跨領域再生醫學研究：發展具前瞻性的神經再生治療策略

Develop therapeutic strategies for neural regeneration

Chiao CC[1]*, Chen LY[2], Lu SC[3], Lin YC[4], Chen H[3], Chang CR[5], and Chang YC[1]

[1]Institute of Systems Neuroscience, [2]Department of Medical Science, [3]Department of Electrical Engineering, [4]Institute of Molecular Medicine, [5]Institute of Biotechnology
E-mail: ccchiao@life.nthu.edu.tw

In this research project, 7 PIs from two colleges (Life Science and EE-CS) have worked together to develop novel and alternative therapeutic strategies for neural regeneration. We have demonstrated that these novel neural regeneration strategies can be used in clinical application of treating brain injury. Here, we briefly summarize our research findings.

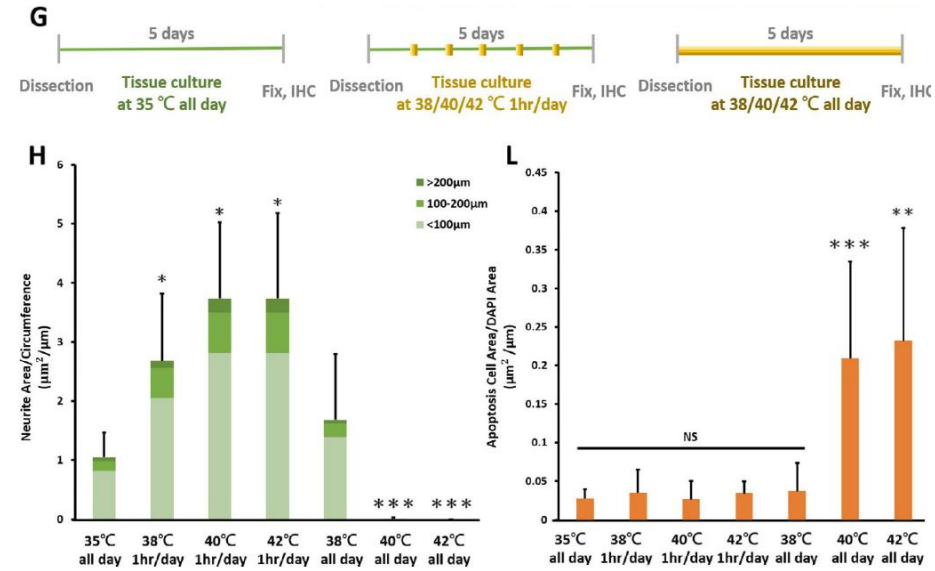
We found that RGC neurite outgrowth from P9-P11 mouse explants was significantly enhanced when the concentration of the culture medium was increased by 1.25 fold, but not when increased by 1.5 fold. Similarly, retinal explants from P9-P11 mice grew longer neurites when the overall temperature was increased from 35 °C to 38 °C, 40 °C or 42 °C for one hour each day. The present study thus provides insights into the cellular mechanism of retinal axon regeneration under the mild stress conditions.

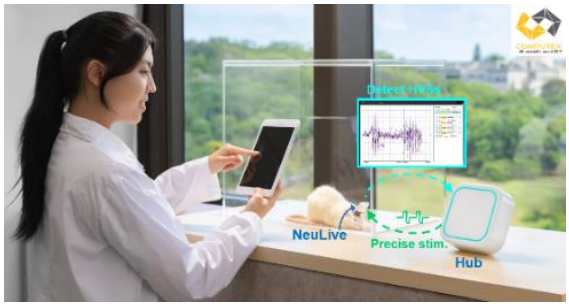
Intranasal administration of WNT3A protein to TBI mice increased number of $NeuN^+$ neurons without affecting $GFAP^+$ glial cells, compared to control mice, as well as retained motor function based on functional behavior analysis. A novel enhancer region for induced *WNT3A* transcription during regeneration of injured cortical neurons has been identified. Together, our findings report a novel mechanism for *WNT3A* gene transcription and reveal a potential therapeutic intervention for neuronal regeneration.

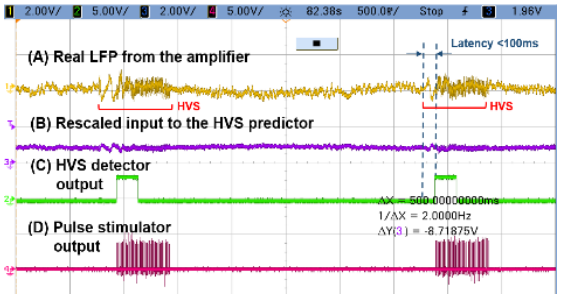
Inspired from the assumption that several parallel amino acid substitutions of Prestin may be involved in adaptive ultrasound hearing, we introduced two evolution-based mutants N7T and N308S into Prestin protein of non-echolocating mice. Heterogeneous expression of this construct has allowed mammalian cells to sense ultrasound stimulation, which evoked a calcium influx from the extracellular space into their cytosol under a low-frequency and low-pressure ultrasound condition

Our results elucidate how mitochondria were regulated by dynamic processes and coordinated with cytoskeleton. This information provided us not only how to maintain mitochondria integrity, but also influence mitochondria through cytoskeleton. This result provided information to develop tools to preserve and re-active mitochondria after transplantation. Furthermore, our work also contributed to elucidation the mechanism of how autophagy regulates cancer plasticity.

