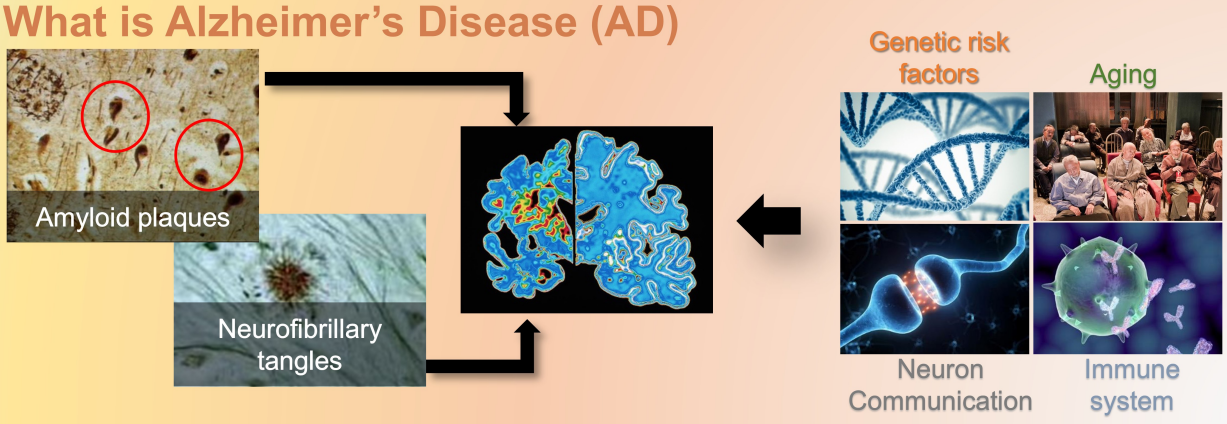
TRS THEME-BASED RESEARCH SCHEME
PUBLIC SYMPOSIUM 2024
主題研究計劃研討會

A Stem Cell Approach to Dissect the Molecular Basis of Neurodegenerative Diseases

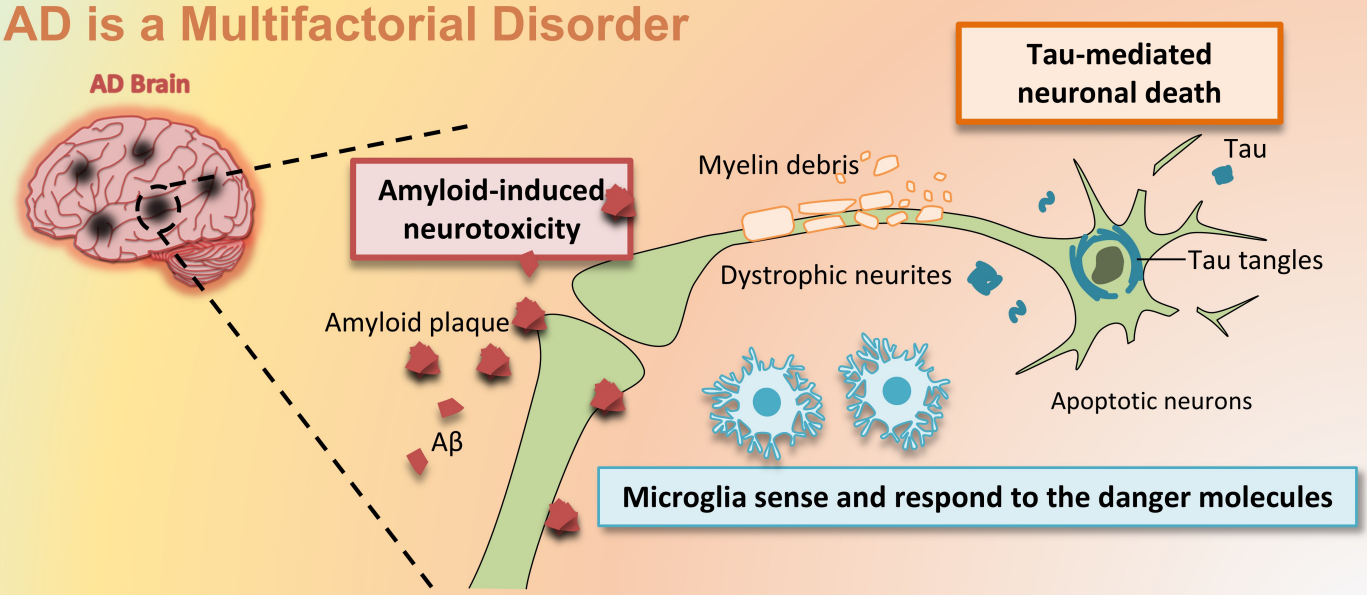
Overview

This inter-institutional initiative led by HKUST, in collaboration with CityU, CUHK, HKU, aims to use human induced pluripotent stem cells (iPSCs) to investigate pathological mechanisms of Alzheimer's disease (AD).

