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Cellular modeling of trisomy 21 as an approach to understand Alzheimer's disease

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Down Syndrome (DS) is the most common genetic cause of intellectual disability and is associated with an increased risk of Alzheimer's disease (AD). The LonDownS consortium aims to draw correlations between dementia, cognitive defects, mouse models and genetics with *in vitro* defects in neurons derived from DS induced pluripotent stem cells (iPSCs). For iPSCs, our strategies are: (1) Isogenic iPSC DS models, (2) iPSCs from dupAPP and (3) iPSCs generated from adults and infants, at extremes of the DS spectrum for intensity of pathology. For (1); we developed an integration-free isogenic DS iPSC model by using fibroblasts of an adult with constitutional mosaicism for DS that reproduce several cellular pathologies, including increased β-amyloid, mitochondrial abnormalities and an increase in DNA double strand breaks indicating accelerated ageing. 3D cerebral organoids differentiated from isogenic iPSCs were found to recapitulate aspects of human brain structure and layering. As for (2); iPSCs have been generated from one dupAPP patient and for (3); to maximize consent, hair follicles and/or blood samples are collected from participants clinically stratified for cognitive ability and dementia. So far, >400 DS adults have been recruited with >120 keratinocyte lines isolated with 14 adults considered as extremes. iPSC lines have been established from 8 extremes, 4 with early onset dementia and 4 with late/no diagnosis of dementia. We have also reproduced some of the cellular phenotypes on primary human fetal neurospheres of T21 and gestational age matched normal controls, sampled in the Singaporean population.

Biography

Dean Nizetic has become one of the leading researchers and opinion-makers in molecular research into Down Syndrome (DS), in particular its relation to stem cell pathology, ageing and cancer. He has recently generated isogenic induced Pluripotent Stem Cells (iPSC) by re-programming the skin fibroblasts from an adult individual with mosaic DS and then cloning separately the genetically identical T21 and euploid (D21) iPSC lines. He is currently leading the Ipsc-cellular modeling stream within the LonDownS consortium. From February 2014, he is a Professor of Molecular Medicine at Lee Kong Chian School of Medicine, Singapore.

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