for characterizing a novel model for CSVD, using salt-sensitive 'Sabra' hypertension-prone rats (SBH/y) which display chronic hypertension and enhanced peripheral oxidative stress.

Methods: SBH/y rats were either administered deoxycorticosteroid acetate (DOCA) (referred to as SBH/y-DOCA rats) or sham operated and provided with 1% NaCl in drinking water. Rats underwent neurological assessment and behavioral testing, followed by ex-vivo MRI, biochemical and histological analyses.

Results: SBH/y-DOCA rats show neurological decline and cognitive impairment, and present multiple cerebrovascular pathologies associated with CSVD such as ICH, lacunes, enlarged perivascular spaces, blood vessel stenosis, BBB permeability and inflammation. Remarkably, SBH/y-DOCA rats show severe white matter pathology as well as WMH, which are rarely reported in commonly used models.

Conclusion: Our model may serve as a novel platform for further understanding the mechanisms underlying CSVD and for discovery of novel therapies for this disease.

Biography

Reut Guy is a PhD student in Prof. Daniel Offen's lab at Tel Aviv University in Israel. Her research focuses on mesenchymal stem cell (MSC)- derived exosomes for the treatment of stroke and cerebral small vessel disease (CSVD). She earned her BSc in biomedical engineering from the Technion – Israel Institute of Technology, and her MSc in human molecular genetics and biochemistry from Tel Aviv University.

Neurovascular 5-Hydroxytryptamine 2A Receptor Agonist Autoantibodies Increase and are a Marker of Severe Covid-19 Infection

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Abstract

Severe Covid-19 infection causes widespread microvascular occlusion in the lung, liver, kidney, heart, and brain via unknown mechanisms. The 5-hydroxytryptamine 2A receptor (5-HT2AR) is widely expressed in peripheral vascular tissue and brain. Previously, we reported increased circulating agonist 5-HT2AR-targeting, IgG autoantibodies in older adults with neurodegenerative disorders including stroke, dementia, Parkinson's disease, or traumatic brain injury. Using an ELISA for the 5-HT2AR second extracellular loop, seventeen of nineteen (89.5%) Covid-19 patients (mean age 67 years) harbored plasma 5-HT2AR autoantibodies. Binding (30 μg/mL IgG) was significantly higher in severe vs mild Covid-19 disease (0.17 vs 0.08 AU; P=0.02), background 0.04 AU, and mean level was 0.13 AU in three patients having co-morbid neurodegenerative disease. Hyperinflammation was associated with highest level of 5-HT2AR, Covid-19 plasma autoantibodies (0.23 AU). After excluding preexisting autoantibodies, white blood cell count correlated with plasma 5-HT2AR autoantibody ($R = 0.845$; $P < 0.01$;N=15). Acute neurite retraction in mouse N2A neuroblastoma cells was ~50% after 5 minutes exposure to 130 nM concentration of severe Covid-19 plasma vs. 60% after 5 minutes exposure to 38 nM concentration of dementia/stroke/severe Covid-19 plasma IgG. Acute neurite retraction (in N2a cells) was nearly completely prevented by selective 5-HT2AR antagonists or antagonists of Gq11/phospholipase C/inositol triphosphate and RhoA/Rho kinase pathways signaling. Severe Covid-19 plasma IgG (n=4) substantially decreased endothelial cell survival (66% vs 103%; P=0.003) compared to 48 hours incubation with identical (30 μg/mL) concentration of IgG from age-matched patients without Covid-19 (n=5). 5-HT2AR-targeting autoantibodies increase and may contribute to pathophysiology in Covid-19 infection.

Biography

Dr. Mark Zimering M.D., Ph.D. is the Chief, Endocrinology at the Veterans Affairs New Jersey Healthcare System and Associate Professor of Medicine at Rutgers-Robert Wood Johnson Medical School. Dr. Zimering is a past recipient of the Arthur S. Flemming Award (2003) from the George Washington University for Outstanding Government Service. He has made groundbreaking discovers linking circulating autoantibodies with diabetic micro- and neurovascular complications. Recent work in his laboratory is focused on the 5-hydroxytryptamine 2A receptor as a target of long-acting agonist plasma IgG autoantibodies expressed in conditions of heightened inflammation including traumatic brain injury, dementia, Parkinsons disease and Covid-19.

Hypoxia Couples Dopaminergic Regulation of Locomotor Development and Motor Neuron Synaptogenesis

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Abstract

Hypoxic injury to the developing human brain from prematurity increases the risk of long-term impairment of motor function. Disruptions of axon and synaptic connectivity have been linked to developmental hypoxia, but the precise mechanisms of hypoxic injury impacting motor function from altered connectivity

are poorly understood. Here, we have investigated the effects of hypoxia on the dopaminergic regulation of locomotor development coupled with motor neuron synaptogenesis in zebrafish. We have found that developmental hypoxia resulted in a significantly decreased spontaneous swimming behavior in larva and that this motor impairment persisted into adulthood. In evaluating the diencephalic dopaminergic neurons, known to regulate early development of locomotion and constitute an evolutionarily conserved component of the vertebrate dopaminergic system, hypoxia caused a decrease in the number of synapses from descending dopaminergic diencephalospinal tract (DDT) to spinal cord motor neurons. Moreover, dopamine signaling from the DDT was coupled jointly to motor neuron synaptogenesis and locomotor development. Together, these results demonstrate the developmental processes regulation early locomotor development and a requirement for dopaminergic projections and motor neuron synaptogenesis. This study further expands our knowledge of hypoxic injury from prematurity in the vertebrate brain development in general, synaptogenesis in particular, as well as the pathological mechanisms of motor disability from hypoxic injury of prematurity.

Biography

Dr. Son, of Salt Lake City, Utah, was named assistant professor of biology. He earned his bachelor's degree in animal science from Dankook University, South Korea, a master's degree in biological science from Western Illinois University, and a doctorate in neuroscience and experimental therapeutics from Texas A&M University of the Health Sciences. For the past eight years he has worked for the University of Utah, as a postdoctoral fellow in the department of pharmacology and toxicology and as a postdoctoral research associate in the School of Medicine.

Does the Brush-Sign Reflect Collateral Status and DWI-ASPECTS in Large Vessel Occlusion?

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Abstract

Background: In acute ischemic stroke (AIS), the brush-sign reflects an increase of blood deoxyhemoglobin concentration within deep medullary veins in relation to hemodynamic impairment. A poor collateral status is likely to increase these anomalies. We aimed to assess the relationship between the brush-sign and collateral status and its potential impact on baseline diffusion-weighted imaging–Alberta Stroke Program Early Computed Tomography Score (DWI-ASPECTS) in AIS patients with large vessel occlusion (LVO) eligible for mechanical thrombectomy (MT).

Methods: From 2015 to 2020, consecutive anterior circulation AIS patients with LVO on admission MRI and eligible for MT were collected from the RELATE registry. The brush-sign and DWI-ASPECTS were assessed on baseline T2*-weighted imaging and DWI, respectively. Collateral status was classified as poor for Higashida score < 3. Predictors of DWI-ASPECTS were identified using a multivariable logistic regression analysis.

Results: 503 patients were included. Of them, 171 (34.0%) patients had a brush-sign. Patients with a brush-sign more frequently had a poor collateral status (72 (42.1%) vs 103 (30.9%); p=0.017). In multivariable analysis, a DWI-ASPECTS<7 was not associated with the brushsign but with a younger age (OR 0.97, 95% CI 0.96-0.99), male sex (OR 1.79, 95% CI 1.08-2.99), a higher NIHSS score (OR 1.16, 95% CI 1.10-1.21), a poor collateral status (OR 9.35,95% CI 5.59-16.02), M1 middle cerebral artery segment (OR 2.54, 95%

CI 1.25-5.38) and intracranial internal carotid artery (OR 3.01, 95% CI 1.16-8.00) occlusion.

Conclusion: The brush-sign is a marker of poor collateral status but did not independently predict a low DWI-ASPECTS.

Biography

Dr Laura Mechtouff, MD, PhD, is the deputy head of the Stroke Center of Lyon (France). She has extensively published on the prognostic role of biomarkers in AIS patients treated by thrombectomy and coordinates ongoing clinical trials targeting acute ischemic stroke and post-stroke neuroinflammation.

