Effects of equilibrative nucleoside transporter 1 (ENT1) inhibitor on cognitive deficits and sleep disruptions in sporadic Alzheimer's mice

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Abstract

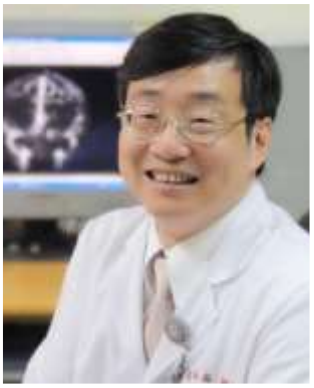
Alzheimer's disease (AD) is one of the most common neurodegenerative diseases in the elderly and there is no adequate medicine for the treatment. We employs the intracerebroventricular (icv) injection of streptozotocin (STZ; 3 mg/kg, the total injection volume is 1 μl) and intrahippocampal (ih) injection of amyloid-beta (Aβ1-42;1 μg/μl, the total volume is 1 μl) in consecutive 4 days to establish a reliable animal model of sporadic AD (sAD) and determined the efficacy of equilibrative nucleoside transporter (ENT)1 inhibitor on sAD treatment. The expression of pathological hallmarks of amyloid-beta plaques and phosphorylated tau proteins, the indicator of apoptosis, the marker of broken DNA double-strand, the nitrite levels of oxidative stress, the cell number of cholinergic, the Morris water maze (MWM) and novel object recognition (NOR) task were evaluated after oral administration of the ENT1 inhibitor. A 24h sleep-wake activity was acquired by analyzing electroencephalogram (EEG) and electromyogram (EMG). Our results indicated that the ENT1 inhibitor blocked the increases of nitric oxide, caspase 3 and phosphorylated γ-H2AX, increased activities of nuclear DNA-dependent serine/threonine protein kinase (DNA-PKcs) through the non-homologous end joining (NHEJ) pathway to repair DNA double-strand breaks and alleviated cholinergic neuronal loss in sAD mice. The ENT1 inhibitor also improved the cognitive deficits in the MWM and NOR tasks. Furthermore, sAD mice increased non-rapid eye movement (NREM) sleep during dark period and decreased NREM and REM sleep during light period, while the elevation of extracellular adenosine by ENT1 inhibitor exhibited beneficial for recovering the homeostatic sleep. In conclusion, our results indicated that the ENT1 inhibitor could be potential for sAD treatment.

Selected recent publications:

1. Yun Lo, Pei-Lu Yi, Yi-Tse Hsiao, **Fang-Chia Chang***. Hypocretin in locus coeruleus and dorsal raphe nucleus mediates inescapable footshock stimulation (IFS)-induced REM sleep alteration. *Sleep* 2021; https://doi.org/10.1093/sleep/zsab301.
2. I-Chen Li, Ting-Wei Lin, Tung-Yen Lee, Yun Lo, Yih-Min Jiang, Yu-Hsuan Kuo, Chin-Chu Chen, **Fang-Chia Chang***. Oral delivered Armillaria mellea promotes non-rapid eye movement and rapid eye movement sleep in rats. *Journal of Fungi* 2021; 7(5): 371.
3. Yi-Tse Hsiao, Yun Lo, Pei-Lu Yi, **Fang-Chia Chang***. Hypocretin in median raphe nucleus modulates footshock stimuli-induced REM sleep alteration. *Scientific Reports* 2019; 9: 8198.
4. Pei-Lu Yi, Ying-Ju Chen, Chung-Tien Lin, **Fang-Chia Chang***. Occurrence of epilepsy at different zeitgeber times alters sleep homeostasis differently in rats. *Sleep* 2012; 35(12):1651-1665.
5. Yi-Tse Hsiao, Pei-Lu Yi, Chia-Ling Li, **Fang-Chia Chang***. Effect of cannabidiol on sleep disruption induced by the repeated combination tests consisting of open field and elevated plus-maze in rats. *Neuropharmacology* 2012; 62:373-384.

Sleep and restless leg syndrome: perspectives beyond dopaminergic pathway

Chung-Yao Hsu(徐崇堯)



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Abstract

Restless legs syndrome (RLS) belongs to sleep-related movement disorder but the underlying pathogenesis is not completely clarified. There is a breakthrough change regarding the treatment of RLS. The dopamine agonists, which have been the evidence-based first choice treatment of RLS, leadto a severe “augmentation” of RLS symptoms. This big change comes from a new concept that RLS is basically a dopamine “hyperactivity” instead of “hypoactivity” state. We started from the dopamine-related “reward system”, coming up with an experimental design using the stimuli based on the idea of “novelty seeking” and “risk taking” behavior, to investigate changes of dopaminergic and opioidreceptor genes, circadian rhythm-related melatonin and clock genes, sleep homeostasis-related cytokines and alpha-2/delta-1 calcium channel receptor gene before and after the stimuli. We chose iron deficiency anemia model of RLS to control the severity and step-wise progression of anemia and conduct a two-axis interventional study in terms of human “full-spectrum light exposure” via retino-thalamic tract and animal low frequency “deep brain stimulation” via bilateral A11 subthalamic nuclei. We analyzed the sleep microstructure, the clock genes expression and changes of melatonin concentration in both humans and animals. We also measured “cognition and balance“related with “sleep deprivation and degree of “impulsivity” and “novelty” related with “dopamine hyperactivity”. We quantified the changes of neurotransmitters and localize the changes using immunohistochemistry in the hypothalamus and basal ganglia-related brain regions. The goal of our study is trying to find out a “point-of-no-return” to promote the pathogenesis of RLS and its interaction with “circadian rhythm”, “homeostasis” and “extra-dopaminergic pathways”.

Selected recent publications:

1. WC Yeh, YC Chuang, CW Yen, MC Liu, MN Wu, LM Liou, CFang Hsieh, CF Chien, CY Hsu*. Static Postural Stability and Neuropsychological Performance After Awakening From REM and NREM Sleep in Patients With Chronic Insomnia: A Randomized, Crossover, Overnight Polysomnography Study. Journal of Clinical SleepMedicine, https://doi.org/10.5664/jcsm.10052, 2022 (SCIE, 69/208, CLINICAL NEUROLOGY).

