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JULIANA CHAN



 06 DIABETES AND OBESITY

Research Progress Summary

Using Data Science to Monitor Trends, Identify Unmet Needs and Evaluate Effectiveness

Led by Andrea Luk, the team has curated data from the Hospital Authority (HA) territory-wide Electronic Medical Record (EMR) system to establish the Hong Kong Diabetes Surveillance Database (HKDSD) consisting of 4 million people who ever had blood glucose measurement (2000-2019). Using this dataset, they have reported the persistently high rate of pneumonia as a leading cause of death as well as the failure for the incidence of end stage kidney disease (ESKD) to decline in contrast to the declining trend of cardiovascular disease and all-cause death over the years. The amplifying effect of young age of diagnosis on ESKD and the high mortality rate even after renal replacement therapy especially in young people is particularly worrying. Despite these unmet clinical needs, in a pooled analysis of national data on mortality rate in people with diabetes (2000-2016), Hong Kong had the largest decline in death rate with 4% per year amongst 16 high income countries/ areas. This impressive drop of nearly 70% in death rate during this 16-year period was in part driven by the territory-wide implementation of data-driven diabetes assessment, education and management program in both primary and secondary settings, complemented by public awareness programs, health care reform and public health policies in Hong Kong.

Led by Elaine Chow, they have developed comprehensive methodologies to evaluate the real-world evidence (RWE) of impacts of common drugs in type 2 diabetes, adjusted for multiple biases. Using the HKDSD and Hong Kong Diabetes Register (HKDR), they had reported reduced risks of pneumonia and related death amongst metformin and renin angiotensin system inhibitors (RASi) users compared with non-users in type 2 diabetes. They also found that use of both drugs was associated with reduced

risk of all-cause death including cardiovascular-renal-cancer death, further supporting the need to develop systems to ensure that patients with diabetes are assessed and put on these lifesaving drugs.

On an international front, Juliana Chan was a lead investigator in the International Diabetes Mellitus Practice Survey where The Chinese University of Hong Kong contributed to the reporting of lack of improvement in glycaemic control in countries outside Western Europe and North America despite the introduction of many new glucose lowering drugs. Although there was increasing screening for albuminuria, there remained high rate of chronic kidney disease in these low- and middle-income countries. In this survey, they also found that 20-30% of patients with type 2 diabetes had depressive symptoms while 1 in 7 insulin-treated patients discontinued insulin at some stage averaging 1-2 months during their course of treatment in both patients with type 1 and type 2 diabetes.

In two large scale multicentre randomised studies, they evaluated the effectiveness of using the web-based Joint Asia Diabetes Evaluation (JADE®) Platform, designed and operated by the Asia Diabetes Foundation as a knowledge transfer project, to improve quality of care in 25,000 patients with type 2 diabetes from 10 countries in Asia versus usual care. In agreement with their previous studies conducted in China and Hong Kong, they confirmed once again the utility of the JADE-assisted care delivered by a doctor-nurse team in reducing multiple cardiometabolic risk factors, reducing default rate and improving clinical outcomes in patients with or without complications such as diabetic kidney disease.



Principal Investigator

Juliana Chan



Team members

Ronald Ma, Alice Kong, Andrea Luk, Elaine Chow, Wing Yee So, Hongjiang Wu, Risa Ozaki, Kitty Cheung, Cadmon Lim, Stephanie Cheung, Natural Chu, Baoqi Fan, Heung Man Lee, Dandan Mao, Mei Shi, Ming Wai Poon, Claudia Tam, Raymond Wan, Feifei Cheng, Eric Lau, Noel Ng, Aimin Yang, Chun Hei Tam, Hou Yong, Huanyi Cao, Jamie Cheung, Sandra Choi, Yingnan Fan, Chuiguo Huang, Qiao Jin, He Jia, Wang Ke, Andy Kuo, James Ling, Kit Ying Tsoi, Tsz Fung Tsoi, Sylvia Qiu, Kwun Kiu Wong, Rebecca Yue, Xinge Zhang

Using Precision Medicine to Predict, Classify and Personalise Care in Young Onset Diabetes

