Nanosymposium (II)-1

Target glioma recurrence and resistance, from invisible to visible

對抗復發腦癌-從看不見的分子到高階的影像

Host: Pin-Yuan Chen (陳品元)、Cheng-Ta Hsieh (謝政達)

Location: 生物醫學科學研究所 B1B會議室
Institute of Biomedical Sciences (IBMS) B1B room

Time: Sep. 12, 11:15-12:30

Participate societies: Taiwan Society for Neuro-Oncology (台灣神經腫瘤學會)、Taiwan Neurotrauma Society (台灣神經創傷學會)

The five-year survival rate of patients with gliomas is less than 10%, which is due to the frequent recurrence of tumor growth after chemotherapy. Therefore, it is important to understand how gliomas acquire drug resistance, and hope to develop new therapeutic options and possible strategies to predict their relapse. Glioma recurrence could be due to changes in the genome or metabolome of tumor cells to increase their drug resistance or suppress immunity against tumors. In this nanosymposium, we will discuss how to target glioma recurrence from the aspects of immunity, radiomic imaging, genomics and lipid metabolomics.

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Target glioma recurrence and resistance, in immune aspect

Pin-Yuan Chen (陳品元) MD., PhD.
Chief, Department of Neurosurgery
Vice chairmen, Department of surgery
Professor, Chang Gung Memorial Hospital
Associate Professor, Chang Gung University

Abstract

Glioma is a grave brain cancer. Inevitable drug resistance and recurrence of tumor growth after surgical excision, radiation and chemotherapy cause that the five-year overall survival rate of patients with gliomas is less than 10%. The components of tumor microenvironment and how these cells react to therapy play important roles in glioma recurrence. Here, we focus on immune cells, especially glioma-associated microglia/macrophages (GAMs) and tumor-infiltrating T cells (TILs) and try to understand how glioma cells attract them, how glioma cells escape from the immune surveillance, and how glioma cells transform GAMs and TILs to facilitate tumor progression. Hope that we could break the vicious cycle and develop some new therapeutic options and possible strategies to prevent tumor relapse.

Selected recent publications:

Wu CY, Chen CH, Lin CY, Feng LY, Lin YC, Wei KC, Huang CY, Fang JY*, **Chen PY***. CCL5 of glioma-associated microglia/macrophages regulates glioma migration and invasion via calcium-dependent matrix metalloproteinase-2. *Neuro-Oncology* 2020 Feb 20;22(2):253-266. doi: 10.1093/neuonc/noz189.

Chen PY[%], Wu CY[%], Fang JH, Chen HC, Feng LY, Huang CY, Wei KC, Fang JY, Lin CY. Functional Change of Effector Tumor-Infiltrating $CCR5^{+}CD38^{+}HLA\text{-}DR^{+}CD8^{+}$ T Cells in Glioma Microenvironment. *Frontiers in Immunology* 2019 Oct 9;10:2395. doi: 10.3389/fimmu.2019.02395.

Wang YC, Lee CC, Takami H, Shen S, Chen KT, Wei KC, Wu MH, Worrell G, **Chen PY** *. Awake craniotomies for epileptic gliomas: intraoperative and postoperative seizure control and prognostic factors. *Journal of Neuro-Oncology* 2019 May, doi.org/10.1007/ s11060-019-03131-0

Pang HH[%], **Chen PY**[%], Wei KC, Huang CW, Shiue YL, Huang CY, Yang HW. Convection-Enhanced Delivery of a Virus-Like Nanotherapeutic Agent with Dual-Modal Imaging for Besiegement and Eradication of Brain Tumors. *Theranostics* 2019 Feb, doi:10.7150/ thno.30977 [%]Equal contribution: first author.

Application of the Advanced Neuroimaging with Artificial Intelligence in Glioblastoma

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College of Medicine, Chang Gung University, Taoyuan, Taiwan

Abstract

Glioblastoma (GBM) is the most common and malignant primary brain tumor. However, there are limited knowledge of its progression pattern. Current conventional magnetic resonance imaging (MRI) constrains the precision of the treatment due to the difficulty to differentiate the characteristics among them before treatment. One of the possible limitations is the limited information provided by the conventional MRI. Our study intends to identify tumor progression pattern by using advanced MR techniques with radiomics and artificial intelligence method.

The radiomics is an emerging technique that can converge conventional imaging into high dimension quantitative data. Further analysis with classifier or machine learning, imaging data can be associated with clinical data, to improve clinical decision. Among 842 radiomics features, 153 of them were significant different in glioblastoma that progress “diffusely” and “localised”. Further analyzed with different machine learning model can have an 80% of prediction accuracy.

In addition, we further analyzed the pre-operative glioblastoma MR imaging by using the neural network such as ResNet and VGG for the identification of the progression pattern. The results showed 94.1%-100% of prediction accuracy in several repeated trainings.

The application of the neural network and advanced neuroimaging analysis techniques can provide a substantial information beyond visualization.

Selected recent publications:

Yan JL, Li C, Hoorn AV, Boonzaier NR, Matys T, Price SJ. (2020, Jun). A Neural Network Approach to Identify the Peritumoral Invasive Areas in Glioblastoma Patients by Using MR Radiomics. Scientific Reports, 2020 Jun 16;10(1):9748.

Yan JL, Li C, Boonzaier NR, Fountain DM, Larkin TJ, Matys T, van der Hoorn A, Price SJ (2019, May). Multimodal MRI Characteristics of the Glioblastoma Infiltration Beyond Contrast Enhancement. Therapeutic Advances in Neurological Disorders, 2019 May 14;12:1756286419844664.

Yan JL*, Hoorn AV, Larkin TJ, Boonzaier NR, Matys T, Price SJ. (2017, Jan). Extent of resection of peritumoural DTI abnormality as a predictor of survival in adult glioblastoma patients. Journal of Neurosurgery, 2017 Jan;126(1):234-241.

Hoorn AV, Yan JL*, Larkin TJ, Boonzaier NR, Matys T, Price SJ (2016, Jul). Validation of a semi-automatic co-registration of MRI scans in patients with brain tumors during treatment follow up. NMR in Biomedicine, 29(7):882-9.

Transcription Therapy: A Potential Strategies Overcoming the Drug Resistance for Glioblastoma

Jian-Ying Chuang (莊健盈)

The Ph.D. Program for Neural Regenerative Medicine, College of Medical Science and Technology, Taipei Medical University, Taiwan

PhD., National Cheng Kung University

Abstract

Background: Glioblastoma is associated with poor prognosis and high mortality. Although the use of first-line temozolomide can reduce tumor growth, therapy-induced stress drives stem cells out of quiescence, leading to chemo-resistance and glioblastoma recurrence. The Sp1 transcription factor is known to protect glioblastoma cells against temozolomide; however, how tumor cells hijack this factor to gain resistance to therapy is not known. Methods: Sp1 acetylation in temozolomide-resistant cells and stem-like tumorspheres was analyzed by immunoprecipitation and immunoblotting experiments. Effects of the HDAC/Sp1 axis on malignant growth were examined using cell proliferation–related assays and *in vivo* experiments. Furthermore, integrative analysis of gene expression with ChIP-seq and the recurrent glioblastoma omics data were also used to further determine the target genes of the HDAC/Sp1 axis. Results: We identified Sp1 as a novel substrate of HDAC6, and observed that the HDAC1/2/6/Sp1 pathway promotes self-renewal of malignancy by upregulating BMI1 and hTERT, as well as by regulating G2/M progression and DNA repair via alteration of the transcription of various genes. Importantly, HDAC1/2/6/Sp1 activation is associated with poor clinical outcome in both glioblastoma and low-grade gliomas. However, treatment with azaindolylsulfonamide, a potent HDAC6 inhibitor with partial efficacy against HDAC1/2, induced G2/M arrest and senescence in both temozolomide-resistant cells and stem-like tumorspheres. Conclusions: Our study uncovers a previously unknown regulatory mechanism in which the HDAC6-Sp1 axis induces cell division and maintains the stem cell population to fuel tumor growth and therapeutic resistance.

