

Research Assessment Exercise 2020

Impact Case Study

University: The Hong Kong University of Science and Technology

Unit of Assessment (UoA): 1 - Biological Sciences

Title: Novel approaches and therapeutic strategies for meeting the challenges of dementia

(1) Summary of the impact

Alzheimer's disease (AD) is a devastating neurodegenerative condition affecting over 45 million individuals worldwide, primarily over the age of 65. The World Health Organization estimates that by 2050, there will be a threefold jump in AD dementia cases to 115.4 million, as populations age. Division of Life Science scientists, led by Morningside Professor of Life Science Nancy Ip (h-factor 67) and Chair Professor Karl Herrup (h-factor 61), approach this challenge as questions of science and research strategy, and are international leaders in the search for new approaches, understanding, and cures. While current understanding of AD has been questioned as expensive clinical trials repeatedly fail, the HKUST scientists have made important progress by identifying novel molecular therapeutic targets and new concepts of disease mechanisms. Technology has been transferred into treatments for enhancing brain health, and licenses for clinical trials and development; as well as protocols for identifying at-risk populations. These breakthroughs have attracted global and local attention from policy leaders; NGOs striving for solutions for dementia; and health practitioners.

(2) Underpinning research

Neurodegenerative diseases are complex conditions with loss of cognition and many associated symptoms. However, existing US Food and Drug Administration (FDA)-approved AD drugs offer only symptomatic relief and are associated with side-effects, from mild to life threatening.

The HKUST team's premise is that a major obstacle for effective drug development is incomplete understanding of the pathophysiology of the disease. Professor Nancy Ip's laboratory, including Dr Amy Fu and a team of around 50 research associates, assistants, students, visiting scientists and scientific officers, has focused on deciphering the molecular mechanisms underlying the dysfunctions of hippocampal synapses, and the damage caused by dysfunctions of the innate immune system. While the main strategies for developing therapeutic interventions center on the two main proteins implicated in AD – tau and amyloid β – the group has sought to understand the effects of other biological processes on AD pathology, namely synapse maintenance and innate immunity. These efforts have unveiled alternative approaches to developing therapeutic interventions for AD. Specifically, the group uncovered the role of the protein EphA4 in AD pathogenesis and identified a number of small molecule EphA4 inhibitors [R1, R2, R3]. These include *Rhynchophylline*, a component in a traditional Chinese medicinal herb. Testing in AD mice models revealed that it rescued synaptic impairment and reduced AD pathology. *Rhynchophylline* and other newly developed EphA4 inhibitors are presently in pre-clinical development. In a collaboration with the University of Glasgow, the Ip group has also revealed the role of innate immunity and anti-inflammatory interleukin-33 (IL-33) and is developing IL-33 for therapeutic use to reduce AD pathology and reverse AD-related cognitive deficits [R4].

Furthermore, the Ip lab has been among the first to examine the entire genomes of AD in non-Caucasian populations that are underrepresented in AD genetic studies, in particular ethnic Chinese. By conducting the first whole-genome sequencing study for AD genetic risk in the Chinese population, in partnership with Hardy (who discovered the amyloid gene) from University College London, and collaborating hospitals and research institutes in Hong Kong and mainland China, the team identified genetic risk factors associated with AD pathogenesis. This led them to establish internationally standardized pipelines and protocols, from patient diagnosis and sample collection to the most advanced analytical pipeline for genetic analysis. Importantly, they developed the biomarker and in-house algorithm for evaluating AD risk, for use in clinical settings in Hong Kong and mainland China, accelerating best practices in AD clinical research in these locations. [R5].

Meanwhile, since 2010, Herrup's research has drawn attention to the deep flaws in the linear pathway model of AD that currently dominates the field, and its failure to account for the role of

aging in AD pathogenesis. In a “Highly Cited Paper” in *Nature Neuroscience* (2015) [R6], he suggested that the field should not only focus on the “amyloid cascade hypothesis”, but should explore the involvement of other disease mechanisms on AD pathology [R7], including myelin integrity. His Hong Kong laboratory has methodically developed new and innovative alternatives that paint a more complex and realistic picture of AD [R8].

