Axonal stress granules: Novel target to improve axon regeneration post nerve injury

*Sahoo, P.K.[1], Lee, S.J.[1], Jaiswal, P.B.[2], Alber, S.[3], Kar, A.N.[1], Miller-Randolph, S.[6], Smith T.[1], Singh, B.[4], Ho, T.S.[4], Urisman, A.[7], Chand, S.[5], Burlingame, A.L.[8], Woolf, C.J.[9], Fainzilber, M.[10], English, A.W.[11], and Twiss, J.L.[12].

[1] Post-doctoral fellow, Department of Biological Sciences, University of South Carolina, Columbia, SC USA, [2] Post-doctoral fellow, Department of Cell Biology, Emory University College of Medicine, Atlanta, GA USA, [3] PhD Student, Department of Biomolecular Sciences, Weizmann Institute of Science, Rehovot, Israel, [4] Post-doctoral fellow, FM Kirby Neurobiology Center and Boston Children's Hospital and Harvard Medical School, Boston, MA, USA, [5]Post-doctoral fellow, Department of Pharmaceutical Chemistry, University of California San Francisco, San Francisco, CA USA, [6] Technical assistant, Department of Biological Sciences, University of South Carolina, Columbia, SC USA, [7] Assistant Professor, Department of Pharmaceutical Chemistry, University of California San Francisco, San Francisco, CA USA, [8] Professor, Department of Pharmaceutical Chemistry, University of California San Francisco, San Francisco, CA, USA, [9] Professor, FM Kirby Neurobiology Center and Boston Children's Hospital and Harvard Medical School, Boston, MA, USA, [10] Professor, Department of Biomolecular Sciences, Weizmann Institute of Science, Rehovot, Israel, [11] Professor, Department of Cell Biology, Emory University College of Medicine, Atlanta, GA USA, [12] Professor, Department of Biological Sciences, University of South Carolina, Columbia, SC USA

sahoop@mailbox.sc.edu

Keywords: Stress granule, protein aggregation, translational control, axon injury, axon regeneration

Abstract: Critical functions of intra-axonally synthesized proteins are thought to depend on regulated recruitment of mRNA from storage depots in axons. Here we show that axotomy induces translation of stored axonal mRNAs via regulation of the stress granule protein G3BP1, to support regeneration of peripheral nerves. G3BP1 aggregates in axons of peripheral nerves in stress granule-like structures that decrease during regeneration, with a commensurate increase in phosphorylated G3BP1. Colocalization of G3BP1 with axonal mRNAs is also correlated with the growth state of the neuron. Disrupting G3BP functions by overexpressing a dominant-negative protein activates intra-axonal mRNA translation, increases axon growth in cultured neurons, disassembles axonal stress granule-like structures, and accelerates nerve regeneration *in vivo*.