Current Status of Opioid Prescribing for Cancer and Non-Cancer Pain in Taiwan

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Abstract

Opioids are the mainstay treatment for severe pain, both cancer pain and non-cancer pain. However, over the past two decades, North America, Oceania and European countries experienced a marked increase of opioid prescribing in especially chronic non-cancer pain that resulted in “opioid epidemic”.

In Taiwan, those patients with cancer diagnosis can be prescribed with opioid without too much limitation. However, lack of different strong opioid options remains major barrier to adequate cancer pain management in Taiwan until late 2014. Our recent studies demonstrated that approximately 50% of cancer patients used analgesics, 50% of which were opioids; the proportions were stable in the pass 2 decades. However, the annual cumulative opioid dose significantly decreased while the annual cumulative strong opioid use per patient increased significantly. In parallel, the annual cumulative weak opioids use per patient decreased. Among extended-release strong opioids, the use of transdermal fentanyl significantly decreased after oxycodone and hydromorphone were introduced. These finding implied that increased therapeutic options in strong opioid prescriptions led opioid prescription patterns to evolve towards international cancer pain management guidelines and may facilitate more efficient opioid titration and rotation and thus decrease, not increase, the opioid usage.

On the contrary, opioid prescription for non-cancer pain is strictly limited in Taiwan. According to Controlled Drugs Management Information System of Taiwan Food and Drug Administration data, we have only less than 500 chronic non-cancer pain patients were prescribed with long term strong opioids. Most of the strong opioid prescription were used in acute pain service. Specifically, weak opioid tramadol is categorized as schedule 4 controlled substance that is not strictly regulated. So the utilization of tramadol prescribed to patients without cancer diagnosis increased drastically in the past decades.

Selected recent publications:

1. Wu TC, Hsu CH, Sun WZ, Chen HM, Lin CP*, Shao YY*: Impact of expanded strong opioid availability on opioid prescription patterns in patients with cancer: A population-wide cohort study in Taiwan. Lancet Reg Health West Pac. 2021 Aug 26;16:100255.

2. Chen TC, Wang TC, Lin CP, Bonar K, Ashcroft DM, Chan KA, Chen LC: Increasing tramadol utilisation under strict regulatory control of opioid prescribing - A cross-sectional study in Taiwan from 2002 through 2016. Journal of Formosan Medical Association, 2021 Feb;120(2):810-818

3. Lin CP, Hsu CH, Fu WM, Chen HM, Lee YH, Lai MS, Shao YY: Key opioid prescription concerns in cancer patients: A nationwide study. Acta Anaesthesiol Taiwan 2016 Jun;54(2):51-6

4. Wang JJ, Teng SF, Chu YR, Chu CC, Ho CH, Chu LL: Evaluation of opioid consumption trends for pain in Taiwan and comparison with neighboring Asian countries. J Food Drug Anal. 2022 Mar 15;30(1):104-110.

5. Wang JJ, Chu YR, Teng SF, Chu CC, Ho CH, Chu LL: Prevalence of opioid prescriptions in Taiwan (2008-2018). J Chin Med Assoc. 2022 May 1;85(5):603-609.

Mesoporous polydopamine nanoparticles attenuates morphine tolerance in neuropathic pain rats: Morphine sparing effect

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Abstract

In 2017, more than 70,000 died from drug overdoses, making a leading cause of injury-related death in the US. Of those deaths, almost 68% involved a prescription or illicit opioid. More than 25 million US adults are affected by daily pain and 2 million individuals have an opioid use disorder, most starting with opioids prescription, then to addiction. NIH initiates the HEAL in 2018; it focuses on 2 primary goals, improving treatments for opioid misuse and addiction, and enhancing strategies for pain management. Study showed that ultra-restrictive opioid prescription protocol provided adequate postoperative pain control without any negative health consequences; this radical opioid-sparing for postoperative pain is expected to reduce health care costs and limited opioids circulating in communities. Ultimately protect patients and their family members from opioid misuse and abuse. Good perioperative pain management is a key matter to enhance surgery recovery and limited CPSP, opioid-sparing is advised; it can be achieved by potentiate the effect of opioids, reduce dosage and duration with MMA. Antioxidation is considered an efficient strategy to eliminate excessive ROS for neuropathic pain. Nanoparticles with natural enzyme-like activities have been developed, which enhanced biological stability with improved half-life, multi-functionality and ease of preparation. We, by using of PSNL model, developed nanocarriers, which provided antioxidative effect to enhance morphine's antinociception with prolong action. MPDA-nanocarrier effectively scavenges ROS and alleviated neuropathic pain with prolonged duration.

Selected recent publications:

1. Kuthati Y, Busa P, Davuluri VNG, Wong CS*. Manganese oxide nanozymes ameliorate mechanical allodynia in a rat mode of partial sciatic nerve-transection induced neuropathic pain. Int J Nanomed 2019:14:10105-10117.

2. Kuthati Y, Navakanth RV, Pabby P, Tummala S, Davuluri VNG, Wong CS*. Scope and applications of nanomedicines for the management of neuropathic pain. Molecular Pharmaceutics, DOI: 10.1021/acs.molpharmaceut.9b01027, 2020.

3. Kuthay Y, Busa P, Tummala S, Rao VN, Davuluri VNG, Ho YP, Wong CS*. Mesoporous polydopamine nanoparticles attenuates morphine tolerance in neuropathic rats by inhibition oxidative stress and restoration of endogenous antioxidant system. Antioxidants 2021, 10, 195 https//doi.org/10.3990/antiox100201195.

4. Kuthati Y, Rao VN, P, Busa P, Wong CS.* Teneligliptin exerts antinociceptive effects in rat model of partial sciatic nerve transection induced neuropathic pain. Antioxidants **2021**, 10, 1438.

5. Busa P, Kuthati Y, Huang NC, Wong CS.* New advances on pathophysiology of diabetes neuropathy and pain management: potential role of melatonin and DPP-4 inhibitors. Frontier Pharm Doi:10.3389/fphar.2022.864088.

The striatal dopamine transporter, novelty seeking and cognitive flexibility in patient with opioid dependence

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Abstract

Novelty seeking (NS) is a core personality trait that primes the susceptibility to drug addiction. Striatal dopamine activity contributes to cognitive flexibility, an important cognitive strategy to inhibit impulsivity and compulsive drug seeking behavior. Evidence supports the association between dopamine and NS, which is higher in opioid-dependent patients. Moreover, repeated opioid exposure can cause cognitive deficits including poor cognitive flexibility and impaired impulse control. However, in opioid-dependent patients, the link between NS, striatal dopamine activity, and cognitive flexibility is still unclear. We recruited 22 opioid-dependent individuals and 30 age- and sex-matched healthy controls. Single-photon emission computed tomography with [99mTc]TRODAT-1 as a ligand was used to measure the striatal dopamine transporter (DAT) availability. The Trial Making Test (TMT) was performed to assess cognitive flexibility. We found that in opioid-dependent patients, the striatal DAT availability was lower and negatively associated with TMT Part B ÷ Part A. Moreover, an inverted-U shape significantly matched the scores of NS as a function of the striatal DAT availability, with maximum NS potential in the midrange of the DAT availability. An extra sum-of-squares F test was conducted, indicating that a quadratic model fitted the association between the DAT and NS better than a linear model did. In brief, in opioid-dependent patients, the striatal DAT availability is nonlinearly linked to NS and linearly linked to cognitive flexibility. The role of the striatal DAT in the transition from controlled to compulsive opioid use warrants further research.