2. WC Yeh, HL, YS Li, CF Chien, MN Wu, LM Liou, CF Hsieh, CY Hsu*. Non-rapid eye movement (NREM) sleep instability in adults with epilepsy: a systematic review and meta-analysis of cyclic alternating pattern (CAP). SLEEP 45(4), 2022. (SCI, 33/208, CLINICAL NEUROLOGY).

3. CY Hsu, YC Chuang, FC Chang, HY Chuang, TY Chiou, CT Lee*. Disrupted Sleep Homeostasis and Altered Expressions of Clock Genes in Rats with Chronic Lead Exposure. Toxics, 9(9):217, 2021. (SCIE, 30/93, TOXICOLOGY).

4. WC Yeh, PJ Lin, YC Chuang, CY Hsu*. Quantitative evaluation of the microstructure of rapid eye movement sleep in refractory epilepsy: a preliminary study using electroencephalography and heart rate variability analysis. Sleep Medicine, 85:239-245, 2021. (SCIE, 94/208, CLINICAL NEUROLOGY).

5. HJ Lin, JH Yeh, MT Hsieh, CY Hsu*. Continuous positive airway pressure with good adherence can reduce risk of stroke in patients with moderate to severe obstructive sleep apnea: An updated systematic review and meta-analysis. Sleep Medicine Reviews, 54:101354, 2020. (SCI, 8/204, CLINICAL NEUROLOGY).

Brain Functional Reorganizations in Light Sleep

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Abstract

Compared with the rapid-eye-movement (REM) sleep, non-REM (NREM) sleep is associated with fading consciousness and memory consolidation. A decade ago, neuroimaging literature has demonstrated the spatiotemporal alterations of the brain functional connectivity (FC) in NREM sleep, especially in the deep sleep (NREM sleep stage 3, *N3 sleep*) or slow-wave sleep (SWS). In contrast, the light sleep (NREM sleep stage 2, *N2 sleep*), over 50% of total sleep time, does not draw lots of attention in sleep neuroimaging. Recently, we measured the sleeping brain using simultaneous EEG-fMRI recordings at midnight. Beyond the FC changes, we adopted multiverse analytical indices to probe the brain functional alterations across NREM sleep stages, such as complexity to FC variability across distinct spatial scales. Interestingly, we found that the intrinsic brain networks, such as default-mode network (DMN) and attention networks, would experience an extremely unstable long-range connection with enhanced entropy in the N2 sleep. Around the local regional space, the brain in the N2 sleep comes with the elevated local connectivity with reduced local entropy. Altogether, these phenomena indicate that, in contrast to the general inactive brain functions in N3 sleep, the brain in the N2 sleep is undergoing a series of unstable information exchange without the constraints of network boundaries, which relates to an intensive functional reorganizations and implies why we fall into the unresponsive consciousness dissipation every night.

Selected recent publications:

1. Kung, Y.-C., Li, C.-W., Hsiao, F.-C., Tsai, P.-J., Chen, S., Li, M.-K., Lee, H.-C., Chang, C.-Y., **Wu, C.W.**, Lin, C.- P., May 17 2022, Cross-Scale Dynamicity of Entropy and Connectivity in the Sleeping Brain, In: *Brain Connectivity* (In press).

2. Wu, H., Qi, Z., Wu, X., Zhang, J., **Wu, C.**, Huang, Z., Zang, D., Fogel, S., Tanabe, S., Hudetz, A. G., Northoff, G., Mao, Y. & Qin, P., Jan 2022, Anterior precuneus related to the recovery of consciousness, In: *NeuroImage: Clinical*. 33, 102951.

3. Qin, P., Wu, X., **Wu, C., Wu**, H., Zhang, J., Huang, Z., Weng, X., Zang, D., Qi, Z., Tang, W., Hiromi, T., Tan, J., Tanabe, S., Fogel, S., Hudetz, A. G., Yang, Y., Stamatakis, E. A., Mao, Y. & Northoff, G., May 1 2021, Higher-order sensorimotor circuit of the brain's global network supports human consciousness, In: *NeuroImage*. 231, 117850.

4. **Wu, C.W.**, Tsai, P.-J., Chen, C.-J., Li, C.-W., Hsu, A.-L., Wu, H.-Y., Ko, Y.-T., Hung, P.-C., Chang, C.-Y., Lin, C.- P., Lane, T.J., Chen, C.-Y., Aug 2 2019, Indication of Dynamic Neurovascular Coupling from Inconsistency between EEG and fMRI Indices across Sleep-wake States, In: *Sleep and Biological Rhythms*. 17, 423.

5. Kung, Y.-C., Li, C.-W., Chen, S., Chen, C.-J., Lo, C.-Y., Ko, Y.-T., Biswal, B.B., Chang, C.-Y., **Wu, C.W.**, Lin, C.- P., Aug 1 2019, Instability of Brain Connectivity during NREM Sleep Reflects Altered Properties of Information Integration, In: *Human Brain Mapping*. 40, 3192.

Resting state brain oscillatory dynamics in people with varying degree of anxiety and mindfulness

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Abstract

Anxiety and mindfulness are two inversely linked traits shown to be involved in various physiological domains. We used resting state electroencephalography (EEG) to explore differences between people with low mindfulness-high anxiety (LMHA) and high mindfulness-low anxiety (HMLA). The resting EEG was collected for a total of 6 minutes, with a randomized sequence of eyes closed and eyes opened conditions. Two advanced EEG analysis methods, Holo-Hilbert Spectral Analysis and Holo-Hilbert cross-frequency phase clustering (HHCFPC), were employed to estimate the power-based amplitude modulation of brain oscillations, and cross-frequency coupling between low and high frequencies, respectively. The unique advantage of Holo-based methods is that they can reveal the nonlinear and nonstationary characteristics of EEG signals. The presence of higher oscillation power across the delta and theta frequencies in the LMHA group than the HMLA group might have been due to the similarity between the resting state and situations of uncertainty, which reportedly triggers motivational and emotional arousal. Additionally, a higher δ-β and δ-γ CFC in LMHA suggested greater local-global neural integration, consequently a greater functional association between cortex and limbic system than in the HMLA group. The present cross-sectional study may guide future longitudinal studies on anxiety aiming with interventions such as mindfulness to characterize the individuals based on their resting state physiology.