What is Alzheimer's Disease (AD)



AD is a Multifactorial Disorder

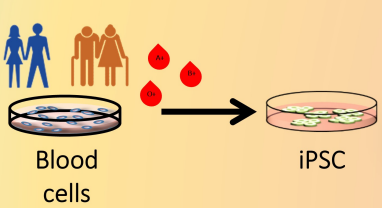


The function of multiple brain cell-types are adversely affected in AD

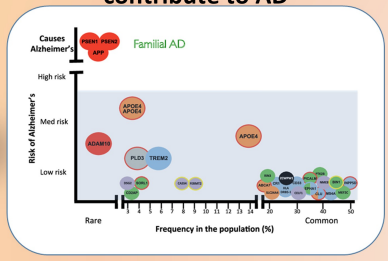
Aims & Objectives

1. Investigate deregulation of disease-associated pathways in iPSC-derived brain cells of AD patients
2. Identify and elucidate molecular pathways that contribute to AD in iPSC-derived models and isogenic controls
3. Perform preclinical drug screening and drug development in iPSC-derived platforms and established animal models

Establish human iPSC core for *in vitro* modeling and functional studies



Examine how genetic variants contribute to AD



Drug screening and preclinical neuro-drug development

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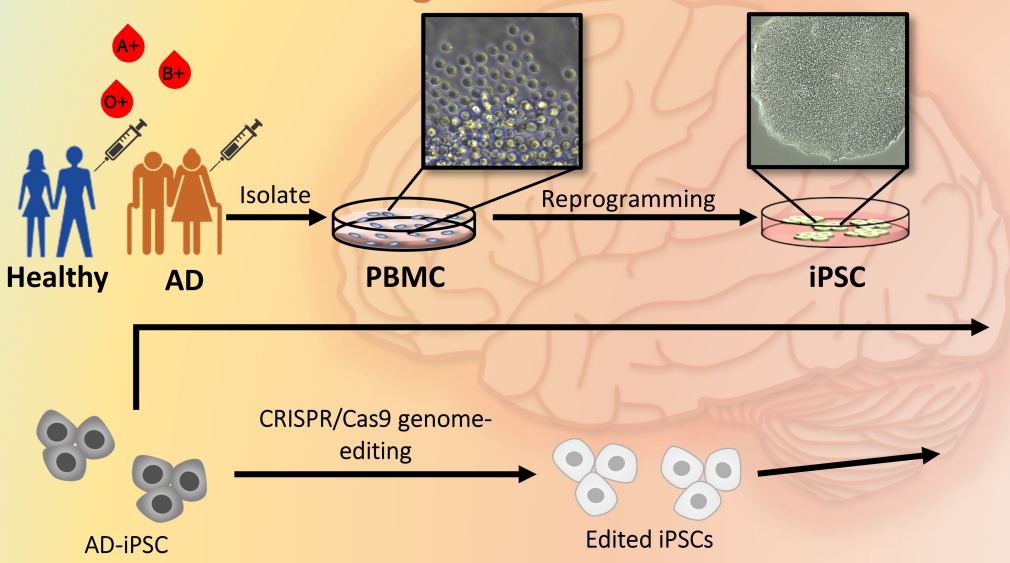
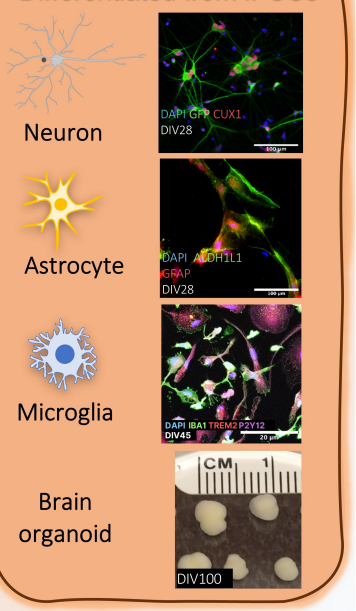
Human iPSC core
For *in vitro* modeling and functional studies

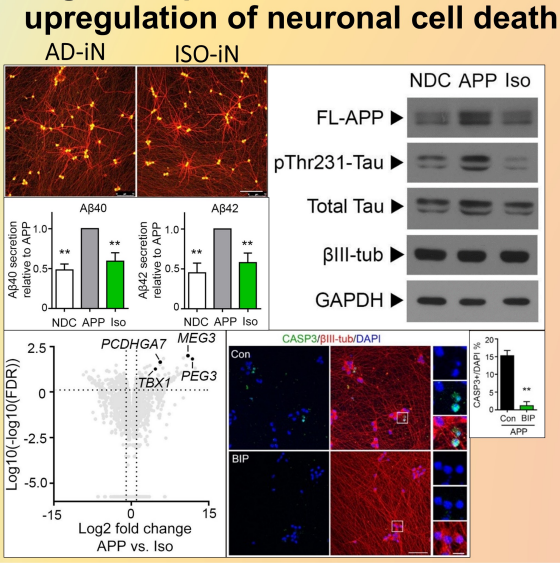


Types of Brain Cells Differentiated from iPSCs



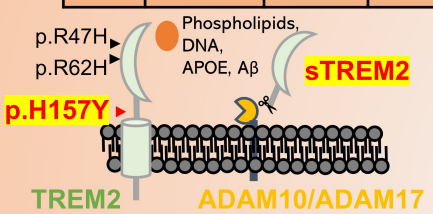
Examine how genetic variants contribute to AD