In their ongoing PRISM Project (**P**recision Medicine to **R**edefine **I**nsulin **S**ecretion and **M**onogenic Diabetes in Chinese Patients with Young Onset Diabetes, YOD) commissioned by the Health and Medical Research Fund (HMRF), they have completed the recruitment of 884 patients with YOD with 442 randomised to receive multidisciplinary care guided by clinical and biogenetic markers. In this project, they discovered that 5% of patients with YOD had autoimmune markers whilst 3% had monogenic diabetes or maturity onset diabetes of the young (MODY). Early identification of

patients with latent autoimmune diabetes of the young (LADA) is important to avoid delayed insulin treatment while patients with MODY may be switched back from insulin to oral glucose lowering drugs. In addition, these young patients carried varying combinations of common genetic variants for YOD, late onset type 2 diabetes and cardiovascular-renal complications which interact to modify clinical course. Due to the silent nature of monogenic diabetes and high penetrance, screening of family members of these index patients is important to avoid delayed diagnosis and intervention of affected

family members. Furthermore, they discovered that more than 10% of these young patients had variants of unknown origin which required ascertainment through functional studies or family co-segregation studies. With detailed clinical evaluation, they noted the phenotypic heterogeneity of these young patients in whom genetic, life course, autoimmune, non-genetic hereditary, hormonal and psychosocial-behavioural risk factors interact in a complex manner to contribute to the diversity of clinical presentation, trajectories and outcomes in these young patients.

Using their community-, family- and clinic-based cohorts including healthy subjects, high risk individuals and patients with diabetes, the team has measured fasting plasma C peptide and glucose to define the insulin resistance and deficiency status during the progression from normal glucose tolerance to diabetes in community-dwelling individuals as well as glycaemic deterioration and insulin requirement in patients with diabetes. In young people without diabetes, insulin resistance was a major predictor for incident diabetes in addition to sex, obesity and lipid abnormalities. In patients without auto-

antibodies and preserved beta cell function, both insulin deficiency and resistance predicted early insulin requirement after adjusting for confounders.

In patients with type 2 diabetes, 8% had LADA although only 50% of them were insulin deficient based on absolute plasma C peptide level. On the other hand, 35% of patients with type 2 diabetes had insulin deficiency although only 50% of them had autoimmune markers. Patients with autoantibodies and/or insulin insufficiency were highly responsive to insulin treatment albeit also at high risk of severe hypoglycaemia. While their pharmacoepidemiological analysis using HKDSD indicated declining use of sulphonylureas (SU) in their patients with type 2 diabetes, supported by the Theme-Based Research Scheme led by Ronald Ma and Elaine Chow, they had reported the greater glucose lowering effects of SU amongst patients with type 2 diabetes who carried genetic variants of *CYP2C9*. The latter is known to be associated with reduced metabolism of gliclazide, which is the most common SU used in their community. These studies emphasised the importance of using comprehensive clinical profiling and biogenetic markers to classify patients in order to personalise care.

Translational Research in Beta Cell Biology and Diabetes-Cancer Link

In collaboration with Xiaoyu Tian from the School of Biomedical Science and Guy Rutter from Imperial College London, Alice Kong continues to use experimental models to elucidate the role of SIRT3 pathway in the development of diabetes. Using transgenic mice, she had reported silencing of this pathway had led to the development of fatty liver and dedifferentiation of beta cells. In support of their previous experiments regarding the cancer-promoting effect of hyperglycaemia on cancer growth in a diabetes-cancer animal model, using colon cancer cell lines, they demonstrated the legacy effect of high glucose medium on promoting the continuing cancer cell growth despite return to a normoglycemic environment. This programming effect of hyperglycaemia was in part mediated through endoplasmic reticulum (ER) stress resulting in reduced apoptosis of the cancer

cells and resistance to anti-cancer drugs which used ER pathway to induce cell death.

In support of the deleterious effect of hyperglycaemia on abnormal cell growth, led by Juliana, they have reported the risk association of glycaemic burden with liver cancer and that of glycaemic variability and all-site cancer as well as death due to cardiovascular and cancer events in patients with more than 10 years of diabetes and especially in those with obesity. To this end, supported by an Innovation Technology Commission (ITC) grant and using the HKDR biobank, Alice had reported the predictive role of several miRNAs on incident liver cancer 4-6 years before its occurrence making them potential markers for early detection and intervention.