The HKUST team’s flagship role in neurodegenerative disease research in Hong Kong, and globally, is reflected in and supported by the Ministry of Science and Technology of China’s approval in 2010 for the establishment of the State Key Laboratory of Molecular Neuroscience, which Ip directs, and by the Hong Kong government identifying the Hong Kong Center for Neurodegenerative Diseases, established in 2019, as one of the first clusters in its Health@InnoHK scheme to build up Hong Kong as a hub for research collaboration. The new center involves collaborations with leading scientists in the field, from University College London; Boston Children’s Hospital – a Harvard Medical School Teaching Hospital; the Paul F. Glenn Center for the Biology of Aging at Stanford University School of Medicine; and clinical partners in Hong Kong and mainland China.

(3) References to the research

[R1] Fu WY, Chen Y, Sahin M, ... Ip NY (2007) Cdk5 regulates EphA4-mediated dendritic spine retraction through an ephexin1-dependent mechanism. *Nature Neuroscience*. 10(1):67-76. (213 citations, Sept. 2019).

[R2] Fu AK, Hung KW, Fu WY, Shen C, Chen Y, Xia J, Lai KO, Ip NY (2011) APC(Cdh1) mediates EphA4-dependent downregulation of AMPA receptors in homeostatic plasticity. *Nature Neuroscience*. 14(2):181-9. (103 citations, Sept. 2019).

[R3] Fu AK, Hung KW, Huang H, ... Ip NY (2014) Blockade of EphA4 signaling ameliorates hippocampal synaptic dysfunctions in mouse models of Alzheimer's disease. *Proc Natl Acad Sci US*. 111(27):9959-64. (78 citations, Sept. 2019).

[R4] Fu AK, Hung KW, ... Ip NY (2016) IL-33 ameliorates Alzheimer’s disease-like pathology and cognitive decline. *Proc Natl Acad Sci US*. 113(19): E2705-2713. (79 citations, Sept. 2019, Clarivate Analytics - top 1% of the academic field of Neuroscience & Behavior).

[R5] Zhou, X., Chen, Y. Mok, ... Ip, NY. Alzheimer's Disease Neuroimaging (2018). Identification of genetic risk factors in the Chinese population implicates a role of immune system in Alzheimer's disease pathogenesis. *Proc Natl Acad Sci US*. 115(8): 1697-1706. (7 citations, Sept. 2019).

[R6] Herrup, K (2015). The case for rejecting the amyloid cascade hypothesis. *Nature Neuroscience*. 18(6): 794-799 (279 citations, Sept 2019, top 1% in Neuroscience & Behavior - Clarivate Analytics).

[R7] Herrup K, Tse KH (2017). Re-imagining Alzheimer's disease - the diminishing importance of amyloid and a glimpse of what lies ahead. *J Neurochem*. 143:432-444. (20 citations, Sept. 2019).

[R8] Herrup, K, Carrillo, MC, Schenk, D, et. al. (2013). Beyond amyloid: Getting real about nonamyloid targets in Alzheimer's disease. *Alzheimers Dement*. 9:452-458. (37 citations, Sept. 2019).

Patents: EphA4 inhibitors as neuroprotective agents (US 9629830); Human EphA4 monoclonal antibodies that show specificity to the ligand binding domain of EphA4 (pending); Heterocyclic compounds as EphA4 inhibitors (pending).

(4) Details of the impact

Ground-breaking research led by Ip and Herrup is now being translated, preparing for novel therapeutic products that will benefit millions of people with AD, including AD patients and those at risk of developing the disease. It also benefits governments and healthcare providers facing the challenge of managing the human and economic costs of this disease. With the field currently “stuck” in pursuit of a disease model that has suffered nearly three dozen advanced, and high-cost Phase III clinical trial failures, the work of the HKUST team benefits the biotech and pharmaceutical industries, which are increasingly abandoning AD as a profitable area of development. Re-engaging them through a “reset” of their approach to this hypercomplex neurological disease will galvanize the field and lead to further dividends in discovery and therapeutic development.