Selected recent publications:

1. **Wei-Kuang Liang***, Philip Tseng, Jia-Rong Yeh, Norden E Huang, Chi-Hung Juan, 2021/04, Frontoparietal beta amplitude modulation and its interareal cross-frequency coupling in visual working memory, NEUROSCIENCE, 460 69-87.
2. Chong-Chih Tsai, **Wei-Kuang Liang***, 2021/03, Event-related components are structurally represented by intrinsic event-related potentials, Scientific Reports, 11 1 5670.
3. Satish Jaiswal, Shao-Yang Tsai, Chi-Hung Juan, Neil G Muggleton, **Wei-Kuang Liang*** (2019, Jun). Low delta and high alpha power are associated with better conflict control and working memory in high mindfulness, low anxiety individuals. *Social Cognitive and Affective Neuroscience*, 14 (6), 645-655
4. Andrew J. Quinn, Vítor Lopes-dos-Santos, Norden Huang, **Wei-Kuang Liang**, Chi-Hung Juan, Jia-Rong Yeh, Anna C. Nobre, David Dupret, and Mark W. Woolrich, 2021/09, Within-cycle instantaneous frequency profiles report oscillatory waveform dynamics, Journal of Neurophysiology, 2021 126:4, 1190-1208
5. Chun-Hao Wang*, **Wei-Kuang Liang***, David Moreau, 2020/01, Differential Modulation of Brain SignalVariability During Cognitive Control in Athletes with Different Domains of Expertise, NEUROSCIENCE, 425 267-279

Automatic sleep staging using intrinsic multi-scale entropy features of five-channel EEG recordings

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Abstract

Sleep is an interesting research topic with growing applications in neuroscience and sleep medicine. This present works proposes a systemic method named as intrinsic multi-scale entropy (iMSE) to quantify a scale-sensitive entropy of electroencephalography (EEG) over two dimensions of filtering and coarse-graining timescales, which performs as a good measure for monitoring sleep status. Methods: A database of polysomnography (PSG) downloaded from PhysioNet with clear notations of sleep stages was used as the material of this study. The five-channels EEG recordings were analyzedby iMSE using 20 filtering and 60 coarse-graining timescales. Two intrinsic entropies sensitively correlated to consciousness level in sleep were defined as indicators for monitoring sleep cycles. Different specific intrinsic entropies perform well in different classifications among six sleep stages (the average of area under ROC curve is 0.925). The dimensionless and objective physical measure of entropy is a good biomarker for monitoring consciousness level in sleep. Entropies calculated from the filtered and coarse-grained time series using specific filtering and coarse-graining timescales work well for automatic sleep staging. A systemic approaching method for determining specific timescales in entropy analysis is the most important contribution in this study. Entropy measure can be a candidate with high scale resolution and high time resolution for investigating the dynamic properties in sleep.

Selected recent publications:

How Dendrites and Spine Layouts can Increase Storage Capacity for Episodic Memory

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Abstract

In order to record the stream of autobiographical information that defines our unique personal history, our brains must form durable memories from single brief exposures to the patterned stimuli that impinge on them continuously throughout life. However, little is known about the computational strategies or neural mechanisms that underlie the brain's ability to perform this type of one-shot "episodic" learning. We present findings at two levels. First, based on evidence that dendrites can act as both signaling and learning units in the brain, we developed a model that relates memory capacity to numerous dendritic, network, pattern, and task-related parameters. We used the model to determine what dendrite size maximizes storage capacity under various conditions. We show that over a several-fold range of both of these parameters and multiple orders-of-magnitude of memory size, capacity is maximized when dendrites contain a few hundred synapses—roughly the natural number found in memory-related areas of the brain. Thus, in comparison to entire neurons, dendrites increase storage capacity by providing a larger number of better-sized learning units (Wu et al. 2019). Second, at a more fine-grained level of analysis, we show that the spine density profile strongly influences a dendrite's nonlinear signaling behavior. In particular, when spine density declines moving outward along individual dendrites – as seen both in the hippocampus and the neocortex – individual dendrites function as more reliable binary-valued thresholding devices which, coming full circle, benefits one-shot learning (Ramdas and Mel, 2021).

Selected recent publications:

1. Mel, B.W., Schiller, J., and Poirazi, P. (2017). Synaptic plasticity in dendrites: complications and coping strategies. *CurrOpinNeurobiol*, 43:177-186, PMID: 28453975.

2. Kumar, A., Schiff, O., Barkai, E., Mel, B.W., Poleg-Polsky, A. and Schiller, J. (2018). NMDA spikes mediate amplification of inputs in the rat pyriform cortex. *eLife, 7:e38446 DOI: 10.7554/elife.38446*

3. Wu, X.E., Strouse, D.J., Mel, G.C., and Mel, B.W. (2019). How dendrites affect online recognition memory. *PLoSComput Biol, 15(5): e1006892. DOI: https://doi.org/10.1371/journal.pcbi.1006892*

4. Jin, L., Behabadi, B. F., Jadi, M. P., Ramachandra, C. A., & Mel, B. W. (2022). Classical-contextual interactions in V1 may rely on dendritic computations. *Neuroscience*, S0306452222001038. *DOI*:https://doi.org/10.1016/j.neuroscience.2022.02.033.

5. Ramdas, T. and Mel, B.W. (2021) Optimizing a neuron for reliable dendritic subunit pooling. Neuroscience, Oct 26;S0306-4522(21)00526-1. *DOI*: https://doi.org/10.1016/j.neuroscience.2021.10.017.

Deep Exposure: hidden behind natural images

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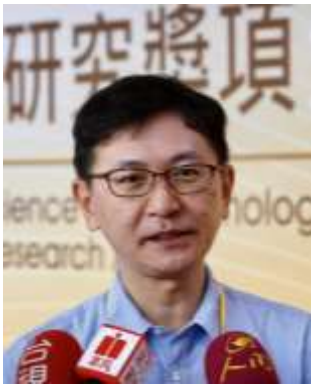

Abstract

Human vision is a powerful sensory system for detecting environmental information. However, its efficiency comes along with built-in fallacies often neglected. Utilizing a machine-learning approach, we reveal a universal hidden structures embedded in most natural images and show that 2D natural images can be compressed and thus encoded faithfully by vorticities along 1D boundaries. In addition, a hierarchy of visual information can be constructed according to the human-eye sensitivity. By projecting out the principal components for human vision, the invisible textures of the natural images emerge, providing a promising tool for medical image analysis in the future.

