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Development of a 3D *in vitro* model mimicking the changes occurring at the blood-brain barrier in Alzheimer's disease

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A striking challenge in diagnosis and therapy of neurodegenerative diseases is the design of drugs able to cross the blood-brain barrier (BBB). *In vitro* BBB models are available, but they mimic only healthy conditions without taking into account the BBB alterations identified in neurodegenerative diseases, such as Alzheimer's disease (AD). Therefore, NAB₃ Project (funded by H2020 ERA-NET Co-fund JPND Programme) aims to develop and fully characterize a complex *in vitro* model of the AD-like BBB by combining different modified cellular models with both neuronal and organotypic brain slice cultures. NAB₃ aims at both (i) manipulating/engineering the BBB in order to mimic the disease state as well as (ii) modulating 'brain'-side towards a disease-like state in order to analyze its influence on the integrity of the BBB. NAB₃ plans a three steps approach: 1) starting from present knowledge of the BBB alterations, these changes will be reproduced by drug-mediated manipulation (e.g. up- or down-regulation of metabolic pathways) and/or genetically engineering (e.g. over-expression of candidate genes or gene-silencing by RNA interference). 2) The project will further increase the knowledge on the disease-related changes occurring at the BBB by performing a transcriptomic and proteomic analysis on brain capillaries isolated from normal and Braak-staged brains. 3) The 'brain'-side will be manipulated/engineered (e.g. increasing b-amyloid production or using organotypic brain slices) in order to analyze the influence of the emerging pathology on the integrity of the BBB. The designed AD-like BBB model may allow to better design diagnostic and therapeutic tools in the pre-clinical phase.