Project number: T12-402/13N

**RESEARCH GRANTS COUNCIL**
**THEME-BASED RESEARCH SCHEME (TRS)**

**Completion Report on Funded Project**

*Project start date:* *1st January 2014*
*Project completion date:* *31st December 2018*

**1. Project Title:** An Integrated Transomics Approach to Diabetic Cardio-renal Complications: From Novel Discoveries to Personalized Medicine

**2. Names and Academic Affiliations of Project Team Members#**

| Project team member | Name / Post | Unit / Department / Institution | Average number of hours per week spent on this project in the whole project period |
|---|---|---|---|
| Project Coordinator (PC) | Ma, Ching Wan Ronald/ Professor | Endocrinology & Diabetes/Department of Medicine & Therapeutics/The Chinese University of Hong Kong | 15hrs/week |
| (Co)-Principal Investigator(s) (Deputy Project Coordinator) | Chan, Juliana Chung Ngor / Professor of Medicine and Therapeutics | Director, Hong Kong Institute of Diabetes and Obesity, The Chinese University of Hong Kong | 10hrs/week |
| Co-Principal Investigator(s) | Huang, Yu/ Professor | Institute of Vascular Medicine, The Chinese University of Hong Kong | 10hrs/week |
| | Lan, Hui Yao/ Professor | Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong | 10hrs/week |
| | Lok, Si/ Professor | Centre for Applied Genomics, The Hospital for Sick Children, Toronto, Canada | 2hrs/week |
| | Tomlinson, Brian/ Professor | Dept. of Medicine and Therapeutics, CUHK | 6hrs/week |
| | Tsui, Kwok Wing Stephen/ Professor | Director, Hong Kong Bioinformatics Centre, The Chinese University of Hong Kong | 10hrs/week |
| | Yu, Weichuan/ Associate Professor | Dept. of Electronic and Computer Engineering, HKUST | 10hrs/week |

| | | | |
|---|---|---|---|
| Co-Investigator(s) | Chan, Ting Fung/ Associate Professor | School of Life Sciences, CUHK | 8hrs/week |
| | Fan, Xiaodan/ Associate Professor | Department of Statistics, CUHK | 6hrs/week |
| | Luk, On Yan Andrea/ Associate Professor | Dept. of Medicine and Therapeutics, Prince of Wales Hospital, CUHK | 6hrs/week<br>Added on 16.12.16 |
| | So, Wing Yee/ Consultant and Honorary Associate Professor | Dept. of Medicine and Therapeutics, Prince of Wales Hospital, CUHK | 6hrs/week |
| | Szeto, Cheuk Chun/ Professor | Renal Division, Dept. of Medicine and Therapeutics, CUHK | 5hrs/week |
| | Tang, Leung Sang Nelson/ Professor | Dept. of Chemical Pathology, CUHK | 2hrs/week |
| | Tian, Xiaoyu/ Research Assistant Professor | School of Biomedical Sciences, CUHK | 8hrs/week<br>Added on 16.12.16 |
| | Yip, Yuk Lap/ Assistant Professor | Dept. of Computer Science and Engineering, CUHK | 8hrs/week |
| Collaborators | Lau, Ip Tim/ Consultant | Dept. of Medicine, Tseung Kwan O Hospital, Hong Kong | N.A. |
| | Lau, Kam Piu/ Consultant | Dept. of Medicine, Northern District Hospital, Hong Kong | N.A. |
| | Lee, Ka Fai/ Consultant | Dept. of Medicine and Geriatrics, Kwong Wah Hospital, HK | N.A. |
| | Leung, Jenny/ Consultant | Dept. of Medicine and Geriatrics, Ruttonjee Hospital, Hong Kong | N.A. |
| | Li, Kam Yin June/ Senior Medical Officer | Dept. of Medicine, Yan Chai Hospital, Hong Kong | N.A. |
| | Siu, Shing Chung/ Consultant | Dept. of Medicine, Tung Wah Eastern Hospital, HK | N.A. |
| | Tsang, Chiu Chi/ Associate Consultant | Dept. of Medicine, Alice Ho Miu Ling Hospital, Hong Kong | N.A. |
| | Tsang, Man Wo/ Consultant | Dept. of Medicine and Geriatrics, United Christian Hospital, HK | N.A. |
| | Yeung, Tok Fai Vincent/ Consultant | Dept. of Medicine and Geriatrics, Our Lady of Maryknoll Hospital, Hong Kong | N.A. |
| | Yu, Cheuk Man/ Honorary Clinical Professor | Dept. of Medicine and Therapeutics, CUHK | N.A. |

| | | | |
|---|---|---|---|
| | Xu, Gang/ Adjunct Assistant Professor | Hong Kong Institute of Diabetes and Obesity, The Chinese University of Hong Kong | N.A. |
| | Hu, Cheng/ Associate Professor | Shanghai Institute of Diabetes, Shanghai, China | N.A. |
| | Cho, Yoon Shin/ Professor | Dept. of Biomedical Science, Hallym University, Rep. of Korea | N.A. |
| | Deloukas, Panos/ Sen. Group Leader | Wellcome Trust Sanger Institute, Hixton, UK | N.A. |
| | Groop, Leif/ Professor | Lund University Diabetes Centre, Malmo, Sweden | N.A. |

*# Please highlight the approved changes in the project team composition and quote the date when the RGC granted approval of such changes. For changes in the project team composition, please submit a separate request, together with the justification and the curriculum vitae of the new member(s), to the RGC three months prior to the intended effective date of the change.*

## 3. Project Objectives

Summary of objectives addressed/achieved:

| Objectives* | Percentage achieved | Remarks** |
|---|---|---|
| 1. Utilize advanced genomic technologies and an integrated trans-omics approach to define a molecular signatory for diabetic cardiovascular and renal complications | 1. 100% | 1. |
| 2. Establish a territory-wide diabetes registry and biobank for large-scale replication | 2. 100% | 2. |
| 3. Within the context of the trans-omics findings, examine the regulatory roles of the PPAR δ and TGF-β/Smad extended pathways in diabetic cardiovascular and renal complications | 3. 100% | 3. |
| 4. Translate the genomic discoveries to improve the prediction and treatment of diabetic complications through personalized diabetes care | 4. 100% | 4. |