Selected recent publications:

1. U(1) dynamics in neuronal activities. CY Lin, PH Chen, HH Lin, WM Huang. arXiv:2109.12608 (2021)
2. Manipulating exchange bias by spin–orbit torque. PH Lin, BY Yang, MH Tsai, PC Chen, KF Huang, HH Lin, CH Lai. *Nature Materials* 18, 335-341 (2019).
3. Initialization-free multilevel states driven by spin-orbit torque switching. KF Huang, DS Wang, MH Tsai, HH Lin, CH Lai. *Advanced Materials* 29, 1601575 (2017).
4. Pairing mechanism in multiband superconductors. WM Huang, HH Lin. *Scientific Reports* 10, 7439 (2020).
5. Anomalous isotope effect in iron-based superconductors. WM Huang and HH Lin. *Scientific Reports* 9, 5547 (2019).

Seeking Thermodynamics in Computing Networks of Neurons

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Abstract

Computing networks in intelligent machines and animals alike consist of large numbers of neurons. While the states of these constituent neurons are relatively simple, their collective dynamics gives rise to a very rich repertoire of functional dynamics. With the large degrees of freedom, statistical approaches are desirable in sifting through the voluminous of data for relevant insights into the mechanisms these networks deploy to serve their functional requirements. By matching the statistical properties of the observed data from the dynamics of the neural systems, we can solve for simplified model networks that reproduce the observed statistics. Through these uncovered models, increased possibilities of theoretical and computational analysis from statistical thermodynamics and complex networks can be applied for various characterizations of their states. Similar to statistical physics for understanding the phase behavior of materials, these quantitative descriptions can hopefully lead to better understanding of functional behavior of the neural systems.

Selected recent publications:

1. Yi-Ling Chen, **Chun-Chung Chen**, Yu-Ying Mei, Ning Zhou, Dongchuan Wu, and Ting-Kuo Lee. Ubiquitous proximity to a critical state for collective neural activity in the CA1 region of freely moving mice. Chinese Journal of Physics, 77:497–510, 2022.

2. Kevin Sean Chen, **Chun-Chung Chen**, and C. K. Chan. Characterization of Predictive Behavior of a Retina by Mutual Information. Frontiers in Computational Neuroscience, 11:66, 2017.

3. Chih-Hsu Huang, Yu-Ting Huang, **Chun-Chung Chen**, and C. K. Chan. Propagation and synchronization of reverberatory bursts in developing cultured networks. Journal of Computational Neuroscience, 42(2):177–185, 2017.

4. Yu-Ting Huang, Yu-Lin Chang, **Chun-Chung Chen**, Pik-Yin Lai, and C. K. Chan. Positive feedback and synchronized bursts in neuronal cultures. PLoS ONE, 12(11):e0187276, November 2017.

5. Kai-Yi Wang, Jei-Wei Wu, Jen-Kun Cheng, **Chun-Chung Chen**, Wai-Yi Wong, Robert G. Averkin, Gábor Tamás, Kazu Nakazawa, and Cheng-Chang Lien. Elevation of hilar mossy cell activity suppresses hippocampal excitability and avoidance behavior. Cell Reports, 36(11):109702, 2021.

Nanosymposium session V

Worms in maze:

Spatial learning and decision making in a structured environment

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Abstract

Mazes are broadly used to investigate animal decision-making and spatial learning. However, they have been sparsely employed to explore *C. elegans* behavior and training-improved performance. We have developed a highly reproducible, low-cost maze platform, made of the standard, agar-based, nematode culturing material. Using this"Worm-Maze" platform, we show that *C. elegans* nematodes learn to associate food with a combination of proprioceptive cues and information on the structure of their surroundings (maze), perceived through mechanosensation. We demonstrated that *C. elegans* young adults can locate food in T-shaped mazes and, following that experience, learn to reach a specific maze arm.*C. elegans* learning inside the maze is possible after a single training session, it resembles working memory, and it prevails over conflicting environmental cues. We provide evidence that the observed learning is a food-triggered multisensory behavior, which requires mechanosensory and proprioceptive input, and utilizes cues about the structural features of nematodes' environment and their body actions. The CREB-like transcription factor and dopamine signaling are also involved in maze performance. Lastly, we show that the observed aging-driven decline of *C. elegans* learning ability in the maze can be reversed by starvation.

Selected recent publications:

1. Lim CY, Lin HT, Kumsta C, Lu TC, Kang YH, Hansen M, Ching TT*, Hsu AL*. (2022) "SAMS-1 coordinates HLH-30/TFEB and PHA-4/FOXA activities through histone methylation to regulate autophagy and longevity." ***Autophagy.****in press*.

2. Gourgou E, Adiga K, Goettemoeller A, Chen C, Hsu AL*.(2021)"*C. elegans* learning in a structured maze is a multisensory behavior." ***iScience.*** 24(4): 102284.

3. Lin JL, Kuo WL, Huang YH, Jong TL, Hsu AL*****, Hsu WH*. (2021) "Using convolutional neural network to measure the physiological age of *C. elegans*." ***IEEE/ACM Trans. Comput. Biol. Bioinform.*** 18(6): 2724-2732. doi: 10.1109/TCBB.2020.2971992.

4. Sural S, Liang CY, Wang FY, Ching TT*, Hsu AL*. (2020) "HSB-1/HSF-1 pathway modulates histone H4 in mitochondria to control mtDNA transcription and longevity."***Science Advances***. 6(43): eaaz4452.

5. Li G, Gond JK, Liu J, Liu JZ, Li HH, Hsu AL, Liu J, Xu XZS. (2019) "Genetic and pharmacological interventions in the aging motor nervous system slow motor aging and extend lifespan in *C. elegans*." ***Science Advances***. 5(1): eaau5041.