Selected recent publications:

1. Tsou CC, Chou HW, Ho PS, Kuo SC, , ***Huang SY (correspondence).**DRD2 and ANKK1 genes associate with late-onset heroin dependence in men.. World J Biol Psychiatry. 2019 Oct;20(8):605-615.
2. Huang CC, Kuo SC, Yeh TC, Yeh YW, Chen CY, Liang CS, Tsou CC, Lin CL, Ho PS, ***Huang SY (correspondence).** OPRD1 Gene Affects Disease Vulnerability and Environmental Stress in Patients with Heroin Dependence Prog Neuropsychopharmacol Biol Psychiatry. 2019 Mar 8;89:109-116 (accepted on 25 Aug 2018) ICF 4.185（28/142 Psychiatry）
3. Tsou CC, Kuo SC, Chen CY, Lu RB, Wang TJ, ***Huang SY (correspondence).**. NGF gene polymorphisms are not associated with heroin dependence in a Taiwanese male population. Am J Addict. 2018 Sep;27(6):516-523
4. Kuo SC, Yeh YW, Chen CY, Huang CC, Ho PS, Liang CS, Lin CL, Yeh TC, Kuo SC, Yang BZ , Lu RB, ***Huang SY (correspondence).** Differential effect of the DRD3 genotype on inflammatory cytokine responses during abstinence in amphetamine-dependent women Psychoneuroendocrinology. 2018 Nov;97:37-46.
5. Yen CH, Mei-Chen Shih, MS, Cheng-Yi Cheng, …...Lu RB, ***Huang SY (correspondence) Differential cytokine levels between early withdrawal and remission states in patients with alcohol dependence.** Psychoneuroendocrinology. 2017 Mar. 20;76:183-191.

Development of Novel Therapeutic Drugs for Treatment and Prevention of Opioid Addiction

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Abstract

The opioids addiction is a serious global problem that affects the health, social, and economic welfare of all societies. Methadone or Buprenorphine is a long-acting synthetic opioid agonist medication that can prevent withdrawal symptoms and reduce craving in opioid-addicted individuals. However, those who take these drugs are still addicts and the heroin relapse rate is relatively high. Therefore, there is no cure for opioids addiction until now. Opioids addiction continue to be global unmet medical needs. Recently, we found that Scla711 (xCT), which encodes system x_c^-, knockout mice lack the heroin or methadone-seeking and craving behaviors compared to wild-type mice while mice were habituated to receive the heroin or methadone administration, indicting system x_c^- has a critical role in the process of opioids addiction. Importantly, the wild-type mice with heroin or methadone-dependence treated with the inhibitor of system x_c^-, sulfasalazine (SSZ)) suppressed the heroin or methadone-seeking and craving behaviors. Moreover, we also finished the PI-initiated clinical trials for SSZ in treatment of patients with opioid addiction. Our results indicate that oral administration of SSZ is able to promote the detoxification and inhibit the opioid craving and withdrawal symptoms in patients with opioid addiction. Moreover, our big data analysis also demonstrates that long-term use of SSZ decreased incidence rate of opioid-addictive disorders in human. These findings show the inhibitors of system x_c^- represent new class of therapeutics against opioids addiction.

Selected recent publications:

1. Wei ST, Huang YC, Hsieh ML, Lin YJ, Shyu WC, Chen HC, Hsieh CH*. Atypical chemokine receptor ACKR3/CXCR7 controls postnatal vasculogenesis and arterial specification by mesenchymal stem cells via Notch signaling. Cell Death Dis. 2020;11(5):307. IF=9.705, R/C=45/203, CELL BIOLOGY

2. Chiang CS, Lin YJ, Lee R, Lai YH, Cheng HW, Hsieh CH*, Shyu WC*, Chen SW*. Combination of fucoidan-based magnetic nanoparticles and immunomodulators enhances tumour-localized immunotherapy. Nature Nanotechnology. 2018;13:746–754. IF=40.523, R/C=2/109, NANOSCIENCE & NANOTECHNOLOGY.

3. Huang MW, Lin YJ, Chang CW, Lei FJ, Ho EP, Liu RS, Shyu WC, Hsieh CH*. RGS4 Deficit in Prefrontal Cortex Contributes to the Behaviors related to Schizophrenia via System xc–-mediated Glutamatergic Dysfunction in Mice. Theranostics. 2018; 8(17): 4781–4794. IF=11.6, R/C=13/139, MEDICINE, RESEARCH& EXPERIMENTAL.

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5. Hsieh CH*, Lin YJ, Chen WL, Huang YC, Chang CW, Cheng FC, Liu RS, Shyu WC*. HIF-1α triggers long-lasting glutamate excitotoxicity via system xc- in cerebral ischaemia-reperfusion. J Pathol. 2017. doi: 10.1002/path.4838. IF=9.883, R/C=4/77 ,PATHOLOGY.

Nanosymposium session IV

Roles of Neutrophils in Glioma

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Abstract

Neutrophils, which are the most abundant circulating leukocytes in humans, are the first line of defense against bacterial and fungal infections. Recent studies have reported the role and importance of neutrophils in cancers. Glioma are the most common primary malignant tumors of the brain. The tumor microenvironment (TME) in the brain is complex and unique owing to the brain-blood barrier or brain-tumor barrier, which may prevent drug penetration and decrease the efficacy of immunotherapy. However, there are limited studies on the correlation between glioma and neutrophils. Here, we reviewed the current knowledge on the correlation between neutrophil-to-lymphocyte ratio and prognosis of glioma, and the implications of tumor-associated neutrophil (TAN) phenotypes and the functions in glioma microenvironment as well. Definitely, we also look into the potential effects of various treatments on TANs and the ability of neutrophils to function as a nanocarrier of drugs to the brain TME. Indeed, further studies are needed to elucidate the complex interactions between neutrophils, other immune cells, and glioma cells inside TME.

Selected recent publications:

1. **Lin YJ**, Wei KC, Chen PY, Lim M, Hwang TL. Roles of Neutrophils in Glioma and Brain Metastases. Front Immunol. 2021 Aug 13;12:701383.
2. Chen KT, Chai WY, **Lin YJ**, Lin CJ, Chen PY, Tsai HC, Huang CY, Kuo JS, Liu HL, Wei KC. Neuronavigation-guided focused ultrasound for transcranial blood-brain barrier opening and immunostimulation in brain tumors. Sci Adv. 2021 Feb 5;7(6):eabd0772.
3. **Lin YJ**, Mashouf LA, Lim M. CAR T Cell Therapy in Primary Brain Tumors: Current Investigations and the Future. Front Immunol. 2022 Feb 21;13:817296.
4. **Lin YJ**, Huang CY, Shen YC, Wei KC, Chuang CC, Hsu PW, Huang YC, Hwang TL, Chen PY. A manzamine-derived compound as a potential therapeutic agent for glioma by inducing apoptosis and cell cycle arrest. Am J Cancer Res. 2022 Apr 15;12(4):1740-1751.
5. Chen CH, **Lin YJ**, Lin YY, Lin CH, Feng LY, Chang IY, Wei KC, Huang CY. Glioblastoma Primary Cells Retain the Most Copy Number Alterations That Predict Poor Survival in Glioma Patients. Front Oncol. 2021 Apr 26;11:621432.