** Please highlight the approved changes in objectives and quote the date when the RGC granted approval of such changes.*

******* *Please provide reasons for significantly slower rate of progress than originally planned.*

## 6. Research Highlights and Outputs

6.1 What are the most exciting research accomplishments of the project?

*(Please list five or more of the team's best research accomplishments, such as journal and conference papers, software codes, research infrastructure, etc. For each item, please clearly justify how it has achieved international excellence (e.g. best paper award, invited presentation, citations, product licensed to industry, etc.))*

1. **Identification of a panel of genetic markers associated with diabetic kidney disease and cardiovascular complications in diabetes**- Through support from the TRS project and the genotyping of a large number of well-phenotyped samples with detailed information on risk of diabetic kidney disease and cardiovascular complications, we have been able to identify a panel of genetic variants associated with the risk of diabetic kidney disease and cardiovascular complications in Chinese with type 2 diabetes, and construct genetic risk scores incorporating these novel markers for prediction of diabetic cardio-renal complications in Chinese subjects with type 2 diabetes. These are now being evaluated in large number of samples both collected locally as well as for overseas collaborators, as well as some functional follow-up for the final publication. The polygenic genetic risk scores for diabetes complications generated from the project represent one of the first examples of polygenic risk scores being developed for the clinical prediction of diabetes complications.

2. **Completion of one of the largest genome-wide association study for diabetic kidney disease**- Our current meta-analysis, including more than 20,000 subjects characterized for diabetic kidney disease, represents one of the largest global study on the genetics of diabetic kidney disease. As a result, we have been invited to join different international initiatives, including the Accelerating Medicines Partnership Type 2 Diabetes Knowledge portal, as well as a grant application on genetics of diabetic kidney disease by an international consortia. An abstract summarizing some of the work from our DKD GWAS was selected for the Young Investigator Award at the 10$^{th}$ Asian Association for the Study of Diabetes (AASD) Scientific Meeting, Kuala Lumpur, 2018.

3. **Establishment of the multi-centre Hong Kong Diabetes Biobank**- With more than 25,000 subjects (>12,000 genotyped to date) recruited into this multi-centre register and biobank with prospective follow-up, this represents one of the largest biorepository dedicated to the study of diabetes and its complications. The HKDB is comparable to other large-scale biobanks such as the UK Biobank (13,250 of 379,411 with diabetes, approximately 3.5% of study population), and China Kadoorie Biobank (30,280 out of 512,869 recruited subjects have diabetes, representing 5.9% of study population) for the study of diabetes-related outcomes.

4. **Elucidation of the downstream effector pathways for smad3 and identification of smad3 dependent lncRNAs**- In addition to expanding on previous work on the role of smad3 in the pathogenesis of diabetic kidney complications, the project has identified a few novel smad-3 dependent transcriptome/lncRNAs with therapeutic potential, including upregulation of lncRNA _5318 as well as lncRNA_9884 in db/db mice with cardiac and renal diseases, and loss of PAX6 with deficient islet beta cell function. Pilot studies utilizing a patented smad3 inhibitor has also been undertaken to examine its potential to prevent diabetes as well as diabetic kidney disease. Abstracts reporting some of the work in this area has received several young investigator awards at international conferences (details see appendix III).

5. **Elucidation of the functional role of unconjugated bilirubin in protection against**

**endothelial dysfunction in diabetic state**- Experimental studies have identified novel biological roles of unconjugated bilirubin as mediator of the vaso-protective effects of Heme oxygenase-1 under hyperglycaemic conditions. The clinical relevance of this finding has further been explored in epidemiological analyses demonstrating the clinical association between increased levels of bilirubin and reduction in diabetes-related vascular outcomes in the Hong Kong Diabetes Register.

6. **Identification of novel genetic loci for type 2 diabetes in East Asians**- Using genotype data generated from the project, we were one of the major contributors to an East Asian meta-analysis of GWAS for type 2 diabetes. With a total of 433,540 genotyped subjects, this represent one of the largest meta-analysis for type 2 diabetes, and led to the identification of 61 novel loci for T2D. This paper has shed new insights on the genetics of T2D in East Asians compared to European population. The paper is now under 3rd review for publication in Nature.

7. **Identification of latent trajectories of renal function decline in type 2 diabetes**- Our novel analysis utilizing latent trajectory analysis has identified a subgroup of individuals with "accelerated decline" in renal function on prospective follow-up, and identified association with several genetic variants. This work has been published in the top nephrology journal *Kidney International*. Additional work to identify novel genetic variants associated with this high risk of renal deterioration is currently ongoing.

6.2 What was the added value of the TRS funding, rather than standard project grant funding?
*(For example, could this work have been achieved with other funding scheme, such as the General Research Fund or Collaborative Research Fund? If not, why?)*

The TRS funding was vital to supporting much of the research infrastructure, as well as the processing of a very large number of patient samples, and the generation of genotyping data on a large number of well-phenotyped individuals. This would not have been possible using standard project funding. The availability of this large dataset has facilitated much work undertaken by the project team, and placed the project team in a strong position in international collaborations as well as providing the opportunity to lead some major efforts. Sustained support from the TRS funding was also vital in providing the support required to establish the Hong Kong Diabetes Biobank, with collaboration of 11 diabetes centres across Hong Kong. This important resource will be invaluable for future work on precision medicine in diabetes.