A wireless neuromodulator called NeuLive is developed for pharmaceutical studies with freely-moving small lab animals, such as rats and mice. The NeuLive system has been recognized by the COMPUTEX d&i with the Specialty Award 2019, in Taipei, Taiwan. The closed-loop function of the NeuLive is further employed to suppress the high-voltage-spindle episodes by STN-DBS (deep-brain-stimulation delivered at the subthalamic nucleus) in Parkinsonian rats.

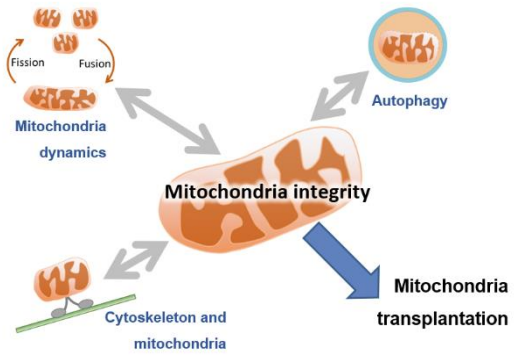


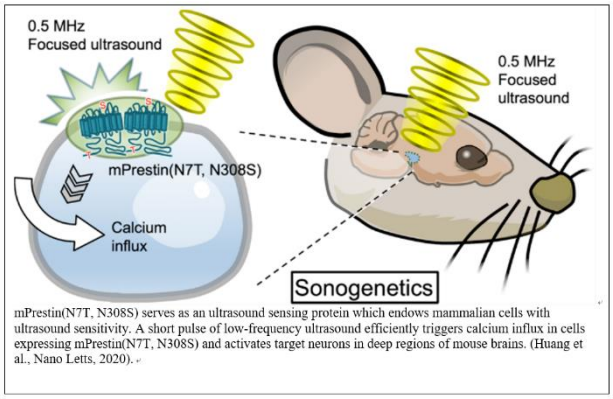




(a) (b)

(a) The NeuLive system (b)The snapshot showing two HVS episodes are detected and suppressed by STN-DBS with latency < 100ms.





mPrestin(N7T, N308S) serves as an ultrasound sensing protein which endows mammalian cells with ultrasound sensitivity. A short pulse of low-frequency ultrasound efficiently triggers calcium influx in cells expressing mPrestin(N7T, N308S) and activates target neurons in deep regions of mouse brains. (Huang et al., Nano Letts, 2020).

References

[1] Chen G.H. and Chiao C.-C. Mild stress culture conditions promote neurite outgrowth of retinal explants from postnatal mice. Brain Research 1747:147050 (2020).
[2] Chu-Yuan Chang, Jui-Hung Hung, Joye Li, Ka Shing Fung, Cheng-Fu Kao, Linyi Chen*. (2020) Epigenetic regulation of WNT3A enhancer during regeneration of injured cortical neurons. International Journal of Molecular Sciences, 21(5), 1891.
[3] Chu-Yuan Chang, Min-Zong Liang, Ching-Chih Wu, Pei-Yuan Huang, Hong-I Chen, Shaw-Fang Yet, Jin-Wu Tsai, Cheng-Fu Kao and Linyi Chen. (2020) WNT3A promotes neuronal regeneration upon traumatic brain injury. International Journal of Molecular Sciences, 21(4), 1463.
[4] Y. W. Chen and M. S.-C. Lu, "Highly sensitive DNA detection beyond the Debye screening length using CMOS field effect transistors,"IEEE Elec. Dev. Lett., vol. 42, no. 8, pp. 1220-1223, Aug. 2021.
[5] C. Lee, Y. W. Chen and M. S.-C. Lu, "CMOS biosensors for the detection of DNA hybridization in high ionic-strength solutions," IEEE Sensors Journal, vol. 21, no. 4, pp. 4135-4142, Feb. 2021.
[6] C. F. Chang and M. S.-C. Lu, "CMOS ion sensitive field effect transistors for highly sensitive detection of DNA hybridization, IEEE Sensors Journal, vol. 20, no. 16, pp. 8930-8937, Aug. 2020.
[7] Huang, Y. S.; Fan, C. H.; Hsu, N.; Chiu, N. H.; Wu, C. Y.; Chang, C. Y.; Wu, B. H.; Hong, S. R.; Chang, Y.C.; Yan-Tang Wu, A.; et al. Sonogenetic Modulation of Cellular Activities Using an Engineered Auditory-Sensing Protein. *Nano Lett.* **2020**, *20* (2), 1089–1100.
[8] Chen YC, Cheng TH, Lin WL, Chen CL, Yang WY, Blackstone C, Chang CR. (2019) Srv2 is a pro-fission factor that modulates yeast mitochondrial morphology and respiration by regulating actin assembly. iScience. 2019 Jan 25;11:305-317.
[9] R. Perumal†, V. Vigneron, C.F. Chuang, Y.C. Chang, S.R. Yeh, H. Chen, A Computationally-efficient, Online-learning Algorithm for Detecting High-voltage Spindles in the Parkinsonian Rats, *Annals of Biomedical Engineering, 48(12), 2809-2820*, 2020.