Multiple Novel approach for GBM therapy

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Abstract

Glioblastoma multiforme is one of the most malignant tumors, and it has an aggressive pattern and a high recurrence rate. Despite multimodalities treatment with surgery and concomitant radiation and chemotherapy, patients with GBM still have a poor prognosis, with a mean survival of <15 months. We used the multiple bioinformatics algorithms tools for multiple modality approach. The goals and aims from novel approach for new drug development and drug repurposing. Simultaneously, biomarker prediction could be fully assessed and applied. Moreover, we performed basic research methods to confirm the big data results and reach the satisfied conclusions. Herein, we presented three studies for demonstration for GBM therapy.

Selected recent publications:

1. **Cheng-Yu Tsai,** Huey-Jiun Ko, Joon-Khim Loh, Aij-Lie Kwan, Tsung-Hsien Chuang, Yi-Ren Hong. **(2021)** Ionizing Radiation Induces Resistant Glioblastoma Stem-Like Cells by Promoting Autophagy via the Wnt/β-Catenin Pathway. Life 11 (5), 451.

2. **Cheng-Yu Tsai,** Huey-Jiun Ko, Shean-Jaw Chiou, Tsung-Hsien Chuang, Chi-Ying F Huang, Joon-Khim Loh, Yi-Ren Hong. **(2021)** NBM-BMX, an HDAC8 Inhibitor, Overcomes Temozolomide Resistance in Glioblastoma Multiforme by Downregulating the β-Catenin/c-Myc/SOX2 Pathway and Upregulating p53-Mediated MGMT Inhibition. International journal of molecular sciences 22 (11), 5907.

3. Huey-Jiun Ko, **Cheng-Yu Tsai,** Shean-Jaw Chiou, Joon-Khim Loh, Yi-Ren Hong. **(2021)** The Phosphorylation Status of Drp1-Ser637 by PKA in Mitochondrial Fission Modulates Mitophagy via PINK1/Parkin to Exert Multipolar Spindles Assembly during Mitosis. Biomolecules 11 (3), 424.

4. Cheng-Jung Ho, **Cheng-Yu Tsai,** Yi-Ren Hong, Chihuei Wang. **(2022)** Compound cellular stress maximizes apoptosis independently of p53 in glioblastoma. Cell Cycle, 1-13.

5. **Cheng-Yu Tsai,** Shean-Jaw Chiou, Huey-Jiun Ko, Aij-Li Kwan, Joon-Khim Loh, Yi-Ren Hong. **(2022)** Deciphering the evolution of composite-type GSKIP in mitochondria and Wnt signaling pathways PloS one 17 (1), e0262138.

Translational Research of Glioma Tumor Therapy: Magic Bullet of Targeting Drug Delivery? Precision Medicine? Tumor Microenvironment? Energy Metabolism?

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Abstract

Among the broad range of tumors, malignant tumors in the central nervous system (CNS) represent the greatest challenge for effective drug delivery due to the blood-brain barrier (BBB). Nanotechnologies may have great clinical potential in overcoming this formidable obstacle in traditional brain cancer treatment. Nanoparticles are purposely constructed on the nanometer scale, and nanoparticles can penetrate more deeply into inflammatory sites, the epithelium and tumors. Moreover, nanoparticles can be loaded with various chemotherapeutic drugs and modified with targeting molecules to provide the targeted delivery of drugs to tumors. Ferritin, the natural iron storage protein complex, self-assembles into a uniform cage-like structure. Human H-ferritin (HFn) has been shown to transverse the BBB by binding to transferrin receptor 1 (TfR1), which is abundant in endothelial cells and overexpressed in tumors, and enters cells via endocytosis. Ferritin is easily genetically modified with various functional molecules, justifying that it possesses great potential for development into a nanocarrier drug delivery system. Hence, with modifications of versatile molecules on ferritin, the tumor-targeting or the tumor microenvironment (TME)-targeting ferritin nanocarrier can be established and encapsulated with various types of drugs/small molecules to specifically deliver them to the GBM tumor or GBM TME, respectively.

Selected recent publications:

1. Huang CW, Hsieh WC, Hsu ST, Lin YW, Chung YH, Chang WC, Chiu H, Lin YH, Wu CP, Yen TC*, **Huang FT*** (2017) The Use of PET Imaging for Prognostic Integrin α2β1 Phenotyping to Detect Non-Small Cell Lung Cancer and Monitor Drug Resistance Responses. *Theranostics* 7(16):4013-4028.

2. Huang CW, Chang YH, Lee HH, Wu JY, Huang JX, Chung YH, Hsu ST, Chow LP, Wei KC, **Huang FT*** (2020) Irisin, an exercise myokine, potently suppresses tumor proliferation, invasion and growth in glioma. *FASEB J*, 34(7):9678-9693.

3. Huang CW, Chuang CP, Chen YJ, Wang HY, Lin JJ, Huang CY, Wei KC, **Huang FT*** (2021) Integrin α2β1-targeting ferritin nanocarrier traverses the blood-brain barrier for effective glioma chemotherapy. *Journal of Nanobiotechnology* 19(1):180.

4. Lin JJ, Chuang CP, Lin JY, **Huang FT***, Huang CW* (2021) Rational Design, Pharmacomodulation, and Synthesis of [^{68}Ga]Ga-Alb-FAPtp-01, a Selective Tumor-Associated Fibroblast Activation Protein Tracer for PET Imaging of Glioma. *ACS Sensors* 6: 3424-3435.

The role of histone deacetylases in promoting glioblastoma process

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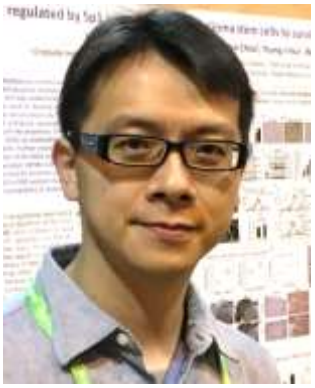

Abstract

Glioblastoma is associated with poor prognosis and high mortality. Although the use of first-line temozolomide (TMZ) can reduce tumor growth, therapy-induced stress drives stem cells out of quiescence, leading to chemo-resistance and glioblastoma recurrence. Histone deacetylases (HDACs) are known to involve in multiple different stages of tumor development; however, how HDACs contribute to more malignant transformation and adaptation of glioblastoma cells to evade drug treatment is not known. Here we observed that HDAC1/HDAC2/HDAC6 are highly overexpressed in TMZ-resistant glioblastoma cells and glioblastoma stem-like tumorspheres. These HDACs can activate Sp1 transcription factor to promote self-renewal of the malignancy by upregulating BMI1 and telomerase reverse transcriptase (TERT), as well as to induce the DNA damage response and repair (DDR) pathway by altering the transcription of various DDR genes. In addition, we also identified a lncRNA, *LINC00461*, as a novel downstream target of HDAC6, and highlighted that the HDAC6/RNA-binding proteins (CCR4-NOT)/*LINC00461* axis increases glioblastoma cell proliferation by maintaining the expression of cell-cycle-related proteins via a sponge function of tumor-suppressive miRNAs. Importantly, HDAC1/HDAC2/HDAC6 expression is associated with poor clinical outcome in both glioblastoma and low-grade gliomas. However, treatment with azaindolylsulfonamide (MPT0B291), a potent HDAC6 inhibitor with partial efficacy against HDAC1/2, induced G2/M arrest and senescence in both TMZ-resistant cells and stem-like tumorspheres. Our study uncovers a previously unknown regulatory mechanism in which the HDACs-mediated Sp1 activation and *LINC00461* expression enable to induce maintains the stem cell population to fuel tumor growth and therapeutic resistance.