6.3 If the project has not met its original objectives, why?

N/A

6.4 (a) Peer-reviewed journal publication(s) arising directly from this project:
*(Please attach a copy of the publication and/or the letter of acceptance if not yet submitted in the previous progress report(s). All listed publications must acknowledge RGC's funding support by quoting the specific grant reference. Please mark the symbol "#" next to the publications involving inter-institutional collaboration s)*

Please find below selected examples of publications arising from the project.

| The Latest Status of Publications | | | | Author(s) *(denote the corresponding author with an asterisk*)* | Title and journal/book *(with the volume, pages and other necessary publishing details specified)* | Submitted to the RGC *(indicate the year ending of the relevant progress report)* | Attached to this report *(Yes or No)* | Acknow-ledged the support of RGC *(Yes or No)* | Accessible from the institutional repository *(Yes or No)* |
|---|---|---|---|---|---|---|---|---|---|
| Year of publication | Year of acceptance *(for paper accepted but not yet published)* | Under review | Under preparation *(optional)* | | | | | | |
| 2015# | | | | Zhou Q, Xiong Y, Huang XR, Tang P, Yu X, **Lan HY*** | Identification of Genes Associated with Smad3-dependent Renal Injury by RNA-seq-based Transcriptome Analysis/***Sci Rep.***/ 5:17901. | 2016 | No | Yes | No |
| 2015 | | | | Yang G, Jiang W, Yang Q, **Yu W**. | PBOOST: A GPU-based tool for parallel permutation tests in genome-wide association studies. ***Bioinformatics***, 31(9):1460-2, 2015. | Yes | No | Yes | No |

| The Latest Status of Publications | | | | Author(s) *(denote the corresponding author with an asterisk*)* | Title and journal/book *(with the volume, pages and other necessary publishing details specified)* | Submitted to the RGC *(indicate the year ending of the relevant progress report)* | Attached to this report *(Yes or No)* | Acknow-ledged the support of RGC *(Yes or No)* | Accessible from the institutional repository *(Yes or No)* |
|---|---|---|---|---|---|---|---|---|---|
| Year of publication | Year of acceptance *(for paper accepted but not yet published)* | Under review | Under preparation *(optional)* | | | | | | |
| 2015# | | | | Liu J, Wang L, Tian XY, Liu LM, Wong WT, Zhang Y, Han Q, Ho HM, Wang N, Wong, SL, Chen ZY, Yu J, Ng CF, Yao X & **Huang Y**. | Unconjugated bilirubin mediates heme oxygenase-1-induced vascular benefits in diabetic mice. ***Diabetes** 2015;* 64(5):1564-1575 with commentary 64(5):1506-1508. | Yes | No | Yes | No |
| 2016# | | | | Jiang G, Hu C, Tam CH, [10authors], **Tsui SK**, Ng MC, **Szeto CC**, Jia W, **Fan X, So WY, Chan JC**, **Ma RC*** | Genetic and Clinical Variables identify predictors of chronic kidney disease in type 2 diabetes/ ***Kid Int***/89(2): 411-20 | 2016 | No | Yes | No |

| The Latest Status of Publications | | | | Author(s) *(denote the corresponding author with an asterisk*)* | Title and journal/book *(with the volume, pages and other necessary publishing details specified)* | Submitted to the RGC *(indicate the year ending of the relevant progress report)* | Attached to this report *(Yes or No)* | Acknow-ledged the support of RGC *(Yes or No)* | Accessible from the institutional repository *(Yes or No)* |
|---|---|---|---|---|---|---|---|---|---|
| Year of publication | Year of acceptance *(for paper accepted but not yet published)* | Under review | Under preparation *(optional)* | | | | | | |
| 2017 | | | | W. Jiang and W. Yu | Jointly determining significance levels of primary and replication studies by controlling the false discovery rate in two-stage genome-wide association studies/ ***Statistical Methods in Medical Research***/ 2017. doi: 10.1177/0962280216687168 | 2017 | No | Yes | No |
| 2017# | | | | Cao Q, Anyansi C, Hu X, Xu L, Xiong L, Tang W, Mok MT, Cheng C, **Fan X**, Gerstein M, Cheng AS, **Yip KY*** | Reconstruction enhancer-target networks in 935 samples of human primary cells, tissues and cell lines, /***Nature Genetics***/9(10):1428-1436 | 2017 | No | Yes | No |

| The Latest Status of Publications | | | | Author(s) *(denote the corresponding author with an asterisk*)* | Title and journal/book *(with the volume, pages and other necessary publishing details specified)* | Submitted to the RGC *(indicate the year ending of the relevant progress report)* | Attached to this report *(Yes or No)* | Acknow-ledged the support of RGC *(Yes or No)* | Accessible from the institutional repository *(Yes or No)* |
|---|---|---|---|---|---|---|---|---|---|
| Year of publication | Year of acceptance *(for paper accepted but not yet published)* | Under review | Under preparation *(optional)* | | | | | | |
| 2017 | | | | **W. Jiang, J. Xue,** and **W. Yu*** | What is the probability of replicating a statistically significant association in Genome-Wide Association Studies/ ***Briefings in Bioinformatics,*** 18(6):928–939 | 2017 | Yes | Yes | No |
| 2017 | | | | **W. Jiang** and **W. Yu*** | Controlling the joint local false discovery rate is more powerful than meta-analysis methods in joint analysis of summary statistics from multiple genome-wide association studies, /***Bioinformatics***/33(4): 500-507, 2017 | 2017 | No | Yes | No |

| The Latest Status of Publications | | | | Author(s) *(denote the corresponding author with an asterisk*)* | Title and journal/book *(with the volume, pages and other necessary publishing details specified)* | Submitted to the RGC *(indicate the year ending of the relevant progress report)* | Attached to this report *(Yes or No)* | Acknow-ledged the support of RGC *(Yes or No)* | Accessible from the institutional repository *(Yes or No)* |
|---|---|---|---|---|---|---|---|---|---|
| Year of publication | Year of acceptance *(for paper accepted but not yet published)* | Under review | Under preparation *(optional)* | | | | | | |
| 2018# | | | | Sun SF, Tang PM, Feng M, Jun X, Huang X, Li P, **Ma RC**, **Lan HY*** | Novel lncRNA Erbb4-IR Promotes Diabetic Kidney Injury in db/db mice by Targeting miR-29b /***Diabetes*** 2018 Apr;67(4): 731-744. | 2017 | Yes | Yes | No |
| 2018# | | | | Zhang H, Liu J, Qu D, Wang L, Wong CM, Lau CW, Huang Y, Wang YF, Huang H, Xia Y, Xiang L, Cai Z, Liu P, Wei Y, Yao X, Ma RC, **Huang Y*** | Serum exosomes mediate delivery of arginase 1 as a novel mechanism for endothelial dysfunctio n in diabetes. ***Proc Natl Acad Sci (PNAS) USA.*** 2018 Jul 17; 115 (29); E6927-E69 36 | No | Yes | Yes | No |