Mitochondrial Transplantation a Therapeutic Approach for Neurological Disorders

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Abstract

Mitochondria are vital for metabolic homeostasis in all multicellular eukaryotes. In the nervous system, mitochondria generated adenosine triphosphate is required to establish proper electrochemical gradients and reliable synaptic transmission. Notably, several mitochondrial defects have been identified in central nervous system (CNS) disorders. Membrane leakage and electrolyte imbalances, pro-apoptotic pathway activation, and mitophagy are among the mechanisms involved in the pathogenesis of neurodegenerative diseases, including Alzheimer's, Parkinson's, and Huntington's disease, as well ischemic stroke. In current review, we summarize mitochondrial pathways that contribute to disease progression. Mitochondrial transplantation therapy is an innovative strategy for the mitochondrial dysfunction treatment. The approach has been reported to be useful in the treatment of myocardial ischemic reperfusion insults in human clinical trials and has been demonstrated to be useful in animal studies as a method for treating mitochondrial dysfunction in numerous tissues, including the heart, liver, lungs, and brain. On the other hand, there is no methodology for using preserved mitochondria. Research into the pharmaceutical formulation of mitochondria to promote mitotherapy as the next step in treating many patients is instantly needed. We overview previous studies on the therapeutic effects of mitochondrial transplantation and also, discussed strategies and tissue sources for mitochondria isolation as a novel approach for CNS disorders therapy.

Biography

Dr. Leila Hosseini received her PhD in physiology from Tabriz University of Medical Sciences, Iran in 2019. Currently working as postdoctoral researcher in Neurosciences Research Center (NSRC), Tabriz University of Medical Sciences, Iran. Published 22 national and international publications. The goal is to develop therapeutic interventions to restore CNS function and improve quality of life of individuals with neurodegenerative diseases.

Plasmapheresis Treatment Preliminary Study Results in Neurological Diseases

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Abstract

Introduction: Plasmapheresis(PE) is used as a treatment method for neurological disorders. Clinical difficulties may be experienced in patient selection due to lack of definitive results regarding disease type; treatment response; possible serious complications. Our aim is to determine the acute efficacy of plasmapheresis, its complications, long lasting outcome.

Methods: Demographic data, diagnosis and treatment results of 29 patients who underwent plasmapheresis in the intensive care unit of our hospital for the last 5 years were recorded in excel format. Plasmapheresis was applied for a minimum of 7 and a maximum of 10 sessions.

Results: In this clinical trial, 29 people obtained plasmapheresis. About 68% of the research participants were diagnosed with demyelinating disorder, 6.8% with myasthenia gravis, 6.8% with transverse myelitis, 5.3% with autoimmune encephalitis and 5.3% with autonomic neuropathy. Two patients were unable to have a definitive diagnosis. Before the attack, 69% of our patients (n:20) had received pulse steroid, 10.3%(n:3) had received intravenous immunoglobulin, and 3.4%(n:1) had received both. In the plasmapheresis evaluations, a clinical progress was observed in 17(58.9%) patients, a clinical decline in 2(6.9%) patients, and no change in 7(24.1%) patients. One patient died following septicaemia.

Conclusion: Plasmapheresis is a treatment option that has a high success rate for neurological disorders, particularly in demyelinating/autoimmune diseases. Therefore, this group of patients should definitely be considered as a treatment choice.

Diabetes Models in Mice and Risk Factor of Neurodegeneration

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Abstract

Diabetes T2 with insulin resistance is a serious disease all over the world with a tendency to steady increase the number of cases and a risk factor of neurodegenerative diseases development, among them firstly Alzheimer's disease. The aim of this study was to investigate behavior and general characteristic of genetic model of diabetes T2 mice db/db, trying to reveal beginning of development early symptoms of neurodegeneration development and characteristic of symptoms of diabetes T2 during treatment by liraglutide or autophagy inducer trehalose. Mice age was 3 and 5 months db/db mice had an increase in body weight, which progressed with age, a decrease in brain mass. Blood glucose levels were increased in db/db mice. Treatment with trehalose or liraglutide reduces its level. Db/db mice were characterized by decrease of overall orientation-exploratory and locomotor activities, increase in anxiety in the open field test. Liraglutide treatment showed positive change in open field test in db/db mice. Passive avoidance test revealed significant decrease in motivation, locomotor and exploratory activity, decreased learning in db/db mice. Db/db mice of both ages were characterized by an increase in the relative number of PMN and monocytes and a decrease in the number of lymphocytes, indicating an inflammatory response. Treatment with trehalose

or liraglutide restored these indicators. Thus, the identified behavioral changes in db/db mice reflected the development of neurodegeneration signs. Positive effects of liraglutide on behavioral processes have been shown. Trehalose or liraglutide treatment reduced blood glucose levels and the severity of the inflammatory response.

Biography

Prof. Tatiana Korolenko graduated from Novosibirsk State Medical Institute. From 1988–2014: she worked for Institute of Physiology and General Medicine, Head of Laboratory of Cellular Biochemistry. The main topics were Lysosomotropic agents, Lysosomes, Proteases and Inhibitors. From 1984 Korolenko T.A. is Dr. Med Sci., Prof.; Thesis "The structural and functional changes of lysosomes in liver injury and lysosomotropic agents administration", 1984. She was also a Visiting scientist in Tokushima University (Japan), 1990; DGF grant in Aachen University, Germany (1995-1996). She is Head of work for 14 PhD students (biochemistry). Korolenko is working in Laboratory of Experimental Neurodegeneration models, Prof. (Scientific Research Institute of Neurosciences and Medicine, Novosibirsk, Russia).

Rapid Volume Pulsation of the Extracellular Space Coincides with Epileptiform Activity in Mice and Depends on the NBCe1 Transporter

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Abstract

The extracellular space (ECS) of the brain shrinks persistently by approximately 35% during epileptic seizures. We report the discovery of rapid volume pulsation (RVP), further transient drops in ECS volume which accompany events of epileptiform activity. These transient ECS contractions were observed in multiple mouse models both in vivo (Bicuculline Methiodide model) and in vitro (Hyaluronan synthase 3 knock-out, Picrotoxin, Bicuculline, and 4-Aminopyridine models). By using the probe transients quantification (PTQ) method we show that individual pulses of RVP shrank the ECS by almost 15% in vivo. In the 4-Aminopyridine in vitro model, the individual pulses of RVP shrank the ECS by more than 4%, and these transient changes were superimposed on a persistent ECS shrinkage of 36% measured with the real-time iontophoretic method. In this in vitro model, we investigated several channels and transporters that may be required for the generation of RVP and epileptiform activity. Pharmacological blockages of $Na^+/K^+/2Cl^-$ cotransporter type 1 (NKCC1), K^+/Cl^- cotransporter (KCC2), the water channel Aquaporin-4 (AQP4) and inwardly-rectifying potassium channel 4.1 (Kir4.1) were ineffective in halting the RVP and the epileptiform activity. In contrast, pharmacological blockade of the electrogenic Na^+/HCO_3^- cotransporter (NBCe1) by 4,4'-diisothiocyano-2,2'-stilbenedisulfonic acid (DIDS) eliminated both the RVP and the persistent ECS shrinkage. Importantly, this blocker also stopped the epileptiform activity. These results demonstrate that RVP is closely associated with epileptiform activity across several models of epileptiform activity and therefore the underlying mechanism could potentially represent a novel target for epilepsy management and treatment.

Biography

Robert Colbourn is currently an MD/PhD student at SUNY Downstate Health Sciences University. He received a BS in Biology and Chemistry at Brooklyn College. He completed his PhD in the Neural and Be-

havioral Sciences Program at SUNY Downstate, where he studied the dynamics of the brain's extracellular space during epileptiform activity in the labs of Dr. Sabina Hrabetova at SUNY Downstate, and Dr. Jeffrey Goodman at the New York State Institute for Basic Research.

Sex-Dependent Molecular Mechanisms of Lipotoxic Injury in Brain Microvasculature: Implications for Dementia

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Abstract

Cardiovascular risk factors and biologic sex play a role in vascular dementia which is characterized by progressive reduction in cognitive function and memory. Yet, we lack understanding about the role sex plays in the molecular mechanisms whereby lipid stress contributes to cognitive decline. Five-week-old low-density lipoprotein deficient (LDL-R -/-) male and female mice and C57BL/6J wild types (WT) were fed a control or Western Diet for 8 weeks. Differential expression of protein coding and non-protein coding genes (DEG) were determined in laser captured hippocampal microvessels using genome-wide microarray, followed by bioinformatic analysis of gene networks, pathways, transcription factors and sex/gender-based analysis (SGBA). Cognitive function was assessed by Y-maze. Bioinformatic analysis revealed more DEGs in females (2412) compared to males (1972). Hierarchical clusters revealed distinctly different sex-specific gene expression profiles irrespective of diet and genotype. There were also fewer and different biologic responses in males compared to females, as well as different cellular pathways and gene networks (favoring greater neuroprotection in females), together with sex-specific transcription factors and non-protein coding RNAs. Hyperlipidemic stress also resulted in less severe cognitive dysfunction in females. This sex-specific pattern of differential hippocampal microvascular RNA expression might provide therapeutic targets for dementia in males and females.

