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Principal Investigator
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Team members
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Research Progress Summary

Gliovascular Dysfunction in Aging and Neurodegeneration

Brain health critically depends on diverse gliovascular cells, each serving crucial homeostatic functions in the maintenance of neural circuit functionality. Over the past decades, accumulating evidence point to causal roles of gliovascular dysfunction in various neurodegenerative diseases. Owen Ko and his team adopt a multimodal approach combining genetic manipulation, molecular assays, *in vivo* functional and structural imaging to uncover how aging and neurodegenerative disease-related genetic mutations cause gliovascular dysfunction. They are also interested in the development of disease-modifying therapeutics, as exemplified by their recent works identifying glucagon-like peptide-1 receptor agonist (GLP-1RA) as a promising potential treatment for age-related vasculopathy (Zhao, Li and Vong et al., *Nature Communications,* 2020 Sep 4;11(1):4413), which can also reverse transcriptomic aging signature in many brain cell types in a genome-wide manner (Li, Chen, Vong and Zhao et al., *Communications Biology,* 2021 Jun 2;4(1)656), implicating broad applicability of GLP-1RAs to the primary prevention and secondary treatment of age-related neurodegeneration (US/PCT patent application filed in 2021). Currently, the team is extending their works in this direction to (i) further investigate the peripheral effects of GLP-1R agonism in aging via multi-omics, and (ii) develop companion diagnostic tools for assessing the anti-aging effects of GLP-1R agonists.

08 NEUROSCIENCE AND NEUROTECHNOLOGY

Development of Imaging Tools and Methods

Bottlenecks in neural circuit and brain disorder investigations are often due to methodological limitations. The research team is actively developing imaging tools for pre-clinical investigations and potential clinical applications.

(i) They work closely with the Lai lab of LiHS to develop new techniques for high-throughput three-dimensional molecular profiling in intact tissues. These techniques will not only empower their investigations of neural circuit functions in health and disease, but also benefit other fields of biomedical sciences. Their recent works include the development of a new hydrophilic tissue-clearing chemical cocktail solution, and a method for the thermostabilisation of antibodies that permit heat-accelerated deep immunostaining of intact tissues (Lai et al.,

manuscript under revision; 3 US/PCT patent applications filed in 2021).

(ii) Driven by the need for better neuroimaging-based diagnostic tools for age-related neurodegenerative disorders, such as Alzheimer's disease (AD), they have been working with industrial collaborators to develop new neuroimaging probes and techniques. They are exploring two technical approaches, whereby they (1) design molecular targeting MRI probes with both amyloid-binding and T_1 MRI signal-generating properties and undergo *ex vivo* and *in vivo* tests in animal models of AD, and (2) develop workflow for hyperpolarised ^{13}C magnetic resonance spectroscopic imaging (MRSI) of neurodegeneration-associated brain metabolic changes.

Neural Circuit Mechanisms of Sensory Processing and Behaviour in Health and Disease

They aim to attain a better understanding of the neural circuit basis of sensorimotor behaviour and learning. To achieve this goal, they must uncover how neurons across different brain regions encode behavioural task-relevant information, such as sensory features and predicted outcomes, to instruct decision making and the generation of motor commands. In their lab, they develop platforms on which (i) larval zebrafish are subject to spatiotemporally precise chemical stimulation (Sy et al., manuscript under review; preprint: *bioRxiv,* 2021 Feb 20; doi:10.1101/2021.02.20.431946), or (ii) mice

learn to execute complex forelimb motor and general locomotor tasks in response to visual cues, while neuronal activities are recorded from different brain areas by light sheet or multiphoton microscopy. Combined with circuit tracing techniques, they are studying the neural coding of (i) ecologically significant odors and odor mixtures in larval zebrafish, and (ii) distinct task-related information along pathways connecting visual areas to association and motor areas in mouse. In the future, they plan to extend their investigations to animal models of neuropsychiatric diseases.