| The Latest Status of Publications | | | | Author(s) *(denote the corresponding author with an asterisk*)* | Title and journal/book *(with the volume, pages and other necessary publishing details specified)* | Submitted to the RGC *(indicate the year ending of the relevant progress report)* | Attached to this report *(Yes or No)* | Acknow-ledged the support of RGC *(Yes or No)* | Accessible from the institutional repository *(Yes or No)* |
|---|---|---|---|---|---|---|---|---|---|
| Year of publication | Year of acceptance *(for paper accepted but not yet published)* | Under review | Under preparation *(optional)* | | | | | | |
| 2018# | | | | Yip DK, Chan LL, Pang IK, Jiang W, **Tang NL, Yu W, Yip KY*** | A network approach to exploring the functional basis of gene-gene epistatic interactions in disease susceptibility/ ***Bioinformatics*** 34(10):1741-1749. doi: 10.1093/bioinformatics/bty005. | 2017 | No | Yes | No |
| 2018 | | | | **Ma RC*** | Epidemiology of diabetes and diabetic complications in China. ***Diabetologia*** https://doi.org/10.1007/s00125-018-4557-7 | No | Yes | Yes | No |

| The Latest Status of Publications | | | | Author(s) *(denote the corresponding author with an asterisk*)* | Title and journal/book *(with the volume, pages and other necessary publishing details specified)* | Submitted to the RGC *(indicate the year ending of the relevant progress report)* | Attached to this report *(Yes or No)* | Acknow-ledged the support of RGC *(Yes or No)* | Accessible from the institutional repository *(Yes or No)* |
|---|---|---|---|---|---|---|---|---|---|
| Year of publication | Year of acceptance *(for paper accepted but not yet published)* | Under review | Under preparation *(optional)* | | | | | | |
| 2019# | | | | Zhang YY, Tang PM, Tang PC, Xiao J, Huang XR, Yu C, Ma RCW, **Lan HY*.** | LRNA9884, a Novel Smad3-Dependent Long Noncoding RNA, Promotes Diabetic Kidney Injury in db/db Mice via Enhancing MCP-1-Dependent Renal Inflammation. ***Diabetes.*** 2019 Jul;68(7):1485-1498. | No | Yes | Yes | No |

| The Latest Status of Publications | | | | Author(s) *(denote the corresponding author with an asterisk*)* | Title and journal/book *(with the volume, pages and other necessary publishing details specified)* | Submitted to the RGC *(indicate the year ending of the relevant progress report)* | Attached to this report *(Yes or No)* | Acknow-ledged the support of RGC *(Yes or No)* | Accessible from the institutional repository *(Yes or No)* |
|---|---|---|---|---|---|---|---|---|---|
| Year of publication | Year of acceptance *(for paper accepted but not yet published)* | Under review | Under preparation *(optional)* | | | | | | |
| 2019# | | | | Jiang G, **Luk AO**, Tam CH, Xie F, Carstensen B, Lim C, Lee HM, Ng AC, Ng MC, Ozaki R, Kong AP, Chow CC, Yang X, **Lan HY, Tsui S, Fan X, Szeto CC, So WY, Chan JC, Ma RC*** **Hong Kong Diabetes Registry TRS Project Group** | Progression of diabetic kidney disease and trajectory of kidney function decline in patients with type 2 diabetes/ Kidney Int 2019; 95(1): 178-87. | 2017 | No | Yes | No |
| 2019# | | | | Xu BH, Sheng J, You YK, Huang XR, **Ma RC**, Wang Q, **Lan HY*** | Deletion of Smad3 prevents renal fibrosis and inflammation in type 2 diabetic nephropathy. ***Metabolism Clinical and Experimental*** 103 (2020) 154013, 1-11 | No | Yes | Yes | No |

(b) Recognised international conference(s) in which paper(s) related to this project was/were delivered:

| Month/Year/ Place | Title | Conference name | Submitted to the RGC *(indicate the year ending of the relevant progress report)* | Attached to this report *(Yes or No)* | Acknowledged the support of the RGC *(Yes or No)* | Accessible from the institutional repository *(Yes or No)* |
|---|---|---|---|---|---|---|
| Sept/ 2014/ Vienna, Austria | Genome-wide association study identifies novel variants associated with incident kidney disease in Chinese. | European Association for the Study of Diabetes | 2014 | No | Yes | No |
| Dec/ 2015/ Vancouver, Canada | Genome wide association study identifies novel loci associated with coronary heart disease in type 2 diabetes | World Diabetes Congress | 2015 | No | Yes | No |
| Jan/ 2016/ San Francisco, USA | Power Estimation and Sample Size Determination for Replication Studies of Genome-Wide Association Studies | The 14th Asia Pacific Bioinformatics Conference (APBC'16) | 2016 | No | Yes | No |
| June/ 2016/ New Orleans, USA | Genome-wide association study identifies novel loci associated with baseline renal function and the rate of decline in renal function among Chinese patients with T2DM | American Diabetes Association | 2016 | No | Yes | No |
| Sept/ 2016/ Munich, Germany | A genome-wide association study identifies common genetic loci associated with lipid levels in Chinese patients with type 2 diabetes | European Association for the Study of Diabetes | 2017 | No | Yes | No |

