NAM-HLG Innovation-Summit 2021

	Instructions/Description
Title	**Development of a novel Alzheimer's disease treatment method by a unique brain protein-derived peptide with an advanced transdermal absorption device**
PI and co-PI(s)	**Yasuomi Ouchi, M.D., Ph.D. : Hamamatsu University School of Medicine, Department of Biofunctional Imaging** **Toshiharu Suzuki, Ph.D. : Hokkaido University, Graduate School of Pharmaceutical Sciences** **Hiroyasu Akatsu, M.D., Ph.D. : Nagoya City University, Department of Community-based Medical Education**
Background	**In Alzheimer's disease (AD), no satisfactory therapeutic drug is yet available in clinical practice. Our previous study showed that transcutaneous administration of p3-Alcβ9-19 improved AβOligomer-induced cognitive impairment in vivo and reduced the neurotoxicity in vitro using rodents. The peptide p3-Alcβ9-19 could survive Aβ-related neuronal death by activating mitochondrial activity to reduce apoptotic signals (Fig.1). The p3-Alcβ9-19 is totally an endogenous protein originated from amyloid protein precursor (APP) protein in the brain, no adverse effect is expected when administered. These pieces of evidence enable us to acquire pieces of not only non-clinical proofs of concept (POC) but clinical POC about this peptide drug.**
Innovative Idea/Project	
Overview	**We hypothesize that the trajectories of parameters and cognitive indices after the drug treatment are favorable in the course of dementia (Fig.2).**
Innovation	**To do this, the transdermal drug formulation has been evaluated in collaboration with a device company, and in vivo imaging studies of the drug effect on mitochondrial activity has been performed, and in near future, a clinical trial using this peptide drug will be planned after examining the drug toxicity and safety with animals. This epoch-making development of a therapeutic drug for AD is totally different from the strategy of the current immunological anti-Aβ disease-modifying drugs.**
Impact	**The drug effect of mitochondrial activation and neuronal revitalization is beneficial not only to AD patients but also individuals with cognitive decline. Unlike vaccination, the medical cost is much smaller.**
Scope	**Regarding a market size, the sales of donepezil for around 2 million patients were 138.2 billion yen (2011, Eisai report) in Japan. Because action mechanism is different from donepezil and the NMDA receptor antagonist (memantine), there is no competition for our drug. Hence, a market size is expected to be the same level as sales of the existing medicines (about 100 billion yen).**
Project Updates & Status	**After selecting the best drug formulation, the pharmacokinetics tests were completed in animals.** **With the advice of PMDA, we finished safety tests under repetitive drug administration in monkeys.** **We found remarkable changes in PET parameters for mitochondrial activation in the living AD model mice and monkeys after treatment of the drug given subcutaneously. An example of PET images for mitochondrial activity in a monkey is shown in Fig.3.**
Potential Challenges	**Further improvement of the application device (Fig.4) with which the drug is treated and further elucidation of additional mechanisms of the drug on neuronal revitalization are yet to come.**
Next Steps & Future Directions	**Because the preclinical POC of the drug is sure to be obtained and the cohorts of patients have been organized by our collaborator, a clinical study is scheduled in the next step (Fig.5).**