Selected recent publications:

1. Chang KY, Hsu TI, Hsu CC, ……, Chuang CK, Kao TJ, **Chuang JY***. (2017 Oct). Specificity protein 1-modulated superoxide dismutase 2 enhances temozolomide resistance in glioblastoma, which is independent of O ^{6}-methylguanine-DNA methyltransferase. *Redox Biol*, 13:655-64.

2. Chen TC[#], **Chuang JY**[#], Ko CY, ……, Chan H, Chang WC, Hsu TI. (2020 Feb). AR Ubiquitination Induced by the Curcumin Analog Suppresses Growth of Temozolomide-Resistant Glioblastoma through Disrupting GPX4-Mediated Redox Homeostasis. *Redox Biol*, 30:101413.

3. Yang WB, Hsu CC, Hsu TI, ……, Chen RM, Chang WC*, **Chuang JY***. (2020 Oct). Increased activation of HDAC1/2/6 and Sp1 underlies therapeutic resistance and tumor growth in glioblastoma. *Neuro Oncol*, 22(10):1439-1451.

4. Yang WB, Wu AC, Hsu TI, ……, Chang WC, Ko CY, **Chuang JY***. (2021 Sep). Histone deacetylase 6 acts upstream of DNA damage response activation to support the survival of glioblastoma cells. *Cell Death Dis*, 12(10):884.

5. Wu AC, Yang WB, Chang KY, ……, Chang WC, Chen PY*, **Chuang JY***. (2022 Feb). HDAC6 involves in regulating the lncRNA-microRNA-mRNA network to promote the proliferation of glioblastoma cells. *J Exp Clin Cancer Res*, 41(1):47.

Nanosymposium session IV

Cell Therapy in Parkinson Disease

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Abstract

Medication using levodopa, surgery including deep brain stimulation, and rehabilitation have all been established as current therapeutic strategies for Parkinson's disease (PD). Strong therapeutic effects have been demonstrated by these treatment methods, but they have been unable to stop the progression of the disease. Therefore cell therapy might be a key for modification of PD progression by reimplementing or regenerating dopaminergic neurons. Cell therapy for PD began with the transplantation of fetal nigral dopamine-containing neurons that improved motor abnormalities in the PD rodent models with good survival of grafts and axonal outgrowth. Thirty years have passed since the 2 clinical trials using fetal nigral transplantation for PD patients were reported and demonstrated unsatisfactory results. However, some patients receiving fetal nigral cell transplantation showed a continuous improvement of motor symptoms for over a decade. Therefore, a new European Union–funded multicenter clinical trial of fetal nigral cell transplantation, TRANSEURO trial, has been carried out recently. The advancement of biotechnology represented by pluripotent stem cells, mesenchymal stem cells and neural stem cells also brings a new hope to apply cell therapies in treating PD. Transplantation of these cell sources has already proven to reduce parkinsonian symptoms in rodent and primate models. Here we will discuss the history and implications for cell therapies for PD, the advantages and disadvantages of these treatments along with the results of relevant trials. Apart from confronting future with optimism in cell therapies, ethical and safety issues should be seriously concerned, with hope separated from hype.

Selected recent publications:

1. **Chang KH**, Cheng ML, Tang HY, Huang CY, Wu HC, Chen CM (2022). Alterations of sphingolipid and phospholipid pathways and ornithine level in the plasma as biomarkers of Parkinson's disease. Cells 11, 395.

2. **Chang KH**, Huang CY, Ou-Yang CH, Ho CH, Lin HY, Hsu CL, Chen YT, Chou YC, Chen YJ, Chen Y, Lin JL, Wang JK, Lin PW, Lin YR, Lin MH, Tseng CK, Lin CH (2021). In vitro genome editing rescues parkinsonism phenotypes in induced pluripotent stem cells-derived dopaminergic neurons carrying LRRK2 p.G2019S mutation. Stem Cell Res Ther 12(1):508.

3. Cheng YC, Chan YH, Hu CJ, Lu YC, Saek T, Hosoya M, Fujioka M, Okano H, Weng SM, Hsu CJ, **Chang KH** (2019). Generation of a human iPS cell line (CGMH.SLC26A4919-2) from a Pendred syndrome patient carrying SLC26A4 c.919-2A>G splice-site mutation. Stem Cell Res. 40: 101524 (Corresponding author)

4. Chiu CC, Wang HL, Weng YH, Chen RS, Chen CM, Yeh TH, Lu CS, Chen YJ, Huang YZ, **Chang KH** (2019). Generation of induced pluripotent stem cells from a young-onset Parkinson's disease patient carrying the compound heterozygous PLA2G6 p.D331Y/p.M358IfsX mutations. Stem Cell Res. 40: 101552

5. **Chang KH***, Lee-Chen GJ, Huang CC, Lin JL, Chen YJ, Wei PC, Lo YS, Yao CF, Kuo MW, Chen CM (2019). Modeling Alzheimer's Disease by Induced Pluripotent Stem Cells Carrying APP D678H Mutation. Mol Neurobiol. 56:3972-3983

Stem cell therapy – a new drug development experience sharing from Steminent

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Ph.D., University College London

Abstract

Cell-based therapies have been attracting much attention for their potential to provide promising approach for the treatment of unmet medical needs and are considered the fourth pillar of healthcare. Recently, extensive interest has focused on the application of stem cell-based therapies in tissue repair and disease treatments. Among different types of stem cells, mesenchymal stem cells (MSCs) are considered multipotent, which means they are able to differentiate into more than one type of cell and are proved to possess multiple mechanism of actions that are critical for many disease treatments. The unique characteristics of MSCs make them the most studied and applied stem cell type in clinical development.

Research of MSCs in neurodegenerative diseases have revealed encouraging evidence for their therapeutic potentials through multiple mechanism of actions. In the talk, I will share general observations from our clinical trials of stem cell therapy for spinocerebellar ataxia and also discuss the challenges for stem cell new drug development.

Selected recent publications:

1. Yoneda T, Choi BH, Gupta PK, Ho CY, Tsui YP, Wang LM, Fujiwara Y, Karasawa H, Moriya Y, Bando K, Kamiyama Y, Kanki M, Omura K, Watanabe T, Bae Y, Chou FC, Ham DS, Lee JY, Liu G, Liu Y, Ooi J, Tsurumaki Y. Non-clinical assessment of cell therapy products: the perspective from five Asian countries/regions based on regulatory guidelines and the underpinning rationales. Cytotherapy. 2021 Oct;23(10):874-885.

2. Coathup MJ, Blunn GW, Campion C, Ho CY, Hing KA. The effect of increased microporosity on bone formation within silicate-substituted scaffolds in an ovine posterolateral spinal fusion model. J Biomed Mater Res B Appl Biomater. 2017 May;105(4):805-814.

