Brain Tissue-on-a-chip platform to spatiotemporally regulate the cell-to-organ level communication

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The brain organoid, a three-dimensional (3D) and self-organised structure, derived from human pluripotent stem cells (hPSCs) enables recapitulation of the genetic information, cellular composition, functionality, physiological and pathological insight of the human brain[1]. These organ-scaled human models exploded in their use in recent years due to their ability to better recapitulate the human brain in vivo in respect to organization, differentiation, and polarity reminiscing the human brain and prove superior over traditional 2-dimensional (2D) monolayer cells and animal model[2]. To reflect the complexity of the human central nervous system, organoid generation methodologies have ever increased. One of the attempts is to physically assemble two or three different regions of organoid to be integrated into one organoid called as 'assembloid'. However, this physical assembly protocol lacks observation of cell-to-cell level communication[3]. For instance, cell migration or molecule secretion from one cell to another cell, and axonal connections between physically departed brain regions couldn't be modeled. In this study, we developed a novel organoid-on-a-chip platform to spatiotemporally regulate axonal migration, connection, and crosstalk between each organoid. We grew individual brain organoids in novel organ-on-chip platform and guided axonal conjugation to form functional nerve bundles. Further applying genetic engineering, we temporally regulated the expression of TDP-43 protein which is considered a key regulator in neurodegenerative disease including amyotrophic lateral sclerosis and frontotemporal dementia. Our organoid-on-a-chip platform not only enabled the investigation of neuronal crosstalk between distant brain organoids which modelling the interconnection of separate regions in the human brain but also to examine cell-to-cell spreading of protein-of-interest which further impacts tissue scale pathology (Fig 1).

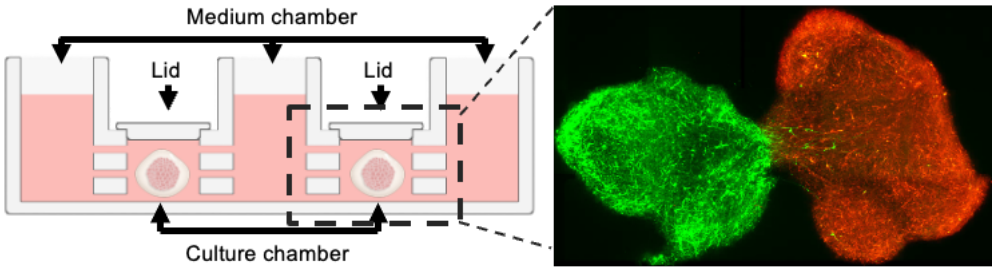

Figure 1: Oraganoid-on-chip model for brain tissue communication and disease modelling.

References:
[1] Cho AN, et al. *Nat Commun*. 2021 Aug 5;12(1):4730.
[2] Cho AN, et al. *Cells*. 2022 Oct 11;11(20):3194. doi: 10.3390/cells11203194.
[3] Martínez-Mármol R, .. Cho AN, et.al. *Sci Adv.* 2023 Jun 9;9(23):eadg2248.