From Genomic Medicine to Drug Discovery

Led by Ronald, their multiomic project, supported by the Impact Research Fund and TRS, continues to generate a wealth of academic output aimed at elucidating the genetic regulation of diabetic complications (see report in Lab 602). Through these projects, they have genotyped more than 30,000 patients in multiple cohorts with detailed phenotypes and multiple outcomes. Using this huge resource, Ronald has performed comprehensive analysis including the use of Mendelian Randomisation and reported the independent predictive role of DNA telomeres on glycemic deterioration, cardiovascular-renal complications and all-cause death. By using genomic data available from publicly available resources together with their proprietary databases, they have developed multiple genetic risk scores consisting of common variants which predicted insulin requirement, deterioration of kidney function as well as multiple lipid traits and cardiovascular disease. Using adipose tissues collected during metabolic surgery, they have also performed multiomic analysis and reported novel epigenetic pathways implicated in both general and visceral adiposity associated with type 2 diabetes.

In their collaborative project with Astra Zeneca, they continued to make progress in using long-read and short-read whole genome sequencing

to discover novel pathways implicated in diabetic kidney disease (DKD) using bioinformatics and computational biology, supplemented by multiomic analysis in their other datasets. They have also developed human glomerular and tubular cell lines which will be used to test the functional significance of novel pathways in DKD discovered in these analyses, in collaboration with the biologists and bioinformaticists of the sponsor for possible drug development.

Technologies and Therapeutics

Both Andrea and Elaine are leading the non-oncology early phase clinical trials at the CUHK Phase 1 Clinical Trial Centre where they have established the insulin/glucose clamp techniques to evaluate the insulin secretory function and its action in controlled settings. Supported by a RGC grant, Andrea is evaluating the insulin secretory function in both lean and obese patients with YOD. Supported by an investigator-initiated study sponsored by Hua Medicine which had taken the first ever glucose kinase activator (GKA) to phase 3 clinical trial, Elaine is evaluating the effects of this novel drug in patients with GK-MODY and early onset type 2 diabetes. These *state-of-the-art* physiological studies continue to provide new insights in their pursuit of precision medicine of reclassifying diabetes for targeted therapies with companion diagnostics.

In a similar vein, Juliana is currently a national lead for a phase 3 study evaluating the efficacy and safety of a novel aldose reductase inhibitor in patients with type 2 diabetes with heart failure and preserved ejection fraction (HFpEF). In this clinical trial, they are working closely with Erik Fung, their cardiologist, to set up the *state-of-the-art* facilities including echocardiogram and cardiopulmonary exercise testing (CPET) along with metabolomic analytical platform for in depth analysis. Given the genetic determinant for the aldose reductase pathway, this is another molecule with potential for precision medicine in diabetes for preventing complications.

Having spearheaded the collaboration with a local biotechnology company in developing a 28-day continuous glucose monitoring (CGM) system, Elaine had been funded by the Innovation and Technology Commission (ITC) to lead a multi-

centre trial in Greater Bay Area for registering this innovative CGM system with National Medical Products Administration (NMPA). Supported by competitive and investigator-initiated industry grants, Elaine is now studying the use of different CGM systems in patients with DKD to improve glycaemic control as well as using CCM to enhance the effects of lifestyle modification in people with pre-diabetes.

Informed by the mechanistic studies conducted by their team which confirmed the effects of 2 Chinese Medicine (CM) formulation in improving beta cell function and insulin resistance, they had been supported by a CUHK Strategic Grant to evaluate the effects of a novel CM formulation with an aim to revert prediabetes in high risk subjects for diabetes. This study was conducted in collaboration with Zhixiu Lin of the CUHK Hong Kong Institute of Integrated Medicine and Phase 1 Clinical Trial Centre. Supported by Paul KS Chan, we are exploring the effects of this novel CM formula on microbiota and multiomic changes and their correlations with beta-cell function and insulin resistance. Guided by the promising results of this pilot study, they have applied for an ITC grant to develop this novel formulation as a proprietary CM with scientific evaluation in phase 1 and phase 2 study aimed at applying for registration with indication for prevention and progression of type 2 diabetes.

Knowledge Transfer, International Profile and People Development

As an International Diabetes Federation (IDF) Centre of Excellence in Diabetes Care, the team continues to build professional capacity through their Master, Diploma and Certificate Courses in Endocrinology, Diabetes and Metabolism and their annual Hong Kong Diabetes and Cardiovascular Risk Factor – East Meets West Symposium organised by the Hong Kong Institute of Diabetes and Obesity. Several of their PhD graduates and fellows have graduated and are now academic leads in other institutions. These include Lee Ling Lim who is now Associate Professor at the University of Malaya; Guozhi Jiang, Associate Professor at the Sun Yat Sun Medical University; Feifei Cheng, Assistant Professor at Shanghai Jiaotong University; Rosemary Yeung, Assistant

Professor at University of Alberti and Dr Calvin Ke, Assistant Professor at University of Toronto in Canada. XL Yang, who used to be a research assistant professor in CUHK, is now Professor at Tianjian University who continues to be a close collaborator in the field of epidemiology, prevention and management of gestational diabetes.