Why burst-dependent synaptic plasticity is relevant for neuromorphic computing

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Abstract

Synaptic plasticity is believed to be a key physiological mechanism for learning. It is well established that it depends on pre- and postsynaptic activity. However, models that rely solely on pre- and postsynaptic activity for synaptic changes have, so far, not been able to account for learning complex tasks that demand credit assignment in hierarchical networks. Here we show that if synaptic plasticity is regulated by high-frequency bursts of spikes, then pyramidal neurons higher in a hierarchical circuit can coordinate the plasticity of lower-level connections. Using simulations and mathematical analyses, we demonstrate that, when paired with short-term synaptic dynamics, regenerative activity in the apical dendrites and synaptic plasticity in feedback pathways, a burst-dependent learning rule can solve challenging tasks that require deep network architectures. Our results demonstrate that well-known properties of dendrites, synapses and synaptic plasticity are sufficient to enable sophisticated learning in hierarchical circuits. We discuss the implications for neuromorphic computing.

Selected recent publications:

1. Payeur, Alexandre, et al. "Burst-dependent synaptic plasticity can coordinate learning in hierarchical circuits." *Nature neuroscience* 24.7 (2021): 1010-1019.
2. Doron, Guy, et al. "Perirhinal input to neocortical layer 1 controls learning." *Science* 370.6523 (2020): eaaz3136.

Blood-based biomarkers for Alzheimer's disease: current status of their clinical implementation in diagnosis, treatment and prevention

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Abstract

Neurodegenerative disorders such as Alzheimer's disease (AD) represent a mounting public health challenge. As these diseases are difficult to diagnose clinically, biomarkers of underlying pathophysiology are playing an ever-increasing role in research, clinical trials, and in the clinical work-up of patients. Though cerebrospinal fluid (CSF) and positron emission tomography (PET)-based measures are available, their use is not widespread due to limitations, including high costs and perceived invasiveness. As a result of rapid advances in the development of ultra-sensitive assays, the levels of pathological brain- and AD-related proteins can now be measured in blood, with recent work showing promising results. To date, several biomarkers have been established that, to a different extent, allow researchers and clinicians to evaluate, diagnose, and more specially exclude other related pathologies. In this talk, we will extensively review data on the currently explored biomarkers in terms of AD pathology-specific and non-specific biomarkers and highlighted the recent developments in the diagnostic and theragnostic domains.

Selected recent publications:

1. Lin SY, Lin PC, Lin YC, Lee YJ, Wang CY, Peng SW, Wang PN*. The Clinical Course of Early and Late Mild Cognitive Impairment. Front Neurol. 2022 May 16;13:685636.

2. Huang YL, Lin CH, Tsai TH, Huang H, Li JL, Chen LK, Li CH, Tsai TF, Wang PN*. Discovery of a Metabolic Signature Predisposing High Risk Patients with Mild Cognitive Impairment to Converting to Alzheimer's Disease. International Journal of Molecular Sciences. 2021 Oct; 22(20):10903.

3. Chen TB, Lin KJ, Lin SY, Lee YJ, Lin YC, Wang CY, Chen JP, Wang PN*. Prediction of Cerebral Amyloid Pathology Based on Plasma Amyloid and Tau Related Markers. Front Neurol.2021 Oct 4;12:619388

4. Wang PN, Lin KJ, Liu HC, Andreasson U, Blennow K, Zetterberg H, Yang SY. Plasma pyroglutamate-modified amyloid beta differentiates amyloid pathology. Alzheimers Dement (Amst). 2020 Apr 30;12(1):e12029.

5. Lin SY, Lin KJ, Lin PC, Huang CC, Chang CC, Lee YC, Hsiao IT, Yen TC, Huang WS, Yang BH, Wang PN*. Plasma amyloid assay as a pre-screening tool for amyloid positron emission tomography imaging in early stage Alzheimer's disease. Alzheimers Res Ther. 2019 Dec 27;11(1):11.

Mild Behavioral Impairment—Novel Prodromal Phenotype of Dementia

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Abstract

Dementia has become a public health priority in aging societies. The limited effects of current treatments for dementia are partly attributable to late diagnoses; therefore, methods for the early identification of dementia must be developed. In addition to cognitive impairment, patients with dementia often experience various neuropsychiatric symptoms before the diagnosis of dementia. A longitudinal study demonstrated that individuals with normal cognition who had neuropsychiatric symptoms exhibited more rapid cognitive decline compared with those without these symptoms. A population-based prospective cohort study reported that the symptoms of irritability, agitation, depression, anxiety, and apathy increased the risk of mild cognitive impairment (MCI) in individuals with normal cognition. Neuropsychiatric symptoms that are observed by clinicians, patients, or informants and persistently occur in middle-aged and older individuals without dementia are named as mild behavioral impairment (MBI), and these symptoms might indicate the prodrome of dementia.

It is a big issue for early detection of dementia. Besides mild cognitive impairment (MCI), diagnosis of mild behavioral impairment (MBI) has been developing recently. Aspects of MBI include decreased motivation, affective dysregulation, impulse dyscontrol, social inappropriateness, and abnormal perception or thought content. MBI-checklist (MBI-C) is developed for assessment of MBI. However, the prevalence and biological etiologies of MBI are still unclear. The learning objects of this talk are 1) to understand how to assess MBI using MBI-C in use in Taiwan, 2) to realize the association between MBI and MCI; 3) to learn the biological markers of MBI.

Selected recent publications:

1.

The Discovery of Novel Therapeutic Targets for Alzheimer's Disease

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Research Fellow

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Abstract

Alzheimer's disease (AD) is characterized by a chronic decline in cognitive functionand is pathologically typified by cerebral deposition of amyloid-β peptide (Aβ). Theproduction of Aβ is mediated by sequential proteolysis of amyloid precursor protein(APP) by β- and γ-secretases, which has been regarded as the amyloidogenic pathway of AD pathogenesis. An RNA interference-based screen has led us to identify an ErbB2-centered signaling network that preferentially govern the proteostasis of APP-C99, a direct substrate of γ-secretases. Down-regulation of ErbB2 by CL-387,785 decreases the levels ofC99 and secreted amyloid-β in cellular, zebrafish, and mouse modelsof AD, through the activation of autophagy. Oral administration of CL-387,785 for 3 wk significantly improves the cognitivefunctions of APP/PS1 transgenic mice, establishing ErbB2 as a novel therapeutic target for AD. A previous report documents the significant correlation between lipid metabolism and incipient AD by using microarray correlation analyses. Given that the level of phosphatidylinositol-4,5-bisphosphate [PI(4,5)P2] in the membrane has been implicated to modulateAβ production, we then investigate whether PIP5Ktype Iα (PIP5K1A) can affect Aβ production by modulating the PIP2 content of the membrane. Our data show that overexpression ofPIP5K1A results in significant enhancement of non-amyloidogenic APP processing, leading to a markeddecrease in secreted Aβ and a concomitant redistribution of APP from endosomal compartments to the cell surface. These results suggesting that PIP5K1A may bea valuable therapeutic target for AD through its effect on promoting non-amyloidogenic processing of APP.