Research and Scholarship

Research Awards and Recognitions

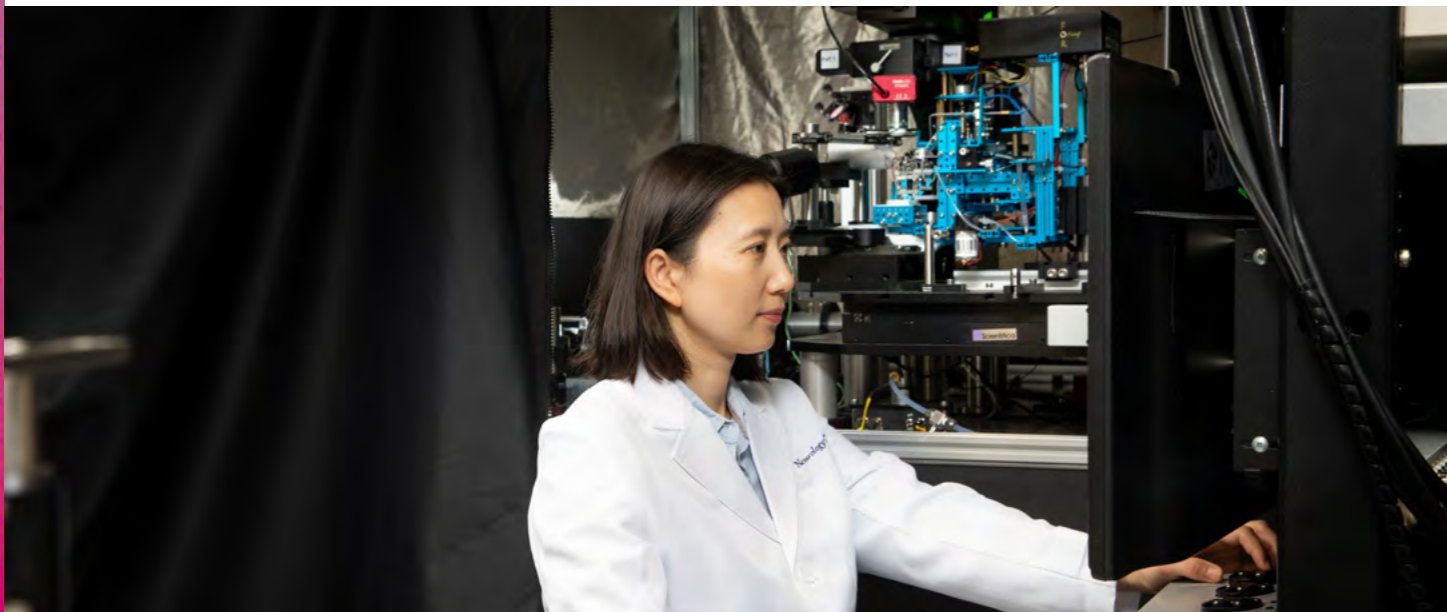| Member's Name	Details	
	Award	**Organisation**
Owen Ko	Awardee of Excellent Young Scientists Fund (Hong Kong and Macau)	The National Natural Science Foundation of China

Academic Editorship

Member's Name	Details	
	Role	**Journal**
Owen Ko	Guest / Associate Editor	BMC Biology

Reviewer of Journal / Conference

Member's Name	Details	
	Role	**Journal / Conference**
Owen Ko	*Ad hoc* reviewer	Nature Communications
		eLife
		Seminars in Cell and Developmental Biology
		Neural Regeneration Research
		Laboratory Investigation
		Frontiers in Neuroscience
		STAR Protocols

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Owen Ko	Development of Novel Therapeutic Drugs for Niemann-Pick Disease, Type C	Science, Technology and Innovation Commission of Shenzhen Municipality	30/07/2021	31/07/2023	RMB 1,000,000