| Month/Year/ Place | Title | Conference name | Submitted to the RGC *(indicate the year ending of the relevant progress report)* | Attached to this report *(Yes or No)* | Acknowledged the support of the RGC *(Yes or No)* | Accessible from the institutional repository *(Yes or No)* |
|---|---|---|---|---|---|---|
| Oct/ 2016/ Taipei, Taiwan | High prevalence of coronary heart disease and chronic kidney disease among Chinese subjects with Type 2 diabetes- The Hong Kong Diabetes Biobank | 11th IDF-WPR Congress 2016 and 8th AASD Scientific Meeting | 2017 | No | Yes | No |
| Dec/ 2016/ Shenzhen, China | GBOOST 2.0: A GPU-based Tool for Detecting Gene-Gene Interactions With Covariates Adjustment in Genome-Wide Association Studies. | In the 2016 Workshop on Accelerator-Enabled Algorithms and Applications in Bioinformatics (WACEBI 2016) in conjunction with IEEE BIBM 2016 | 2017 | No | Yes | No |
| June/ 2017/ San Diego, USA | Clinical and genetic determinants of progression in Type 2 Diabetes | American Diabetes Association 77th Scientific Sessions | 2017 | No | Yes | No |
| Sept/2017/ Lisbon, Portugal | Estimation of heritability for diabetic complications based on genome-wide association study in Chinese population | European Association for the Study of Diabetes 2017 | No | Yes | Yes | No |
| June/2018/ Orlando, USA | Circulating microRNAs associated with incident end-stage renal disease in Chinese with type 2 diabetes | 78th Scientific Sessions, American Diabetes Association, 2018 | No | Yes | Yes | No |
| October/2018/San Diego/USA | Genome-wide association study of diabetes progression in Chinese patients with type 2 diabetes | American Society of Human Genetics 2018 Annual Meeting | No | Yes | Yes | No |

| Month/Year/ Place | Title | Conference name | Submitted to the RGC *(indicate the year ending of the relevant progress report)* | Attached to this report *(Yes or No)* | Acknowledged the support of the RGC *(Yes or No)* | Accessible from the institutional repository *(Yes or No)* |
|---|---|---|---|---|---|---|
| June/2019/ San Francisco, USA | RNA-sequencing of laser-microdissected glomeruli and tubules reveal differentially expressed genes in diabetic kidney disease | 79th Scientific Sessions, American Diabetes Association, 2018 | No | Yes | Yes | No |
| Sep/2019/ Hong Kong | Smad3 Deficiency promotes β cell proliferation and ameliorates diabetes by targeting E2F3, a key regulator for G1/S entry | 21st East Meets West Symposium, Hong Kong, 28-29 Sep 2019 | No | Yes | Yes | No |

(c) RGC funding should have been acknowledged in all publication(s)/conference papers listed in (a) and (b) above. If no acknowledgement has been made in any of the publications/ papers, please indicate and provide explanations.

N/A

6.5 To what extent this project has strengthened inter-institutional collaborations and other partnerships?

There is close collaboration and communication between members of the project team for the different component projects, as evident from the different workshops, meetings and output. Together with some of the key international collaborators, the project team has established an international consortium, the TRANSCEND Consortium (Trans-omics Analysis of Complications and Endpoints in Diabetes). Project Co-PI/CoIs have built on the international collaborations reported in the earlier project reports. In addition to pursuing our research goals, the project team has leveraged the rich phenotype information and the genotype data generated to collaborate with other international investigators, including GIANT (genetics of anthropometric traits), SUMMIT (genetics of diabetes complications), DIAMANTE (trans-ethnic analysis of genetics of type 2 diabetes), MetGen Consortia (genetics of metformin response), to name but a few. Through our work in genetics of diabetes progression, the PC is establishing a new international consortium together with Prof Ewan Pearson on genetic determinants of diabetes progression. The PC has also been invited to join an international collaborative project on genetics of diabetic kidney disease (GENIE-GEnetics of Nephropathy an International Effort) led by Jose Florez.

In addition to collaboration in international consortia, the project team has also strengthened or helped to establish collaborations with particular groups, including at the University of Sydney (Prof Tony Keech/Prof Alicia Jenkins), Joslin Diabetes Centre, Harvard Medical School (Prof Alessandro Doria), Prof Ewan Pearson (Dundee University), Prof Maggie Ng (Vanderbilt

University). These collaborations, along with ongoing collaborations among the project team, will continue in the project supported by the RGC Research Impact Fund.

With support from the respective universities, and building on work initiated through the TRS project, the PC established the Chinese University of Hong Kong-Shanghai Jiao Tong University Joint Research Centre in Diabetes Genomics and Precision Medicine, with its opening officiated by the Vice-chancellor of the two universities in January 2017. The Joint research centre will strengthen collaboration with Professor Weiping Jia and Professor Cheng Hu from the Shanghai Jiao Tong University, key collaborators in our genetics work.
http://www.hkido.cuhk.edu.hk/Centres/CUHK-SJTUJointResearchCentreinDiabetesGenomicsandPrecisionMedicine.aspx

Other investigators from the project team have also strengthened international collaborations through the project, as evidenced by the large proportion of inter-institutional collaborative outputs in the list of publications arising from the project.