3. Ho CY, Sanghani A, Hua J, Coathup M, Kalia P, Blunn G. Mesenchymal stem cells with increased stromal cell-derived factor 1 expression enhanced fracture healing. Tissue Eng Part A. 2015 Feb;21(3-4):594-602.

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5. Lien CY, Chih-Yuan Ho K, Lee OK, Blunn GW, Su Y. Restoration of bone mass and strength in glucocorticoid- treated mice by systemic transplantation of CXCR4 and cbfa-1 co-expressing mesenchymal stem cells. J Bone Miner Res. 2009 May; 24 (5): 837-48.

創新標靶基因編輯CRISPR/Cas9:在視網膜疾病上的應用
Application of Genomic Editing Technology in Retinal Diseases

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Abstract

In recent years, due to advances in regenerative medicine and stem cell technology, as well as the use of health big data, cell therapy has broken through the barriers and bottlenecks in the treatment of many diseases and physiological research in the past, creating various possibilities for personalized precision medicine, and has become the focus of global medical competition. It is also a key policy direction for the government to promote innovative medical care in Taiwan.

The Ministry of Health and Welfare of the Executive Yuan promulgated the "Measures for the Administration of the Implementation or Use of Specific Medical Technical Inspection Instruments " (referred to as the Special management method) in 107, and formulated a draft of the "Regulations on the Administration of Regenerative Medicine Preparations " to promote Taiwan's regenerative medicine industry and emerging organisms. The basis for technological development. In recent years, Taiwan and Japan have been promoting economic structural reforms and industrial innovation measures. It is hoped that this exchange of Taiwanese clinical trials will help Japan’s successful experience in implementing the regenerative medicine industry and provide more complete domestic regenerative medicine products. Benefit the domestic public.

In the future, multi-center and cross-field clinical treatment can be carried out in Taiwan, which is expected to improve the treatment level for Taiwan's stem cell industry.

Selected recent publications:

1. Oncogenic circRNA C190 Promotes Non-Small Cell Lung Cancer via Modulation of the EGFR/ERK Pathway.Ishola AA, Chien CS, Yang YP, Chien Y, Yarmishyn AA, Tsai PH, Chen JC, Hsu PK, Luo YH, Chen YM, Liang KH, Lan YT, Huo TI, Ma HI, Chen MT, Wang ML, Chiou SH.Cancer Res. 2022 Jan 1;82(1):75-89.(IF=12.701;RANK=20/310;ONCOLOGY)

2. METTL3-dependent N6-methyladenosine RNA Modification Mediates the Atherogenic Inflammatory Cascades in Vascular Endothelium. Chien CS, Li Julie YS, YC, Wang ML, Aliaksandr A Yarmishyn, Tsai PH, Juan CC, Phu Neugyn, Cheng HM, Huo TI, **Chiou SH ***, Chien Shu ****Proc. Natl. Acad. Sci. USA*** 2021 118 (7) e2025070118 (IF= 9.412; RANK=8/71;Multidisciplinary Sciences)

3. Supramolecular Nanosubstrate-Mediated Delivery System Enables CRISPR/Cas9 Knockin of Hemoglobin Beta Gene for Hemoglobinopathies. Yang P, Chou SJ, Li J, Hui W, Liu W, Sun N, Zhang RY, Zhu Y, Tsai ML, Lai HI, Smalley M, Zhang X, Chen J, Romero Z, Liu D, Ke Z, Zou C, Lee CF, Jonas SJ, Ban Q, Weiss PS*, Kohn DB*, Chen K*, **Chiou SH***, Tseng HR*.***Science Advances*** 2020 Oct 23;6(43):eabb7107 (IF=13.116;RANK=4/71; MULTIDISCIPLINARY SCIENCES)

4. Dual Supramolecular Nanoparticle Vectors Enable CRISPR/Cas9-Mediated Knockin of Retinoschisin 1 Gene—A Potential Nonviral Therapeutic Solution for X-Linked Juvenile Retinoschisis. SJ Chou,Yang P, Ban Q, Yang YP, Wang ML, Chien CS, Chen SJ, Sun N, Zhu Y, Wang F, Zhang RY, Nguyen VQ, Liu Wnfei, Chen M, Jonas SJ, Weiss PS, Tseng HR*, **Chiou SH*.*****Advanced Science*** 2020 April 16;7(10):1903432 (IF=15.804;RANK=9/103; NANOSCIENCE & NANOTECHNOLOGY)

5. Ash2l interacts with Oct4-stemness circuitry to promote super-enhancer-driven pluripotency network. Tsai PH, Chien Y, Wang ML, Hsu CH, Laurent B, Chou SJ, Chang WC, Chien CS, Li HY, Lee HC, Huo TI, Hung JH, Chen CH, **Chiou SH*** Nucleic Acids Res 2019 Sep 26. (IF= 11.147;RANK= 15/297; BIOCHEMISTRY & MOLECULAR BIOLOGY)

From bench to bedside, a study of mesenchymal stem cell-like cells in the blood

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Abstract

The sustained therapeutic effects and tissue repairment are two significant advantages of cell therapy. Besides the hematopoietic stem cells, stem cells-orientated clinical applications require cell purification, amplification or differentiation. These cellular processes require sophisticated techniques and comprehensive regulations to fulfill strict quality controls and assurance. In order to provide a practical and feasible cell resource for clinical application, we introduce a method to produce a mesenchymal stem cell-like population in the blood that shows strong immunomodulation and tissue repairment activity. These cells are evaluated in animal models and several clinical trials at multiple centers, such as late-stage osteoarthritis, discogenic pain and carpal tunnel syndrome, as a disease-modified drug for long-term pain relief and tissue regeneration.

Selected recent publications:

1. Huang, M,H,, Chou, Y,W,, Li, M.H., et al. (2019). Epigenetic targeting DNMT1 of pancreatic ductal adenocarcinoma using interstitial control release biodegrading polymer reduced tumor growth through hedgehog pathway inhibition..*PharmacologicalResearch.* 139, 50-61.

2. Chang, C. Y. Chen, S. M. Lu, H. E. et al. (2015). Nbutylidenephthalide attenuates Alzheimer's disease-like cytopathy in Down syndrome induced pluripotent stem cell-derived neurons. *Scientific Reports*, 5, 8744.

3. Chen, S.M., Lee, M.S., Chang, C.Y., et al. (2015). Prerequisite Oct4 maintenance potentiates the neural induction of differentiating human embryonic stem cells and induced pluripotent stem cells. *Cell Transplantation.*, 24(5), 829-44.

4. Sun, C. K. Lee, F. Y. Kao, Y. H. et al. (2015). Systemic combined melatonin-mitochondria treatment improves acute respiratory distress syndrome in the rat. *Journal of Pineal Research* , 58(2):137-150. (SCI, 3/83, Physiology).

5. Shen, C.I., Lee, H.C., Kao, Y.H., Wu, C.S., Chen, P.H., Lin, S.Z., Lai, P.S., Su, H.L. (2014). EpCAM induction functionally links to the Wnt-enhanced cell proliferation in human keratinocytes .*Cell Transplantation*, 23: 1031-1044.