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Owen Ko	Novel MRI-based Machine Learning Tool to Detect Mild Cognitive Impairment Associated with Alzheimer's Disease	Food and Health Bureau – Health and Medical Research Fund	01/09/2021	31/08/2023	911,140
	A Comprehensive Survey on Alpha-Synuclein Pathologies in Colonic Submucosal Biopsies of Prodromal Parkinson's Disease Patients – An Exploratory Study	Food and Health Bureau – Health and Medical Research Fund	01/09/2021	31/08/2023	965,803
	Construction of a MesoSPIM Light Sheet Microscope	The Chinese University of Hong Kong Research Committee – Academic Equipment Grant	23/02/2021	31/08/2021	1,063,000
	Clearing the Way for Better Tissue Diagnostics - a Midstream Development Project on Accessible Three-dimensional Histology Methods and Platform	Innovation and Technology Commission – Midstream Research Programme	01/04/2021	31/10/2023	4,700,000
	Investigating Neurovascular and Astrocyte Dysfunction in Neurodegenerative Diseases – Matching Fund	Research Grants Council – Research Matching Grant Scheme	01/06/2020	31/05/2022	1,000,000
	Investigating Neurovascular and Astrocyte dysfunction in neurodegenerative Diseases	The Croucher Foundation	01/06/2020	31/05/2025	5,000,000
	The Role of IL33 in Synaptic Dysfunctions and Pathogenesis of Alzheimer's Disease	Research Grants Council – Collaborative Research Fund	01/04/2020	31/03/2023	5,586,951
	A Pilot Test in Search for Novel Plasma Biomarkers in REM Sleep Behavior Disorder, a Prodromal Stage of Alpha-Synucleinopathy Neurodegeneration, in a Prospective Family Cohort	The Chinese University of Hong Kong Research Committee – Direct Grant	30/06/2020	29/06/2022	149,200

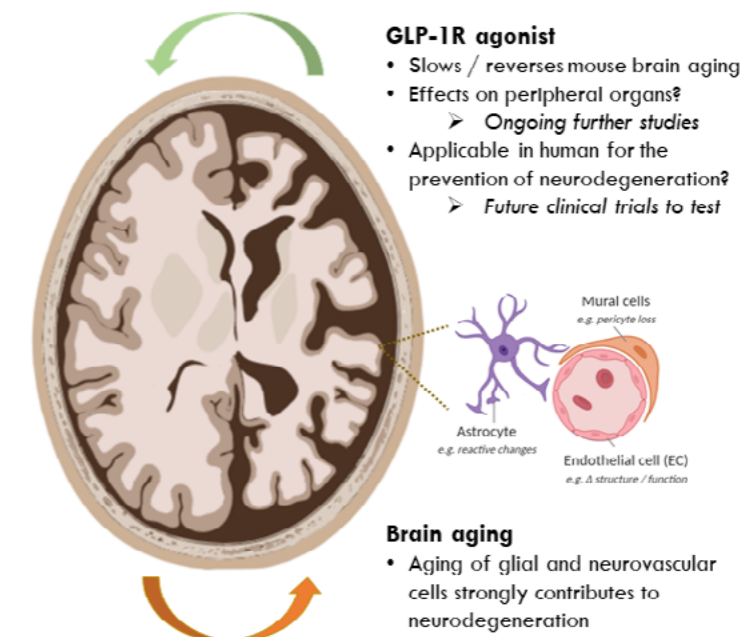| Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Owen Ko	Novel Carbobicyclic Nucleosides and Repurposed Drugs for the Treatment of SARS-CoV-2 Infection	The Chinese University of Hong Kong – Faculty of Medicine	12/03/2020	11/03/2021	1,050,000
	Cellular Mechanisms of Synaptic Functions and Plasticity in Health and Neurodegenerative Diseases	Research Grants Council – Area of Excellence Scheme	01/07/2019	30/06/2025	77,516,000
	Design and Characterization of Novel MRI Contrast Agents for Alzheimer's Disease	Videns Incorporation Ltd.	01/02/2019	30/06/2021	2,560,000
	Elucidating the Cellular Functions of the Spinocerebellar Ataxia-Causing Gene CCDC88C and Its Pathogenic Roles in Neurological Conditions	The Chinese University of Hong Kong Research Committee – Funding for Research Sustainability of Major Research Grants Council Funding Schemes	27/05/2019	30/06/2021	500,000
	Nanorobots Swarm for Stroke Treatment: Pilot Study	The Chinese University of Hong Kong Research Committee – Funding for Research Sustainability of Major Research Grants Council Funding Schemes	01/06/2019	31/05/2021	625,000
	High-content Screening of Small Molecules for Inhibiting Microglia Phagocytotic Clearance of Inhibitory Synapses in the Management of Chronic Pain	The Chinese University of Hong Kong Research Committee – Funding for Research Sustainability of Major Research Grants Council Funding Schemes	15/05/2019	14/05/2021	625,000