Selected recent publications:

Chen TC[#], **Chuang JY[#]**, Ko CY, Kao TJ, Yang PY, Yu CH, Liu MS, Hu SL, Tsai YT, Chan H, Chang WC, Hsu TI. (2020). AR Ubiquitination Induced by the Curcumin Analog Suppresses Growth of Temozolomide-Resistant Glioblastoma through Disrupting GPX4-Mediated Redox Homeostasis. *Redox Biol*, 30:101413. (SCI. IF=**9.986**)

Lo WL, Hsu TI, Yang WB, Kao TJ, Wu MH, Huang YN, Yeh SH, **Chuang JY***. (2020). Betulinic acid-mediated tuning of PERK/CHOP signaling by Sp1 inhibition as a novel therapeutic strategy for glioblastoma. *Cancers*, 12(4). pii:E 981. (SCI. IF=**6.126**)

Yang WB[#], Hsu CC[#], Hsu TI[#], Liou JP[#], Chang KY, Chen PY, Liu JJ, Yang ST, Wang JY, Yeh SH, Chen RM, Chang WC, **Chuang JY***. (2020). Increased activation of HDAC1/2/6 and Sp1 underlies therapeutic resistance and tumor growth in glioblastoma. *Neuro Oncol*, In press. (SCI. IF=**10.247**)

Degradation of Androgen Receptor Inhibits Growth of Temozolomide-Resistant Glioblastoma through Inducing Ferroptosis

Tsung-I Hsu (徐宗溢)

Ph.D. Program for Neural Regenerative Medicine, College of Medical Science and Technology, Taipei Medical University and National Health Research Institutes, Taipei, Taiwan.

Graduate Institute of Medical Sciences, College of Medicine, Taipei Medical University, Taipei, Taiwan

Abstract

Androgen receptor (AR) overexpression was shown to promote drug resistance in prostate cancer. However, the role of AR in acquiring resistance of glioblastoma enriched by androgen-typed neurosteroids remains unclear. Herein, we observed ALZ003, a curcumin analog, induced FBXL2-mediated AR ubiquitination, leading to degradation. Compared with FDA-approved AR inhibitor, enzalutamide, ALZ003 exhibited higher activity in degrading AR and in suppressing tumor growth. Importantly, ALZ003 significantly inhibited the survival of glioblastoma with or without temozolomide (TMZ) resistance. The dysregulation of redox homeostasis, and characteristics of ferroptosis, including glutathione peroxidase (GPX) 4 downregulation, were significantly induced by ALZ003, not by enzalutamide. Furthermore, we found that AR regulated GPX4 expression, and overexpression of AR prevented ferroptosis in the presence of GPX4. In addition to inhibiting the growth of glioblastoma in the orthotopic mouse model, ALZ003 significantly extended the survival period of transplanted mice, and significantly decreased AR expression in the tumor area. Particularly, ALZ003 synergistically suppressed growth of glioblastoma with TMZ in the orthotopic model. Taken together, AR potentiates TMZ resistance for glioblastoma, and ALZ003-induced AR degradation provide a new insight into therapeutic strategy for TMZ resistant glioblastoma.

Selected recent publications:

Yang WB#, Hsu CC#, Hsu TI#, Liou JP#, Chang KY, Chen PY, Liu JJ, Yang ST, Wang JY, Yeh SH, Chen RM, Chang WC, Chuang JY*. (Apr, 2020) Increased activation of HDAC1/2/6 and Sp1 underlies therapeutic resistance and tumor growth in glioblastoma. Neuro Oncol. 2020 Apr 24:noaa103.

Chen TC#, Chuang JY#, Ko CY, Kao TJ, Yang PY, Yu CH, Liu MS, Hu SL, Tsai YT, Chan H, Chang WC*, Hsu TI*. (Feb. 2020) AR Ubiquitination Induced by the Curcumin Analog Suppresses Growth of Temozolomide-Resistant Glioblastoma through Disrupting GPX4-Mediated Redox Homeostasis. Redox Biol. 2020 Feb;30:101413.

Tsai YT, Wu AC, Yang WB, Kao TJ, Chuang JY, Chang WC, Hsu TI*. (Nov. 2019) ANGPTL4 Induces TMZ Resistance of Glioblastoma by Promoting Cancer Stemness Enrichment via the EGFR/AKT/4E-BP1 Cascade. Int J Mol Sci. 2019 Nov 11;20(22). pii: E5625.

Lin HY, Ko CY, Kao TJ, Yang WB, Tsai YT, Chuang JY, Hu SL, Yang PY, Lo WL, Hsu TI*. (Sep. 2019) CYP17A1 Maintains the Survival of Glioblastomas by Regulating SAR1-Mediated Endoplasmic Reticulum Health and Redox Homeostasis. Cancers (Basel). 2019 Sep 16; 11(9). pii: E1378.

Yang WB, Chuang JY, Chang WC, Ko CY, Kao TJ, Lo WL, Hsu TI*. (Apr, 2019) Dehydroepiandrosterone induces temozolomide resistance through modulating phosphorylation and acetylation of Sp1 in glioblastoma. Mol Neurobiol. 2019 Apr;56(4):2301-2313.

Microbiome in aging, cognition and dementia
腸道微生物和人類以共生關係進化

Host: Shu-Ping Chao (趙書屏)

Location:生物醫學科學研究所 B1C會議室
Institute of Biomedical Sciences (IBMS) B1C room

Time: Sep. 12, 11:15-12:30

Participate societies: Taiwan Neuroscience Society (台灣基礎神經科學學會)、Taiwan Dementia Society (台灣臨床失智症學會)

Bidirectional communication between the gut microbiome and the central nervous system (also known as the 'microbiota-gut-brain axis') plays a key role in brain function.

Microbial replacement therapy, where changes in the quality and quantity of gut flora restore microbial balance, is a potential treatment option for cognitive disorders. Moreover, certain eating habits have a positive effect on balancing microbiome and may help enhance cognitive function. In this nanosymposium, we will introduce the effect of gut microbiome on cognition and share the latest experience of using medicine or food to improve cognitive function by altering gut microbiota.

The role of microbiota in Alzheimer disease animals and patients

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Department of Neurology, School of Medicine, College of Medicine, Taipei Medical University

Department of Neurology and Dementia Center, Shuang Ho Hospital, Taipei Medical University, Taiwan.

MD., Taipei Medical University

Abstract

Alzheimer disease (AD) is the most common disease of dementia. The pathological landmarks of AD are extracellular senile plaques and intracellular neurofibrillary tangles. The main components in plaques and tangles, amyloid and tau proteins have been considered to pay the most important role of cause of AD. However, many clinical trials of amyloid cleaning therapy failed. Therefore, the real pathophysiological mechanisms of AD might be still unclear.

In recent years, the scientists have begun to study causal effects of the gut microbiota on the neuro-degenerative disorders, including Parkinson disease (PD) and AD. The underlying molecular mechanisms are being elucidated. The pathways of gut–brain communication can be direct. The gut microbiota signals can be delivered to the central nervous system through the vagus nerve around the gut or immune system or some unknown pathways.

Recent studies also have observed abnormal gut microbiota (dysbiosis) in AD and PD patients. Dysbiosis was further found to play important roles in blood-brain-barrier disruption and amyloid accumulation. Fecal microbiota transplantation (FMT) therapy has been applied to many diseases in human, including clostridium difficile colitis, irritable bowel syndrome, PD, autism and stroke. These findings imply modification of gut microbiota could be a therapeutic target of AD.

In this talk, I will review the recent evidence of gut-brain axis in AD and present our results of AD animals treated by FMT.

Selected recent publications:

Huang LK, Chao SP, Hu CJ. (2020) Clinical trials of new drugs for Alzheimer disease. *J Biomed Sci.* 6;27(1):18.

Amelia Nur Vidyanti, Hsieh JY, Lin KJ, Fang YC, Ismail Setyopranoto, **Hu.CJ**. (2020) Role of HMGB1 in an Animal Model of Vascular Cognitive Impairment Induced by Chronic Cerebral Hypoperfusion. *Int J Mol Sci.* 2020 Mar; 21(6): 2176.