Translational neurosciences of personalized medicine for omega-3 fatty acids in depression

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Abstract

Depression is one of the leading causes of morbidity and mortality in medicine. Current available treatments clearly do not meet clinical needs, while clinicians and researchers are facing the huge challenge of developing effective depression treatments despite of the advance of neurosciences. Omega-3 polyunsaturated fatty acids (PUFAs), including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have a range of neurobiological activities in modulation of neurotransmitters, anti-inflammation, anti-oxidation and neuroplasticity, by which could contribute to the antidepressant effects. The committee of the International Society for Nutritional Psychiatry Research (ISNPR) organized an expert panel and conducted a Delphi-process to develop a consensus-based practice guideline for clinical use of n-3 PUFAs in MDD. Evidence from epidemiological, pre-clinical, and clinical studies have revealed that omega-3 PUFAs play an important role in the treatment and prevention of certain subgroups of clinical depression. According to biological specificity and safety consideration, omega-3 PUFAs is a potential antidepressant treatment for pregnant women, children, adolescents, and inflammation-related depression. Omega-3 PUFAs are well tolerated and accepted by general populations for health promoting. Thus, more research on stratifying depression is needed to justify the clinical application of omega-3 PUFAs as one of the first-line antidepressant treatments in specific populations with depression.

Selected recent publications:

1. Guu TW, Mischoulon D, Sarris J, Hibbeln J, McNamara RK, Hamazaki K, Freeman MP, Maes M, Matsuoka Y, Belmaker RH, Jacka FN, Pariante CM, Berk M, Marx W, **Su KP***. International Society for Nutritional Psychiatry Research (ISNPR) Practice Guidelines for Omega-3 Fatty Acids in the Treatment of Major Depressive Disorder. **Psychotherapy and Psychosomatics** 2019;88(5):263-273.

2. Yang B, Lin L, Bazinet RP, Chien YC, Chang JPC, Satyanarayanan SK, Su HX, **Su KP*.** Clinical efficacy and biological regulations of omega-3 PUFA-derived endocannabinoids in major depressive disorder. **Psychotherapy and Psychosomatics** 2019;88(4):215-224.

3. Bosini A, Nicolaou A, Camacho-Munoz MD, Kendall A, Di Benedetto MG, Giacobbe J, **Su KP***. Omega-3 polyunsaturated fatty acids protect against inflammation through production of LOX and CYP450 lipid mediators: relevance for major depression and for human hippocampal neurogenesis. **Molecular psychiatry** 2020Nov;26(11):6773-6788.

4. Lin YW, Wu AIC, Su HX, **Su KP***. Transient receptor potential V1 (TRPV1) modulates the therapeutic effects for comorbidity of pain and depression: The common molecular implication for electroacupuncture and omega-3 polyunsaturated fatty acids. **Brain Behavior and Immunity** 2020 Oct; 89: 604-614.

5. Lin PY, Cheng C, Satyanarayanan SK, Chiu LT, Chien YC, Chuu CP, Lan TH, **Su KP***. Omega-3 fatty acids and blood-based biomarkers in Alzheimer's disease and mild cognitive impairment: A randomized placebo-controlled trial. **Brain Behavior and Immunity** 2022 Jan;99:289-298.

Fish oil alleviates LPS-induced inflammation and depressive-like behavior in mice via restoration of metabolic impairments

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Abstract

Fish oil (FO) pre-treatment could improve the lipopolysaccharides (LPS)-induced depressive-like behavior in mice but did not alter the expression of stress hormones associated with the hypothalamic-pituitary-adrenal (HPA) axis. The exact mechanisms underlying the protective effects of FO remain elusive. Here we applied the metabolomic technique to investigate the potential involvement of FO metabolites in ameliorating depressive-like behaviors in LPS-injected mice. It revealed that LPS-injection stimulated systemic inflammation, exhausted the nicotinamide adenine dinucleotide (NAD) level in the brain, decreased energy metabolism and impaired neuronal function, which collectively contributed to depressive-like behaviors in mice. FO treatment enhanced the production of neuroprotective metabolites including taurine, hypotaurine and tyramine, decreased the generation of neurotoxic agents such as ADPR, glutamate accumulation and oxidized glutathione, and prevented the NAD exhaustion in the brain, which might underlie the beneficial effects of FO against LPS-induced inflammation and depressive-like behaviors.

Selected recent publications:

1. Peng Y, Shi Z, Kumaran Satyanarayanan S, He C, Li P, Wan JB, **Su H***. Fish oil alleviates LPS-induced inflammation and depressive-like behavior in mice via restoration of metabolic impairments. Brain Behav Immun. 2020 Nov;90:393-402.

2. Ke M, Chong CM, Zeng H, Huang M, Huang Z, Zhang K, Cen X, Lu JH, Yao X, Qin D*, **Su H***. Azoramide protects iPSC-derived dopaminergic neurons with PLA2G6 D331Y mutation through restoring ER function and CREB signaling. Cell Death Dis. 2020 Feb 18;11(2):130.

3. Yan L, Xie Y, Satyanarayanan SK, Zeng H, Liu Q, Huang M, Ma Y, Wan JB, Yao X, Su KP, **Su H***. Omega-3 polyunsaturated fatty acids promote brain-to-blood clearance of β-Amyloid in a mouse model with Alzheimer's disease. Brain Behav Immun. 2020 Mar;85:35-45.

4. Tan Y, Ke M, Huang Z, Chong C, Cen X, Lu JH, Yao X*, Qin D*, **Su H***. Hydroxyurea facilitates manifestation of disease relevant phenotypes in patients-derived iPSCs-based modeling of late-onset Parkinson's disease. Aging and disease. 2019 Oct 1;10(5):1037-1048.

5. Luo C, Ren H, Yao X, Shi Z, Liang F, Kang JX, Wan JB, Pei Z, Su KP, **Su H***. Enriched Brain Omega-3 Polyunsaturated Fatty Acids Confer Neuroprotection against Microinfarction. EBioMedicine. 2018 Jun;32:50-61

Diagnosis and quantification of symptoms of psychiatric disorders by digital phenotyping

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Abstract

One of the biggest challenges in the field of psychiatry is the lack of biomarkers. As a result, diagnosis or assessment of disease severity are done through conversations between patients and psychiatrists. Such approaches, which can be influenced by the experience of the evaluator, lack objectivity and reproducibility, and make research and clinical trials difficult. Recently, the utilization of digital phenotype, i.e. behavioral data from smartphones and wearable devices, has become a worldwide trend in the psychiatry field.

Our group has been developing technologies for diagnosing (screening) and assessing the severity of mental disorders using such digital phenotypes. Specifically, we have developed technologies for screening and severity assessment of depression using a wristband-type wearable device, screening technology for depression using Holter ECG, screening technology for dementia using natural language processing.

In this presentation, the research projects above will be presented and the prospects for using digital phenotype will be discussed.

Selected recent publications:

1. **Kishimoto T**, Hagi K, Kurokawa S, Kane JM, Correll CU. Long-acting injectable versus oral antipsychotics for the maintenance treatment of schizophrenia: a systematic review and comparative meta-analysis of randomised, cohort, and pre-post studies. Lancet Psychiatry. 2021 May;8(5):387-404.

