Final Report

Project acronym: nanoPD

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2. Publishable project summary

The neurodegenerative disorder Parkinson's disease (PD) is caused by a degeneration of dopaminergic neurons in one particular region of the human brain, the substantia nigra in the midbrain. The development of drugs for treatment of PD is largely hampered by inability of compounds to cross the blood-brain-barrier (BBB) which separate the brain from the vascular system. In the nanoPD project we have modelled the BBB *in vitro* in multi-compartment microfluidic chips containing human midbrain organoids for development of new theranostics. The midbrain organoids were derived from PD patient specific stem cells (iPSC) and showed the major phenotypes associated with neurodegeneration in PD. BBB-penetrating nanodrug delivery systems (NDDSs) were synthesized based on a BBB-penetrating peptide conjugated with cyclodextrins (CD) as novel NDDSs. the NDDSs could successfully deliver fluorescently labelled therapeutic molecules across the BBB into midbrain organoids. In addition, we have proved on two *in vivo* models that the NDDSs can reach the brain. The presence of fluorescent signal in neuron cells C. elegans was detected, suggesting the effective neuronal cell entry of the NDDSs. In a PD animal model induced by MPTP the NDDSs injected in the blood exhibited the ability of penetrating BBB *in vivo*. The consortium will continue to work on evaluating the rescue of phenotypes by the NDDSs. Molecularly imprinted polymer (MIP)-based electrochemical sensors were designed for detecting α-synuclein (a marker for PD) using a peptide epitope from the protein. Cell culture medium from PD patient specific midbrain organoids generated from induced pluripotent stem cells was analyzed. α-Synuclein levels were found to be significantly reduced in the organoids from PD patients, compared to those generated from age-matched controls. Microfluidic devices integrated with optical and electrical sensors were developed to assess PD-specific phenotypes using immunofluorescence and multi-sensor arrays to monitor the health of the midbrain organoids. The oxygen sensors revealed midbain organoids from PD patients' cells had an abnormal oxygen consumption compared to healthy organoids. Moreover, the electrodes to detect dopamine could show that PD organoids released less neurotransmitter dopamine compared to the healthy organoids. Several prototypes for integrated organs-on-a-chip microfluidic devices have been designed and fabricated by using 3D printing techniques, as well as PDMS-based methods. We could successfully develop a chip device to determine the surface charge of the BBB model by measuring streaming potential, demonstrated the increased BBB properties of the human stem cell-based model and integrated the human BBB model with PD or healthy organoids in one microfluidic and microelectronic device. The consortium will continue to work on testing the NDDSs' therapeutic effect on PD organoids in the integrated model in the chip device. The successful establishment of the technologies described above have resulted in an increase of at least one TRL.