Huang LK, Tsai JC, Lee HH, Kuan YC, Lee YT, Lin CP, Chao SP, Hu CJ. (2020) Dementia screening for elderly in-patients and its association with nursing care satisfaction-an observational study. Medicine (Baltimore).99(2):e18741.

Cheng CH, Lin KJ, Hong CT, Wu D, Chang HM, Liu CH, Hsiao IT, Yang CP, Liu YC, Hu CJ. (2019) Plasmon-Activated Water Reduces Amyloid Burden and Improves Memory in Animals with Alzheimer's Disease. *Sci Rep.* 13;9(1):13252.

Chi NF, Chao SP, Huang LK, Chan L, Chen YR, Chiou HY, Hu CJ. (2019) Plasma Amyloid Beta and Tau Levels Are Predictors of Post-stroke Cognitive Impairment: A Longitudinal Study. *Front Neurol.* 2;10:715.

Associations and potentials for gut microbiota therapies in Alzheimer's disease

徐瑋萱(Wei-Hsuan Hsu)

Assistant Professor, Department of Food Safety/Hygiene and Risk Management, National Cheng Kung University

Researcher, Industrial Technology Research Institute
Postdoctoral Researcher, Purdue University
Ph.D., National Taiwan University

Abstract

Ageing is a world trend. Alzheimer's disease (AD) is the most common degenerative brain disease. Burden of AD has far-reaching effects on families and society. Currently there is neither a cure nor a treatment that addresses the underlying cause of AD. Gut microbes are associated with human health, and gut microbiota affect brain function through brain-gut axis. The aim of this study is to clarify whether specific gut microbiota are key targets of AD therapy. We anticipate using specific probiotics to regulate gut microbiota and act as a therapeutic target for AD treatment to accelerate the successful of AD therapeutics in the future. We compared the gut microbiota of AD patients (AD group) with healthy controls (H group). Fecal samples were collected and analyzed by next generation sequencing (NGS). The results indicated that gut microbiota composition was different between AD and H groups. Family *Lachnospiracea* was increased in AD patients when compared with H controls whereas family *Muribaculaceae* was decreased. We also found that when compared with the H group, genus *Fusobacterium*, *Klebsiella*, and *Streptococcus* were significantly higher in AD group, whereas genus *Akkermansia* and *Faecalibacterium* showed a tendency decreased, which referred as the next generation probiotics. Thus, probiotics are likely to be key microorganisms for AD development. In summary, AD patients have a similar gut microbiota composition with metabolic related diseases such as obesity. It coincided with the theory that obesity may aggravate AD symptoms in previous studies.

Selected recent publications:

Bao-Hong Lee, **Wei-Hsuan Hsu**, Cheng-Hui Lin. 2019. The anti-bacterial and anti-adherent effects of Pentraxin-3 on porcine kidney epithelial PK15 cells against *Staphylococcus aureus* infection. Int. J. Pept. Res. Ther. 25, 645-652.

Wei-Hsuan Hsu, Yu-Chun Lin, Bo-Rui Chen, *She-Ching Wu, *Bao-Hong Lee. 2018. The neuronal protection of a zinc-binding protein isolated from oyster. Food Chem. Toxicol. 114, 61-68.

Liang-Tzung Lin, Ying-Jang Lai, She-Ching Wu, ***Wei-Hsuan Hsu**, *Chen-Jei Tai. 2018. Optimal conditions for cordycepin production in surface liquid-cultured *Cordyceps* 3 *militaris* treated with porcine liver extracts for suppression of oral cancer. J. Food Drug Anal. 26, 135-144. (***Co-corresponding author**)

Rui Zhang, Sherri Y. Huang, Kay Ka-Wai Li, Yen-Hsing Li, **Wei-Hsuan Hsu**, GuangJun Zhang, Chun-Ju Chang, *Jer-Yen Yang. 2017. Dual degradation signals destruct GLI1: AMPK inhibits GLI1 through β-TrCP-mediated proteasome degradation. Oncotarget 8, 49869-49881.

Chia-Woei Wang, **Wei-Hsuan Hsu**, *Chen-Jei Tai. 2017. Antimetastatic effects of cordycepin mediated by the inhibition of mitochondrial activity and estrogen-related receptor α in human ovarian carcinoma cells. Oncotarget 8, 3049-3058.

Boost memory function by eating right: the role of gut microbiota

Pei-Yu Wang (王培育)

Associate Professor

Graduate Institute of Brain and Mind Sciences,

College of Medicine, National Taiwan University

PhD. University of Otago, NZ

Abstract

Graduate Institute of Brain and Mind Sciences, College of Medicine, National Taiwan University Age-related cognitive decline is a critical health and social issue in aging populations. It is well established that dietary restriction (DR, 20~40% reduction in food intake) enhances longevity and prolongs healthy lifespan, with striking attenuation of age-related cognitive decline. Given that it is difficult to practice DR in our normal daily lives, discovering the mechanisms underlying the beneficial effects of DR and identifying potential drug targets may shed the light on the future treatment of age-related dysfunction. DR has been shown to lead to alterations in the gut microbiota, which has been heavily implicated in neural regulation through the so-called microbiota-gut-brain axis. In this study, we discovered a critical role for gut microbiota in the mediation of DR-related beneficial effects, in particularly on memory function, and we aim to explore the potential for this model in the prevention and treatment of age-related cognitive decline. Our goal is to identify nextgeneration probiotics, microbiota-derived compounds, and host metabolites with the potential to ameliorate cognitive aging.

Selected recent publications:

Teng LL, Lu GL, Chiou LC, Lin WS, Cheng YY, Hsueh TE, Huang YC, Hwang NH, Yeh JW, Liao RM, Fan SZ, Yen JH, Fu TF, Tsai TF, Wu MS, Wang PY (2019) Serotonin receptor HTR6-mediated mTORC1

signaling regulates dietary restriction-induced memory enhancement. *PLOS Biology* 17(3):e2007097.

Lin WS, Yeh SR, Fan SZ, Chen LY, Yen JH, Fu TF, Wu MS, Wang PY (2018) Insulin signaling in female Drosophila links diet and sexual attractiveness. *FASEB J.* 32:3870-3877.

Chen HH, Tsai LK, Liao KY, Wu TC, Huang YH, Huang YC, Chang SW, Wang PY, Tsao YP, Chen SL (2018). Muscle-restricted nuclear receptor interaction protein knockout causes motor neuron degeneration through down-regulation of myogenin at the neuromuscular junction. *J Cachexia Sarcopenia Muscle*. 9:771-785.

Huang CW, Wang HD, Bai H, Wu MS, Yen JH, Tatar M, Fu TF, Wang PY (2015) Tequila regulates insulin-like signaling and extends life span in Drosophila melanogaster. *J. Gerontol. Ser. A-Biol. Sci.Med. Sci.*70 (12): 1461-1469.

Kuo SY, Wu CL, Hsieh MY, Lin CT, Wen RK, Chen LC, Chen YH, Yu YW, Wang HD, Su YJ, Lin CJ, Yang CY, Guan HY, Wang PY, Lan TH, and Fu TF (2015) PPL2ab neurons restore sexual responses in aged Drosophila males through dopamine. *Nature Communications* 6:7490

Gut-brain axis: microbial dysbiosis exacerbates Alzheimer's Disease

Jyh-Lyh Juang (莊志立)

Associate Director, Institute of Molecular & Genomic Medicine, National Health Research Institutes, Taiwan

PhD, University of Wisconsin-Madison

Abstract

Inter-organ communication is an important and highly evolutionarily conserved mechanism to maintain body homeostasis. However, studies of the role of inter-organ communication in disease and its underlying molecular mechanisms have only recently just emerged. Alzheimer's disease (AD) is a biologically complex neurodegenerative dementia. The amyloid cascade is a compelling hypothesis suggesting that pathological accumulation of A 42 in the brain triggers inflammatory response and oxidative damage in AD. However, the brain inflammatory response is not restricted to local primary insults only. Neuroinflammation in that organ may also be provoked by peripheral stimulatory signals driven by a remote organ. However, whether the gut-brain axis influences the progression of AD remains to be elucidated. By using a *Drosophila* AD model, we were able to test the possible involvement of the gut-brain axis in neurodegeneration. We showed that the induction of intestinal dysbiosis by enterobacteria infection exacerbated neurodegeneration. It led to the aggravation of an array of AD-related phenotypes, including increases in neuronal apoptosis, humoral inflammatory response, and reactive oxygen species (ROS) and decreases in lifespan and locomotor activity. These results suggest the existence of a gut-brain axis that can modulate AD neurodegeneration in *Drosophila*. We found that immune hemocytes pass signals from the dysbiotic gut to the AD brain that exacerbate neurodegeneration. Enteric infection increased motility of the cells, which were readily attracted to the AD brain in an ROS-dependent manner. This finding is important because it highlights the role of gut-brain crosstalk as a fundamental system for modulating AD neurodegeneration.