The Chinese University of Hong Kong, as one of the leading universities in diabetes research, most of the Principal Investigators (PIs) of the diabetes research team are serving on editorial boards of leading diabetes journals and committees of international organisations in the field of diabetes, obesity and related disease, including the IDF (Diabetes Atlas), American Diabetes Association (Precision Medicine) and KDIGO (Kidney Disease Improving Global Outcome) Practice Guidelines. Some are members of steering committees of global outcome clinical trials and consultants of global and regional advisory boards of multinational companies including Astra Zeneca, Bayer, Boehringer Ingelheim, Celltrion, Merck Sharpe Dohme, Sanofi, Pfizer and Viatrix Pharmaceuticals. Apart from serving on Food and Health Bureau and Hospital Authority committees on diabetes, noncommunicable disease (NCD) and drug utilisation, most of the PIs are members of grant review committees of ITC, RGC and HMRF and contribute to the scholastic development in Hong Kong.

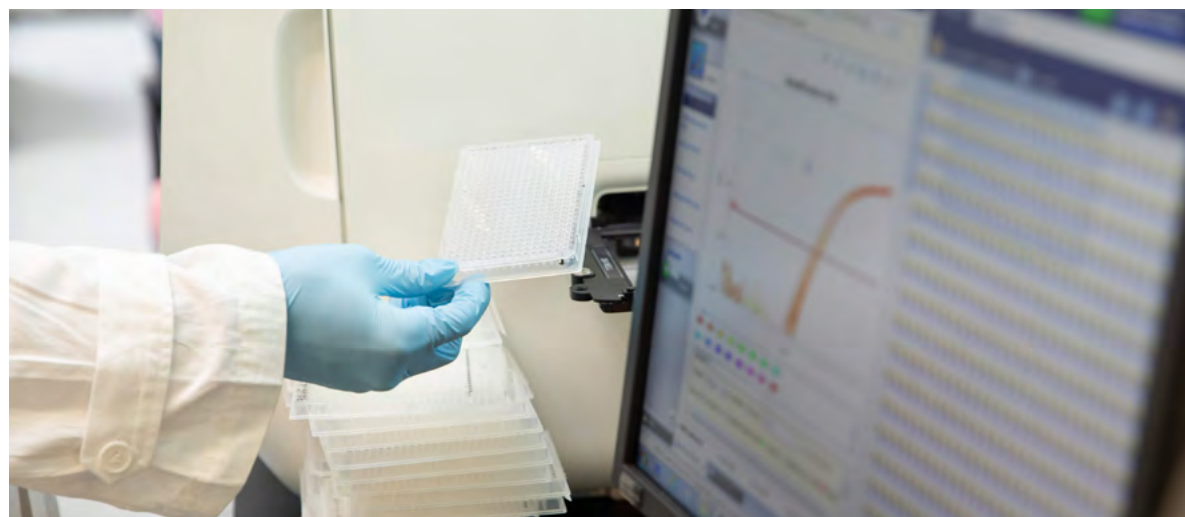
On the knowledge transfer front, the team continues to promote the JADE platform through the ADF, governed by the CUHK Foundation and implement the JADE-assisted data-driven diabetes prevention and care program at the

CUHK Yao Chung Kit Diabetes Assessment Centre in partnership with the CU Medical Centre.

Awards and Recognitions

Several of their postgraduate students have received awards from the Faculty of Medicine or conferences for their excellent performance. Jamie Cheung, a PhD student and a qualified pharmacist from Canada received the Hong Kong PhD Fellowship Scheme (HKPFS) 2020-2021 award under the mentorship of Alice. Noel Ng, their PhD graduate, received a 3-year postdoctoral fellowship from the new RGC scheme on a topic related to polycystic ovarian syndrome under the mentorship of Ronald.