Impact on industry, human health, and practitioners through research translation: Translating research into treatments for patients takes many years. But Ip’s group has made important

progress, with discoveries now licensed for development, pre-clinical trial, and production. The Morningside Group, a private equity and venture capital investment firm specializing in early-stage technologies, has licensed a number of technologies in a biotech startup company, Orthogonal Neuroscience. These include inhibitors of the EphA4 receptor, and the immune protein IL-33. Gerald L Chan, Morningside Chairman and CEO, [S1] affirmed that these are in pre-clinical development, generating promising data. He stated: *“Clinical trials will begin soon and our initial commitment towards this effort is USD12 million.”* The number of beneficiaries and potential financial impact from this are *“far too huge to ignore”*, with the estimated global size of the therapeutics and diagnostics market almost USD11 billion in 2018 and estimated to reach USD13.8 billion in 2023.

Ip’s discoveries related to the therapeutic effects of five formulae of traditional Chinese medicine (TCM) herbs have been licensed [Text removed for publication] [S2].

Ip’s discoveries related to genetic factors and biomarkers for AD are achieving impact on medical research, practice, and human health during on-going development in Hong Kong and mainland China. Dr Lam Ching-choi, Chief Executive Officer, Haven of Hope Christian Service (HOHCS), confirmed that HOHCS has signed an MOU with HKUST involving use of the proprietary pipelines and algorithm from the research to evaluate AD risk in the Hong Kong community [S3]. This would inform *“both policy development and clinical interventions that will benefit the elderly as well as their care-givers. This is a first step towards positive and important changes in elderly management, involving early diagnosis of the disease, and respective health consultation as well as greater public understanding of elderly health in Hong Kong.”* Leaders of partner hospitals Shanghai Sixth People's Hospital and Beijing Tiantan Hospital also attested to using the screening methods to evaluate AD risk among local populations, for research and the benefit of patients involved [e.g. S4].

Impact on AD research strategy and policy: Ip’s global influence on policy related to AD and its research is indicated by her membership of World Economic Forum councils on brain research and related topics since 2014; membership of the Swiss-based The Brain Forum’s International Advisory Panel; and as a founder of the China Brain Science Project (established 2015). For example, as a member of the WEF Global Future Council on Neurotechnologies and Brain Science (2016-18), she contributed to its mandate to *“explore how developments in neurotechnologies and brain science could impact industry, governments and society in the future, and design innovative governance models that ensure that their benefits are maximized ...”* [S5]. Her presentations at the WEF, Brain Forum [S6], and Boao Forum for Asia, among many others, on drug discovery strategies for dementia prove her persistence in bringing the critical question of dementia, and potential solutions to different stakeholders. Ip is also an organizing committee member of the International Common Disease Alliance, comprising global scientists across sectors seeking to propose disease solutions using genetic advances and developing white papers with effective plans for implementing these solutions. [S7]

The recognition and confidence that the Hong Kong government has for the HKUST AD work is reflected in the Hong Kong Center for Neurodegenerative Diseases, established by the researchers and awarded up to HKD500 million funding under the Health@InnoHK program. Hong Kong’s Chief Executive Carrie Lam stated at the Center’s signing ceremony, attended by Consul Generals from the US and UK: *“One could not help thinking that this is clear and compelling testimony of Hong Kong’s singular ability to create connections, to help people, businesses and institutions excel.”* [S8]

