Research Assessment Exercise 2020
Impact Case Study

University: The University of Hong Kong (HKU)
Unit of Assessment (UoA): 02 - Pre-Clinical Studies
Title of case study: Commercialization of biomarkers for prediction and therapeutic intervention of cardiometabolic diseases: from bench to bedsides and beyond

(1) Summary of the Impact

Hong Kong University (HKU) researchers have discovered and characterized four fat-derived biomarkers and metabolic hormones which can be utilized for risk prediction, early diagnosis and therapeutic interventions for diabetes and its cardiovascular complications. The team has developed proprietary rapid assays for these biomarkers and validated the clinical utility of these assays in different ethnic groups. Based on their patented discovery, a strategic alliance with Servier was established to develop novel therapies for obesity-related cardiometabolic diseases. A HKU spin-off biotech company has been formed in 2016 for licensing and commercialization of the diagnostic products in the global market. Sufficient money has been raised and research staffs have been employed for production development and registration in Hong Kong Science Park. A community-based screening program for diabetes using our assays has been initiated in 2019 in Dongguan city, China.

(2) Underpinning research - key research insights and findings

Key HKU Researchers (Dept. of Medicine, Dept. of Pharmacology and Pharmacy, and State Key Laboratory of Pharmaceutical Biotechnology):
Professor Aimin Xu (Chair Professor, 2002 – present)
Professor Yu Wang (Professor, 2004 – present)
Dr Ruby Hoo (Assistant Professor, 2004 – present)

Early diagnosis and interventions are still the most effective strategy to manage diabetes and its complications, the major cause of disability and death in our rapidly ageing population. In this connection, our team has discovered several adipose (fat)-derived metabolic hormones which can be exploited as diagnostic biomarkers for risk prediction and therapeutic targets for early intervention of diabetes and its complications.

In 2002, HKU researchers were the first to identify several bioactive glycol-isoforms of adiponectin, a fat cell-secreted insulin-sensitizing hormone with anti-diabetic activity (3.1) *(US patent 7,365,170*), and demonstrated that O-glycosylation of the collagenous domain is crucial for the formation of oligomeric structure required for the insulin-sensitizing activity of adiponectin. These novel findings set the foundation for studying the structural and molecular basis of this anti-diabetic hormone in the coming decade. Our subsequent study uncovered a key function of adiponectin in protection against obesity-related fatty liver disease (3.2), and demonstrated that low level of adiponectin (hypoadiponectinemia) is a risk factor for obesity-related metabolic and vascular diseases (*Tan K, JCEM, 2004* DOI 10.1210/jc.2003-031012). We also discovered a key mechanism to explain why males have lower level of adiponectin than females, which may contribute to the fact that men have higher incidence of diabetes and cardiovascular diseases than women. Since then, thousands of studies from different ethnic groups have consistently demonstrated that low circulating level of adiponectin is an independent predictor for future development of diabetes. To further promote its clinical application, in 2015, our team developed the first immunoturbulent assay (ITA), which enables rapid and automatic detection of plasma adiponectin.

In 2006-7, we identified another two fat-secreted hormones (adipocyte fatty acid binding protein (A-FABP) and lipocalin-2), both of which play key roles in linking obesity with diabetes and its

complications (3.3, 3.4*, US patents* ***8,030,097 B2 & 8,481,032B2***). Our subsequent studies discovered that A-FABP exacerbates obesity-induced cardio-metabolic diseases by potentiating toxic lipids-induced pro-inflammatory responses, while lipocalin-2 triggers metabolic inflammation by facilitating the crosstalk between neutrophils and macrophages. In collaboration with several medical centers in Mainland China and overseas, we discovered the predictive value of these two adipokines in the future development of diabetes, metabolic syndrome and cardiovascular events, in several community-based prospective studies in Hong Kong (CRISP), Shanghai (SHDHS) and Australia (FIELD) (3.5). We also demonstrated that pharmacological or genetic inhibition of these two adipokines is effective for treating a cluster of obesity-related cardio-metabolic diseases (3.*6*).

(3) References to the research

3.1 **Yu Wang, Aimin Xu,** Catriona Knight, Lance Yi Xu, Garth JS Cooper. Hydroxylation and Glycosylation of the Four Conserved Lysine Residues in the Collagenous Domain of Adiponectin: Potential role in the modulation of its insulin-sensitizing activity. **Journal of Biological Chemistry**, 2002, 277(22): 19521-9. DOI: 10.1074/jbc.M200601200 **(cited 490 times, US patent No 7,365,170).**

3.2 **Aimin Xu, Yu Wang,** Hussila Keshaw, Lance Yi Xu, **Karen SL Lam**, Garth JS Cooper. The fat-derived hormone adiponectin alleviates alcoholic and nonalcoholic fatty liver diseases in mice. **Journal of Clinical Investigation**, 2003, 112 (1), 91-100. DOI: 10.1172/JCI17797 (**cited 1448 times)**.

