Symposium 19: Neural organoids for studying human development and diseases (Sat July 31, 1400-1600 JST)
Chairs: Woong Sun (Korea University, Seoul) and Hyunsoo Shawn Je (Duke-NUS, Singapore)

14:00-14:30 Hyunsoo Shawn Je (Duke-National University of Singapore Medical School Singapore)
Modeling Neural Disorders Using Human Pluripotent Stem Cells

14:30-15:00 Jinsoo Seo (Daegu Gyeongbuk Institute of Science & Technology, Korea)
Modeling Alzheimer's disease with human iPSC-derived cerebral organoids

15:00-15:30 Yoshiho Ikeuchi (Institute of Industrial Science, The Univ of Tokyo, Japan)
An Organoid-on-a-chip Approach for Modeling Macroscopic Neural Circuits in vitro

15:30-16:00 Kinichi Nakashima (Grad Sch Med Sci, Kyushu University, Japan)
MeCP2 controls neural stem cell fate specification through microRNA-mediated inhibition of BMP-Smad signaling

Symposium 19 Speaker 1

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Modeling Neural Disorders Using Human Pluripotent Stem Cells

The ability to make functional neural cells from human pluripotent stem cells (hPSCs) provides a unique opportunity to study human brain development and neural disorders. In this seminar, I will present recent findings from our laboratory -1) the direct induction and functional maturation of human forebrain glutamatergic and GABAergic neurons derived from hPSCs, 2) the generation of human midbrain-like organoids from hPSCs, and 3) their utilities in modeling human brain disorders.

Symposium 19 Speaker 2

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Modeling Alzheimer's disease with human iPSC-derived cerebral organoids

Tremendous efforts have been made to cure Alzheimer's disease (AD) over 100 years since the disease was first identified. However, we still lack a clear understanding of earlier pathological features for the disease and their underlying mechanisms. Previously, we showed that human induced pluripotent stem cells (iPSCs)-derived cerebral organoids carrying either familial AD-causing mutations or *APOE4* isoform nicely recapitulate some of AD-related phenotypes such as extracellular amyloid-beta accumulation and hyperphosphorylation of tau. We found that this model system displays early neuronal differentiation that leads to increased neuronal activity, which also was recently reported with mouse models for AD. Using iPSCs-derived neural progenitor cells, we further revealed that altered reactive oxygen species (ROS) levels and metabolic reprogramming are associated with early neuronal differentiation/maturation by AD-causing genetic factors. In addition, we utilized multi-electrode array to determine alterations of neuronal firing and network activity in AD cerebral organoids compared to control. These approaches provide us a human in vitro model system for prodromal AD to investigate the pathogenesis of disease thus to intervene related signaling pathways before the disease onset.

Symposium 19 Speaker 3:

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An Organoid-on-a-chip Approach for Modeling Macroscopic Neural Circuits in vitro

Macroscopic axonal connections in the human brain distribute information and neuronal activity across the brain. Although this complexity previously hindered elucidation of functional connectivity mechanisms, brain organoid technologies have recently provided novel avenues to investigate human brain function by constructing small segments of the brain in vitro. I will introduce our "organoid-on-a-chip" approach to model macroscopic circuits in the brain by applying microfluidic technologies. By providing physical guidance by our custom-made culture chip, we direct axons grown from organoids to self-assemble into bundle tissue. This approach can be applied to model motor nerves which are unidirectionally aligned axons from spinal cord to skeletal muscle. Also, two organoids can extend axons to each other and connect reciprocally. We have demonstrated this approach can structurally mimic cortical connections through cerebral tracts. Mutations in L1CAM cause agenesis of corpus callosum (ACC). To model the developmental defect of cerebral tract formation including ACC, we knocked down L1CAM gene in cells in our model tissue. Axons from the L1CAM knockdown cells exhibited significantly lower ratio of axons assembled into a bundle than the control cells, demonstrating that the axon fascicle formation process in our tissue is relevant to cerebral tract formation *in vivo* and that the tissue can be used to model developmental disease related to cerebral tract. Interestingly, the connected organoids produced significantly more intense and complex oscillatory activity than conventional organoids. I will discuss potential of the connected organoids and the organoid-on-a-chip further.

Symposium 19 Speaker 4:
Kinichi Nakashima
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MeCP2 controls neural stem cell fate specification through microRNA-mediated inhibition of BMP-Smad signaling

Rett syndrome (RTT) is a severe neurological disorder with impaired brain development caused by mutations in MECP2, yet the underlying mechanism remains elusive. We have previously discovered that MeCP2 facilitates processing of a specific microRNA, miR-199a, by associating with Drosha complex to regulate neuronal functions. Here, we show that the MeCP2/miR-199a axis regulates neural stem/precursor cell (NS/PC) differentiation. We found a shift from neuronal to astrocytic differentiation of MeCP2- and miR-199a-deficient NS/PCs due to the upregulation of a miR-199a target, Smad1, a downstream transcription factor of bone morphogenetic protein (BMP) signaling. Moreover, miR-199a expression and treatment with BMP inhibitors rectified differentiation of RTT patient-derived NS/PCs and development of brain organoids, respectively, suggesting that facilitation of BMP signaling accounts for the impaired RTT brain development. Our study provides new insights into the molecular pathology of RTT and reveals the MeCP2/miR-199a/Smad1 axis as a potential therapeutic target for RTT.