

Stimulating Corticospinal Tract Axon Regeneration

July 7

Tuesday, 12:30 pm

Live Webinar
via Zoom Conference



Speaker: Jian Zhong, Ph.D.
Lab Director
Molecular Regeneration and
Neuroimaging Laboratory
Burke Neurological Institute
Associate Professor of Neuroscience
Brain and Mind Research Institute
Weill Cornell Medicine
Co-Director
Center for Pain & Sensory Recovery
Burke Neurological Institute

For more information, please contact
Lindsey Echevarria
lechevarria@med.cornell.edu

Burke Neurological Institute
Academic Affiliate of Weill Cornell Medicine
785 Mamaroneck Avenue
White Plains, NY 10605
burke.weill.cornell.edu

Abstract

In our laboratory we study how limited numbers of genes orchestrate the axon growth program to build the neuronal network in the mammalian fetus, and then attempt to activate these same mechanisms to enable axon regeneration in the injured adult nervous system. Failure of axonal rewiring after spinal cord injury is the reason that its victims typically remain paralyzed for life. We have identified the RAF - MEK kinase pathway as a key signaling mediator in the program of axon growth. Activation of this pathway in genetically modified mice triggers the expression of multiple regeneration-associated genes and promotes robust regenerative corticospinal tract axon growth, both elongation and collateral sprouting. Newly extending corticospinal axons form synaptic connections with spinal interneurons, and we documented improved recovery of voluntary locomotion in murine models of spinal cord injury. Aiming to translate the finding into the clinic, we found that high-frequency repetitive transcranial magnetic stimulation (HF-rTMS), a non-invasive and clinically applicable technique, activated the kinases MEK1/2 in motor cortex. Post-injury HF-rTMS treatment triggered substantial CST axon regeneration and sprouting as well as sustained recovery of fine motor performance in wild type mice with spinal cord injuries. Moreover, its effects on regeneration and motor behaviors were fully abolished by conditional ablation of MEK1/2 in corticospinal neurons. Collectively, these data demonstrate a central role of neuron-intrinsic RAF - MEK signaling for the rebooting of intrinsic axon growth programs in adult CSNs. We are now teaming up with clinicians to examine the feasibility and efficacy of HF-rTMS as a treatment option for spinal cord injury patients.

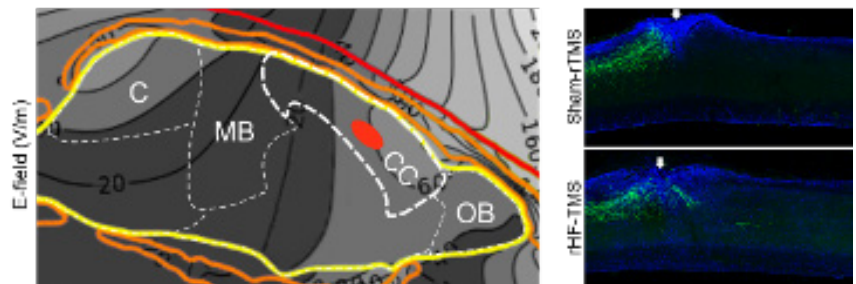


Fig. High Frequency transcranial magnetic stimulation facilitates CST axon regeneration in the spinal cord after injury (Manuscript submitted).

1. Boato Ft, Guan Xt, Nicola F, Zhu Y, Voutounou M, Freschlin F, Matho K, Sergey N, Makarov SN, Wu Z, Son Y-J, Z. Huang J, Nummenmaa A, Edwards DJ, Zhong J. HF-rTMS instruments MAPK kinase signaling for axon growth and enhances recovery of voluntary motor control after CST injury (Submitted).
2. Garg A, Hannan A, Wang Q, Makrides N, Zhong J, Li H, Yoon S, Mao Y, Zhang X. Etv transcription factors functionally diverge from their upstream FGF signaling in lens development. *Elife*. 2020 Feb 11;9. doi: 10.7554/eLife.51915. PubMed PMID: 32043969; PubMed Central PMCID: PMC7069720.
3. O'Donovan KJ, Ma K, Guo H, Wang C, Sun F, Han SB, Kim H, Wong J, Charron J, Zou H, Son Y-J, He Z, Zhong J (2014) B-RAF kinase drives developmental axon growth and promotes axon regeneration in the injured mature CNS. *J Exp Med* 211:801-14. PMID: 24733831 PMCID: PMC4010899.