Selected recent publications:

Wu SC, Cao ZS, Chang KM, **Juang JL***. (2017) Intestinal microbial dysbiosis aggravates the progression of Alzheimer's disease in Drosophila. Nature Comm. 8(1):24. doi:10.1038/s41467-017-00040-6

Wu SC, Liao CW, Pan RL, **Juang JL***. (2012) Infection-induced intestinal oxidative stress triggers organ-to-organ immunological communication in *Drosophila*. Cell Host & Microbe. 11(4): 410–417. (featured by Cell Host & Microbe. 11: 323-324)

Chen PC, Huang YY, and **Juang JL***. (2011) MEMS microwell and microcolumn arrays: novel methods for high-throughput cell-based assays. Lab Chip. 11(21): 3619-3625.

Lin TY, Huang CH, Kao HH, Liou GG, Yeh, SR, Cheng CM, Chen MH, Pan, RL, **Juang JL***. (2009) Abi plays an opposing role to Abl in *Drosophila* axonogenesis and synaptogenesis. Development. 136(18): 3099-107.

Liu SC, Jen YM, Jiang SS, Chang JL, Hsiung CA, Wang CH, **Juang JL***. (2009) G 12-mediated pathway promotes invasiveness of nasopharyngeal carcinoma by modulating actin cytoskeleton reorganization. Cancer Research. 69(15): 6122-30.

Application of focus ultrasound on brain tumor
具焦超音波於腦腫瘤的應用

Host: Kuo-Chen Wei (魏國珍)

Location: 跨领域大楼
Interdisciplinary Research Building for Science and Technology (IRB)

Time: Sep. 12, 11:15-12:30

Participate societies: Taiwan Neurosurgical Society (台灣神經外科醫學會)、Taiwanese Society of Biomedical Engineering (中華民國生物醫學工程學會)

Malignant brain tumor is a devastating disease, and the average remaining life after diagnosis is only about one and a half years. Despite active treatment, the prognosis is still poor because the blood-brain barrier hinders the delivery of anti-cancer drugs. Our team uses non-invasive focused ultrasound to open the blood-brain barrier, which can significantly enhance drug transmission into the brain and consequently improve the therapeutic effect in the animal model. We have applied this approach in glioblastoma patients and completed the first phase of clinical trials. In this nanosymposium, we will present the results of clinical trials, the biomedical properties and engineering of focused ultrasound, and its application on facilitating adjuvant nano-drug delivery and radiotherapy.

Neuronavigation-Guided Focused Ultrasound (NaviFUS) for Transcranial Blood-Brain Barrier Opening in Recurrent Glioblastoma Patients

Wei, Kuo-Chen (魏國珍)

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Adjunct assistant professor, School of Medicine, Chang Gung University, Taiwan
Associate professor, Chang Gung Memorial Hospital, Linkou Branch, Taiwan
Assistant professor, School of Medicine, Chang Gung University, Taiwan
Professor, Chang Gung Memorial Hospital, Linkou Branch, Taiwan
Associate professor, School of Medicine, Chang Gung University, Taiwan

M.D., Chung Shan Medical University, Taichung, Taiwan.
Post MD research, Brain Tumor Research Center, University of California, San Francisco, CA

Abstract

BACKGROUND Blood-brain barrier (BBB) limits over 95% of drugs' penetration into brain, which has been a major obstacle in treating patients with glioblastoma. Transient BBB opening in glioblastoma (GBM) is feasible by combining focused ultrasound (FUS) with systemic infusion of microbubbles (MB).

OBJECTIVES Navigation guided focused ultrasound, a novel device that integrates neuronavigation and FUS-MB system, is able to intraoperatively direct the ultrasound energy precisely and repeatedly at targeted CNS areas. This clinical trial evaluates the safety and feasibility of navigation guided focused ultrasound, in recurrent glioblastoma patients.

METHODS The study is a first-in-human, prospective, open-label, single-center, single-arm, dose escalation phase 1 clinical trial. A total of 6 patients will be enrolled. Patients will be enrolled into three groups, each group receiving an escalating dose of FUS energy (acoustic power is 4, 8, and 12W) with concomitant systemic microbubbles (0.1ml/kg) applied 1 week before surgical resection.

EXPECTED OUTCOMES Dynamic contrast-enhanced MRI will be obtained immediately and 24 hours after FUS procedures, while heavily T2-weighted sequence will be obtained to evaluate for any micro-hemorrhages. We anticipate that there will be minimal side effects associated with NaviFUS-mediated transient BBB opening.

DISCUSSION Obtained results will support a planned phase 2 trial to evaluate whether navigation guided focused ultrasound can effectively enhance the delivery of chemotherapeutic agents and improve tumor control.

Selected recent publications:

Lin TY[1], **Wei KC**[1], Ju SP, Huang CY, Yang HW*. Diagnosis by simplicity: an aptachip for dopamine capture and accurate detection with a dual colorimetric and fluorometric system. Journal of Materials Chemistry B. 2018 May; 6(20): 3387-3394. (SCI; IF2018=5.047; Materials science, biomaterials 6/32) ([1]co-first author)

Yen HC*, Lin CL, Chen BS, Chen CW, **Wei KC**, Yang ML, Hsu JC, Hsu YH. Alterations of the levels of primary antioxidant enzymes in different grades of human astrocytoma tissues. Free Radical Research. 2018 Aug; 52(8): 856-871. (SCI; IF2018=2.825; Biochemistry & molecular biology 153/298)

Tsai HC, Tsai CH, Chen WS, Inserra C, **Wei KC***, Liu HL*. Safety evaluation of frequent application of microbubble-enhanced focused ultrasound blood-brain-barrier opening. Scientific Reports. 2018 Dec; 8(1): 17720. (SCI; IF2018=4.011; Multidisciplinary sciences 15/69) (co-corresponding author)

Pang HH, Chen PY, **Wei KC**, Huang CW, Shiue YL, Huang CY*, Yang HW*. Convection-Enhanced Delivery of a Virus-Like Nanotherapeutic Agent with Dual-Modal Imaging for Besiegement and Eradication of Brain Tumors. Theranostics. 2019 Feb; 9(6): 1752–1763. (SCI; IF2018=8.063; Medicine, research & experimental 10/136)

Pang HH, Huang CY , Chou YW , Lin CJ , Zhou ZL , Shiue YL , **Wei KC*** , Yang HW*. Bioengineering fluorescent virus-like particle/RNAi nanocomplexes act synergistically with temozolomide to eradicate brain tumors. Nanoscale. 2019 Apr; 11(17): 8102-8109. (SCI; IF2018=6.970; Physics, applied 18/148) (co-corresponding author)

Focused Ultrasound: Biomedical Application, Biosystem Manipulation, and Device Design

Hao-Li Liu (劉浩澧)

Distinguished Professor, Department of Electrical Engineering, Chang Gung University, Taoyuan, Taiwan 2018
Adjunct Researcher, Division of Medical Engineering Research, National Health Research Institutes, Miaoli, Taiwan
Director, Department of Electrical Engineering, Chang Gung University, Taoyuan, Taiwan
Professor, Department of Electrical Engineering, Chang Gung University, Taoyuan, Taiwan 2011

Ph.D., Department of Engineering, National Taiwan University, 2003, Taiwan.
M.S., Department of Engineering, National Taiwan University, 1998, Taiwan.