HOHCS’ Lam, who has played leading roles in Hong Kong’s policy and services for the elderly, as Chairman of the Elderly Commission and Elderly Care Service Industry Training Advisory Committee, member of the Steering Committee on Primary Healthcare Development and ex-officio member of the Family Council, attested to Ip’s influence: *“Prof Ip’s research has gone further than any other in Hong Kong in creating new understanding of Alzheimer’s disease and its causes and identifying potential breakthroughs for its early detection and treatment. These bodies, which advise government on policies to meet the challenge of ensuring the optimum health and well-being of the elderly in our aging population, are well aware of the global and local significance of Prof. Ip’s work.”* He also attested to the *“high profile, esteem and influence that Prof Ip most deservedly enjoys in our society, among policy-makers, the health sector and wider public”* [S3]. Indeed, Ip has aroused

widespread public awareness of the importance of neurodegenerative diseases research in Hong Kong and the HKUST breakthroughs through extensive local and international media coverage, for example being featured in the RTHK series “Our Scientists”, and in BBC news [S9, S10].

Herrup’s arguments have also been widely noticed and relayed to policymakers, clinicians, and the research community. With Ip, he has organized well-attended international meetings in Hong Kong, drawing representatives from the US FDA, pharmaceutical industry, economists, the Alzheimer’s Association and US National Institute on Aging, and addressed and led many other high-profile international discussions of policy and direction for the entire field, including at successive Alzheimer’s Association International Conferences (AAIC) and Basic Science Sessions, for all stakeholders [e.g. S11]. His passion to educate the public about the disease and suggest better, more efficient strategies for research and development has led to opinion pieces in high-profile journals that have been widely cited by academicians, federal regulators, funding agencies (government and private) and pharmaceutical houses [e.g. S12]. He is under contract with MIT Press as sole author of a book targeted to inform a lay audience entitled, “*How Not to Study a Human Disease – A History of Alzheimer’s Disease Research*” [S13]. As Maria Carrillo, Chief Science Officer of the Alzheimer’s Association in the US, testified: “*The work that Dr Karl Herrup has done in the field of Alzheimer’s research is continuously noticed and has clearly helped guide the thinking of scientists and policy makers – both young and old, and is advancing our field forward in important ways.*” [S14]

(5) Sources to corroborate the impact

[S1] Letter, Gerald L Chan, Chairman and Chief Executive Officer, Morningside Group. [On file]

[S2] Letter, [Name anonymized for publication]. [On file]

[S3] Letter, Dr. Lam Ching-choi, CEO, Haven of Hope Christian Service. [On file]

[S4] Letter, Professor Yongjun Wang, Executive Vice President, Beijing Tiantan Hospital. [On file]

[S5] World Economic Forum. Network of Global Future Councils: The future of neurotechnologies and brain science (p56).

http://www3.weforum.org/docs/WEF_2016_2018_Network_of_Global_Future_Councils_Final_Report.pdf

[S6] The Brain Forum, Presentation by Prof Nancy Ip, on The China Brain Science Project, 30 March, 2015 <https://www.youtube.com/watch?v=SHQJnjCCMuw>

[S7] International Common Disease Alliance. <https://www.icda.bio/people>

[S8] HKSAR Chief Executive, Carrie Lam. “Hong Kong a medical research hub – international collaboration on establishing The Center for Neurodegenerative Diseases”

<https://www.hketosf.gov.hk/sf/whatsnew/2019/medhub.htm>

[S9] RTHK. Our Scientists. https://www.rthk.hk/tv/dtt31/programme/ourscientists_eng

[S10] BBC. “Protein injection hope for Alzheimer’s”. <http://www.bbc.com/news/health-36070987>

[S11] AAIC 20. 2019 Emerging Concepts in Basic Science Sessions.

<https://www.alz.org/aaic/program/emerging-concepts.asp>

[S12] MinnPost. “Alzheimer’s researchers are (finally) shifting their focus away...”

www.minnpost.com/second-opinion/2015/08/alzheimers-researchers-are-finally-shifting-their-focus-away-amyloid-plaques

[S13] Letter of Agreement, The MIT Press, Massachusetts Institute of Technology. [On file]

[S14] Letter, Maria C Carrillo, Chief Science Officer, Alzheimer’s Association. [On file]