In 2021, Ronald Ma received the Senior Croucher Fellowship and Elaine received the Hong Kong College of Physician Young Researcher Award. At the International Congress of Diabetes and Metabolism and Asian Association for Study of Diabetes (AASD) Scientific Meeting, Ronald delivered the Pan Xiao Ren Epidemiology Award Lecture bestowed by the Asian Association for Study in Diabetes. At the Virtual IDF Congress, Juliana delivered the Hellmut Mehnert Award Lecture in recognition of her extensive knowledge in the field of diabetes. For the second consecutive year, the CUHK was ranked number 1 in Asia for Endocrinology and Metabolism by the United States News Best Global Universities Rankings. In recognition of the impacts of their 3 decades of research, their JADE-assisted, data-driven diabetes care model was published as one of the 5 CUHK impact stories in the 2020 Research Assessment Exercise.



Research Awards and Recognitions

Member's Name	Details	
	Award / Recognition	Organisation
The Chinese University of Hong Kong Endocrine and Diabetes Team	Number 1 in Asia for Endocrinology and Metabolism	Best Global Universities Rankings U.S. News
The Chinese University of Hong Kong	Transforming Diabetes Care: From Research to Practice to Community	Impact Case of Research Assessment Exercise 2020 from the University Grants Committee
Juliana Chan	Hellmut Mehnert Award	University of Oxford
Ronald Ma	Xiaoren Pan Distinguished Research Award for Epidemiology of Diabetes in Asia	Asian Association for Study of Diabetes
Dandan Mao	Young Investigator Award	American Diabetes Association

Fellowships

Member's Name	Details	
	Fellowship	Organisation
Ronald Ma	Croucher Senior Medical Research Fellowship	Croucher Foundation
Eric Lau	Faculty Postdoctoral Fellowship	The Chinese University of Hong Kong Faculty of Medicine
Aimin Yang	Impact Research Fellowship	The Chinese University of Hong Kong Research Committee

Academic Editorship

Member's Name	Details	
	Role	Journal
Juliana Chan	International Advisor	The Lancet Diabetes and Endocrinology

Member's Name	Details	
	Role	Journal
Juliana Chan	Editorial Board Member	Diabetes Metabolism Research Review
		Journal of Diabetes
Ronald Ma	Expert Editor	Journal of Diabetes Investigation
	Editorial Board Member	PLOS Medicine
		Obesity Reviews
Associate Editor	Journal of Diabetes Investigation	
Alice Kong	Editor-in-chief	Primary Care Diabetes
	Editorial Board Member	Diabetes Technology & Therapeutics
Andrea Luk	Associate Editor	Diabetic Medicine
Elaine Chow	Associate Editor	Primary Care Diabetes

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK\$)
Juliana Chan Ronald Ma	Using Whole Genome Sequencing, Computational Biology and Functional Analysis to Discover Biological Pathways Implicated in Diabetic Kidney Disease	AstraZeneca Investigator Initiated Study	2019	2022	8,970,000
Juliana Chan Andrea Luk	Precision Medicine to Redefine Insulin Secretion and Monogenic Diabetes (PRISM) in Chinese Patients with Young Onset Diabetes	Food and Health Bureau – Health and Medical Research Fund Commissioned Grant	2019	2024	8,457,718
Juliana Chan	Self-managing Healthy Eating & Active Lifestyle for Impeding 3-Highs (High Blood Glucose, High Blood Pressure and High Cholesterol) Mobile Application (SHEALF3 APP) (Renamed as Citybite APP)	Innovation and Technology Fund for Better Living via Asia Diabetes Foundation	2018	2022	4,247,006
	Conducting Diabetes Health Seminars and Weight Management Short Courses for Clinical Research	The Chinese University of Hong Kong Jockey Club Multi-Cancer Prevention Programme	2019	2021	600,000