2. Shiga K, Izumi K, Minato K, Sugio T, Yoshimura M, Kitazawa M, Hanashiro S, Cortright K, Kurokawa S, Momota Y, Sado M, Maeno T, Takebayashi T, Mimura M, **Kishimoto T**. Subjective well-being and month-long LF/HF ratio among deskworkers. PLoS One. 2021 Sep 7;16(9): e0257062.

3. Horigome T, Sumali B, Kitazawa M, Yoshimura M, Liang KC, Tazawa Y, Fujita T, Mimura M, **Kishimoto T**. Evaluating the severity of depressive symptoms using upper body motion captured by RGB-depth sensors and machine learning in a clinical interview setting: A preliminary study. Comprehensive Psychiatry. 2020 Feb 20;98:152169.

4. Tazawa Y, Liang KC, Yoshimura M, Kitazawa M, Kaise Y, Takamiya A, Kishi A, Horigome T, Mitsukura Y, Mimura M, K**ishimoto T**. Evaluating depression with multimodal wristband-type wearable device: screening and assessing patient severity utilizing machine-learning, Heliyon. 2020 Feb 4;6(2):e03274. doi: 10.1016/j.heliyon.2020.e03274. PMID: 32055728; PMCID: PMC7005437.

5. **Kishimoto T**, Hagi K, Nitta M, Kane JM, Correll CU. Long-term effectiveness of oral second-generation antipsychotics in patients with schizophrenia and related disorders: a systematic review and meta-analysis of direct head-to-head comparisons. World Psychiatry. 2019 Jun;18(2):208-224.

Associations of leptin, C-reactive protein and corticostriatal connectivity in bipolar disorder

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Abstract

Bipolar disorder (BD) and metabolic disturbance represent a chronic state of low-grade inflammation and corticostriatal circuitry alterations. Herein, we aimed to investigate whether plasma leptin, an adipokine that plays a key role in the interplay of metabolism and inflammation, is associated with corticostriatal connectivity in patients with BD. Twenty-eight BD I patients, 36 BD II patients and 66 healthy controls were enrolled and completed the Hamilton Depression Rating Scale, the Young Mania Rating Scale, and the Recent Life Change Questionnaire. Fasting plasma leptin and C-reactive protein (CRP) levels were measured, and corticostriatal connectivity was examined using functional magnetic resonance imaging (fMRI). The relationships between leptin, CRP and body mass index (BMI) identified in the controls and BD II patients were absent in the BD I patients. We did not find a significant group difference in the leptin level; nevertheless, the negative correlation between leptin level and corticostriatal connectivity (ventrolateral prefrontal cortex and inferior temporal gyrus) observed in the healthy controls was absent in the BD patients. The disproportionate increase in leptin level with increasing BMI in BD indicated a potential inflammatory role of white adipose tissue in BD. Furthermore, higher CRP levels in BD I patients might induce leptin resistance. Collectively, our results implied vulnerability to inflammatory and metabolic diseases in patients with BD, especially BD I.

Selected recent publications:

1. Wei SY, Tseng HH, Chang HH, Lu TH, Chang WH, Chiu NT, Yang YK, **Chen PS**: Dysregulation of oxytocin and dopamine in the corticostriatal circuitry in bipolar II disorder. Translational Psychiatry 2020 Aug;10:281~1-281~8.
2. **Chen PS**, Jamil A, Tseng HH, Wei SY, Liu LC, Nitsche MA, Kuo MF: Nonlinear Effects of Dopamine D1 Receptor Activation on Visuomotor Coordination Task Performance. Cerebral Cortex 2020 Oct;30(10):5346-5355.
3. Chang HH, Tseng HH, Chang WH, Huang KC, Lu TH, Yang YK, **Chen PS**: Peripheral insulin sensitivity predicting cognitive function in euthymic bipolar disorder patients. CNS Spectr. 2021 Mar 11;1-6.
4. Hsueh YS, Lin CY, Chiu NT, Yang YK, **Chen PS**, Chang HH: Changes in striatal dopamine transporters in bipolar disorder and valproate treatment. European Psychiatry 2021 Jan 8;64(1):e9~1-e9~7.
5. Tseng HH, Chang HH, Wei SY, Lu TH, Hsieh YT, Yang YK, **Chen PS**: Peripheral inflammation is associated with dysfunctional corticostriatal circuitry and executive dysfunction in bipolar disorder patients. Brain, Behavior, and Immunity 2021 Jan;91:695-702.

Cortical maps following peripheral nerve reconstruction

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Abstract

The conventional dogma indicates that the removal of sensory inputs to the sensory cortex results in massive reorganization in the brain, but recent studies support a different theory by showing a stability of cortical topography without reorganization. It is important to understand the neuronal mechanisms underlying neuroplasticity after deafferentation. To this end, we designed anexperimental model that deliberately induces aberrant reinnervation of peripheral nerve to evaluate the change of cortical topography and direction tuning in neurons in the somatosensory cortex (S1BF).

We applied two-photon calcium imaging on awake animal and developed a long-term brain window method to chronically record the topographicalreorganization of neuronal selectivity.In addition, electrophysiological recording of spiking activities was applied at multiple time points after reinnervation surgery to observe the chronological changes of neuronal tuning over time. After the induction of aberrant reinnervation in the periphery,whisker-wise topography in S1BF was systematically shiftedand the shift can be predicted by the pattern of aberrant inputs. A proportion of barrels whose original whisker inputs were absent also responded to whisker stimulations and, most importantly,tuned to whiskers of the same row, a property suggesting a mechanism of lateral sprouting.Onemonth after reinnervation surgery, a proportion of neurons showed extremely strong direction selectivity, a property we dubbed as “nascent tuning”. Interestingly, the proportion of neurons with nascent tuning gradually decreased afterwards, implying that nascent tuning is mediated by the early restoration of sensory inputs after the reinnervation surgery.

Selected recent publications:

1. Pu SW, et al. Decoupling Finger Joint Motion in an Exoskeletal Hand: A Design for Robot-assisted Rehabilitation. IEEE transactions on industrial electronics. 2020 Jan. 67(1) 686-697.
2. Pei Y, et al. Neural mechanisms of tactile motion integration in primary somatosensory cortex. Neuron. 2011; 69(3):536-547.
3. Pei Y, et al. Shape invariant coding of motion direction in primary somatosensory cortex. PLoS Biology. 2010;8(2):e1000305.
4. Pei Y, et al. The tactile integration of local motion cues is analogous to its visual counterpart. Proc Natl Acad Sci USA. 2008 Jun 10;105(23):8130-5.

Habitual physical activity mediates the acute exercise-induced modulation of anxiety-related amygdala functional connectivity

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Abstract

Aerobic exercise, in relation to physical activity, has been shown to have beneficial effects on anxiety. However, the underlyig neural mechanism remains elusive. Using a within-subject crossover design, this fMRI study examined how exercise (12-min treadmill running versus walking) mediated amygdala reactivity to explicit and implicit (backward masked) perception of emotional faces in young adults (N = 40). Results showed that acute exercise-induced differences of state anxiety (STAI-S) varied as a function of individual's habitual physical activity (IPAQ). Subjects with high IPAQ levels showed significant STAI-S reduction (P< .05). Path analyses indicated that IPAQ explained 14.67% of the variance in acute exercise-induced STAI-S differences. Running elicited stronger amygdala reactivity to implicit happiness than fear, whereas walking did the opposite. The exercise-induced amygdala reactivity to explicit fear was associated with the IPAQ scores and STAI-S differences. Moreover, after running, the amygdala exhibited a positive functional connectivity with the orbitofrontal cortex and insula to implicit happiness, but a negative connectivity with the parahippocampus and subgenual cingulate to implicit fear. The findings suggest that habitual physical activity could mediate acute exercise-induced anxiolytic effects in regards to amygdala reactivity, and help establish exercise training as a form of anxiolytic therapy towards clinical applications.