3.3 **Aimin Xu, Yu Wang,** Jian Yu Xu, David Stejskal, Sidney Tam, Jialiang Zhang, Nelson MS Wat, Wai Keung Wong, **Karen SL Lam**. Adipocyte Fatty Acid-Binding Protein Is a Plasma Biomarker Closely Associated with Obesity and Metabolic Syndrome. **Clinical Chemistry**, 2006, 52(3): 405-13. DOI: 10.1373/clinchem.2005.062463 (**cited 522 times**).

3.4 **Wang Y, Lam KS**, Kraegen EW, Sweeney G, Zhang J, Tso AW, Chow WS, Wat NM, Xu JY, Hoo RL and **Xu A***. Lipocalin-2 is an inflammatory marker closely associated with obesity, insulin resistance and hyperglycemia in humans. **Clin Chem**, 2007, 53(1):34-41. DOI: 10.1373/clinchem.2006.075614 (cited >490 times, with US patent **8,030,097 B2***)*

3.5 **Xu A**, Tso AW, **Cheung BM, Wang Y**, Wat NM, Fong CHY, Yeung DCY, Janus ED, Sham PC and Lam KS. Circulating adipocyte-fatty acid binding protein levels predict the development of the metabolic syndrome: a 5-year prospective study. **Circulation**, 2007, 115(12):1537-43. DOI: 10.1161/CIRCULATIONAHA.106.647503 **(cited 588 times)**

3.6 Law IK, Xu A, Lam KS, Berger T, Mak TW, Vanhoutte PM, Liu JT, Sweeney G, Zhou M, Yang B, Wang Y. Lipocalin-2 deficiency attenuates insulin resistance associated with aging and obesity. **Diabetes.** 2010, 59(4): 872-82. DOI: 10.2337/db09-1541 (US patent ***8,481,032B2).*** **(cited 203 times)**

Key grants

Grant 1. Xu A et al. A Multi-disciplinary Approach to Investigate Vascular Dysfunction in Obesity and Diabetes: From Molecular Mechanism to Therapeutic Intervention. The Research Grants Council Collaborative Research Fund (RGC CRF, C7055-14G) (6/2015 – 6/2018) HK$8,780,850

Grant 2. Lam KSL, Xu A et al. To Establish a Metabolic Study Center in Hong Kong: Focusing on the Emerging Metabolic Hormones. The Research Grants Council Collaborative Research Fund (RGC CRF, HKU3/CRF/09) (6/2013-5/2016) HK$8,000,000

Grant 3. Xu A et al. A Multi-disciplinary Approach to Investigate Vascular Dysfunction in Obesity and Diabetes: From Molecular Mechanism to Therapeutic Intervention. The Research Grants Council Collaborative Research Fund (RGC CRF, HKU4/CRF/10) (6/2011 – 6/2014) HK$7,280,000

Grant 4: Xu A, Development of Innovative Chemiluminescent Immunoassays for Diabetes and its Cardiovascular Complications, Hong Kong Government - Innovation and Technology Commission (ITC) - (UIM/270) (4/2015-12/2017) HK$4,002,608.

Grant 5: Xu A, Vascular dysfunction in obesity and diabetes: from risk prediction to therapeutic intervention. The Research Grants Council Collaborative Research Fund (RGC CRF,HKU2/07C)

(06/2008-06/2011), HK$ 5,500,000
Grant-6: Xu A, Adiponectin as a novel diagnostic marker and therapeutic target for the treatment of diabetes, steatohepatitis and other metabolic disorders, Hong Kong Government - Innovation and Technology Commission (ITC), (ITS/048/03) (07/2003-01/2006), HK$ 2,538,960

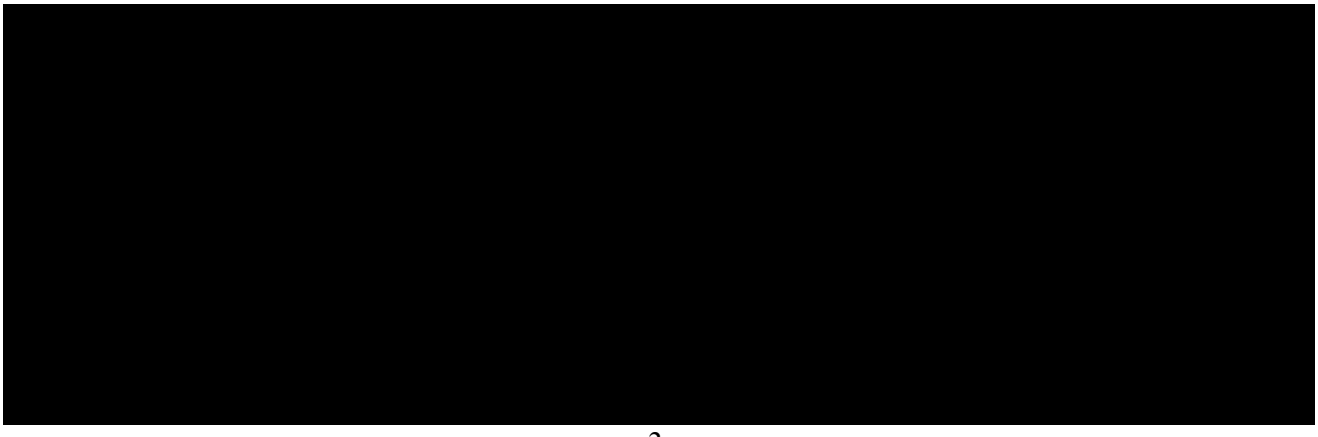
(4) Details of the impact (For supporting evidence cited, please refer to Section 5)
Impacts include: health and welfare, commercial, public policy and services
Main Beneficiaries include: Governments in Mainland China and Hong Kong, World Health Organisation (WHO), Food and Agriculture Organisation (FAO) and World Organisation for Animal Health (OIE)