Biography

She is an Assistant Project Scientist in the laboratory of Dr. Amparo Villablanca in the Department of Internal Medicine, Cardiovascular medicine division, University of California, Davis. She has more than 12 years of experience in molecular biology, cell biology, genomics and epigenomics. My research interests are in understanding how vascular risk factors and inflammatory processes contribute to the development and progression of vascular cognitive impairment and Alzheimer's disease (AD), the two leading causes of cognitive dysfunction. My research focuses on identifying the molecular mechanisms of high fat diet induced cerebrovascular damage and sex differences using murine models.

Altered Postnatal Development as Premise of Neurodegeneration and Alzheimer's Disease: Experimental Study

Ekaterina Rudnitskaya*, Tatiana Kozlova, Alena Burnyasheva, Natalia Stefanova, Nataliya Kolosova

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Abstract

Aging is the major risk factor for neurodegeneration including development of Alzheimer's disease (AD). The most common sporadic AD develops asymptomatically for many years prior to its manifestation. To date several experimental and epidemiological studies have shown that risk factors for the development of AD may materialize early in life during postnatal brain maturation. However, the mechanisms and substrates underlying its long-lasting effects remain unclear. Using OXYS rats as suitable model of sporadic AD may shed a light on long-lasting effects of brain developmental alterations.

We showed shortened duration of gestation in OXYS rats compared to control Wistar rats, which resulted in developmental retardation and delay of emergence of postural and locomotor skills. These changes may reflect deterioration of brain development. Indeed, we demonstrated delay of hippocampal development in OXYS rats: peaks of postnatal neurogenesis and apoptosis fall later compared to Wistar rats which led to alterations of mossy-fiber formation. Besides we found altered astrocytic migration from dentate gyrus in OXYS rats. It should be mentioned, that there were long-lasting consequences of these abnormalities of hippocampal development such as lower intensity of neurogenesis during lifespan: indeed, the density of stem quiescence neuronal progenitors was higher in OXYS rats at 18 months of age.

We suppose that the observed features of early hippocampal development are the one of predictors of AD-like pathology in OXYS rats and may be one of risk factors for sporadic AD in humans.

This work was supported by the Russian Science Foundation (# 19-15-00044).

Biography

Dr. Ekaterina Rudnitskaya received her degree in human and animals' physiology from Novosibirsk State University and her PhD in pathological physiology from Federal research center Institute of Cytology and Genetics, Siberian Branch of Russian Academy of Sciences in Russia. To date she is a researcher in the Department of molecular mechanisms of aging. Research interests include investigation of neuroplasticity during development of Alzheimer's disease. She investigates changes of neurotropic supply and neurogenesis in hippocampus prior to manifestation and during progression of signs of Alzheimer's disease using OXYS rats as unique animal model of sporadic form of the disease.

The Role of Alzheimer's disease relevant Tau modifications in Neurodegeneration and Mitochondrial dysfunction

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Abstract

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder whose pathological hallmarks include intraneuronal neurofibrillary tangles (NFTs) composed of the microtubule-associated protein Tau. Tau isolated from AD brain exhibits abnormally high levels of post-translational modifications

(PTMs) including phosphorylation and acetylation at specific epitopes that increase with disease severity and age. In addition, mitochondrial dysfunction is an early feature of AD, and abnormal, toxic tau PTMs may contribute to disease pathogenesis. A major bottleneck in understanding the mechanisms behind the neurotoxicity of pathological forms of Tau is the lack of genetically tractable models that can recapitulate the effects of Tau PTMs in a short time frame without artifacts associated with Tau overexpression.

Method: Human 0N4R Tau (wild type) was expressed in touch receptor neurons through single-copy gene insertion. Mutations were introduced into the single-copy tau transgene through CRISPR-Cas9 genome editing, including T231E, to mimic phosphorylation of a commonly observed pathological epitope, and K274/281Q, to mimic disease-associated lysine acetylation. We then assessed their impact on age-dependent response to light touch, neurodegeneration, and mitochondrial parameters such as abundance, morphology, trafficking, and turnover, using fluorescent biosensors including mito-mKeima.

Result: Unlike existing tau overexpression models, C. elegans single-copy expression of wild type human tau did not elicit overt pathological phenotypes at baseline. However, strains expressing disease associated PTM-mimetics (T231E and K274/281Q) exhibited reduced touch sensation and neuronal morphological abnormalities that increased with age. Remarkably, the PTM-mimetics selectively impaired mitophagy following mitochondrial oxidative stress, but had no effect on macroautophagy, and furthermore reduced mitolysosomal trafficking.

Conclusion: Single copy expression limits pathological phenotypes to strains expressing disease-associated Tau mutants. In addition to overt pathology, these mutants eliminate oxidative stress-induced mitophagy and reduce trafficking of mitolysosomes. Our findings highlight a selective mechanism through which disease-associated Tau PTMs may suppress compensatory responses to mitochondrial stress that occur with age and provide a new perspective into the pathogenic mechanisms underlying AD.

Biography

Sanjib Guha completed his Ph.D. in Neuroscience with strong research background in mitochondrial biology and stress related pathways, aging and longevity, neurometabolic disorders and neurodegenerative diseases.

Investigating the Role of Hydrogen Sulfide in Neurodegeneration: Focus on Amyotrophic Lateral Sclerosis

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Abstract

Over the past 30 years a considerable amount of data has accumulated on the multifaceted role of hydrogen sulfide (H2S) in the central nervous system. H2S is recognized as an endogenous gasotransmitter with a dual, biphasic action. Depending on its concentrations, H2S can act as an antioxidant and a cytoprotective, but also as a poison with a high probability of causing brain damage when present at noxious levels. Nowadays, accurate determination of H2S is still an important challenge to understand its biochemistry and functions. We have developed an analytical chromatographic method to detect H2S levels in cerebrospinal

fluid (CSF), key biofluid for neurological studies to assess alleged correlations with neuroinflammatory and neurodegenerative mechanisms. A cohort of CSF samples was analyzed from patients with inflammatory and demyelinating disorders (acute disseminated encephalomyelitis; multiple sclerosis), chronic neurodegenerative diseases (Alzheimer disease; Parkinson disease), and motor neuron disease (Amyotrophic lateral sclerosis, ALS).

Interestingly, toxic H2S levels have been shown in ALS patients and in neuronal tissues from the familial ALS mouse model, SOD1G93A, as well. ALS is a fatal disease characterized by neurodegeneration of upper and lower motor neurons. A complex interaction of both genetic and environmental factors contributes to motorneurons damage. Despite considerable research efforts, the exact mechanism underlying ALS pathogenesis is not yet fully understood. We experimentally demonstrated that H2S is extremely and selectively toxic to motor neurons by accurate multi-omics investigations. Therefore, in this perspective, H2S signalling could act as an additional player in already compromised ALS motorneurons.

Biography

Viviana Greco is Assistant Professor in Biochemistry at the Catholic University of the Sacred Hearth, Rome, Italy. Since her PhD, her main research topic has been addressed to the study of redox unbalance affecting protein and metabolic pathways underlying neurodegeneration, and specifically Amyotrophic Lateral Sclerosis, using multi-omics (mainly proteomics and metabolomics) based investigations.

Currently, she is member of the Executive Committee board of Italian Proteomics Association (ItPA); Member Chair for COST-CA16113 CliniMARK.; member of HUPO mitochondrial Human Proteome Project (mtHPP); member of HUPO Human Brain Proteome Project (HBPP); member of EuPA Funding Committee and EuPA Young proteomics investigators club.

The Regular Intake of Sicilian Honey Prevents Neurodegeneration in Mice with Diet-Induced Obesity

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Abstract

Oxidative stress, inflammation, obesity, insulin resistance are common factors involved in the etiopathology of neurodegenerative diseases. Dietary interventions promoting food rich in antioxidant and anti-inflammatory compounds can be helpful tools for preventing or reversing the course of neurodegenerative diseases. The aim of the present study was to analyze the preventive effects of regular intake of Sicilian honey, rich in flavonoids and phenolic acids, in obesity dysmetabolisms including neurodegeneration. Three groups of mice were fed with standard diet (STD), High Fat Diet (HFD) or HFD supplemented with honey (HFD-H) for 16 weeks. Neuronal apoptosis (TUNEL assay and brain genes expression of Fas-L, Bim and P27), peripheral and central insulin sensitivity (cerebral cortex protein expression of pAKT, pERK and pGSK3 and microarray analysis) were analyzed and compared between the different groups of animals. The HFD cerebral cortex showed an higher number of apoptotic nuclei and upregulation of Fas-L, Bim and P27 genes (pro-apoptosis markers) compared to STD- and HFD-H mice, suggesting honey neuroprotection. Moreover, honey intake significantly improved peripheral and central insulin resistance. HFD-H mice showed reduced plasma fasting glucose and insulin, and significantly ameliorated glucose tolerance and insulin sensitivity in comparison with HFD. In HFD-H brain, PCR-array analysis showing upregulation of insulin signalling targets (InsR, AdipoR and Irs1) and downregulation of pro-inflammatory genes (Rbp4, Cd36 and Stat3). In addition, in HFD-H mouse cortex, p-AKT and p-ERK protein expression was increased, while

p-GSK3 was reduced compared to HFD cortex, suggesting that honey ingestion prrevents insulin resistance in HFD-brain. In conclusion the present results suggest that honey intake has protective effects against neurodegeneration and central insulin resistance resulting from obesity.

Biography

Antonella Amato is Associate Professor of Physiology - Department of Biological- Chemical- Pharmaceutical Science and Technology, University of Palermo - Italy. She teaches Nutrition Physiology in Master Degrees courses. Prof. Amato is guest Editor of journal "Nutrients" and director of the Advance Course in "Nutrition and Health" - University of Palermo. Her main research interest is aimed to analyze the effects of natural bioactive compounds contained in dietary supplements and functional foods on the metabolism dysfunctions related to obesity, including neurodegeneration. Prof. Amato has published over 50 papers and she has contributed with many original papers in neurodegeneration field identifying natural compounds able to counteract onset of Alzheimer's disease in an animal model with diet-induced obesity.

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Drug Delivery Strategies to Suppress HIV in the CNS Reservoirs

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Abstract

Due to the inability of antiretroviral drugs (ARVs) to cross the blood-brain-barrier (BBB) and ARV-induced neurotoxicity, the current ARV regimens are incapable of suppressing HIV in the CNS reservoirs. We propose to design and develop pharmacologically relevant and clinically significant drug delivery strategies using novel nanocarrier and drug regimens that target CNS HIV reservoirs. Our drug delivery strategies are designed for enhanced BBB permeability, facilitating drug passage across the BBB and effectively suppressing the virus in CNS reservoirs, especially in macrophages and microglia, with minimal/tolerable neurotoxicity. We are developing FDA-approved poly (lactic-co-glycolic acid) (PLGA)-based elvitegravir (EVG) as well as a novel "biological nanoparticle" delivery system using "extracellular vesicles (EVs)". For drug loading, we are using EVG, an integrase inhibitor, in combination with chemodietary agent cucurbitacin-D (cur-D). Cur-D has been proven to be effective in treating many CNS diseases and in reducing inflammation and oxidative stress, the hallmark of HIV pathogenesis. In this meeting will discuss the results obtained from PLGA-EVG nanoformulation and its ability to cross the BBB to effectively suppress HIV in macrophages and microglia using an in vitro BBB model. We will also discuss the ability of PLGA-EVG formulation to enhance the EVG concentration in the brain and suppress CNS HIV in an animal model. Further, we will discuss the ability of cur-D to effectively suppress HIV not only in macrophages using direct treatment, but also across the BBB model. Cur-D also reduces the levels pro-inflammatory agents. Finally, we will discuss the preparation and formulation of EVs as nanocarrier with both EVG and cur-D and their ability to enhance the concentrations of EVG and cur-D across the BBB and suppress HIV in CNS reservoirs macrophages and microglia.

Biography

Dr. Kumar graduated from the Indian Institute of Technology (IIT)-Bombay, India. He did his postdoctorate fellowship from the University of Missouri-Kansas City (UMKC) followed by worked as a junior faculty at the University of Texas Medical Branch. He then went back to UMKC where he worked as an Assistant Professor before coming to UTHSC in 2014. Dr. Kumar is a trained biochemist and enzymologist with

expertise in drug metabolism, HIV, substance abuse, and exosomes. Dr. Kumar's group has published substantially in this field (>70 papers), with a total of ~115 papers. He has mentored six graduate students and three post-doctorate fellows along with numerous other trainees. Currently, he is mentoring three graduate students and one PDF. In addition to research, Dr. Kumar participate significantly in classroom teaching to both professional pharmacy students and graduate students. Dr. Kumar has been actively engaged in serving the Society on Neuroimmune Pharmacology as Chair of "Early Career Investigator (ECI) Committee, as well as Secretary and President-elect of the society. As a result of his distinguished contributions to research, teaching, mentoring, and service, Dr. Kumar has received numerous awards and honors.

MicroRNAs in Breast Cancer Brain Metastases: From Biomarkers Discovery to Targets Identification and Validation

Joana Godinho Pereira

Universidade de Lisboa, Portugal

Abstract

Patients with brain metastases have a poor prognosis, particularly in triple negative breast cancer (BC), due to the lack of early biomarkers and the absence of targeted therapies. We hypothesized that along BC brain metastases (BCBM) development the microRNAs (miRNAs; miR-) signature in plasma is deregulated and that specific miRNAs' targets expression in brain metastases is related with disease severity. Using a mouse model of BCBM, we performed next-generation sequencing to establish the miRNAome alterations in plasma, followed by RT-qPCR validation, and in situ hybridization to relate with the brain miRNA profile. We further performed bioinformatics analysis to identify selected miRNAs' targets and validated the altered expression in the brain. We additionally analyzed resected brain metastases of BC patients, and matched primary tumors, to translate the findings to humans. Finally, we assessed relevant signaling molecules to disclose underlying mechanisms of action. The results obtained showed that prior to BCBM detection, miR-194-5p and miR-802-5p are downregulated, while miR-92a-1-5p, miR-205-5p, and miR-181a-1-3p are upregulated in plasma, with parallel changes in the brain. Myocyte enhancer factor 2C (MEF2C) emerged as a common target of both miR-802-5p and miR-194-5p. MEF2C was detected in primary BC samples and was increasing expressed and translocated into the nucleus as brain metastases developed, features that were associated with malignant cells' proliferative activity, as well as with VEGFR-2 and β-catenin signaling. Collectively, the deregulated miRNAs appear as early biomarkers of BCBM in liquid biopsies, while parenchymal MEF2C arises as a prognosis biomarker and as a potential target for modulation.

Work funded by the Portuguese Foundation for Science and Technology.

Biography

Joana Godinho Pereira, PhD student, completed her masters' in Molecular Biology and Genetics in 2013, From Faculty of Sciences, Lisboa, Portugal. Godinho-Pereira research has been focused on the understanding of cellular and molecular mechanisms, particularly from age-related, chronic diseases and neoplastic (e.g. brain metastases formation from triple-negative breast cancer), to further accomplish prevention and/or treatment for those pathologies. Throughout the research experiment Godinho-Pereira was trained as a cellular and molecular biologist, with expertise ranging from molecular biology, natural compound testing, development of improved cell models of brain diseases to imaging techniques.

Imaging Neurovascular Abnormalities in Neurodegenerative Diseases

Jun Hua[1,2]

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[2]*F.M. Kirby Research Center for Functional Brain Imaging, Kennedy Krieger Institute, Baltimore, Maryland, United States. Address: 707 N Broadway, Baltimore, MD, 21205;*

Abstract

Neurovascular abnormalities have been associated with many neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. Advanced MRI approaches have been developed to probe functional, microvascular, metabolic and lymphatic changes in the human brain. In this presentation, we will discuss the application of these techniques in neurodegenerative diseases.

Biography

Dr. Hua's research has centered on the development and application of novel MRI technologies for in vivo functional and physiological imaging in the brain. These include the development of human and animal MRI methods to measure functional brain activities, cerebral perfusion and oxygen metabolism at high (3 Tesla) and ultra-high (7 Tesla and above) magnetic fields. He is particularly interested in novel MRI approaches to image small blood and lymphatic vessels in the brain. Collaborating with clinical investigators, these techniques have been applied to detect functional, vascular and metabolic abnormalities in the brain in neurodegenerative diseases.

Novel Therapies for Manganese- Asssociated Neurodegenerative and Cognitive Leasioning

Jack T. Rogers, Ning Xia, Rachit Bakshi and Catherine Cahill

Neurochemistry, Masachusetts General Hospital , Harvard, Boston, Massachusetts

Abstract

Manganese (Mn) toxicity has long been linked to the neurodegenerative movement disorder of occupational manganism and also was recently associated with Parkinson's disease (PD). We collaborated with Prof. Fudi Wang (Zhejiang University) to conduct a meta-analysis demonstrating that environmental excesses of Mn is associated with impaired childhood neurodevelopment and cognition (Liu W, et al, Environ Health. 2020, 2;19(1):104). Here, we will present supporting data that Mn exposures to brain neurons dysregulates iron transport causing accumulation of excess Fe in the neurodegenerative brain. High Mn exposures perturb pathways of iron homeostasis (Rogers JT, et al 2019.. Int. J Mol. Sci. 2019;20(4). PMID: 30823541).

The Alzheimer's amyloid precursor protein (APP) cytoprotectively exports excess toxic Fe from neurons after binding to the central iron exporter ferroportin (FPN) (Venkataramani et al, 2018). As a part of normal cellular physiology, increases in intracellular iron concentrations induce the up-regulation of APP gene expression at the level of translation by relieving of repression by the Iron-regulatory Protein-1 (IRP1) acting at the site of an iron-responsive element RNA stem loop (IRE) in the 5'untranslated region (5'UTR) or APP mRNA. Resulting from these events, increased APP(s) levels have a protective role to promote excess iron efflux, the iron storage protein ferritin also is translationally up-regulated to confer cyto-protection via its ferroxidase activity (in the H- subunit). We discuss our model that Mn was shown to operate in SH-SY5Y neural cell lines and in rodents to selectively interfere with the translation of ferritin and APP by a post-tran-

scriptional mechanism to explain Mn neurotoxicity both ex vivo and in vivo. We review our findings that Mn mediates metal toxicity by targeting the IREs amongst the network of iron-associated transcripts encoding proteins that promotes neuronal viability; this includes APP and ferritin whose Mn induced absence increases iron load and may generate ferroptosis and cell death.

Urate's elevation recently emerged as a neuroprotective strategy to treat neurologic disorders based on convergent epidemiological and clinical biomarker data as well as on its potent antioxidant and metal chelator properties. We present data suppport the use of urate and our neuroprotective APP 5'UTR activators to therapeutically mitigate Mn-induced degeneration of dopaminergic neurons. APP activators are to be tested to act via IRE target sequences to then restore translation of the mRNAs for APP (neuroprotective iron export) and ferritin (neuroprotective iron storage) after their inhibition in the presence of Mn. These studies offer insight into the mechanisms of Mn- and APP-mediated neurotoxicity while exploring urate's neuroprotective potential to Mn dependent neuronal injury.

Biography

Jack Rogers, PhD. is a leading authority on the role that RNA plays in the maintenance of iron homeostasis related to disease processes in neurodegeneration, including manganese neurotoxicity and Parkinson's disease. He is the Director of the Neurochemistry Laboratory in the Psychiatry/ NEUROSCIENCE Department at Massachusetts General Hospital. Jack is an Associate Professor at the Harvard Medical School, having a funded track-record in established scientific journals (Cell, J. Biol. Chem. including a cover issue, and PNAS). His peer review publications won him a Zenith award from the Alzheimer's Association on the subject of iron metabolism, and on translational control of related disease progression. Currently, he is contibuting his efforts to treat Mn toxicity and PD by pharmacological modulation of iron homeostasis towards neural survival.

Discrimination of Normal Brain Tissue From Dysplastic Tissue in Focal Cortical Dysplasia Using Raman Spectroscopy

Trang Tran[*1,2], Frederick Dallaire[1], Romain Cayrol[2], Steffen Albrecht[3], Frederic Leblond[1,2], Roy Dudley[3]

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Abstract

Focal cortical dysplasias (FCD), characterized by abnormal cortical architecture, are the most common cause of refractory focal epilepsy in the pediatric population. Only surgery can remove FCD lesions to cure focal epilepsy, but surgical success depends on the ability to resect the lesion completely while minimizing damage to perilesional normal tissues. Therefore, it remains extremely challenging to remove FCD lesions completely. Thus, better methods of delineating FCD lesions and their borders are needed to improve post-surgical seizure outcomes. Raman spectroscopy induces vibrations in the molecules of a sample and the scattered radiation is used to characterize it. The goal of this in vitro prospective study is to use Raman spectroscopy to discriminate between normal brain tissue and dysplastic tissue using specimens of focal cortical dysplasia patients. Stained sections of biopsy specimens from 20 patients with focal epilepsy were acquired and assessed by a pediatric neuropathologist. Raman map points were recorded from targeted abnormal regions with structures characterizing FCD: dysmorphic neurons, balloon cells and cortical dyslamination.

Significant spectral differences were observed between the dysplastic tissue regions and normal regions in the cortex. Indeed, FCD tissues exhibit significantly increased spectral at 1302 cm-1, 1660 cm-1and 1156

cm-1peaks, indicating a higher intensity of protein components and abnormal stretching mode of protein, lower quantity of lipids and most interestingly, a higher intensity of glycogen in the dysplastic tissues, respectively. In addition, the fingerprint region between FCDIIa and FCDIIb differs in intensity in specific biomolecules. These findings suggest the potential spectral fingerprint of dysplastic tissues as an aid to delineating FCD borders.

Biography

Trang has joined the LRO lab in 2020 as Research Associate with an interest in Raman spectroscopy in Clinical environment, with years in the domain of neurosciences and clinical research, Trang wishes to combine her knowledge of these fields to the applications of Raman Spectroscopy

Pharmacogenetic and Association Studies on the Influence of HLA Alleles and Rivastigmine on the Iranian patients with Late Onset Alzheimer's Disease

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[2]*University of Medical Sciences, Tehran, Iran;*

Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder affecting cognitive function. Number of allelic genes from HLA complex have shown variable associations with AD in different populations. In this study, we investigated the association of DQB1*06:00/x, DRB1*04:00/x, DRB1*15:00/x and B*07:00/x genotypes with AD and their relevance to the efficacy of Rivastigmine treatment in Iranian population. Our findings suggest that DQB1*06:00/x genotype offers strong protection against AD (P=0.0074), while B*07:00/x genotype imposes a significant susceptibility for sporadic Alzheimer's disease (SAD) (P=0.009). Interestingly, B*07:00/x genotype does not show any apparent associations with familial Alzheimer's disease (FAD). Our studies also suggest a pharmacogenetic relationship between drug treatment and presence of a particular genotype in the Iranian LOAD patient population. The Clinical Dementia Rating analysis showed that LOAD patients carrying DRB1*04:00/x genotype tend to display a downward trend in the disease severity and symptoms after two year follow up with Rivastigmine treatment. Moreover, in our total patient population, the carriers of DQB1*06:00/x and B*07:00/x alleles have better and worse responses to Rivastigmine respectively. We also measured the clinical relevance of the testing for these genotypes employing PcPPV formula. The PcPPV of testing for DQB1*06:00/x in the Iranian LOAD patients was 1.17% which means that people carrying this genotype have half of the probability of the absolute risk for developing LOAD. Whereas the PcPPV of testing for B*07:00/x was 4.45% for SAD, which can be interpreted as a doubling chance for developing LOAD among the Iranian population carrying this genotype. These results also suggest that DQβ1peptide containing positively charged AAs histidine30 and arginine55 and HLA class I β chain containing negatively charges aspartic acid114 and glutamic acid45, 152 in their binding groove play important roles in protection against and susceptibility for LOAD respectively.

Biography

Fatemeh Rezaei Rad is 27 years old. She was graduated from Arak University of Medical Science with B.S. in Clinical Laboratory Science in 2017. She also completed my M.S. program in Human Genetics at Tehran University of Medical Science in 2020 with a dissertation on Pharmacogenetic and Association Studies on the Influence of HLA Alleles and Rivastigmine on the Iranian patients with Late Onset Alzheimer's Disease under the supervision of Prof. Mahdi Zamani. She is currently working for Hematology Oncology and SCT research center. She tries to spend most of her time on study and research.

Acute and Chronic Synaptic Pathology in Multiple Sclerosis Gray Matter

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Abstract

Accumulating evidence from several studies suggests that synaptic dysfunction contributes to multiple sclerosis (MS) pathophysiology; however limited data is available on the relationship between synaptic pathology and grey matter (GM) inflammation[1,2]. In this study we aimed to investigate synaptic loss in MS GM and the contribution of GM inflammation and demyelination to synaptic loss, using two different post-mortem series of MS and control brains, including deep GM and cortical GM. MS brain samples were specifically selected for the presence of active demyelinating GM lesions (GMLs). Over 1,000,000 synapses were identified using immunofluorescence for synaptophysin and further characterized as glutamatergic/GABAergic by colocalization of the pre-synaptic vesicular transporters of glutamate (VGLUT1) and GABA (VGAT) in double immunofluorescence. Important synaptic loss was observed in active demyelinating GMLs (-58.9%), while in chronic inactive GMLs, synaptic density was only mildly reduced compared to adjacent non-lesional GM (-12.6%). Synaptic loss in MS equally affected glutamatergic and GABAergic presynaptic terminals during and following GM demyelination, at least in the structures assessed in this study. Compared to control GM, a diffuse loss of synapses was observed in MS non-lesional GM, independent from local axonal or neuronal loss (-21.2% overall). These findings suggest that, in MS brain tissue, acute synaptic damage/loss occurs during active GM inflammatory demyelination, affecting equally glutamatergic and GABAergic synapses, and is followed by synaptic reorganization in chronically demyelinated GM. Furthermore, this study provides a strong indication of widespread synaptic loss in MS non-lesional GM, also independently from focal GM demyelination and from local axonal/neuronal loss.

Biography

Stella Marasciulo, a cellular and molecular biologist at the Department of Neuroscience "Rita Levi Montalcini" in Turin, received her Master's Degree from the University of Turin with thesis on adult neurogenesis "The brainstem serotonin system and cell proliferation in adult male rat SVZ are regulated by gonadal hormones (Supervisor Panzica Giancarlo). In 2017 she worked at Loyola University Chicago with Toni Pak's team to study the molecular signaling pathway for estrogen receptor-beta (ERβ) creating phosphomutants of ERβ protein and using reporter gene assays for transcriptional activity analyses and co-immunoprecipitations. Current research interests are focused on the synaptic pathology in multiple sclerosis gray matter (GM), including investigation of neuropathologic mechanisms and the contribution of GM inflammation and demyelination to synaptic loss, using immunofluorescence, immunohistochemistry and confocal microscopy.

Progressive Reduction in Glymphatic Clearance in a Patient with MCI Developing Over 14 Months

Charles R Joseph, MD

Associate Professor of Internal Medicine and Neurology Liberty University College of Osteopathic Medicine

Abstract

Objective: Reduced glymphatic clearance determined by 3D TGSE PASL MRI in patients with Alzheimer Disease (AD) has been described in our previous pilot study. We present findings in a single subject diagnosed with mild cognitive impairment of separate studies performed a year apart, demonstrating progressive reduction in glymphatic clearance.

Background: The early pathophysiologic changes in AD are associated with BBB leak and consequent alteration in glymphatic flow . Non-invasive identification of this is possible using arterial spin labeling (ASL) MRI. We report results of a one year longitudinal follow up study in a single patient.

Design: 3D ASL was employed utilizing seven sequential long time to inversions (TI) as described previously. Signal averages using region of interest were recorded and signal clearance graphed for 6 separate brain regions: bilateral temporal, frontal, and parietal lobes. After informed consent this 69-year-old volunteer subject with mild cognitive impairment was studied. The first and second studies were performed 14 months apart and a third confirmatory study one month after the second.

Results: The first study demonstrated significantly reduced rate of clearance in only the left temporal lobe. The second study demonstrated significant reduction in bilateral temporal and frontal lobes, with increased rate of clearance in the bilateral parietal lobes. The results of the second study recapitulated the third. His spouse noted mild decline in cognitive function corresponding to slight reduction in MMSE score in second study.

Conclusions: Non-invasive 3D ASL may provide a necessary tool identifying early preclinical BBB integrity loss in AD, providing physiologic measure of potential therapeutic benefits in future trials addressing it.

Biography

Charles Joseph is an Associate Professor of neurology and Internal medicine boarded in Neurology and Internal Medicine at Liberty university College of Osteopathic Medicine. Prior to that he was in private practice Neurology and as part of that performed Neuroimaging studies at Centra Health in Lynchburg Virginia. He have published 2 articles on my MRI concept and soon to be released a third. He is currently conducting a larger study using 3D ASL PASL in early dementia.

Vestibular Rehabilitation is the Most Effective Intervention to Improve Balance and Decrease Fatigue in Patients with Multiple Sclerosis: A Network Meta-Analysis

Mélanie Giannesini-Gorrichon, PT[1*], Aurélien Hugues, PT, MS[1,2], Sophie Jacquin-Courtois, MD, PhD[1,2] Sébastien Mateo, PT, PhD[1,2]

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[2]Université de Lyon, Université Lyon 1, INSERM U1028, CNRS UMR5292, Lyon Neuroscience Research Center, Trajectoires Team, 69676 Lyon, France;

Abstract

1) Background: Multiple sclerosis (MS) is characterized by an inflammation of the central nervous system and the demyelination of axons. In 50% of cases, those structural disorders lead to balance disorders and/or vertiginous sensations (1). Rehabilitation is recommended over no rehabilitation for MS patients to reduce unbalance, gait disorders, fatigue, and dizziness (2). However, the most effective intervention between conventional, and/or vestibular, or no rehabilitation (CT, VR, CT+VR, or NR) for MS patients remains unknown. **2) Methods:** A network meta-analysis was conducted to extent the Garcia-Munoz et al. meta-analysis (3) and determine the most effective interventions by estimating the ranking probabilities (i.e. p-score) considering balance, gait, fatigue, and dizziness. Random effect analysis was conducted only in case of significant heterogeneity within studies and/or inconsistency between studies. Methodological quality was assessed using the Cochrane risk of bias toolbox. **3) Results:** Among 45 studies, 7 studies totaling 364 MS patients were used for the fixed-effect network meta-analysis for all outcomes but balance. Insufficient study number (n<3) prevented dizziness analysis. The mean risk of bias was 6.5/10 (Standard Deviation=1.3). VR induced significantly greater improvement of balance (than CT or NR), and of gait and fatigue (than CT, CT+VR, or NR); VR was systematically ranked first. Discussion: VR appears as a promising intervention to improve balance, fatigue, and gait in MS patients but further studies should investigate the rehabilitation effect by separating intensity, task-specificity, and MS characteristics.

Biography

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The Role of Astrocytes in SMA Motor Neuron Synaptic Defects

Emily Welby, Allison Ebert

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Abstract

Spinal muscular atrophy (SMA) is a neurodegenerative disease characterized by the loss of lower spinal motor neurons. Evidence suggests that survival motor neuron (SMN) protein deficiency in other cell types can contribute to SMA pathology. We and others have demonstrated astrocytes derived from patient induced pluripotent stem cells (iPSCs) show SMN-dependent intrinsic defects. In addition to providing neurotrophic support, astrocytes play an important regulatory role in synapse development and function. Motor neuron peripheral and central synaptic defects have been described in SMA, but it remains to be fully determined how human glial cells contribute to synapse pathogenesis.

RNA seq data from iPSC-derived astrocytes demonstrate a significant down-regulation of genes associated with synaptic transmission and plasma membrane cell projections in patient-derived samples. Using the SurfaceGenie prediction tool, we verified many of these down-regulated genes likely encode cell surface proteins and are associated with ion gradient regulation, glutamate receptors and transporters, and synaptic formation and integrity. We therefore hypothesize that SMA astrocytes may lack important synaptic-related cell surface genes and their encoding proteins, which could contribute towards motor neuron synaptic defects. We are currently using a mass spectrometry approach to define healthy and SMA iPSC-derived astrocyte cell surface proteins. We will assess if candidate proteins are implicated in synaptic defects by applying super resolution microscopy and multi-electrode array (MEA) techniques to our iPSC-derived motor neuron astrocyte co-cultures. Preliminary MEA data from SMA iPSC-derived motor neurons suggest mean firing rate abnormalities; we will investigate if SMA astrocytes could further compound this synaptic deficit.

