

## Report for Joint/Usage Research Program for Endocrine/Metabolism (Fiscal Year 2024)

Date : 2025/6/26

To Director of Institute for Molecular and Cellular Regulation, Gunma University

Principal Applicant	
Institution	Beijing Tongren Hospital, Capital Medical University
Position	Professor
Name	Jinkui Yang

We report on the results of joint research in fiscal year 2024 as below.

(Program No. 22005)

1. Research Title	Berberine promotes GLP-1 secretion through hERG potassium channel in enteroendocrine L-cells.				
2. Purpose and Significance of the research project	Berberine (BBR), one kind of Chinese traditional medicine, has applications as a drug in treating type 2 diabetes mellitus and hyperlipidemia for hundreds of years. However, the mechanism is still unknown. This study is to explore the function of BBR on GLP-1 exocytosis and clarify the molecular mechanism of BBR in enteroendocrine L-cells.				
3. Period of The Program	April 1, 2024 ~ March 31, 2025				
4. Project Members					
Name	Age	Sex	Affiliation	Position	Role
(Principal Applicant) Jin-Kui Yang	61	M	Beijing Diabetes Institute, Beijing Tongren Hospital, Capital Medical University	Position : Professor Degree : MD, PhD	Project director
(Research Collaborators) Hao Wang	41	M	Beijing Diabetes Institute, Beijing Tongren Hospital, Capital Medical University	Position : Associate Professor Degree : MD, PhD	Experimental designer and executor
Ying-Chao Yuan	29	F	Beijing Diabetes Institute, Beijing Tongren Hospital, Capital Medical University	Graduate stu- dent	Experimental executor
Ze-Ju Jiang	25	M	Beijing Diabetes Institute, Beijing Tongren Hospital, Capital Medical University	Graduate stu- dent	Experimental executor
※If additional space is required, please attach a separate sheet.					
5. Collaborating Researcher of IMCR	Name of Laboratory	Endocrine and Metabolic System Regulation	Name	Katsuhide Okunishi	



6. Research Plans

1. Generation of GCG-venus mouse for isolating primary murine intestinal L-cells by FACS.
2. Check Kv currents and action potential duration (APD) of BBR treated intestinal L cells and GLUTag cells.
3. Check Kv currents and action potential duration (APD) of BBR treated hERG deficient intestinal L cells and hERG deficient GLUTag cells.
4. Check GLP-1 secretion in BBR treated ileac organoids derived from WT and hERG L-cell deficient mice.
5. Summary all of results and prepare manuscript for publication.

7. Research results:

Please describe the details of the contribution of the joint research with IMCR in obtaining the results.

1. BBR reduced Kv currents and extended APD in intestinal L cells and GLUTag cells.
2. BBR showed no effect on Kv currents and APD on hERG deficient intestinal L cells and hERG deficient GLUTag cells.
3. BBR enhanced GLP-1 secretion in ileac organoids derived from WT mice.
4. BBR showed no effect on GLP-1 secretion in ileac organoids derived from hERG L-cell deficient mice.
5. Summary all of results and prepare manuscript for publication.

8. Present status of academic conference presentations and research papers associated with the results of the joint research, and exchange of information on the joint research with the collaborating researcher at IMCR.

(As much as possible, please state papers that include the names of the collaborating researcher at IMCR or papers stating that the research was supported by the Joint Research Program with IMCR.

Regarding papers, please send a PDF file together with the report to the email address of the general affairs section of the Institute.) Office of General Affairs: [kk-msomu4@ml.gunma-u.ac.jp](mailto:kk-msomu4@ml.gunma-u.ac.jp)

① Please list the publications that include the name of the collaborating researcher from IMCR and send a reprint of each publication to IMCR.

- (a) Zhao MM, Lu J, Li S, Wang H, Cao X, Li Q, Shi TT, Matsunaga K, Chen C, Huang H, Izumi T, Yang JK. