Bio-Magnetogenetic Control of Spatially Restricted Intracellular Protein-Activity During Rodent Embryonic Neuronal Development And in Neurodevelopmental Pathologies

ABSTRACT

All cellular events controlling cell morphogenesis or physiological functions, in all cells, all organisms, are determined by localized and timed activity of specific intracellular proteins. Furthermore, fundamental events in mammalian embryonic brain development, including axon development during neuronal polarization, are regulated by localized intracellular protein-activity and subsequent downstream signaling. The causative role of an intracellular-protein in a cellular process or the ability to control that process can only be achieved by subcellular localization/confinement of the protein's activity, especially if prolonged protein-activity in localized subcellular compartments is needed. Spatio-temporal control of intracellular protein-activity will allow directed regulation of neuronal/brain development and repair of neurodevelopmental pathologies resulting from break-down of polarity, intellectual/motor disabilities, psychiatric disorders, and autism. We develop a robust Bio-Magnetogenetic approach for localization of intracellular proteins' activity in neuronal subcellular compartments, using functionalized magnetic nanoparticles (fMNPs) chemo-genetically modified to carry target proteins into the neuronal cytoplasm, wherein protein-functionalized-fMNPs are mobilized and localized to desired subcellular compartments using a localized magnetic force. fMNPs assemble localized signaling nanoplatform downstream of the target protein, retained in these locations as-long-as the magnetic force is applied. We use magnetogenetics to control a fundamental process of axon formation in developing neurons *in vitro* and in the live rodent embryonic brain. We further repair axon formation in a mouse model for a human neurodevelopmental pathology, and in models of Parkinson's disease. *Study's appropriateness for Biomedical Innovation Fund for Interdisciplinary Research* is high, as Magnetogenetics can be used to: 1) trigger protein-signaling to locally control basic events in embryonic neuronal morphogenesis/structural plasticity, 2) repair protein-activity in central/peripheral neuropathologies, and 3) be broadly applied to many intracellular proteins and cell-types, with broad application in cell- and neuro-biology. This *highly multi-disciplinary proposal* incorporates expertise in magnetogenetics, developmental-neurobiology, molecular-genetics, material-nanoengineering, particle-nanofabrication, and magneto-electronics, as exemplified by the expertise of our team.