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK\$)
Juliana Chan Elaine Chow	Real-World Evidence on the Effects of Metformin on Clinical Outcomes in Patients with Type 2 Diabetes at Different Stages of Chronic Kidney Disease	Merck (Germany) Investigator Initiated Study via Asia Diabetes Foundation	2020	2021	1,265,000
Elaine Chow	Effects of Dorzagliatin on 1 st Phase Insulin and Beta-Cell Glucose Sensitivity in Individuals with Recent-Onset Type 2 Diabetes and Monogenic Diabetes	Hua Medicine Investigator Initiated Study	2020	2021	1,290,863
Juliana Chan Andrea Luk	Development of an ABC-S Model to Predict Atherosclerotic Cardiovascular Disease in Chinese Patients with Type 2 Diabetes for Early Intervention	Lilly (USA) Investigator Initiated Study via Asia Diabetes Foundation	2020	2021	780,000
Juliana Chan	Transforming Diabetes Care: From Research to Practice to Community	The Chinese University of Hong Kong Research Committee's One-off Project Impact Enhancement Fund	2019	2021	500,000
	Using Modern and Traditional Technologies to Redefine and Prevent Young Onset Diabetes	The Chinese University of Hong Kong Funding for Research Sustainability of Major Research Grants Council Funding Schemes	2019	2022	500,000
	Aldose Reductase Inhibition for Stabilisation of Exercise Capacity in Heart Failure: A Multicenter, Randomised, Placebo-controlled Study to Evaluate the Safety and Efficacy of AT-001 in Patients with Diabetic Cardiomyopathy / Stage B Heart Failure at High Risk of Progression to Overt Heart Failure (Stage C Heart Failure)	Applied Therapeutics	2021	2024	1,500,000

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK\$)
Ronald Ma	A Nanotechnology Platform for Profiling Diabetes-related MiRNA for Precision Medicine	Innovation and Technology Commission – Midstream Research Programme for Universities	2021	2023	5,998,400
	Croucher Senior Medical Research Fellowship	Croucher Foundation	2021	2022	2,272,948
	Precision Medicine in Diabetes	Croucher Foundation	2021	2022	2,000,000
	Unraveling the Link between Maternal Hyperglycaemia and Childhood Obesity: Genome-Wide Methylation Analysis in a Prospective Cohort of Untreated Gestational Diabetes	Research Grants Council – General Research Fund	2019	2021	970,517
Ronald Ma Juliana Chan	Translating Multi-Omic Discoveries to Transform Diabetes Care and Reduce Diabetic Complications	Research Grants Council – Research Impact Fund	2019	2024	8,400,000
Ronald Ma	Translating Multi-Omic Discoveries to Transform Diabetes Care and Reduce Diabetic Complications	Research Committee Funding for Research Sustainability of Major Research Grants Council Funding Schemes	2019	2024	500,000
Alice Kong	The Impact of Cognitive Behavioral Therapy for Insomnia on Glycemic Control in Older Type 2 Diabetes Comorbid with Insomnia	Food and Health Bureau – Health and Medical Research Fund	2021	2023	1,484,694
Andrea Luk	Delineating The Metabolic Architecture and Response to Anti-Hyperglycaemic Drug Treatment in Lean Type 2 Diabetes in Chinese	Research Grants Council – General Research Fund	2021	2023	1,178,778
Elaine Chow	Effectiveness and Safety Study of the Continuous Glucose Monitoring System (Fibersense) for Home Use (Including In-Clinic Sessions) in Patients with Diabetes	Innovation and Technology Commission – Guangdong Hong Kong Technology Cooperation Funding Scheme	2020	2022	5,674,000

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK\$)
Elaine Chow Juliana Chan	A Phase 1b/2a Ascending Dose Study of the Safety, Tolerability and Preliminary Efficacy of Sublingual Liraglutide in Patients with Type 2 Diabetes	Innovation and Technology Commission – Partnership Research Programme	2020	2021	3,680,203
Elaine Chow	Continuous Glucose Monitoring as An Adjunct to Lifestyle Modification in Individuals with Impaired Glucose Tolerance: A Randomised Controlled Trial	Food and Health Bureau – Health and Medical Research Fund	2020	2023	1,344,796



