Abstract

Background:
Neurodegenerative disorders (NDDs) are currently a health crisis around the world. By the ageing of the population, the incidence rates of these diseases increases and the current treatments can only alleviate symptoms. Among NDDs, Alzheimer's disease (AD) is the most common cause of dementia worldwide and the disease progression always results in patient's death. Despite years of the research on its treatment, no progress has been made. Making a drug with an efficient and early curative response demands a deeper understanding the pathophysiology of the earliest stages of the disease. Studies have shown that the changes that result in symptoms of AD start 20-30 years earlier.
Along with the extensive development of medicine, researchers have worked on the potential of the use of stem cells, both indirectly in the modelling of the disease and directly by cell therapy. Several studies has shown promissing treatment potential of stem cells derived from the permanent teeth pulp of children in NDDs, based on the ability of such cells to prevent cellular death. For instance, Stem Cells from Human Exfoliated Deciduous teeth (SHED), isolated from human milk teeth can differentiate into fully functional cells, including various types of neurons and has been suggested as a suitable therapeutic method for NDDs. Accordingly, in this study, we study the effects of SHED treatment against AD-related changes, emphasising the earliest stages of the disease and precicing treamtment conditions, e.g. how many cells are required?
Methodology:
For this purpose, we will test neuroregenerative, migratory, and other pro-neuro-functional properties of SHED using neurons 2D cultures or cerebral organoids 3D model differentiated from induced pluripotent stem cells (iPSCs) derived upon reprogramming from various AD patients. For comparing the effect of interventions, we included 6 groups in this study: one control group (iPSC-derived neurons/brain organoids from healthy whole-plan-match donors), one saline sham group (control group [1] + Aβ solvent, saline), one control group with amyloid-β (Aβ, a marker of AD development), endogenous Aβ group (iPSC-derived neurons/brain organoids from (pre-)symptomatic FAD, early-symptomatic mild SAD, and prodromal MCI cases), and two experimental groups with SHED: experimental group I (control group one + Aβ + SHED), and experimental group II (endogenous Aβ group +SHED).
Expected outcomes
This study will be in line with the Sustainable Development Goals, adopted by United Nations, to create good health and well-being in patients with AD and can provide an in-deep understanding of the mechanisms of action of SHED in the treatment of AD, which opens the door to a novel therapeutic methods for AD. We propose that could be related to anti-oxidant, calcium-blocking, and anti-apoptotic neuronal response. The task will be fulfilled using cerebral organoids / neuronal model, derived from AD patients, based on induced pluripotent stem cells (iPSC) reprogramming. In detail, we aim to answer the following questions:

1. Does the use of stem cells change the rate of cell survival?
2. Can stem cells be effective in regulating the level of free radicals?
3. Is the use of stem cells effective in regulating intracellular calcium levels?
4. Does the use of stem cells affect tau protein hyperphosphorylation?
5. Does the use of stem cells affect the mitochondrial membrane potential?
6. Does the use of stem cells change the electrophysiological recording of synapses?

Future perspectives:
This study can also lay the foundation for **future** interdisciplinary research joining 1) tissue engineering (design of the biological scaffolds for therapeutic use of SHED stem cells), 2) the use of nanoparticles to carry medicine or stem cells, and 3) advances inanatomical science, i.e. providing details on sites of injections of stem cells (by stereotaxic surgery in the animal models).