Selected recent publications:

1. Chen YC, Chen C, Martínez RM, Fan YT, Liu CC, Chen CY, Cheng Y* (2021) An amygdala-centered hyper-connectivity signature of threatening face processing predicts anxiety in youths with autism spectrum conditions. *Autism Research* 14 (11):2287-99

2. Chen C, Martínez RM, Cheng Y* (2020) The key to group fitness: the presence of another synchronizes moral attitudes and neural responses during moral decision-making. *NeuroImage* 213: 116732.

3. Chen C, Martínez RM, Liao TT, Chen CY, Yang CY, Cheng Y* (2020) An integrative analysis of 5HTT-mediated mechanism of hyperactivity to non-threatening voices. *Communications Biology* 3: 113.

4. Chen YC, Chen C, Martínez RM, Etnier J, Cheng Y* (2019) Habitual physical activity mediates the acute exercise-induced modulation of anxiety-related amygdala functional connectivity. *Scientific Reports* 9: 19787.

5. Chen C, Hu CH, Cheng Y* (2017) Mismatch negativity stands at the crossroads between explicit and implicit emotional processing. *Human Brain Mapping* 38(1): 140-150.

The function of cortical layers in the sensory cortex

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Abstract

In macaques and humans, the cerebral cortexoccupies >70% of the brain volume (<30% in rodents), and consists of six distinct layers of neurons that differ in both morphology and neurophysiology. A main question in cortical neurophysiology is to understand the function of cortical layers and how incoming information is transformed through different layers to form perceptions. Measuring neural activity simultaneouslyacross cortical layers will be critical for revealing the computational roleand effect of each cortical layer. We did this by applying a multiple-electrode array (8 parallel shanks x 8 contacts each shank, 200 um spacing, Neuronexus) to simultaneously record from different layers of macaque monkey primary visual cortex V1. We studied both physiological responses to sensory stimuli and synchronous responses of pairs of cells according to their laminar location. We used different stimulus ensembles to measure response properties of V1 neurons and found that both receptive-field dissimilarity and response bias were smaller for neurons in the granular layerthan those in the supragranular layer. Analysesof spike triggered local field potential (st-LFP) signals also revealed laminar difference:the lateral space constant of the st- LFP was significantly shorter and lateral propagation speed of the st-LFP was significantly slower in the in thesupragranular layer than in the granular and infragranular layers. Moreover, the preferred frequency of gamma oscillation differs between the supragranularlayer and the granular layer.These results provide some insight about general rules of cortical processing across different laminar structures.

Selected recent publications:

1. Yeh CI, Xing D, Williams PE, Shapley RM (2009). Stimulus ensemble and cortical layer determine V1 spatial receptive fields. Proceedings of the National Academy of Sciences of the United States of America, 106, 14652-14657.

2. Yeh CI, Xing D, Shapley RM (2009). “Black” responses dominate macaque primary visual cortex V1. Journal of Neuroscience, 29, 11753-11760.

3. .Xing D, Yeh CI, Gordon J, Shapley RM (2014). Cortical brightness adaptation when darkness and brightness produce different dynamical states in the visual cortex. Proceedings of the National Academy of Sciences of the United States of America, 111, 1210-1215.

4. Huang WN, Wu HY, Pei YC, Yeh CI (2019). Response asymmetry of red and green in macaque primary visual cortex. Society for Neuroscience Abstract No 143.09.

5. Han C, Wang T, Yang Y, Wu Y, Li Y, Dai W, Zhang Y, Wang B, Yang G, Cao Z, Kang J, Wang D, Li L, Yu H, Yeh CI, Xing D (2021). Multiple gamma rhythms carry distinct spatial frequency information in primary visual cortex. Public Library of Science: Biology 19: e3001466.

Interactive dynamics of the sensorimotor cortices during dexterous forelimb movement in mice

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Abstract

Understanding how the primary motor cortical (M1) neural activity coordinates to achieve fine movement control is a central challenge in comprehending brain function. The M1 neural activity state can be described as a dynamic system, and its spiking patterns are strongly influenced by external inputs from other brain regions, such as the somatosensory cortex (S1) and the pre-motor cortex (M2), and the thalamus. However, the spatiotemporally detailed interactive dynamics across sensorimotor cortices are largely unexplored due lacking an adequate method. Here, we established a large-scale in vivo cortical extracellular electrophysiology platform consisting of a microwire bundle and a CMOS multielectrode array (MEA) (Obaid *et al*., 2020) to concurrently record the M1, M2, and S1spiking activity during a forelimb food-pallet reaching movement. We conducted spike sorting and monitored over 2000 units across multiple cortices chronically with this platform. We applied a machine learning framework, Latent Factor Analysis via Dynamical Systems or LFADS (Pandarinat*et al*., 2018), to search for low-dimensional neural states' dynamics and provide high-quality denoised spike rates across the M1, M2, and S1. Our results reveal the interactive dynamics undying the movement kinematic variables. In addition, using the denoised firing rates, we decoded the neural dynamics and predicted forelimb positions with high performance (R^2> 0.9), suggesting this framework is also suitable to apply in brain-computer interfaces (BCIs).

Selected recent publications:

1. Obaid A*, Hanna M*, **Wu YW* (co-first author)**, Kollo M*, Racz R, Angle MR, Muller J, Wray W, Franke F, Blackbill N, Chichilinsky EJ, Hierlemann A, Ding JB, Schaefer AT, Melosh NA (2019) Massively parallel microwire arrays integrated with CMOS chips for neural recording. ***Science Advances*** 6(12) eaay2789

2. **Wu YW*(co-corresponding author)**, Gordleeva S, Tang X, Shih PY, Dembitskaya Y, Semyanov A* (2019) Morphological profile determines frequency of spontaneous calcium events in thin astrocytic processes. ***Glia*** 67(2):246-262

3. Du K*, **Wu YW* (co-first author)**, Lindroos R, Liu Y, Rózsa B, Katona G, Ding JB, Kotaleski JH (2017) Cell-type specific inhibition of the dendritic plateau potential in striatal spiny projection neurons. ***Proceedings of the National Academy of Sciences (PNAS)*** 114(36): E7612-E7621.

4. Guo L*, Xiong H*, Kim JI*, **Wu YW* (*co-first author)**, Lalchandani RR, Cui Y, Shu Y, Xu T, Ding JB (2015) Dynamic rewiring of neural circuits in the motor cortex in mouse models of Parkinson's disease. ***Nature Neuroscience*** 18(9):1299-309

5. **Wu YW**, Kim JI, Tawfik VL, Lalchandani RR, Scherrer G, Ding JB (2015) Input- and cell type-specific Endocannabinoid-Dependent LTD in the striatum. ***Cell Reports*** 10(1):75-87