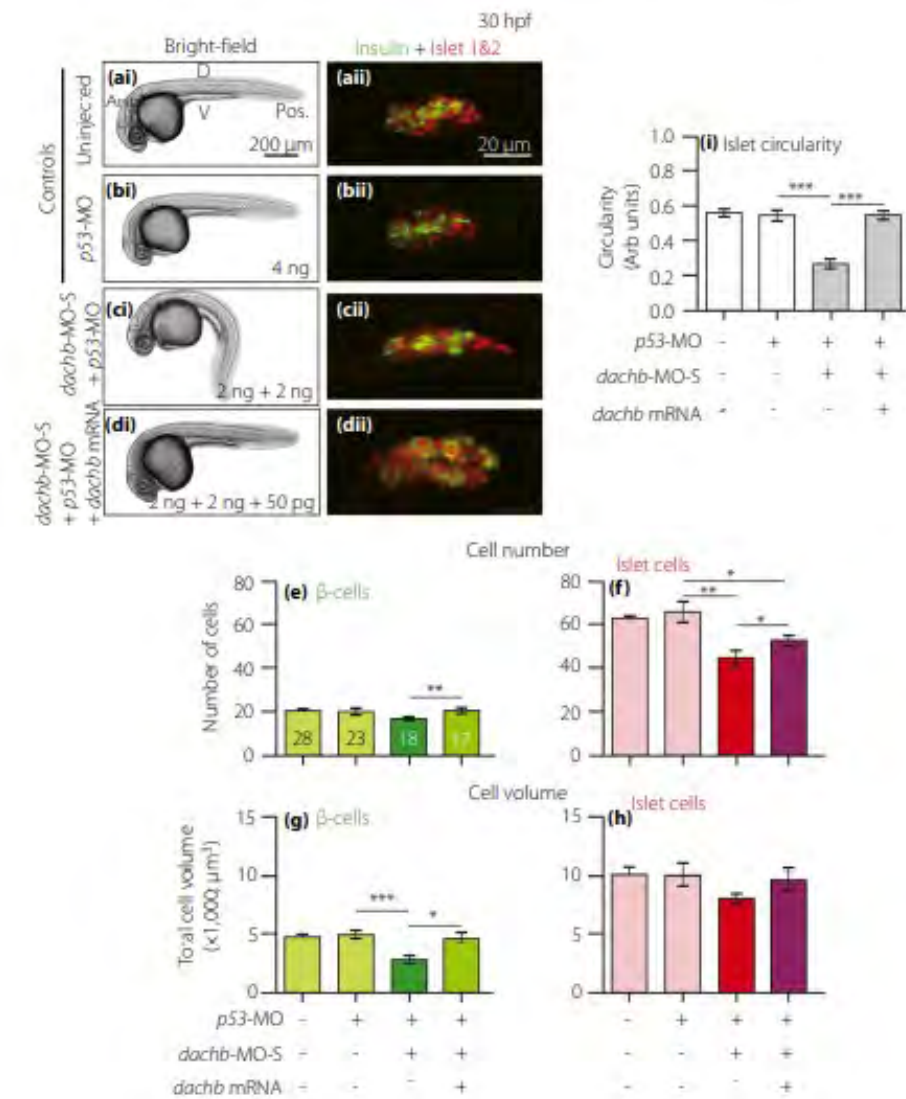
Publications

A. Journal Papers

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Genetic variation of DACH1 was first discovered by the research team in Chinese patients with young onset diabetes which had been validated in multiple Asian cohorts. In collaboration with Hong Kong University of Science and Technology, they used zebra fish models to elucidate the functional significance of this gene.

Injection of dachb messenger ribonucleic acid (mRNA) rescues the effect of splice-blocking dachb-morpholino (dachb-MO-S) on the development of the pancreatic islet in embryos at 30 h post-fertilization (hpf). Embryos were (a) uninjected (control) or they were injected at the one-cell stage with (b) p53-MO (control), (c) 2 ng dachb-MO-S + 2 ng p53-MO or (d) 2 ng dachb-MO-S + 2 ng p53-MO + 50 pg dachb mRNA. (ai–dii) Bright-field images were acquired at 30 hpf, after which the embryos were whole-mount double-immunolabeled with antibodies to insulin (green) and islet 1 and 2 (red) to show the localization of the β -cells and islet cells in the endocrine pancreas, respectively. (aii–dii) These are all single optical sections taken through the middle of pancreatic islet. (e,f) The number of (e) β -cells and (f) islet cells, and (g,h) the volume of (g) β -cells and (h) islet cells. (i) The circularity of the pancreatic islet. The data are presented as the mean – standard error of $n = 10$ to 28 embryos, such that the number is shown in the respective bars in panel (e). The asterisks indicate significant differences at $P < 0.05^*$, $P < 0.01^{**}$ or $P < 0.001^{***}$ using the Mann–Whitney U-test. Ant., anterior; D, dorsal; NS, not significant; Pos. posterior; V, ventra

Source: Yang L, Webb SE, Jin N, Lee HM, Chan TF, Xu G, Chan JC, Miller AL, Ma RC. Investigating the role of dachshund b in the development of the pancreatic islet in zebrafish. *Journal of Diabetes Investigation*. 2021;12(5):710-727. doi: 10.1111/jdi.13503.