Selected recent publications:

1. B.-J. Wang, G. M. Her, M.-K. Hu, Y.-W. Chen, Y.-T. Tung, P.-Y. Wu, W.-M. Hsu, H. Lee, L.-W. Jin, S.-P. L. Hwang, R. P.-Y. Chen, C.-J. Huang, and **Y.-F. Liao*.** (2017) ErbB2 regulates autophagic flux to modulate the proteostasis of APP-CTFs in Alzheimer's disease. *Proc. Natl. Acad. Sci. U.S.A., 114: E3129-E3138*.

2. P.-Y. Wu, P.-Y. Chuang, G.-D. Chang, Y.-Y. Chan, T.-C. Tsai, B.-J. Wang, K.-H. Lin, W.-M. Hsu*, **Y.-F. Liao***, and H. Lee*. (2019) Novel Endogenous Ligands of Aryl Hydrocarbon Receptor Mediate Neural Development and Differentiation of Neuroblastoma. *ACS Chem. Neurosci., 10: 4031-4042*.

3. P.-Y. Wu, I-S. Yu, Y.-C. Lin, Y.-T. Chang, C.-C. Chen, K.-H. Lin, T.-H. Tseng, M. Kargren, Y.-L. Tai, T.-L. Shen, Y.-L. Liu, B.-J. Wang, C.-H. Chang, W.-M. Chen, H.-F. Juan, S.-F. Huang, Y.-Y. Chan, **Y.-F. Liao***, W.-M. Hsu*, and H. Lee*. (2019) Activation of Aryl Hydrocarbon Receptor by Kynurenine Impairs Progression and Metastasis of Neuroblastoma. *Cancer Res., 79: 5550-5562*.

4. P.-F. Wu, N. Bhore, Y.-L. Lee, J.-Y. Chou, Y.-W. Chen, P.-Y. Wu, W.-M. Hsu, H. Lee, Y.-S. Huang, P.-J. Lu, **Y.-F. Liao***. (2020) Phosphatidylinositol-4-Phosphate 5-Kinase Type 1α Attenuates Aβ Production by Promoting Non-amyloidogenic Processing of Amyloid Precursor Protein. *FASEB J., 34: 12127-12146*.

5. N. Bhore, B.-J. Wang, P.-F. Wu, Y.-L. Lee, Y.-W. Chen, W.- M. Hsu, H. Lee, Y.-S. Huang, D.-I Yang, and **Y.-F. Liao***. (2021) Dual-specificity phosphatase 15 (DUSP15) modulates Notch signaling by enhancing the stability of Notch protein. *Mol. Neurobiol., 58: 2204-2214*.

Investigation of TDP-43 in Alzheimer's disease and the therapeutic development

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Abstract

TDP-43 is an RNA binding protein normally resided in the nucleus. Since 2006, TDP-43 inclusions are found in brain and/or spinal cord tissue of amyotrophic lateral sclerosis (ALS) and frontotemporal lobar dementia (FTLD) patients. The inclusions were also found in nearly 57% Alzheimer's disease (AD) patients who present faster disease progression and greater brain atrophy. In 2014, we found that recombinant full-length human TDP-43 forms toxic spherical oligomers and perturbs amyloid-β (Aβ) fibrillization. We generated TDP-43 oligomer-specific antibody, TDP-O, and identified the species in FTLD patients by immunostaining and immunoprecipitation. In this talk, I will first present our study to investigate the role of TDP-43 in AD. We identified the interaction of TDP-43 and Aβ and examined the effect of TDP-43 in Aβ fibrillization and in AD mouse models. We also showed that TDP-43 oligomers mostly colocalized with intraneuronal Aβ in the brain of AD patients. Together, we demonstrated that TDP-43 inhibits Aβ fibrillization through its Aβ interaction and exacerbates AD pathology3. In addition, I will discuss our latest results on the therapeutic and diagnostic potential of TDP-43 oligomer-specific monoclonal antibody for neurodegenerative diseases.

Selected recent publications:

1. Fang YS, Tsai KJ, Chang YJ, Kao P, Woods R, Kuo PH, Wu CC, Liao JY, Chou SC, Lin V, Jin LW, Yuan H, Cheng IH, Tu PH, and **Chen YR***."Full-Length TDP-43 Forms Toxic Amyloid Oligomers that are Present in Frontotemporal Lobar Dementia-TDP Patients." **Nature Communications,** 5:4824**(2014)**

2. Tu LH, Tseng NH, Tsai YR, Lin, Lo YW, Charng JL, Hsu HT, Chen YS, Chen RJ, WuYD, Chan YT, Chen CS, Fang JM*, and**Chen YR***.Rationally Designed Divalent Caffeic Amides Inhibit Amyloid-β Fibrillization, Induce Fibril Dissociation, and Ameliorate Cytotoxicity. **European Journal of Medicinal Chemistry**. 158: 393-404 **(2018)**

3. Lee MC, Yu WC, Shih YH, Chen CY, Guo ZH, Huang SJ, Chan JCC, and **Chen YR***. Zinc ion rapidly induces toxic, off-pathway amyloid-β oligomers distinct from amyloid-β derived diffusible ligands in Alzheimer's disease. **Scientific Reports** 8, Article number: 4772 **(2018)**

4. Shih YH§, Tu LH§, Chang TY, Ganesan K, Chang WW,Chang PS, Fang YS, Lin YT, Jin LW, and **Chen YR***.TDP-43 interacts with amyloid-β, inhibits fibrillization, and worsens pathology in a model of Alzheimer's disease. **Nature Communications**. 11: 5950 **(2020)**