Abstract

Scientists have been devoted into the understanding of using focused ultrasound as a therapeutic tool since 1950. Yet, before the diagnostic ultrasound has even been clinically adopted much earlier in the 80s, focused ultrasound clinically proved its therapeutic efficacy and biomedical value way behind until this early century. Focused ultrasound has unique niche to be able to sharply steer radiation force energy into deep-seated soft tissue and can induce localized thermal or mechanical related biophysical effect. Focused ultrasound can even penetrate through the human skull to achieve noninvasive brain therapy. Regulatory approved its clinical practice in abdomen, bone, and brain, and more and more clinical applications are under discovery, development and clinical validation. Clinician relies on engineers dedicating on comprehensive system design to secure focused ultrasound energy delivery and to eventually achieve therapeutic bioeffect. In this presentation, the view angle from the engineering design perspective on focused ultrasound will be explored. Topics such as biosystem consideration, concept in biosystem control, medical electronics design experience, as well as medical device design experience on focused ultrasound will be covered.

Selected recent publications:

CJ Lin, CY Lin, YT Lin, CY Huang, KC Wei, JC Chen, GJL Chen, HL Liu*, “Microbubble-Facilitated Ultrasound Pulsation Promotes Direct α-Synuclein Gene Delivery,” Biochemical and Biophysical Research Communications, Vol. 517, No. 1, pp. 77-83, 2019

CH Wu, HL Liu, CT Ho, PH Hsu, CH Fan, CK Yeh, ST Kang, WS Chen, FN Wang, HH Peng, “Monitoring of acoustic cavitation in microbubble-presented focused ultrasound exposure using gradient-echo magnetic resonance imaging,” Journal of Magnetic Resonance Imaging, Accepted, 2019

CY Lin, CH Tsai, LY Feng, WY Chai, CJ Lin, CY Huang, KC Wei, CK Yeh, CM Chen, HL Liu, “Focused Ultrasound-Induced Blood Brain-Barrier Opening Enhanced Vascular Permeability for GDNF Delivery in Huntington's Disease Mouse Model,” Brain Stimulation, Accepted, 2019

KT Chen, KC Wei and HL Liu*, “Theranostic Strategy of Focused Ultrasound Induced Blood-Brain Barrier Opening for CNS Disease Treatment,” Frontiers in Pharmacology, Vol. 10, pp. 1-16, 2019

IC Lee, HJ Wu, HL Liu*, “Dual-frequency ultrasound induces neural stem/progenitor cell differentiation and growth factor utilization by enhancing stable cavitation,” ACS Chemical Neuroscience, Vol. 10, pp. 1-18, DOI: 10.1021/acschemneuro.8b00483, 2018

Self-assembly of functional RNAs in VLPs for glioma targeting therapy

楊閎蔚

Associate Professor, Institute of Medical Science and Technology

Chemical and Biomolecular Engineering, Georgia Institute of Technology, Georgia, U.S.A.
Chemical Engineering, National Tsing Hua University,, Taiwan.
Ph.D., Chemical and Materials Engineering, Chang Gung University, 2011, Taiwan.

Abstract

How to deliver effectively the RNAi or plasmid DNA (pDNA) into cells is the key point for successful gene therapy. The nanoparticles-based and adeno-associated viral vector (AAV)-based delivery systems are commonly used to enhance the transfection efficiency, but their disadvantages are the manufacturing cost and complicated processes. In this grant, we propose one-pot synthesis of self-assembly fluorescent virus-like-particle (fVLP)-miRNA complexes, which can be used for imaging tracking and gene down-regulation (c-Met and β-catenin) to further enhance the sensitivity of Temozolomide (TMZ) toward to Brain tumor cells. The innovation in this grant is our designed RNA scaffold can induce green fluorescence that can be monitored the RNA processing in cells in real time instead of gel electrophoresis. We will also modify the cell-penetrating peptide (CPP)- and Apolipoprotein E (ApoE)-peptides on the exterior surface of fVLP-RNAi complexes to enhance the cell uptake and penetration of blood-brain barrier (BBB). Intravenous administration of this formulation enhanced the curative efficacy of TMZ by downregulating the hepatocyte growth factor receptor (c-MET) gene in GBM U87 cells. Furthermore, upon gene-chemotherapy, the methylated DNA in GBM U87 cells was significantly enhanced by inhibiting the DNA repair mechanism, leading to significant brain tumor suppression. The results of this study could be critical for the design of RNAi-based genetic therapeutics for promoting chemotherapy against brain tumors.

Selected recent publications:

H.H. Pang, Y.C. Ke, N.S. Li, Y.T. Chen, C.Y. Huang, K.C. Wei*, **H.W. Yang***. A new lateral flow plasmonic biosensor based on gold-viral biomineralized nanozyme for on-site intracellular glutathione detection to predict drug-resistance level. *Biosensors and Bioelectronics* 165, 112325 (2020).

N.S. Li, Y.T. Chen, Y.P. Hsu, H.H. Pang, C.Y. Huang, Y.L. Shiue, K.C. Wei*, **H.W. Yang***. Mobile healthcare system based on the combination of lateral flow pad and smartphone for rapid detection of uric acid detection in whole blood. *Biosensors and Bioelectronics* 164, 112309 (2020).

W.L. Hsu, C.Y. Huang, Y.P. Hsu, T.L. Hwang, S.H. Chang, H.Y.J. Wang, L.Y. Feng, S.J. Tzou, K.C. Wei*, **H.W. Yang***. On-skin glucose-biosensing and hyperglycaemia-triggered insulin-zinc hexamers delivery using microneedles for syringe-free diabetes management. *Chemical Engineering Journal* 398, 125536 (2020).

Y.P. Hsu, N.S. Li, Y.T. Chen, H.H. Pang, K.C. Wei, **H.W. Yang***. A serological point-of-care test for Zika virus detection and infection surveillance using an enzyme-free vial immunosensor with a smartphone. *Biosensors and Bioelectronics* 151, 111960 (2020).

Y.P. Hsu, **H.W. Yang***, N.S. Li, Y.T. Chen, H.H. Pang, S.T. Pang*. A urological point-of-care FXYD3 test for early urothelial carcinoma screening and postoperative monitoring. *ACS Sensors* 5, 928-935 (2020).

Evaluation the combination effect of radiation and focused ultrasound in treatment of brain tumor model animals

黃瓊瑩

Senior postdoctoral research fellow, Department of Medicine, Chang Gung University

Ph.D., Graduate Institute of Tropical Medicine, National Yang-Ming University, 2005, Taiwan.

M.S., Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, 1995, Taiwan

Abstract

The standard treatment of malignant brain tumor is surgical resection followed by adjuvant chemo/radiotherapy. However, in spite of these aggressive treatments, tumor may still recur and resulting in poor survival. In solid tumors, the hypoxia condition presented in most of tumor area may contribute to treatment failure in both adjuvant therapies. It had been proven that systemic delivered oxygen may not sufficient for ionizing radiation to produce cytotoxic effect. A recent study reported using focused ultrasound combined with oxygen-contained microbubbles prior to radiation significantly increased the oxygen content in breast cancers and statistically improved animal survival. Therefore, providing sufficient oxygen in tumor area may be beneficial for radiation therapy. To study the potential role of such strategy for brain tumor treatment, we used focused ultrasound to treat brain tumor bearing animals before radiation therapy. As compared with non-ultrasound treatment groups, the tumor growth rate was significantly inhibited, and the animal survival is prolonged. We also analysis the gene expression changes, reveal some potential pathway that may involve in the process. Furthermore, we found focused ultrasound combined with non-oxygen-containing microbubbles also represented similar results, demonstrate the focused ultrasound induced cerebral vascular permeability increment may also contribute to the radiation therapy effect for brain tumor treatment.