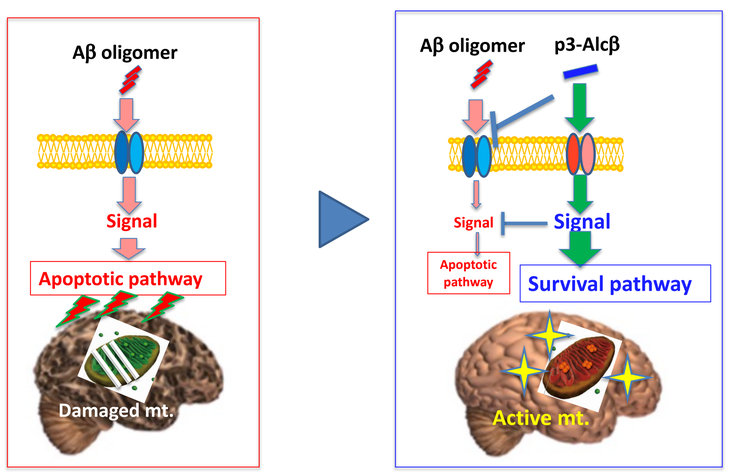


Fig.1: Mechanism of p3-Alcβ action

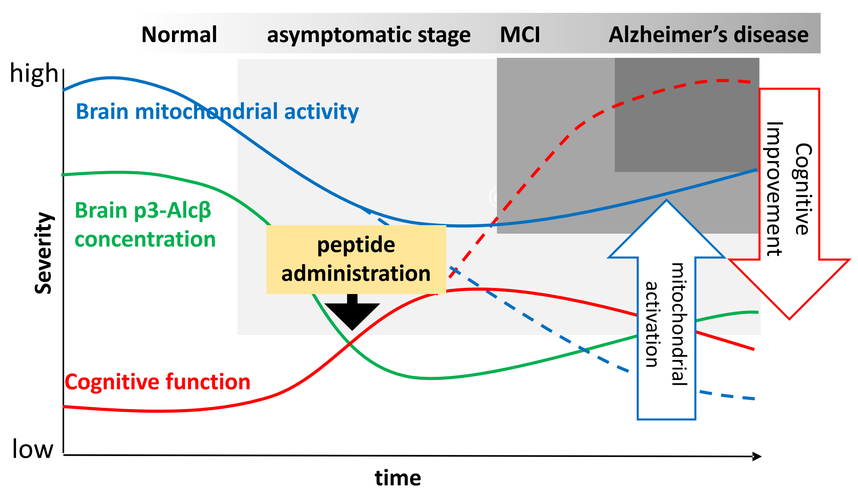
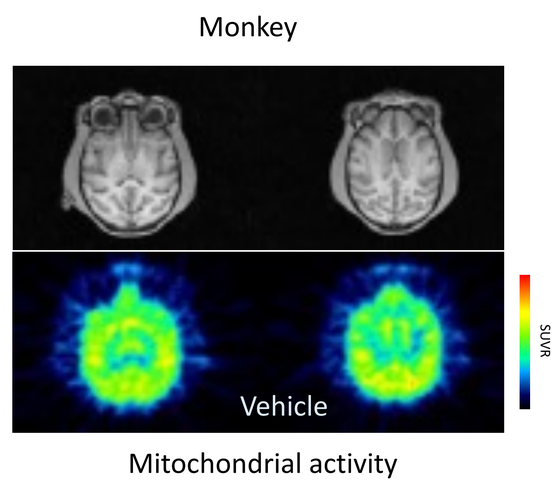


Fig.2: Trajectories of parameters after peptide treatment



Mitochondrial activity

Fig.3: PET data with [18F]BCPP-EF

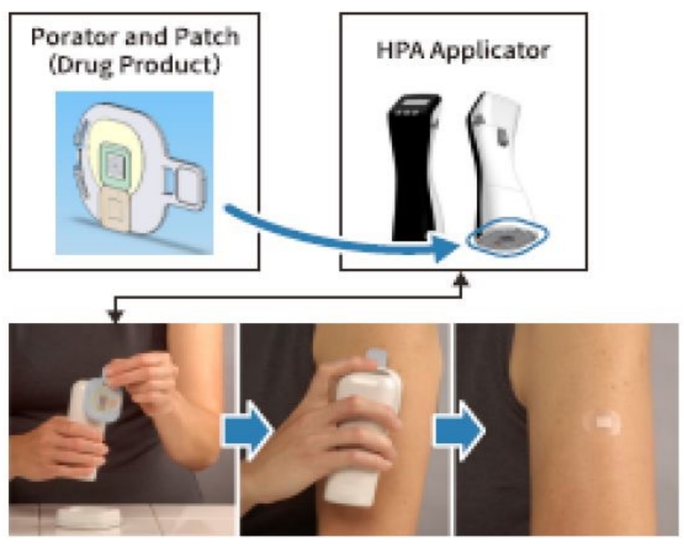
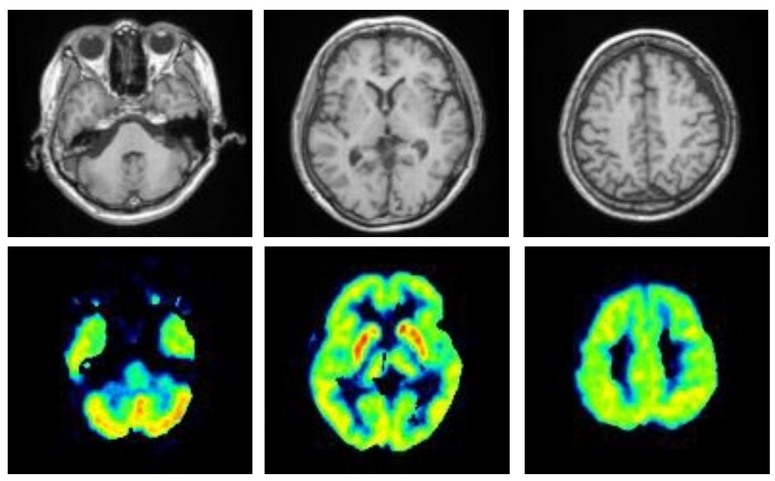


Fig.4: PassPort® transdermal drug delivery system (PassPort Technologies, Inc., USA)

Next step

Human study



+ Cognitive evaluations

Mitochondrial activity in a healthy subject

Fig.5: PET data of [18F]BCPP-EF binding