Metabolic diseases such as diabetes and its vascular complications have reached epidemic proportions worldwide. According to the latest WHO statistics, there were 425 million diabetic patients in the world in 2017, while China accounted for 114 million. Furthermore, nearly 400 million prediabetic individuals are at high-risk of developing diabetes in China. Therefore, there is huge market potential for biomarkers which can be used for risk prediction and early therapeutic intervention for diabetes and its complications.

Impact on health, wellbeing and commerce: Influencing Commercial R&D

Although data from our group and others have demonstrated the potential of using adiponectin as a biomarker for diabetes prediction and monitoring，promoting the clinical application of adiponectin as a diagnostic marker has been constrained by the lack of a standardized and simple assay. We have developed a proprietary immunoturbidimetric assay (ITA) for rapid and accurate measurement of plasma adiponectin levels in an Automatic Chemical Analyzer, a machine widely used in clinical diagnostics laboratories. Thus, our innovation makes it possible to measure adiponectin as a cheap and routine assay, and to standardize the data among different clinical laboratories (CN patent application no: 201810211206.7) **[A**]. In 2017, we formed a joint venture with Guangdong Uniten Biotechnology Co., LTD in Mainland China to market our adiponectin ITA products in global market for diabetic care **[B]**. In 2018, our adiponectin ITA product was granted with approvals from CFDA (Chinese Food and Drug Administration) (Registration no: 20182400947) and CE certification from Europe (no. 2891) **[C] i, ii**. This Joint Venture has annual sales volume of approximately 25 million RMB **[F]**.

Based on our series of findings that high plasma levels of A-FABP and lipocalin-2 predict the future development of cardiovascular events and heart attack, we also developed chemiluminescent immunoassays (CLIA) for these two adipokines for risk prediction of cardiovascular diseases, via partnership with Zhong Long Industrial Co. Ltd (a subsidiary company of Pien Tze Huang Co LTD, a biotech company listed in stock market of China). We have obtained support of 4 million $HK from Hong Kong ITC University-industrial Matching Fund between 2015-17 to develop and validate the diagnostic assays **[E]**. The diagnostic products are now under CFDA review for registration and will be used clinically in coming years.



[redacted]

Impact on health, wellbeing and commerce: Spin-Off Biotech companies for the management of cardiometabolic diseases

To facilitate the clinical and industrial applications of our laboratory-based discoveries and technology development, we founded Immunodiagnostics Co Ltd as a HKU spin-off biotech company (supported by ITC "Technology Start-up Support Scheme for Universities" (TSSSU)) in 2015 **[I, G]**, focusing on discovery of novel biomarkers and development of assays for cardiometabolic diseases. Thus far, we have successfully developed over 20 highly-specific assays which are widely for research, high throughput drug screening and clinical diagnosis [I] (www.immunodiagnostics.com.hk). The end users are from a large number of major research institutes, hospitals and biotech companies globally **(G)**. We have established our R&D center in Hong Kong Science Park, and are expanding our R&D capacity in Shenzhen, with the objective to be a world-leading biotech company in this field. Additionally, our joint venture with Guangdong Uniten Biotech Co. Ltd, which has over 6,000 square meter of GMP-certified manufacturing factory with over 70 technical staff (http://www.unitenbio.com/) **(B, F),** to become a bio-incubator for Hong Kong's small biotech companies for licensing and commercialization of their diagnostic products in China and overseas.

Impact on health, well-being and public policy

Our joint venture company Guangdong Uniten Biotech Co. Ltd is now actively promoting the clinical application of the adiponectin ITA assay for routine diabetic screening tests in the community, and for early diagnosis of prediabetes in both Mainland China and Hong Kong. A population-based diabetes screening program using our adiponectin ITA assay has been initiated in Dongguan City, China in 2019 **[H]** to screen 2 million local residents with our adiponectin ITA assay. We are promoting our adiponectin ITA assay as a routine test for screening and precision diagnosis of diabetes in communities and physical examination centers and medical diagnostic laboratories globally.

(5) Sources to corroborate the impact

[A] A Letter from China Patent Burea stating that the adiponectom ITA assay patent is under process with the PRC patent application no. 201810211206.7

[B] [redacted]

[C] i) CFDA approval in Chinese (Registration no. 20182400947)

ii) CE certification from Europe (no. 2891) for adiponectin assay products

[D] [redacted]

[E] ITC supported industry-university collaboration with our industrial partner for development of diagnostic assays

[F] [redacted]

[G] [redacted]

[H] [redacted]

[I] Registration certificate of Immunodiagnostics Ltd in Hong Kong