Selected recent publications:

Chang EL, Ting CY, Hsu PH, Lin YC, Liao EC, **Huang CY**, Chang YC, Chan HL, Chiang CS, Liu HL, Wei KC, Fan CH, Yeh CK. Angiogenesis-targeting microbubbles combined with ultrasound-mediated gene therapy in brain tumors. *Journal of Controlled Release*. 2017 Jun; 255: 164-175. (SCI; IF2016=7.786; Pharmacology & pharmacy 10/256)

Lin FW, Chen PY, Wei KC, **Huang CY**, Wang CK, Yang HW. Rapid *In Situ* MRI Traceable Gel-forming Dual-drug Delivery for Synergistic Therapy of Brain Tumor. *Theranostics*. 2017 Jun; 7(9): 2524-2536. (SCI; IF2016=8.712; Medicine, research & experimental 8/128)

Chang EL, Ting CY, Hsu PH, Lin YC, Liao EC, **Huang CY**, Chang YC, Chan HL, Chiang CS, Liu HL, Wei KC, Fan CH, Yeh CK*. Angiogenesis-targeting microbubbles combined with ultrasound-mediated gene therapy in brain tumors. *Journal of Controlled Release*. 2017 Jun; 255: 164-175. (SCI; IF2018=7.901; Pharmacology & pharmacy 9/267)

Liu YS, Lin HY, Lai SW, **Huang CY**, Huang BR, Chen PY, Wei KC, Lu DY. MiR-181b modulates EGFR-dependent VCAM-1 expression and monocyte adhesion in glioblastoma. *Oncogene*. 2017 Aug; 36(35): 5006-5022. (SCI; IF2016=7.519; Genetics & heredity 12/166)

Lin CY, Li RJ, **Huang CY**, Wei KC, Chen PY. Controlled release of liposome-encapsulated temozolomide for brain tumour treatment by convection-enhanced delivery. *Journal of Drug Targeting*. 2018 Apr; 26(4): 325-332. (SCI; IF2018=7.901; Pharmacology & pharmacy 9/267)

Cellular stimulation
細胞刺激

Host: Ya-Cherng Chu (朱亞成)

Location:分子生物研究所 Institute of Molecular Biology (IMB)

Time: Sep. 12, 11:15-12:30

Participate societies: Taiwan Neurosurgical Society(台灣神經外科醫學會)、Taiwanese Society of Biomedical Engineering (中華民國生物醫學工程學會)

When facing brain trauma and neurological diseases, clinicians like to try non-invasive external stimulation for neuromodulation as a treatment option even in the absence of molecular basis to corroborate its curative effect. However, to pass three-phase clinical trials and to further optimize stimulation parameters for therapeutic efficacy, it is necessary to elucidate molecular mechanisms as the theoretical basis underlying clinical efficacy. Therefore, we will discuss how external stimuli, such as ultrasound and red light, regulate neuronal function at the molecular level and introduce a new chemo/opto-genetics method to control neuronal connectivity.

ASIC1a plays a role as the mechanosensor of low-intensity ultrasound stimulation for mouse brain neuronal activation

林若梅

Postdoc, Biomechanical Lab (Jaw-Lin Wang Lab)

National Taiwan University

PhD Institute of Molecular and Cell Biology, National University of Singapore

Abstract

Accumulating evidence has shown transcranial low-intensity ultrasound can be potentially a non-invasive neural modulation tool to treat brain diseases. However, the majority of studies on animal models applying rather high-intensity ultrasound that cannot be safely used in humans. In addition, the mechanical and molecular mechanisms remain elusive. Therefore, we aim to set up a study platform to investigate the neuronal responses upon ultrasound stimulations. Here we showed low-intensity ultrasound can activate neurons in the mouse brain. *In vitro* calcium imaging studies showed that the ultrasound delivered by micropipette, which generates both ultrasound and acoustic streaming in a local site, is required to activate primary culture of neonatal cortical neurons. By using candicate approach of testing various inhibitors, ASIC1a and the tether-mode mechanotransduction are demonstrated to be involved in the low-intensity ultrasound-mediated mechanotransduction and cultured neuron activation. In particular, neuronal calcium response induced by micropipette delivered ultrasound is specifically inhibited by ASIC1a blockade and cytoskeleton-modified agents. In contrast, the inhibition of mechanical sensitive channels involved in bilayer-model mechanotransduction like Piezo proteins do not affect the micropipette delivered ultrasound mediated neuronal activation. Most importantly, repeated ultrasound stimulation results in adult neurogenesis in specific brain regions, implicating a potential adult neurogenesis upon specific ultrasonic neuromodulations.

Selected recent publications:

Lim J, Chu Y-S, Chu Y-C, Lo C-M, Wang J-L (2020) Low Intensity Ultrasound Induces Epithelial Cell Adhesion Responses. *J Biomech Eng* 142: 091014

Lim J, Li X, Yuan X, Yang S, Han L, Yang S (2020) Primary cilia control cell alignment and patterning in bone development via ceramide-PKCζ-β-catenin signaling. *Commun Biol* 3:45

Chu Y-C, **Lim J**, Hong C-W, Chu Y-S, Wang J-L (2019) Design of an ultrasound chamber for cellular excitation and observation. *J ACOUST SOC AM* 145: EL547

Lim J, Thiery JP (2012) Epithelial-mesenchymal transitions: insights from development. *Development* 139: 3471-3486

Lim J, Balastik M, Lee TH, Nakamura K, Liou Y-C, Sun A, Finn G, Pastorino L, Lee VM-Y, Lu KP (2008) Pin1 has opposite effects on wild-type and P301L tau stability and tauopathy. *J Clin Invest* 118:1877-1889

Mechanoregulation of mitochondrial dynamics in axons/neurites

Yeh-Shiu Chu (朱業修)

Assistant Researcher, Brain Research Center, National Yang-Ming University, Taipei, Taiwan

PhD, Paris VI University, Paris, France

Abstract

Cells regulate mitochondrial movement and positioning in order to balance energy needs. Neurons are particularly susceptible to disturbance of mitochondrial motility and distribution due to their highly extended structures and specialized function. Regulation of mitochondrial motility thus plays a vital role in neuronal physiology. Ultrasound is used as therapeutics for neurologic diseases over the years; however, the fundamental knowledge as how neurons are affected by ultrasound remains poorly understood. We applied very low intensity ultrasound (1MHz) as a source of mechanical forces to stimulate living cortical neurons and monitored mitochondrial movement and fusion/fission events in axon/neurite by TIRF microscopy. Motility and membrane dynamics of mitochondria are reduced at ultrasound stimulation. Moreover, FLIM analyses reveal that ultrasound can modulate membrane tension and the topology of axon/neurite. Our study establishes a mechanobiolgical model to demonstrate that very low intensity ultrasound can exert effects on mitochondria dynamics at various cellular contexts through a outside-in spatial sequence of mechanotransducive events.

Selected recent publications:

Lim J*, YS Chu*, Chu YC, Lo CM, JL Wang, Low intensity ultrasound induces epithelial cell adhesion responses, J Biomechanical Engineering, 142:091014-1, 2020 (* co-first author),

Lai YT, YS Chu, Lo JC, YH Hung, Lo MC, Effects of electrode diameter on the detection sensitivity and frequency characteristics of electric cell-substrate impedance sensing, Biosensor and Actuator B: Chemical, 228: 707-715, 2019

Al-Aghbar MA, YS Chu, Chen BM, Roffler S High-affinity ligands can trigger T cell receptor signaling without CD45 segregation, Front Immunology. 9:713, 2018

Neurite regrowth induced by a red-light spot focused on the soma

Chau-Hwang Lee (李超煌)
Research Fellow/Professor, Research Center for Applied Sciences, Academia Sinica, Taiwan; Institute of Biophotonics, National Yang-Ming University, Taiwan

Ph.D. in Electrical Engineering, National Taiwan University

Abstract

Light produces various effects in biological cells; and these effects are dependent on wavelengths. For example, infrared light could raise the temperature of the illuminated site, while blue or violet light generates reactive oxygen species in cells. Numerous reports suggest that light-induced neurite growth could be a clinically useful technique for neuron repair. Most previous studies used either a large illumination area to accelerate overall neurite growth or a light spot to guide a growing neurite. It is not clear if optical stimulation can really "repair," or induce the regrowth of a retracted neurite. In this presentation, we demonstrate using blue light (wavelength: 473 nm) to cause neurite retraction, and then using a red-light (wavelength: 650 nm) spot to illuminate the soma and induce neurite regrowth. We found that the initialization of the neurite regrowth was wavelength dependent, while the regrowth length seemed to be independent of wavelength. Moreover, the neurite regrowth length was increased by the pre-treatment with inhibitors of myosin II activities. We also observed actin propagation from the soma to the tip of the re-growing neurite following red-light stimulation. This red light-induced regrowth did not occur in the calcium-free culture medium. These results suggest that illumination with a red-light spot on the soma may trigger the regrowth of a retracted neurite.