APP gene duplication is associated with upregulation of neuronal cell death



A genetic variant of TREM2 is associated with altered microglial function

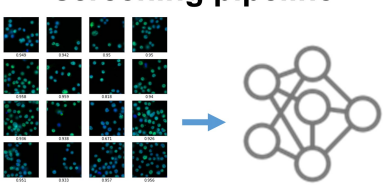
	FREQUENCY			EFFECT SIZE
	European	East Asian population		
		Overall	HK Chinese (Our cohort data)	
R47H	≈ 0.21%	≈ 0		2.83 - 4.59
H157Y	≈ 0.025%	≈ 0.18%	≈ 0.35%	3.65 - 11.01



Patient derived iMGL exhibits impaired phagocytic ability

Drug screening and preclinical neuro-drug development

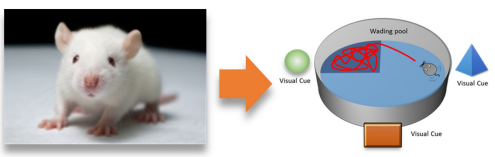
High-throughput drug screening pipeline



Captures cellular features with specific organelle dyes

Recognize distinct features that differ between healthy and disease cells

Methods for *in vivo* validation



Establish transplantation of iPSC-derived brain cells to validate functional circuitry formation within the host brain

Innovative Gene Editing Tool

Develop a “one-for-many” gene editing tool in autosomal dominant diseases

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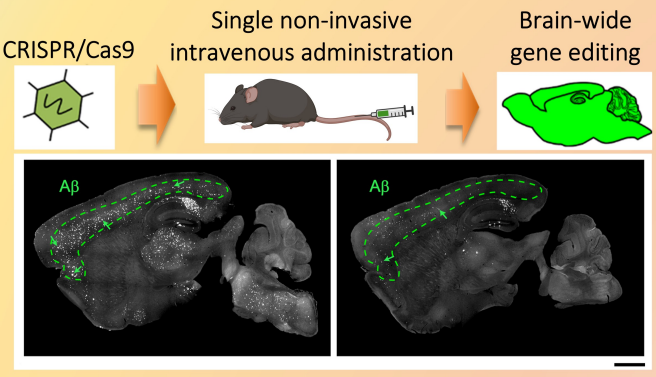
Output Highlights

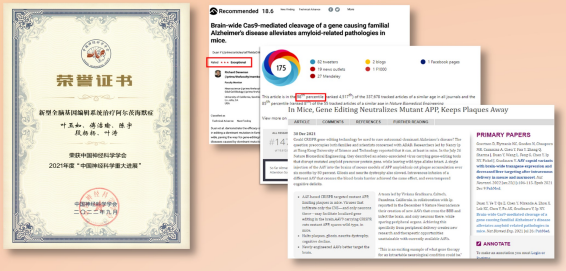
- Establishment and optimization of iPSC-based platforms to generate 2D monolayer neural cell cultures and 3D organoids
- Generation of genome-edited isogenic lines for key AD pathways
- Systematic identification of the molecular and cellular deregulation of AD
- Pipeline development of AI-based high-throughput drug screening platforms
- Training of students and postdocs with expertise at the forefront of neuroscience research
- ~ 200 papers in reputable peer-reviewed journals, i.e. J Alzheimers Dis, Cell Rep, Nat Aging, Nat Commun, PNAS.

Representative Achievement

Genome-editing Strategy for Potential Alzheimer's Disease Therapy
First demonstration of efficient brain-wide genome editing to alleviate AD pathology throughout the whole brain



Duan *et al.*, *Nat Biomed Eng.* 2022 (IF = 26.8)
Ye *et al.*, *Commun Biol.* 2021 (IF= 5.2)



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Top 2% of articles scored by Altmetric
Reported by Alzforum

2021 "Major Breakthrough in Neuroscience" award from the Chinese Neuroscience Society

Gold Medal at the International Exhibition of Inventions Geneva 2024

Among the first selected for the RAISe+ Scheme by the Innovation and Technology Commission

Impact

Address urgent need for new and innovative therapies for AD

Enhance Hong Kong's position in neural regenerative medicine and stem cell research

Provide training opportunities for young scientists

Strengthen Hong Kong's position as an international innovation and technology center