5. Chiang WC§, Fang YS§, Lye YS, Wong TY, Ganesan K, Chou SC, **Chen YR***.Hyperphosphorylation-mimetic TDP-43 Drives Amyloid Formation and Possesses Neuronal Toxicity at the Oligomeric Stage. **ACS Chemical Neuroscience**. In revision. **(2022)**

IGF-1 as a Potential Therapy for Spinocerebellar Ataxia Type 3

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Abstract

Although the effects of growth hormone (GH) therapy on spinocerebellar ataxia type 3 (SCA3) have been examined in transgenic SCA3 mice, it still poses a nonnegligible risk of cancer when used for a long term. This study investigated the efficacy of IGF-1, a downstream mediator of GH, in vivo for SCA3 treatment. IGF-1 (50 mg/kg) or saline, once a week, was intraperitoneally injected to SCA3 84Q transgenic mice harboring a human ATXN3 gene with a pathogenic expanded 84 cytosine-adenine-guanine (CAG) repeat motif at 9 months of age. Compared with the control mice harboring a 15 CAG repeat motif, the SCA3 84Q mice treated with IGF-1 for 9 months exhibited the improvement only in locomotor function and minimized degeneration of the cerebellar cortex as indicated by the survival of more Purkinje cells with a more favorable mitochondrial function along with a decrease in oxidative stress caused by DNA damage. These findings could be attributable to the inhibition of mitochondrial fission, resulting in mitochondrial fusion, and decreased immunofluorescence staining in aggresome formation and ataxin-3 mutant protein levels, possibly through the enhancement of autophagy. The findings of this study show the therapeutic potential effect of IGF-1 injection for SCA3 to prevent the exacerbation of disease progress.

Selected recent publications:

1. Wu SL, Liu KH, Cheng WL, Su SL, Lin YS, Lin TS, Cheng YS, Chang JC, Wu YL, **Liu CS***. Growth hormone rescue cerebellar degeneration in SCA3 transgenic mice. Biochem Biophys Res Commun. 2020 Aug 20;529(2):467-473.

2. Lin YT, Lin YS, Cheng WL, Chang JC, Chao YC, **Liu CS***, Wei AC*. Transcriptomic and Metabolic Network Analysis of Metabolic Reprogramming and IGF-1 Modulation in SCA3 Transgenic Mice. Int J Mol Sci. 2021 Jul 26;22(15):7974. doi: 10.3390/ijms22157974. PMID: 34360740; PMCID: PMC8348158.

3. Chang JC, Chao YC, Chang HS, Wu YL, Chang HJ, Lin YS, Cheng WL, Lin TT, **Liu CS**. Intranasal delivery of mitochondria for treatment of Parkinson's Disease model rats lesioned with 6-hydroxydopamine. Sci Rep. 2021 May 19;11(1):10597. doi: 10.1038/ s41598-021- 90094-w. PMID: 34011937; PMCID: PMC8136477.

4. .Chang CC, Chen PS, Lin JR, Chen YA, **Liu CS**, Lin TT, Chang HH. Mitochondrial DNA copy number is associated with treatment response and cognitive function in euthymic bipolar patients receiving valproate. Int J Neuropsychopharmacol. 2022 Jan 3:pyab095.

5. .Lin YS, Cheng WL, Chang JC, Lin TT, Chao YC, **Liu CS***. IGF-1 as a Potential Therapy for Spinocerebellar Ataxia Type 3. Biomedicines 2022, 10(2), 505.

Two independent mechanisms that lower mutant ATXN3 expression

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Abstract

Spinocerebellar ataxia type 3 (SCA3), also known as Machado–Joseph disease, is an autosomal dominant neurological disorder caused by an expansion of CAG repeats in the coding sequence of ATXN3 gene. Synthesis together with accumulation of mutant ATXN3 is detrimental to neurons, and accumulated evidence have indicated that a delay or even prevention of SCA3 onset and progression in animals is achievable by lowering the mutated gene expression. In our recent studies, we found that cellular proteins SUPT4H and PIAS1 via two distinct molecular mechanisms to modulate the production of mutant ATXN3. Genetic knockdown of SUPT4H impairs RNA polymerase II transcription machinery elongating over DNA templates containing pathogenic-length of CAG repeats, including SCA3 mutant gene, whereas a decreased ATXN3 protein abundance by a change in its protein stability and post-translational modification is observed in PIAS1 deficient cells. More intriguingly, a PIAS1 genetic variant identified from clinical samples of SCA3 patients with late onset of disease, exhibits a biochemical characteristic that drives mutant but not wild-type normal ATXN3 protein turnover. SUPT4H and PIAS1 thus enable to modulate mutant ATXN3 at the transcriptional and post-transcriptional level respectively and by targeting these cellular proteins individually or in a combinational manner might serve as a practical approach for treatment of SCA3.

Selected recent publications:

1. CR Liu, CR Chang, Y Chern, TH Wang, WC Hsieh, WC Shen, CY Chang, IC Chu, N Deng, SN Cohen*, and **TH Cheng*** (2012). Spt4 is Selectively Required for Transcription of Extended Trinucleotide Repeats. *Cell* 148, 690-701.

2. HM Cheng, Y Chern, IH Chen, CR Liu, SH Li, S Chun, F Rigo,CF Bennett, N Deng, Y Feng, CS Lin, YT Yan*, SN Cohen*, and **TH Cheng*** (2015). Effects on Murine Behavior and Lifespan by Selectively Decreasing Expression of Mutant Huntingtin Allele by Supt4h knockdown. *PLoS Genetics*11, e1005043.

3. CR Liu and **TH Cheng*** (2015). Allele-selective Suppression of Mutant Genes in Polyglutamine Diseases. *Journal of neurogenetics* 29 (2-3): 41-49.

4. NJ Kramer, Y Carlomagno, YJ Zhang, S Almeida, CN Cook, TF Gendron, M Prudencio, MV Blitterswijk, V Belzil, J Couthouis, JW Paul III, LD Goodman, L Daughrity, J Chew, A Garrett, L Pregent, K Jansen-West, LJ Tabassian, R Rademakers, K Boylan, NR Graff-Radford, KA Josephs, JE Parisi, DS Knopman, RC Petersen, BF Boeve, N Deng, Y Feng, **TH Cheng**, DW Dickson, SN Cohen, NM Bonini, CD Link, FB Gao, L Petrucelli*,AD Gitler* (2016). Spt4 selectively regulates the expression of C9orf72 sense and antisense mutant transcripts. *Science* 353, 708-712.