Biography

Dr. Welby is a postdoctoral fellow in Dr. Allison Ebert's lab at the Medical College of Wisconsin and is a recipient of the Audrey Lewis Young Investigator Award (2020) funded by CureSMA. Dr. Welby obtained her Ph.D. in 2017 from University College London in Stem Cells and Regenerative Medicine, with a primary focus on characterizing cone photoreceptors in stem cell-derived retinal organoids. Dr. Welby has an avid interest in the use of stem cell modeling systems to study the underlying causes of neurodegenerative disorders and how glia-neuron interactions could be implicated in disease pathogenesis.

Genetic Markers as Risk Factors for Impulsive-Compulsive Behavior in Parkinson's Disease Patients on Dopaminergic Therapy

Stepan Tikhomirov[1*], Anna Fedosova[1], Nataliya Titova[2,3], Natalia Shipilova[2,3], Olga Rudko[1], Elena Katunina[2,3], Eugene Klimov[1†]

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† Deceased on July, 8, 2021;

Abstract

Impulsive-compulsive and related behavioral disorders (ICD) are drug-induced non-motor behavioral complications in Parkinson's disease (PD). Since dopaminergic and specifically dopamine agonists therapy is considered the main risk factor for ICD development, a large body of work has focused on pharmacogenetic approaches for prediction and management of ICD in PD. The aim of our study was to evaluate the role of candidate genes such asDBH, DRD2, MAOA, BDNF, COMT, SLC6A4, SLC6A3, ACE, DRD1 polymorphismsand links to pathogenesis of ICD in PD. We compared patients with PD and ICD (n=49), patients with PD without ICD (n=36) and a population control group (n=365). ICD was diagnosed using the QUIP questionnaires and a specific diagnostic criteria for ICD subtypes. Genotyping was conducted using PCR, Real-Time PCR, SNaPshot, and PCR-RFLP techniques. Statistical analysis was performed using WinPepi and APSampler v3.6 software. PCA testing was conducted using RStudio software. The following substitutions showed statistically significant correlations with PD and ICD: DBH (rs2097629, rs1611115), DRD2 (rs6275, rs12364283, rs1076560), ACE (rs4646994), DRD1 (rs686), BDNF (rs6265); and these are novel associations in Russian PD patients. Our findings suggest that polymorphisms in DBH, BDNF, DRD2, ACE genes are associated with an increased risk of ICD development in Russian PD patients. Of specific interest is rs6275 DRD2 gene polymorphism which is associated with a strong clinical genetic risk factor for the development of ICD in PD patients and may therefore enable pharmacogenetic strategies to aid personalized treatment and prophylaxis.

Additional link: Titova N, Chaudhuri KR. 2017. Personalized Medicine and Nonmotor Symptoms in Parkinson's Disease. Int Rev Neurobiol 134:1257-1281. https://doi.org/10.1016/bs.irn.2017.05.015.

Biography

Stepan Tikhomirov, bachelor student, 4th year of the Biological Faculty of Moscow State University, Department of Genetics, medical and veterinary genetics group, Scientific supervisor: leading researcher, Doctor of Biological Science, associate professor Eugene Klimov. Our team has been studying the molecular and genetic features of the response to dopaminergic therapy in Parkinson's disease to develop a personalized approach to prognosis and treatment. Cooperation: Department of Neurology, Neurosurgery and Medical Genetics of the Medical Faculty of the Pirogov Russian National Research Medical University of the Ministry of Health of the Russian Federation.

A Review on Parkinson's Disease Treatment

Tori Lee[1]*, Eva Yankee[2]

Department of Biology, Pacific Union College, USA

Abstract

Parkinson's disease (PD) is a neurodegenerative illness and has a common onset between the ages of 55 and 65 years. There is progressive development of both motor and non-motor symptoms, greatly affecting one's overall quality of life. While there is no cure, various treatments have been developed to help manage the symptoms of PD. Management of PD is a growing field and targets new treatment methods, as well as improvements to old ones. Pharmacological, surgical, and therapeutic treatments have allowed physicians to treat not only the main motor symptoms of PD, but target patient-specific problems as they arise. This review discusses both the established and new possibilities for PD treatment that can provide patient-specific care and mitigate side effects for common treatments.

Biography

Tori Lee is a medical student at Loma Linda University School of Medicine. She wrote this paper while attending Pacific Union College, where she spent two years doing research on Alzheimer's disease and Parkinson's disease.

Adiponectin Reduces the Damages Induced by Cerebrospinal Fluid from Patients Affected by Multiple Sclerosis

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Abstract

Adiponectin (Acrp30) is an adipokine involved in multivalent biological functions such as energy metabolism, proliferation, and immunity[1]. Previously, we found high expression of Acrp30 in the serum as well in cerebrospinal fluid (CSF) related to severity and prognosis from patients affected by Multiple Sclerosis (MS)[2,3].

In this scenario, we investigated the effects of CSF from severe MS patients on U87 and SH-SY5Y cells, tested such as in vitro models of glioblastoma and neuroblastoma respectively. Also, we evaluated whether Acrp30 administration reverts the effects induced by CSF.

U87 and SH-SY5Y cell lines have been treated with CSF and/or Acrp30 and successively, cell viability, oxidative stress, and inflammatory mediators (IL-6, IL-10, TNF-alpha, INF-□) have been evaluated by MTT, nitrite assay and qPCR.

Our results demonstrated that MS CSF has a cytotoxic activity on both cell lines that is partially attenuated by Acrp30 administration in SH-SY5Y but not in U87 cells. The toxic effects due to MS CSF are mediated by oxidative stress, as showed by induction of nitric oxide. In addition, Acrp30 is able to reduce the release of nitric oxide induced by CSF treatment on SH-SY5Y cells but not on U87 cells. Finally, we found that

MS CSF treatment induces an increase of expression of INF-□ on SH-SY5Y cells and that Acrp30 partially reverts this effect.

Taken together, our data demonstrated that Acrp30 protects SH-SY5Y cells against MS CSF-induced cytotoxicity reducing the release of nitric oxide and modulating INF-□ expression, a major mediator involved in inflammatory response in MS.

Biography

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Tranexamic Acid as a Novel Adjunct in the Management of Vessel Perforation During Neurointerventional Procedures

Dr Samuel Wreghitt[1], Dr Kerelus Morkos[9], Dr Julian Maingard [2 3 11], Associate Professor Christen Barras [4 5], Dr Hong Kuan Kok [2 6], Dr Jonathan Hall [7 11], Professor Vincent Thijs [8,] Dr Lee-Anne Slater[3,] Associate Professor Winston Chong [3], Associate Professor Ronil Chandra [3 10], Dr Ash Jhamb[11] Associate Professor Mark Brooks [7 8] Associate Professor Hamed Asadi[2,3,7,11]

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Abstract

We present our experience of the use of Tranexamic Acid as a novel adjunct in the management of vessel perforation during neurointerventional procedures. Iatrogenic vessel perforation is an uncommon but potentially life-threatening complication of endovascular clot retrieval (ECR) for treatment of acute ischaemic stroke. Intracranial vessel perforation is typically managed with a variety of endovascular techniques.

The clot stabilising effect of TXA is well established in trauma to reduce blood loss and mitigate trauma-induced hyperfibrinolysis as well as peri-operative use to improve intraoperative haemostasis and reduce the need for blood transfusions. The role of TXA during intracranial vessel perforation has not been established.

We report a case series of 9 patients describing the use of intra-arterial (IA) catheter directed TXA to facilitate haemostasis post vessel perforation during ECR. Administration of TXA was successful in halting

extravasation post arterial rupture in all but one case. One-third of all patients (3/9) experienced a good functional outcome at 3 months post- procedure. Mortality complicated one-third of our cases (3/9). TXA administration was used as the sole haemostasis method in one-third of our cases (3/9). Balloon occlusion was used as an adjunct to TXA in a further 5 cases.

This case series highlights the feasibility of direct administration of IA TXA as an additional tool in the armamentarium of the neuro-interventionalist in managing iatrogenic vessel perforation.

Is There a Difference Between Microglial Activation and Blood Supply in the Three Different Human Brain Regions Linked to Suicids?

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Abstract

Objectives: Neuroinflammation is suggested to be linked to suicide and microglia is an immune cell of the central nervous system. The aim of this study was to search for indications of neuroinflammation and find out if there is any difference between microglial cells and blood supply between individuals, who had committed suicide and the control group.

Materials and Methods: Post-mortem human brain tissues were obtained from seven individuals, who had committed suicide and from eight individuals (control group), who died from other causes. Quantitative analysis was performed using immunohistochemical staining of activated microglia (CD68+) and blood vessels (CD31+) in the white and gray matter of prefrontal cortex, striatum and substantia nigra.