Publications

A. Journal Papers

1. Sy SKH, Chan DCW, Lai H-M, Li Z, Wong KKY, Choi CHJ, Mok VCT, Hu Y, Ko H. A neural circuit basis for bilateral olfactory input-enhanced chemosensory avoidance navigation. *bioRxiv*. Published online January 1, 2021:2021.02.20.431946. doi:10.1101/2021.02.20.431946. (In press)

2. Wong A, Yin Ka Lam B, Kit Yi Mak M, Chiu Wa Lam L, Wing Chi Au L, Ka Fung Yiu B, Wong C, Yee Tong H, Ki Yeung S, Chiu Wing Chu W, Shi L, Wai Hong Leung T, Oi Yan Soo Y, Yuk Lun Lau A, Yiu Ming Ip B, Chi Yui Kwok T, Ko H, Chung Tong Mok V, Yin Ka LAM B. Aerobic exercise in older people with subclinical sporadic cerebral small vessel disease: A randomized clinical trial. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*. 2021;7(1):e12224. doi:10.1002/trc2.12224.

3. Ismail M, Mok VCT, Wong A, Au L, Yiu B, Wang Z, Chu WCW, Chan AYY, Fan FSY, Ma SH, Ip V, Ip B, Ma K, Leung H, Soo YOY, Leung TWH, Ko H, Lau AYL, Lam BYK. Risk factors for delayed-onset dementia after stroke or transient ischemic attack—a five-year longitudinal cohort study. *International Journal of Stroke*. Published online 2021. doi:10.1177/17474930211026519. (Epub ahead of print)

4. Lam BYK, Yiu B, Ampil E, Chen CLH, Dikot Y, Dominguez JC, Ganeshbhai PV, Hilal S, Kandiah N, Kim SY, Lee JY, Ong AP, Senanarong V, Leung KT, Wang H, Yang YH, Yong T, Arshad F, Alladi S, Wong S, Ko H, Lau AYL, Mok VCT. High burden of cerebral white matter lesion in 9 Asian cities. *Scientific Reports*. 2021;11(1). doi:10.1038/s41598-021-90746-x.

5. Li Z, Chen X, Vong JSL, Zhao L, Huang J, Yan LYC, Ip B, Wing YK, Lai HM, Mok VCT, Ko H. Systemic GLP-1R agonist treatment reverses mouse glial and neurovascular cell transcriptomic aging signatures in a genome-wide manner. *Communications Biology*. 2021;4(1). doi:10.1038/s42003-021-02208-9.

6. Liu W, Au LWC, Abrigo J, Luo Y, Wong A, Lam BYK, Fan X, Kwan PWL, Ma HW, Ng AYT, Chen S, Leung EYL, Ho CL, Wong SHM, Chu WC, Ko H, Lau AYL, Shi L, Mok VCT. MRI-based Alzheimer's disease-resemblance atrophy index in the detection of preclinical and prodromal Alzheimer's disease. *Aging*. 2021;13(10):13496-13514. doi:10.18632/aging.203082.