5. YH Lee, YS Tsai, CC Chang, CC Ho, HM Shih, HM Chen, HL Lai, CW Lee, YC Lee, YC Liao, UC Yang*, **TH Cheng***, YJ Chern*, BW Soong* (2021). A PIAS1 protective variant S510G delays polyQ disease onset by modifying protein homeostasis. *Movement Disorders* (in press)

mRNA capping regulates cerebellar development and motor function

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Abstract

Eukaryotic mRNAs have 7-methylguanosine (m7GpppNN, N: any nucleotide) at the 5' end and poly(A) at the 3' end, both of which are important for mRNA stability and translation. In recent years, several chemical modifications in mRNA have been mapped to a transcriptome-wide scale. However, in contrast to epigenetic regulation, mechanisms underlying epitranscriptome-controlled gene expression remain largely unexplored.Therefore, we began to study molecular and physiological functions of cap methyltransferase 1 (CMTR1) and CMTR2, which catalyze 2'-O-ribose methylation (2'-O-Me) of the first (N1) and second (N2) nucleotides in mRNA, respectively. Addition of 2'-O-Me to the 5'-end nucleotides generates cap1 (m7GpppNmN) and cap2 (m7GpppNmNm) structures that have been identified for almost 50 years, but how cells recognize these chemical moieties to control gene expression for physiological functionsremains a mystery. Thus, we generated conditional knockout (cKO) of CMTR2 mice by crossing with *Nestin*-Cre mice whoseCreexpression begins at E10.5 in pan neuron progenitors. CMTR2-cKO mice showed impaired motor coordination and balance in rotarod and beam walking tests. Anatomical and electrophysiological analyses revealed abnormal axonal and dendritic structures and impaired synaptic transmission in CMTR2-deficient Purkinje cells. Which transcripts are N2 2'-O-Me by CMTR2 to support the development and function of Purkinje cells and whether such a modification is perturbed under pathological conditions are currently under investigation.

Selected recent publications:

1. Lu WH, Chao HW, Lin PY, Lin SH, Liu TH, **Huang YS** (2021) CPEB3-downregulated *Nr3c1* mRNA translation confers resilience to developing posttraumatic stress disorder-like behavior in fear-conditioned mice. *Neuropsychopharmacology* 46:1669-1679

2. Lee YL, Kung FC, Lin CH, **Huang YS** (2020) CMTR1-catalyzed 2'-O-ribose methylation controls neuronal development by regulating *Camk2α* expression independent of RIG-I signaling. *Cell Reports* 33:108269

3. Chen HF, Hsu CM, **Huang YS** (2018) CPEB2-dependent translation of long 3'-UTR Ucp1 mRNA promotes thermogenesis in brown adipose tissue. *EMBO Journal*37: e99071

4. Tseng CS, Chao HW, Huang HS, **Huang YS** (2017) Olfactory experience- and developmental stage-dependent control of CPEB4 regulates c-*Fos* mRNA translation for granule cell survival. *Cell Reports* 21: 2264-2276

5. Lu WH, Yeh NH, **Huang YS** (2017)CPEB2 activates GRASP1 mRNA translation and promotes AMPA receptor surface expression, long-term potentiation and memory. *Cell Reports* 21: 1783-1794

Activation of TrkB signaling reverses *Rbm4* knockout induced cerebellar malformation

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Abstract

A multifunctional splicing regulator, RBM4 is involved in neuronal differentiation of mouse P19 cells *in vitro* and radial migration of cortical progenitors *in utero* by altering splice isoform expression of critical signaling genes. To gain insights into the function of RBM4 during development, we recently generated conventional *Rbm4* double gene knockout (dKO) mice. *Rbm4*dKO showed rather normal cortical morphology but a foliation defect at cerebellar lobules VI and VII, which is clinically reminiscent of a group of individuals with autism spectrum disorder (ASD). These mice exhibited hyperactive exploratory behavior in the open-field test. The absence of RBM4delayed cell cycle exit of granule cell (GC) precursors and radial migration of postmitotic GCs in the developing cerebellum. The mutant mice also exhibited stunted dendritic arborization of Purkinje cells. These features are reminiscent of neurotrophin deficiency. Strikingly, *Rbm4* knockout reduced the level of brain-derived neurotrophic factor (BDNF)-TrkB signaling. Treatment of pregnant *Rbm4*dOK mice with a TrkB agonist restored cerebellar development and reversed hypoplasia of lobules VI-VII. We further demonstrated that RBM4 promotes BDNF expression. This study provides evidence that prenatal activation of the BDNF-TrkB signaling may ameliorate the defects of cerebellar development caused by *Rbm4* deficiency.

Selected recent publications:

1. Su CH, Hung KY, Hung SC,**Tarn, WY** (2017) RBM4 regulates neuronal differentiation of mesenchymal stem cells by modulating alternative splicing of pyruvate kinase M. *Mol. Cell. Biol*. 37: e00466-16

2. D D, Hung KY,**Tarn, WY** (2018) RBM4 modulates radial migration via alternative splicing of Dab1 during cortex development. *Mol. Cell. Biol*. 38: e00007-18

3. Chuang TW, Lu CC, Su CH, Wu PY,Easwvaran S, Lee CC, Kuo HC, Hung KY, Lee KM, Tsai CY,**Tarn WY** (2019) The RNA processing factor Y14 participates in DNA damage response and repair. *iScience*13: 402-415

4. Chen HH, Yu HI, Rudy R, Lim SL, Chen YF, Wu SH, Lin SC, Yang MH,**Tarn, WY** (2021) DDX3 modulates the tumor microenvironment via its role in endoplasmic reticulum-associated translation. *iScience* 24: 103086

5. Su CH, Liao WJ, Ke WC, Yang RB,**Tarn WY** (2021) The Y14-p53 regulatory circuit in megakaryocyte differentiation and thrombocytopenia. *iScience* 24: 103368