6.6 Research students trained (registration/awards):

| | Name | Degree registered for | Date of registration | Date of thesis submission/ graduation |
|---|---|---|---|---|
| 1 | GAO, Zhen | PhD (CUHK) | 08/2011 | Graduated 11/2014 |
| 2 | YANG, Guangyuan | MPhil (HKUST) | | Graduated 11/2014 |
| 3 | XU Chunhua | PhD (CUHK) | 01/01/2016 | 2019 (expected) |
| 4 | HU Weining | PhD (CUHK) | 01/08/2012 | Graduated 07/2016 |
| 5 | Luo Jiang-Yun | PhD (CUHK) | 01/08/2012 | Graduated 07/2015 |
| 6 | TAM Ha Ting | PhD (part-time) (CUHK) | 01/08/2013 | Graduated 02/2016 |
| 7 | YEUNG, Ming-wai | MPhil (CUHK) | 01/08/2014 | Graduated 07/2016 |
| 8 | SONG, Wencong | PhD (CUHK) | 01/02/2014 | Graduated 08/2015 |
| 9 | ZHANG, Hongsong | PhD (CUHK) | 01/08/2014 | Graduated 07/2018 |
| 10 | TANG, Sheung Ho | MPhil (Statistics, CUHK) | 01/08/2014 | Graduated 07/2016 |
| 11 | YOU, Yongke | PhD (CUHK) | 01/09/2013 | Graduated 07/2016 |
| 12 | BIAN, Ning | PhD (CUHK) | 01/01/2014 | Withdrawn due to illness |
| 13 | SHI, Mai | PhD (CUHK) | 01/08/2014 | Graduated 09/2017 |
| 14 | XIE, Fei | MBChB (Global Physician Stream with research work) | 01/08/2014 | Graduated 06/2018 |
| 15 | XIE, Fangying | PhD (CUHK) | 01/09/2014 | Graduated 09/11/2017 |
| 16 | JIANG, Wei | PhD (HKUST) | 02/ 2012 | Graduated 01/2017 |
| 17 | YU, Fengchao | PhD (HKUST) | 09/2012 | Graduated 05/2017 |
| 18 | ZHANG, Sen | MPhil (HKUST) | 08/2014 | Graduated 06/2018 |
| 19 | PU, Yu | MPhil (HKUST) | 08/2014 | Graduated 03/2019 |
| 20 | WANG, Meng | MPhil (HKUST) | 08/2014 | Graduated 03/2017 |
| 21 | DAI, Jiaan | MPhil (HKUST) | 08/2015 | Graduated 03/2018 |
| 22 | ZHAO, Lei | PhD (CUHK) | 08/2013 | Graduated 07/2016 |
| 23 | QU, Dan | PhD (CUHK) | 08/2012 | Graduated 07/2016 |
| 24 | HUO, Mingyu | PhD (CUHK) | 8/2015 | Graduated 7/2019 |
| 25 | FAN, Baoqi | PhD (CUHK) | 01/08/2015 | Graduated 31/07/2019 |
| 26 | JIANG, Hangjin | PhD (CUHK) | 08/2015 | Graduated 07/2018 |

| | Name | Degree registered for | Date of registration | Date of thesis submission/ graduation |
|---|---|---|---|---|
| 27 | JIN, Nana | PhD (CUHK) | 08/2015 | Graduated 07/2018 |
| 28 | LI, Jing-woei Marco | MBChB (CUHK) | 09/2016 | 08/2022 (expected) |
| 29 | WANG, Honglian | PhD (HKUST) | 04/07/2017 | 30/06/2020 (expected) |
| 30 | CHENG, Feifei | PhD (HKUST) | 01/08/2017 | 31/07/2020 (expected) |

Please refer to Appendix III for the list of awards received by research students.

6.7 Specific products (e.g. software or netware, instruments or equipment developed):
OMBlast (https://github.com/aldenleung/OMBlast): A tool for aligning optical mapping data.
OMTools (https://github.com/aldenleung/OMTools): A software package for processing optical mapping data and visualizing structural variations from optical mapping data.
OMSV (http://yiplab.cse.cuhk.edu.hk/omsv/): A tool for identifying structural variations from optical mapping data.
START (http://yiplab.cse.cuhk.edu.hk/start/): A tool for analyzing genomic signal tracks (a corresponding query language called STQL has also been developed).
JEME (http://yiplab.cse.cuhk.edu.hk/jeme/): A method for inferring enhancer-target interaction networks. This web site provides the inferred networks for 935 human primary cells, tissues and cell lines.

Some genetic variants identified through the first-phase GWAS for diabetic kidney disease and cardiovascular complications, have been included in the Illumina Global Screening Array (GSA), a clinically-orientated genotyping array, which facilitated the genotyping of later HKDB samples from our cohorts. A customized version of the Illumina Asian Screening Array (ASA), a genotyping array designed for clinical use in Asian populations, has also been produced. This customized version of the array, incorporating some of the additional novel variants associated with diabetes complications and various clinical outcomes identified through the current project, has been developed in collaboration with Illumina. This customized version of the array, available for future genotyping uses by the group, will facilitate subsequent replication experiments as well as construction of genetic risk scores.

6.8 Other education activities and/or training programmes developed:

The project PC and Co-PI, in collaboration with the Hospital Authority, organized a Commissioned Training on Genetics in Diabetes on 27 Feb 2016. Prof Ewan Pearson was invited as the lead faculty. This was attended by >230 healthcare professionals who were provided latest updates on clinical relevance of genomic medicine in diabetes. Details are as reported in previous report from 2017.

6.9 Please highlight any deliverables indicated in the project implementation timetable endorsed by the RGC which have not been covered or achieved as per sections 6.1 to 6.8 above, and explain/ elaborate.

N/A

Project Management

6.10 Please elaborate how the PC has played his/her role in coordinating and managing the project.

The PC has continued to play a leading role in terms of moving the project forward towards

the different project objectives, facilitating collaborations within the project Co-PIs and CoIs, as well as initiating and developing a large number of collaborations as detailed above. In addition to chairing the steering committee meetings, the international advisory board meetings, the PC also initiated various study group meetings, including those meetings focused on data analyses. The PC played a key role in communicating and establishing collaborations with key international collaborators. The PC also led the successful bid for funding support from the RGC Research Impact Fund to continue some of the work initiated during the TRS project.

## 7. Awards and Recognition

7.1 Have any research grants been awarded that are directly attributable to the results obtained from this project?

1. Foundation of National Institutes of Health, US. Accelerating Medicines Partnership in Type 2 diabetes RFP4 funding "Genetic variants for type 2 diabetes and diabetic complications in East Asians: The Hong Kong Diabetes Registry" to Ronald Ma, Juliana Chan and Wing Yee So.
2. NSFC-NHMRC Joint Research Scheme: "Identifying the epigenomic fingerprint of coronary heart disease in Chinese adults with type 2 diabetes" to Y Huang and JC Chan, in collaboration with Assam El-Osta from Baker IDI/Monash University.
3. HMRF 03140486/2016 "Mechanisms and Therapeutic Implication of a DPP4-I, Sitagliptin, in High CRP-associated Type-2 diabetic nephropathy" to HY Lan.
4. HMRF 14152321/2017 "Treatment of Diabetic Nephropathy by Targeting TGF-β/Smad Signalling with the Combination of Asiatic Acid and Naringenin" to HY Lan.
5. RGC-GRF 14117815 "Role of a novel lncRNA np_5318 in kidney disease" to HY Lan.
6. RGC-GRF 14163317 "The Pathogenic role and therapeutic implication of a novel lncRNA np_9884 in type-2 diabetic kidney disease" to HY Lan.
7. RGC Research Impact Fund (R4012-18) "Translating Multi-omic Discoveries to Transform Diabetes Care and Reduce Diabetic Complications" to RC Ma.
8. Croucher Foundation Senior Medical Research Fellowship (2020-2021) and project funding for project entitled "Precision Medicine in Diabetes" to RC Ma.