Results: Significantly higher number and more diffuse CD68+ cells were found in the white matter of prefrontal cortex compared to its gray matter ($p=0.005$). In addition the significantly lower number of CD31+ microvessels were identified ($p=0.02$). CD68 positivity was different between brain regions, where significantly more CD68+ cells were found in the substantia nigra compared to prefrontal cortex taking into account white and gray matter ($p=0.001$). Furthermore, negative correlation between number of CD68+ cells and number of CD31+ blood vessels in substantia nigra ($r=-0.326$; $p=0$) was found.

Conclusions: As this study could not confirm increased number of CD68+ cells in individuals, who had committed suicide, it suggests that different inflammation pathways could be involved. Interestingly, we found that comparing three different brain regions substantia nigra had the most CD68+ cells, but the least blood supply, that requires further investigation.

Biography

Marika Garnizone received her medical degree from Riga Stradins University. Dr. Garnizone is currently a resident doctor at Riga Psychiatry and Addiction Medicine Centre. Her field of interest is neurobiology of suicidality.

Tianqi Yizhi Granules Improves Cognitive Performance and Inhibits Apoptosis in Senescence-Accelerated Mouse Prone 8 (SAMP8) Mice

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Abstract

Tianqi Yizhi Granules（TQ）, clinical experienced prescription of traditional Chinese Medicine, has been applied to treat Alzheimer's disease（AD）with exhibited remarkable effects. With age-related pathological phenotypes, the senescence-accelerated mouse prone 8 (SAMP8) strain, is considered a robust model for sporadic AD. Aimed to define the effect and investigate the underlying mechanism of TQ, four-month-old male SAMP8 mice were randomly divided into a model, donepezil-treated, or TQ-treated group (multiple doses, respectively), while Senescence-Accelerated Resistant Mouse 1 (SAMR1) mice were set as the control group. Open field test (OFT) and Y-maze were conducted during the 12 weeks treatment period, after that Morris water maze (MWM) was used to test the ability of spatial navigation and memorization. HE staining, Nissl staining , Immunohistochemistry and Thio-S staining were used to analyze neuron loss, Tau deposition, and amyloid-β (Aβ) level. Western blot (WB) analysis was applied to detect the protein expression levels of NeuN, Bcl-2, Bax, caspase-3, cleaved caspase-3, and caspase-9. The current study proved that TQ exerted a protective effect on improving learning and memory, inhibiting apoptosis, and reducing the process of pathological degeneration in the hippocampus of SAMP8 mice, which showed almost similar effects with the positive control group of donepezil.

Biography

Yi Zeng received the Bachelor of Medicine degree in 2018, and is currently working toward a Ph.D. degree in Integrated Traditional and Western Medicine with the School of Traditional Chinese Medicine, Southern Medical University. Her research focuses on the mechanism of traditional Chinese medicine in the treatment of Neurodegenerative Diseases.

Effect of Jin Three-Needle Therapy on Quality of Life in Patients with Parkinson's Disease: A Study Protocol for a Multicenter Randomized Controlled Trial

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Abstract

Background: Acupuncture has been widely applied on treating Parkinson's disease (PD) based on Madopar (L-dopa). Jin three-needle therapy is a unique and common acupuncture and this study is designed to assess the clinical effect of this treatment on quality of life in PD patients with multicenter randomized controlled trail.

Methods: A total of 162 participants will be randomly assigned to treatment group (Jin three-needle therapy and Madopar, n=81) and control group (Madopar, n=81). The whole treatment will last for 8 weeks with

each four-week period as a course and a follow-up whereafter. Several scales like UPDRS will be used four times during treatment and follow-up to grade the changes of symptoms and determine the effects. SPSS22.0 will be adopted for data entry and statistical analysis.

Discussion: The study is a preliminary investigation about acupuncture on improving quality of life in patients with PD, which may contribute to the design for multicenter randomized controlled trials.

Keywords: Jin three-needle; Parkinson's disease; multicenter; clinical effect

Biography

Xiaowen Cai received the B.S. degree in Traditional Chinese Medicine (TCM) in 2018 and the M.S. degree in acupuncture, moxibustion, and tuina in 2021 from Southern Medical University, Guangzhou, China. She is currently continuing her Ph.D. study in integrated Chinese and western medicines in the same university. Her main research field is the mechanism of acupuncture on depression. By 2019, she is a member of the Acupuncture and Moxibustion Preventive Treatment for Disease Subcommittee of Guangdong Provincial Association of Acupuncture and Moxibustion.

De Novo Absence Status Epilepticus in Elderly due to Acute Psychotropic Withdrawal: A Case Report

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Introduction: De novo absence status epilepticus (SE) can occur in the elderly related to benzodiazepine withdrawal and excessive psychotropic drug use. We describe a case of de novo absence SE in a 61-year-old woman related to acute benzodiazepine and zolpidem withdrawal.

Case Report: A 61-year-old woman was brought to the University of Nebraska Medical Center hospital Emergency Room (ER) after being found down and unresponsive at her home. Past medical history was notable for chronic depression and insomnia that were treated with alprazolam and zolpidem respectively. In the ER, she was awake but not following commands and her Glasgow Coma Scale score was 14. She had a generalized convulsive seizure in the ER that was aborted with lorazepam, and she was admitted for further management. An electroencephalogram (EEG) obtained due to persistent confusion showed generalized spike-and-wave discharges (GSWD) at 1-5 Hz lasting 5-40 seconds consistent with absence SE. Clinically, she had ictal delirium, catatonia and facial automatisms. The GSWD were briefly aborted with levetiracetam but they soon recurred. Psychiatry evaluated her and re-started the zolpidem and benzodiazepine that were discontinued abruptly on hospital admission. Subsequently, there was resolution of epileptic activity on EEG and her delirium and catatonia also resolved.

Conclusion: In elderly individuals who present with acute confusion after abrupt psychotropic withdrawal, there should be a high suspicion for de novo absence SE. Urgent EEG should be obtained to confirm the diagnosis. In our case, abrupt withdrawal of benzodiazepine and zolpidem likely precipitated the absence SE.

Biography

Dr. Navnika Gupta is a fourth year neurology resident at the University of Nebraska Medical Center. Her interest includes the neurological diseases affecting the central and peripheral nervous system. She has special interest in epilepsy and her interests include management of status epileptics, and management of refractory epilepsy. She plans to pursue a 2-year epilepsy fellowship after completion of her residency.

Co-Occurrence of Apathy and Impulsivity in Progressive Supranuclear Palsy

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Abstract

Introduction: Apathy and impulsivity are common consequences of progressive supranuclear palsy (PSP) and can worsen its prognosis. They can co-exist in the same patients, although their concomitant prevalence remains unclear. Their relationship to emotional lability is also unknown. Our aim was two-fold: (1) to estimate the co-occurrence of apathy and impulsivity and their relationship to emotional lability in PSP, and (2) to characterize the demographic, clinical, and cognitive features of PSP patients with apathy and impulsivity.

Methods: In a retrospective study of a long-term clinical cohort, we assessed the prevalence of apathy, impulsivity, and emotional lability from clinical interviews, medical records, and contemporary carer questionnaires. 154 patients with a diagnosis of probable or possible PSP were identified, of which 64 patients had neuropathological confirmation of PSP. PSP patients with both apathy and impulsivity were compared in terms of demographic, clinical, and cognitive characteristics to PSP patients with either one or neither of these neuropsychiatric features.

Results: Apathy and impulsivity co-existed in two-thirds of people with PSP. A fifth displayed emotional lability in addition to apathy and impulsivity. Apathy and impulsivity were more commonly coexpressed than by chance. There was no single demographic, clinical or cognitive feature that distinguished between PSP patients with versus without apathy and impulsivity.

Conclusions: The co-existence of apathy and impulsivity in PSP suggests that these neuropsychiatric features may share similar risk factors and etio-pathogenetic mechanisms. Apathy and impulsivity should be jointly assessed when planning symptomatic treatments for detrimental behavioural problems caused by PSP.

Biography

Zi Qi Kok is a final year medical student at the University of Cambridge. She received a Bachelor's degree (Honours) in Neuroscience from the University of Cambridge, and has conducted basic and clinical research at the Anne McLaren Laboratory of Regenerative Medicine, as well as the Cambridge Centre for Frontotemporal Dementia and related disorders. She has collaborated with world-leading professors in neurology, including Professor James B. Rowe and Professor Alasdair Coles. Her research interests includes behavioural presentations in frontotemporal dementia, as well as the interface between neuroinflammation and neurodegeneration.

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