Selected recent publications:

Y.-C. Kao, Y.-C. Liao, P.-L. Cheng, and **C.-H. Lee,** 2019, "Neurite regrowth stimulation by a red-light spot focused on the neuronal cell soma following blue light-induced retraction," *Scientific Reports*, vol. 9, 18210.

C.-W. Lee, Y.-L. Chiang, J.-T. Liu, Y.-X. Chen, **C.-H. Lee,** Y.-L. Chen, and I.-S. Hwang, 2018, "Emerging roles of air gases in lipid bilayers," *Small*, vol. 14, 1802133.

Y.-C. Kao, J.-R. Jheng, H.-J. Pan, W.-Y. Liao, **C.-H. Lee,** and P.-L. Kuo, 2017, "Elevated hydrostatic pressure enhances the motility and enlarges the size of the lung cancer cells through aquaporin upregulation mediated by caveolin-1 and ERK1/2 signaling," *Oncogene*, vol. 36, pp. 863-874.

C.-W. Lee, L.-L. Jang, H.-J. Pan, Y.-R. Chen, C.-C. Chen, and **C.-H. Lee,** 2016, "Membrane roughness as a sensitive parameter reflecting the status of neuronal cells in response to chemical and nanoparticle treatments," *Journal of Nanobiotechnology*, vol. 14, 9.

C.-C. Lan, E. Y. Lu, H.-J. Pan, and **C.-H. Lee,** 2015, "Directional migration of cancer cells induced by a blue light intensity gradient," *Biomedical Optics Express*, vol. 6, pp. 2624-2632.

Chemical Optogenetics for Precise Control and Interrogation of Neurotransmission

Wan-Chen Lin (林宛蓁)
Assistant Research Fellow, Institute of Biomedical Sciences, Academia Sinica, Taiwan

Ph.D., Massachusetts Institute of Technology

Abstract

Neurotransmitters and their receptors are responsible for cell-cell communications in the nervous system. Due to their pivotal roles in signal detection and propagation, neurotransmitter receptors have long been therapeutic targets for neurological, psychiatric, and developmental disorders. Decoding of neurotransmission in the brain, however, is challenging due to the tremendous diversity of neurotransmitter receptors and the complex nature of neural circuitry. Breakthroughs await new approaches that enable control over neurotransmission mediators with high spatial, temporal, and biochemical precision. Our lab integrates chemical, biochemical, and genetic approaches to develop these tools and methods, with a special focus on next-generation optogenetics. Optogenetics is a powerful technique for investigating complex biological phenomena such as cellular signaling and neuronal connectivity. Through the action of a light-sensitive protein, the physiology of a cell or an organism can be optically controlled in defined space and time. We develop strategies to: (1) **engineer light-sensitive neurotransmitter receptors** for precise manipulation of specific signaling components in the brain; and (2) **optically control native neurotransmitter receptors** in defined neuronal types or subcellular compartments. We establish our methodologies with type-A γ-aminobutyric acid receptors ($GABA_A$ receptors), the master mediators of inhibitory neurotransmission in the brain. Ultimately, we aim to enable a comprehensive decoding of GABAergic signaling in the nervous system, and to provide generalizable approaches for optogenetic control of other neurotransmitter pathways.

Selected recent publications:

Lin WC, Tsai MC, Davenport CM, Smith CM, Veit J, Wilson NM, Adesnik H, Kramer RH (2015) A comprehensive optogenetic pharmacology toolkit for in vivo control of $GABA_A$ receptors and synaptic inhibition. *Neuron* 88:879−891.

Lin WC, Tsai MC, Rajappa R, Kramer RH (2018) Design of a highly bi-stable photoswitchable tethered ligand for rapid and sustained manipulation of neurotransmission. *J. Am. Chem. Soc.* 140:7445−7448.

Lin WC, Davenport CM, Mourot A, Vytla D, Smith CM, Medeiros KA, Chambers JJ, Kramer RH (2014) Engineering a light-regulated $GABA_A$ receptor for optical control of neural inhibition. *ACS Chem. Biol.* 9:1414−1419.

Lin WC, Kramer RH (2018) Light-switchable ion channels and receptors for optogenetic interrogation of neuronal signaling. *Bioconjugate Chem.* 29:861−869.

Computation and systems neuroscience
計算與系統神經科學

Host: Chung-Chuan Lo (羅中泉)

Location: 細胞與個體生物研究所
Institute of Cellular and Organismic Biology (ICOB)

Time: Sep. 12, 11:15-12:30

Participate societies: Taiwan Neuroscience Society (台灣基礎神經科學學會)、Taiwanese Society for Computational Neuroscience (台灣計算神經科學學會)

The human brain is an extremely complex computing device that can learn, memorize and make decisions through the interaction between tens of billions of neurons in response to sensory inputs. Computational neuroscience studies how neurons generate and transmit signals by simulating the actions of neurons in mathematical models. Before building a neural network model to accurately quantify or even predict the operation of the nervous system, many parameters need to be obtained from the experimental measurements of systems neuroscience. We will share our studies on the cerebellar plasticity and function, the construction of fly brain map, spatial navigation and memory in mice and flies.

Optogenetic regulation of synaptic plasticity to understand the functions of cerebellar systems

Wataru Kakegawa (掛川 渉)
Associate Professor, Department of Physiology, Keio University School of Medicine, Japan

Ph.D., Gunma University

Abstract

Our brains contain ca. 100 billion neurons which connect to each other through “synapses” to make neuronal circuits essential for higher brain functions, such as learning & memory. It is considered that synaptic plasticity, an activity-dependent change in synaptic properties, is a molecular basis of learning & memory (Kakegawa and Yuzaki, *BRAIN & NERVE*, 2018). Indeed, a lot of mutant mice which lack genes involved in synaptic plasticity exhibit severe memory impairment. However, we don’t know whether synaptic plasticity directly causes behavior dysfunction because we have no means to acutely intervene in synaptic plasticity at the specific synapses in the brain.

Recently, we developed novel chemogenetic and optogenetic tools to regulate the localization and functions of glutamate receptors, which are key players for synaptic transmission and plasticity (Kiyonaka et al., *Nat Chemistry*, 2016; Kakegawa et al., *Neuron*, 2018). In particular, a new optogenetic tool, PhotonSABER, controlled not only long-term depression (LTD), a certain form of synaptic plasticity, but also cerebellum-dependent motor learning in a light-dependent manner, suggesting the direct relationship between LTD and cerebellar motor learning (Kakegawa et al., *Neuron*, 2018). Because synaptic plasticity occurs in almost all neuronal circuits in each brain region, using these technologies, we will know the causal relationship between synaptic functions and the behaviors in more detail.