7.2 Have any project team members participated as invited speakers in or organisers of international conferences as a result of this project?

Several project team members have received invitations to speak at international meetings. For example, the project PC has received several invitations to speak on genetics of diabetes and diabetic complications. The project PC was also invited to be a member of the programme committee and a programme stream lead at the International Diabetes Federation World Diabetes Congress 2019, Busan, Korea.

Please refer to Appendix IV for full list of 106 talks as invited speakers by the project team.

7.3 Have any project team members taken leadership positions in editorial boards, scientific and professional organisations?

1. Prof. Ronald Ma has been appointed as member of editorial board for the top journal PLoS Medicine (from 2017), and continues as editorial board member for Obesity Reviews, Diabetic Medicine, Nutrition, Metabolism and Cardiovascular Disease and Journal of Diabetes Investigation. Prof Ma completed his term as President of International Diabetes Epidemiology Group (IDEG), and is currently member of Exec. Board for the Asian Association for the Study of Diabetes (AASD). He has been

appointed to the board of Worldwide Initiative for Diabetes Education (WorldWIDE Diabetes) http://www.worldwidediabetes.org/ , as well as a Lancet Commissioner on Diabetes. Prof Ma has also been appointed as Regional Editor of Diabetic Medicine (starting 2019-) and has also been invited to join the editorial board of Diabetologia, starting 02/2020. Prof Ma has been invited to join the Medicine and Biology Panel of the Research Grants Council starting from 02/2019.

2. Prof. Juliana Chan has been appointed to chair the Lancet Commission on Diabetes.
3. Prof. Hui Yao Lan is associate Editor of "Clinical and Experimental Pharmacology & Physiology" as well as associate editor of "J Cellular and Molecular Medicine".
4. Asso. Professor Andrea Luk has been appointed as associate editor of Diabetic Medicine.

7.4 Any documentary proof of the application of technologies arising directly from this project?

N/A

7.5 Other awards and recognitions as a result of this project (please specify):
The project team has received several major international awards. A full list of these major awards are listed in Appendix V from the previous TRS report submitted in 2017. Professor Juliana Chan has also been selected by the Lancet to lead a Lancet commission on Diabetes, with the Commission meeting hosted by the Chinese University of Hong Kong in May 2016. (http://www.hkido.cuhk.edu.hk/Research/TheLancet-ClinicalDiabetesCommission.aspx ). The full commission report is currently under review by the Lancet for publication.

Professor Juliana Chan also received the 2019 Harold Rifkin Award for Distinguished International Service in the Cause of Diabetes from the American Diabetes Association (https://www.adameetingnews.org/live-updates/photo/juliana-c-n-chan-mb-chb-md-frcp-receives-the-harold-rifkin-award/ ), and the Epidemiology Stream award Lecture at the IDF World Diabetes Congress, December 2019.

Professor Ronald Ma received the Croucher Senior Medical Research Fellowship in December 2019.
(https://projects.croucher.org.hk/news/croucher-innovation-awards-2019-and-senior-research-fellowships-2020)

In collaboration with Prof Assam El-Osta (Monash University, Australia), the PC and Co-PI have also been selected to start and host a Gordon Research Conference on Epigenomics of Diabetes and other metabolic diseases. This was first held in Hong Kong in May 2018, and helped to enhance the involvement of the project team and other local academics in this fast-evolving field. (https://www.grc.org/programs.aspx?id=17707 ). The next GRC, together with a Gordon Research Seminar (for students and postdoctoral fellows) is scheduled to be held in Hong Kong in May 2021.

## 8. Impacts

8.1 What are the current and expected impacts of the project on the long-term development of Hong Kong (social or economic development, e.g. patent, technology transfer, collaboration with external organisations, etc.)?

The project has led to initiation of several major international collaboration, which will advance research development in Hong Kong. Together with the Hospital Authority, we organized a workshop in January 2016 to advance implementation of genomic medicine in

diabetes by healthcare professionals. Another workshop on precision medicine in diabetes is currently being planned for 2021. Through support from the Technology Start-up Support Scheme for Universities (TSSSU) from the Hong Kong Government Innovation and Technology Commission, R Ma, WY So and J Chan have set up the first Hong Kong based genetic testing company specializing in diabetes: GemVCare (Genetic Evaluation & Management), based at the Hong Kong Science and Technology Park. This technology transfer initiative aims to create a working environment to nurture our young graduates and scientists, and will help develop Hong Kong as a centre for innovative healthcare delivery. The company has begun to provide services for testing of genetic variants associated with Type 2 diabetes or diabetes-related complications.

We have also been selected by the Foundation of National Institute of Health to contribute genotype data into the AMP T2D knowledge portal (http://www.type2diabetesgenetics.org/) in stages (after fulfilling our own research goals). This major academic-industry collaboration aims to develop a platform to provide data and tools to a wider community to advance understanding and treatment of type 2 diabetes and its complications. Being a major contributor of data and a steering committee member of this project will greatly enhance the international profile of diabetes genomic research from Hong Kong, and ensure data generated from our project can be made available to the larger scientific community at an appropriate time and in a manner most conducive to advancing scientific discoveries. The profile of the TRS project has also led to the PC being invited to join as a stakeholder of the discussion of the American Diabetes Association Advancing Precision Diabetes Medicine Symposium, held in Madrid, Spain, 8-9 October 2019. The Lancet Diabetes Commission led by Prof Juliana Chan has also helped establish strong international links, as well as showcase Hong Kong as a centre for innovative diabetes care delivery.

There are much IP and technology transfer activities arising directly from the project. Patents relating to panels of miRNA and methylation markers for risk stratification and management of diabetic complications are being filed, and we expect to identify a few candidate genes to focus on for functional studies and potential drug discovery.

