Seminar Announcement

The following two special seminars related to "**Focused Ultrasound Applications**" will be held on Aug. 1st.

Date: August 1st (Wed), 2018, 15:00-16:30
Place: Academic Hall, 1st floor, Molecular & Life Innovation Bldg., Hongo Campus, The University of Tokyo
（東京大学本郷キャンパス，分子ライフイノベーション棟１階 アカデミックホール）

Seminar 1: 15:00-15:45

Focused ultrasound applications for Alzheimer's disease: From preclinical research to clinical trials

Dr. Isabelle Aubert, Senior Scientist, Sunnybrook Research Institute
Professor, Department of Laboratory Medicine and Pathobiology, University of Toronto

Clinical trials for disorders such as essential tremors and Alzheimer's disease (AD), are ongoing using transcranial MRI-guided focused ultrasound (MRIgFUS) at thermal and non-thermal modalities, respectively. Non-thermal MRIgFUS is achieved in presence of intravenously injected microbubbles and can be used for the delivery of therapeutics from the blood to targeted areas of the brain by increasing the permeability of the blood-brain barrier (BBB) locally and transiently. In addition to modulating the BBB, we have previously shown that MRIgFUS without therapeutic stimulates glial plasticity, reduces plaque load, promotes hippocampal neurogenesis and improved cognitive functions.

This seminar will introduce MRIgFUS applications for neurological disorders, provide up-to-date evidence of the impact of MRIgFUS on neuronal and glial plasticity in the brain, without intravenous therapeutics, and discuss the efficacy of clinically approved antibodies and preclinical therapeutics delivered to the brain using MRIgFUS in a mouse model of AD. It will conclude on challenges and opportunities encountered in the development of MRIgFUS applications from preclinical studies to AD clinical trials.

Seminar 2: 15:45-16:30

Focused ultrasound-mediated gene therapy for synucleinopathies

Dr. Anurag Tandon, Associate Professor, Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto.

Aggregated and misfolded alpha-synuclein (asyn) accumulates progressively in Parkinson's disease, multiple system atrophy, and dementia with Lewy bodies, collectively known as synucleinopathies. The spreading pathology in these disorders appears to involve a prion-like mechanism, whereby asyn assemblies are conveyed between brain regions and amplified by the recruitment of normal asyn in otherwise healthy cells. The underlying intercellular exchange implies at least three critical events: asyn membrane binding and internalization by recipient cells, interaction with intracellular α-syn, and eventual secretion or transport into adjacent cells.

We analyzed these steps in single and co-culture cell-based assays designed to recapitulate the uptake and transmission of misfolded asyn across cellular membranes. Intermixing of exogenous and endogenous asyn is detectable in fluorescent cell assays, and our results suggest that internalized asyn interacts with endogenous asyn by two pathways, including rupture of endocytic vesicles by asyn fibrils and by the fusion of late endosomes with autophagosomes. In addition, murine synucleinopathy models induced by asyn fibril seeding provide useful preclinical platforms to test therapeutics. We will present proof-of-concept that viral-mediated asyn gene suppression can prevent the progressive asyn pathology and that non-invasive brain delivery of systemic AAV-asyn-shRNA vectors can be achieved using MRI-guided focused ultrasound (MRIgFUS) and microbubbles. This work demonstrates that MRIgFUS can effectively deliver anti-asyn shRNA vectors directly into multiple brain areas that are particularly susceptible to Lewy pathology, and this approach may be effective for the clinical treatment of synucleinopathies.

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