Selected recent publications:

Kakegawa W, Miyoshi Y, Hamase K, Matsuda S, Matsuda K, Kohda K, Emi K, Motohashi J, Konno R, Zaitsu K, Yuzaki M (2011) D-Serine regulates cerebellar LTD and motor coordination through the d2 glutamate receptor. *Nat Neurosci* 14:603-611

Unoki T*, Matsuda S*, **Kakegawa W*** (*equally contributed), Bich Van NT, Kohda K, Suzuki A, Funakoshi Y, Hasegawa H, Yuzaki M, Kanaho Y (2012) NMDA receptor-mediated activation of PI(4,5)P_2-producing enzyme PIP5K is essential for AMPA receptor endocytosis during long-term depression. *Neuron* 73:135-148

Kakegawa W, Mitakidis N, Miura E, Abe M, Matsuda K, Takeo YH, Kohda K, Motohashi J, Takahashi A, Nagao S, Muramatsu S, Watanabe M, Sakimura K, Aricescu AR, Yuzaki M (2015) Anterograde C1ql1 signaling is required in order to determine and maintain a single-winner climbing fiber in the mouse cerebellum. *Neuron* 85:316-329

Elegheert J, **Kakegawa W**, Clay EJ, Shanks N, Behiels E, Matsuda K, Kohda K, Miura E, Rossmann M, Mitakidis N, Motohashi J, Chang TV, Siebold C, Greger HI, Nakagawa T, Yuzaki M, Aricescu AR (2016) Structural basis for integration of GluD receptors within synaptic organizer complexes. *Science* 353:295-299

Kakegawa W, Katoh A, Narumi S, Miura E, Motohashi J, Takahashi A, Kohda K, Fukazawa Y, Yuzaki M, Matsuda S (2018) Optogenetic control of synaptic AMPA receptor endocytosis reveals roles of LTD in motor learning. *Neuron* 99:985-998

FlyBrain: This is a small world, but not small everywhere

Chi-Tin Shih (施奇廷)
Professor, Department of Applied Physics, Tunghai University, Taiwan

PhD, Department of Physics, National Tsing-Hua University, Taiwan

Abstract

The structure of the brain network of *Drosophila* was analyzed at two scales – the mesoscopic and microscopic networks describing the connections of the brain regions called local processing units (LPUs), and the single neurons, respectively. The brain network can be organized by some functional modules, or sub-networks, related to the brain functions. The whole-brain showed clear small-world features as many complex networks observed in natural and social sciences. Interestingly, structure of the sub-networks are diverse. Some of them are also small-worlds as the whole brain network, and others are not because they have long path lengths or small clustering coefficients. Statistics of other measurements also show diverse behavior among the sub-networks of the functional modules. The results suggest a correlation between functions and network structures.

Selected recent publications:

Chi-Tin Shih, Yen-Jen Lin, Cheng-Te Wang, Ting-Yuan Wang, Chih-Chen Chen, Ta-Shun Su, Chung-Chuan Lo, and Ann-Shyn Chiang, 2020, Diverse Community Structures in the Neuronal-Level Connectome of the Drosophila Brain, Neuroinformatics 18: 267-281.

Chi-Tin Shih, Olaf Sporns, Shou-Li Yuan, Ta-Shun Su, Yen-Jen Lin, Chao-Chun Chuang, Ting-Yuan Wang, Chung-Chuang Lo, Ralph J. Greenspan, and Ann-Shyn Chiang, 2015, Connectomic-Based Analysis of Information Flow in the Drosophila Brain, Current Biology, 25: 1249-58

Novel cellular mechanism supporting putative prospective coding in spatial navigation

Ching-Lung Hsu (徐經倫)
Assistant Research Fellow, Institute of Biomedical Sciences, Academia Sinica, Taiwan

Research Scientist, Janelia Research Campus, Howard Hughes Medical Institute

Ph.D., National Taiwan University

Abstract

Animals learn to use neural maps of environments to guide behavior. For spatial tasks, the neural codes require localization of the animal's position and planning for subsequent actions, but cellular mechanisms supporting such kinds of prospective spatial code are poorly understood.

In the hippocampus, place cells have been considered critical for both spatial representation and navigation. A subset of place cells, called splitter cells, exhibit place-dependent firing modulated by behavioral motor trajectories, but exact plasticity mechanisms that shape this behavioral-context-dependent spatial code remain unknown. Here, we applied whole-cell patch-clamp recording of CA1 pyramidal neurons in awake mice performing a visually cued two-choice task in virtual reality, which required functionally intact dorsal hippocampus. Under the strict control of visual cues, we found that calcium plateau potentials can rapidly and robustly trigger emergence of splitter cells in CA1, and further experiments unambiguously indicated that task demand is a necessary factor in this process. Finally, I will also discuss one potential implication of splitter cells in a computational framework of reinforcement learning for navigation.

Selected recent publications:

Hsu CL*, Zhao X, Milstein AD, Spruston N. (2018). Persistent sodium current mediates the steep voltage dependence of spatial coding in hippocampal pyramidal neurons. *Neuron*, 99(1): 147-162.

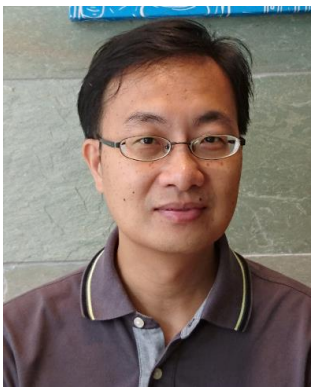
Kim Y*, **Hsu CL***, Cembrowski M, Mensh B, Spruston N. (2015). Dendritic sodium spikes are required for long-term potentiation at distal synapses on hippocampal pyramidal neurons. *eLife*, 4: e06414.

Hsu CL*, Yang HW, Yen CT, Min MY. (2010). Comparison of synaptic transmission and plasticity between sensory and cortical synapses on relay neurons in the ventrobasal nucleus of the rat thalamus. *Journal of Physiology*, 588(22): 4347-4363.

A spiking neural network model of spatial working memory in Drosophila

Chung-Chuan Lo (羅中泉)
Professor and director, Institute of Systems Neuroscience,
National Tsing Hua University, Hsinchu, Taiwan

PhD, Boston University



Abstract

The ability of maintaining spatial orientation is crucial for an animal to perform goal-directed movements. Recent *Drosophila* studies have revealed the critical role of the ellipsoid body (EB) in tracking spatial orientation, but the precise neural computation and underlying mechanisms remain unclear. We analyzed connectomic data of *Drosophila* central complex and discovered that the circuit connecting EB and the protocerebral bridge (PB) form symmetric and asymmetric rings. The asymmetric rings can be further divided into two sub-rings, one with counterclockwise and the other with clockwise patterns. We further constructed a spiking neural circuit model based on the circuits reconstructed from the connectomic data. We demonstrated that the symmetric ring is capable of sustaining persistent neural activity that encodes spatial orientation, while the asymmetric rings perform angular path integration and update orientation when the body rotates in the dark. We tested this model by performing neural functional and behavioral experiments based on a modified Buridan's paradigm. We investigated how orientation working memory is maintained in wild-type flies and in flies with hyperactivated or suppressed ring neurons. We discovered that, as predicted by the model, manipulation of different ring neurons gave rise to distinct behavioral changes, with one characterized by inaccurate working memory of spatial orientation after the offset of the visual cues and the other by loss of spatial orientation even with the presence of the visual cues.

Selected recent publications:

Hung-Hsiu Yen, Rui Han and **Chung-Chuan Lo*** (2019). Quantification of Visual Fixation Behavior and Spatial Orientation Memory in Drosophila melanogaster. *Frontiers in Behavioral Neuroscience* 13:215

Chi-Tin Shih*, Yen-Jen Lin, Cheng-Te Wang, Ting-Yuan Wang, Chih-Chen Chen, Ta-Shun Su, **Chung-Chuang Lo***, and Ann-Shyn Chiang* (2019). Diverse Community Structures in the Neuronal-level Connectome of the Drosophila Brain. *Neuroinformatics* 18:267–281

Yu-Chi Huang, Cheng-Te Wang, Ta-Shun Su, Kuo-Wei Kao, Yen-Jen Lin, Chao-Chun Chuang, Ann-Shyn Chiang and **Chung-Chuan Lo*** (2019). A Single-Cell Level and Connectome-Derived Computational Model of the Drosophila Brain. *Frontiers in Neuroinformatics* 12:99

Ta-Shun Su, Wan-Ju Lee, Yu-Chi Huang, Cheng-Te Wang and **Chung-Chuan Lo*** (2017). Coupled symmetric and asymmetric circuits underlying spatial orientation in fruit flies. *Nature Communications* 8:139.

Po-Yen Chang, Ta-Shun Su, Chi-Tin Shih* and **Chung-Chuan Lo*** (2017). The Topographical Mapping in Drosophila Central Complex Network and its Signal Routing. *Frontiers in Neuroinformatics* 11:26