8.2 Others (please specify):

Please find enclosed Appendix V for summary of steering committee meeting minutes.

## 9. Sustainability of the Project

9.1 Whether there are new ideas evolved directly from this project?

Numerous ideas have evolved directly from this project. These include the panel of genetic markers associated with diabetic kidney disease, diabetic cardiovascular complications, diabetes progression, or other endpoints in diabetes. Through genotyping data generated from the project, we have developed the first polygenic risk scores associated with diabetes progression and need for insulin for subjects with type 2 diabetes. A subsequent GWAS meta-analysis has identified novel genetic variants associated with diabetes progression. We have also identified novel methylation markers, including a prediction model for subsequent change in renal function based on baseline methylation markers. This has established the possibility of using a panel of methylation markers to predict subsequent decline in renal function in diabetes. We have also identified and replicated a number of miRNA associated with risk of diabetes complications, which may become potential biomarkers to predict clinical outcome in clinical practice.

The identification of a novel role of smad3 in pathogenesis of type 2 diabetes, identified through work undertaken in the project, has also provided new ideas that are currently being pursued in continuing research.

9.2 Whether there are new projects evolved directly from this project?

A project entitled "Translating Multi-omic Discoveries to Transform Diabetes Care and Reduce Diabetic Complications" has successfully been funded by the RGC Research Impact Fund, with the PC Professor Ronald Ma has the lead investigator. This project will focus on functional characterization of smad3 targets, novel genes identified through the TRS, and further replication and translational work using biomarkers identified through the TRS project.

Additional funding has also been obtained from a Croucher Senior Research Fellowship, with some research funding provided to support additional genotyping of samples collected into the Hong Kong Diabetes Biobank. The title of the project "Precision Medicine in Diabetes", was based on findings which have arisen from the TRS project. In addition to further downstream translational work, the project will focus on refining some of the polygenic risk scores developed, including that for diabetes progression.

Additional grant funding has also been secured for follow-up work of novel lncRNAs associated with smad3 and diabetic kidney disease.

9.3 Whether there are new collaborations developed directly from this project?

Most of the international collaborations included in section 6.5 are new collaborations which have developed directly from this project.

9.4 Please give details on how much money and from which sources has been obtained/requested for the specific purpose of continuing the work started under this project.

HK$12,000,000 (RGC Research Impact Fund – HK$8,400,000 and Institutional Matching Fund – HK$3,600,000)
HK$2,000,000 (CUHK-SJTU Joint Research Centre in Diabetes Genomics and Precision Medicine
HK$2,000,000 (Croucher Senior Research Fellowship, costs for additional manpower to support analyses and for additional genotyping of collected samples).

## 10. Statistics on Research Outputs

*(Please ensure the statistics in this section are consistent with the information presented in other sections of this report.)*

| | Peer-reviewed journal publications | Conference papers | Scholarly, books, monographs and chapters | Patents awarded | Other research outputs (please specify) | |
|---|---|---|---|---|---|---|
| No. of outputs arising directly from this research project | 66 | 48 abstracts + 106 invited talks | 3 book chapters | 1 awarded, several under filing | Type | No. |
| | | | | | software | 5 |

## 12. The Layman's Summary

*(describe in layman's language the abstracts and research impact of the project.)*

Diabetes is a major health problem worldwide, including in Hong Kong. Healthcare costs associated with diabetes in China was 200 billion RMB in 2007, and is forecasted to exceed 360 billion RMB by 2030. Most of the healthcare burden from diabetes is associated with the management of diabetic complications, in particular, cardiovascular and renal complications. In Hong Kong, diabetes accounts for annual healthcare costs of approximately 5 billion HKD, mostly due to burden from heart and kidney complications. Diabetes is the major cause of end-stage renal disease (ESRD), and increases the risk of cardiovascular disease (CVD) by 3-4 fold. Asian patients with type 2 diabetes (T2D) are particularly prone to renal complications when compared to patients of European origin. Only few genetic markers have so far been identified to predict diabetic cardiovascular-renal complications. Discovery of novel genetic or other biomarkers for diabetic complications can help identify at risk subjects for intensive risk factors management, advance our understanding of disease pathogenesis, revolutionize care and provide novel targets for drug development. In this Grand Challenge, we have utilized the unique resource from the Hong Kong Diabetes Registry, with more than 10,000 patients with T2D with detailed biochemical assessment of risk factors and documentation of medication history, who have been prospectively followed up for a mean duration of 8 years, with an accrual of 4,000 events of cardiovascular and renal complications. We applied a multi-omic approach and used genotyping arrays and new-generation sequencing (NGS) and other technologies to conduct a comprehensive evaluation of the genome, epigenome and transcriptome of diabetic patients with complications and diabetic patients free of complications despite long duration of disease. Through work in the project, the project team has identified a panel of genetic and other molecular markers that can identify patients at higher risk of future diabetes complications. We have utilized advanced bioinformatics analysis to integrate findings from these different approaches. Insights from this multi-faceted investigation was compared to findings from animal models of diabetic complications. We also utilized bioinformatics, in vitro experiments and animal models to explore the functional significance and regulatory pathways of novel genes identified from the genomic studies. In addition to novel biological discoveries, we sought to translate our findings and examine the clinical significance of these novel biomarkers, as well as their interactions with different treatments on disease outcomes. In the project, we have also leveraged on the existing healthcare infrastructure and detailed clinical information available to establish an expanded diabetes registry and biobank with contribution from major diabetes centres across Hong Kong for large-scale replication of any novel biomarkers discovered. This resource is a first-of-its-kind. Ongoing work is focused on large-scale replication of these findings in different populations, application to patients in real-life clinical setting, and studies to understand how these genes affect development of diabetes-related complications. Findings from the project is helping to transform the way we treat patients with diabetes, whereby each patient can receive tailored treatment regimens that are most suitable and effective for them. Discoveries arising from the project are also providing us with new insights and leads for developing new drugs to treat diabetes and prevent its associated complications.
In sum, the translation of our genomic discoveries to clinical care will consolidate Hong Kong as a centre for innovative biomedical research and chronic care excellence.