7. Li Z, Ip B, Mok VCT, Ko H. Neurovascular ageing: transcriptomic readout and implications on therapeutic targeting in Alzheimer's disease. *Neural Regeneration Research*. 2021;16(12):2411-2412. doi:10.4103/1673-5374.313042. (Editorial)

8. Lau AYL, Ming BY, Ko H, Lam BYK, Shi L, Ma KKY, Au LWC, Soo YOY, Leung TWH, Wong A, Mok VCT. Pandemic of the aging society-sporadic cerebral small vessel disease. *Chinese Medical Journal*. 2021;134(2):143-150. doi:10.1097/cm9.0000000000001320. (Review)

9. Wang Q, Tian Y, Du X, Ko H, Ip BYM, Leung TWH, Yu SCH, Zhang L. Magnetic navigation of collective cell microrobots in blood under ultrasound doppler imaging. *IEEE/ASME Transactions on Mechatronics*. Published online 2021. doi:10.1109/tmech.2021.3109346. (Epub ahead of print)

10. Wang Q, Jin D, Wang B, Xia N, Ko H, Ip BYM, Leung TWH, Yu SCH, Zhang L. Reconfigurable magnetic microswarm for accelerating tPA-mediated thrombolysis under ultrasound imaging. *IEEE/ASME Transactions on Mechatronics*. Published online August 11, 2021:1-1. doi:10.1109/tmech.2021.3103994. (Epub ahead of print)

11. Lo HS, Hui KPY, Lai HM, He X, Khan KS, Kaur S, Huang J, Li Z, Chan AKN, Cheung HHY, Ng KC, Ho JCW, Chen YW, Ma B, Cheung PMH, Shin D, Wang K, Lee MH, Selisko B, Eydoux C, Guillemot JC, Canard B, Wu KP, Liang PH, Dikic I, Zuo Z, Chan FKL, Hui DSC, Mok VCT,

Wong KB, Mok CKP, Ko H, Aik WS, Chan MCW, Ng WL. Simeprevir potently suppresses SARS-CoV-2 replication and synergizes with remdesivir. *ACS Central Science*. 2021;7(5):792-802. doi:10.1021/acscentsci.0c01186.

12. Wang B, Chan KF, Yuan K, Wang Q, Xia X, Yang L, Ko H, Wang YXJ, Sung JJY, Chiu PWY, Zhang L. Endoscopy-assisted magnetic navigation of biohybrid soft microrobots with rapid endoluminal delivery and imaging. *Science Robotics*. 2021;6(52). doi:10.1126/scirobotics.abd2813.

B. Patents

1. Ko H, Li Z, Chen X, Huang J, Zhao L, Vong SL, Yan LYC, Lai HM, Mok VCT. A method for reversing aging brain functional decline.
   - PCT Patent Application: 2021 Dec 16; PCT/CN2021/138827.
   - US Provisional Patent Application: 2020 Dec 16; US63/126,122.

2. Lai HM, Ko H. Efficient antibody DNA-barcoding reagents for multiplexed molecular imaging.
   - PCT Patent Application: 2021 Jun 18; PCT/CN2021/100919.
   - US Provisional Patent Application: 2020 Jun 18; US 63/040,557.

3. Lai HM, Tang Y, Ko H. Efficient and effective tissue clearing agents and their compositions.
   - PCT Patent Application: 2021 May 25; PCT/CN2021/095690.
   - US Provisional Patent Application: 2020 Jun 3; US 63/029,582.

4. Lai HM, Lau ZYH, Ko H. Thermodynamically stabilized antibodies for deep immunolabeling and tissue imaging.
   - PCT Patent Application: 2021 May 21; PCT/CN2021/095327.
   - US Provisional Patent Application: 2020 May 21; US 63/028,022.

GLP-1R agonist
- Slows / reverses mouse brain aging
- Effects on peripheral organs?
  - ➤ *Ongoing further studies*
- Applicable in human for the prevention of neurodegeneration?
  - ➤ *Future clinical trials to test*

Mural cells
e.g. pericyte loss

Astrocyte
e.g. reactive changes

Endothelial cell (EC)
e.g. Δ structure / function

Brain aging
- Aging of glial and neurovascular cells strongly contributes to neurodegeneration

Gliovascular dysfunction strongly contributes to age-related neurodegeneration. They demonstrated that GLP-1R agonism can potently slows brain aging. Ongoing further works in their lab are exploring the effects of GLP-1R agonism on peripheral organs in aging, and the role of altered central nervous system GLP-1 signaling in natural aging.

Sources: Owen Ko's laboratory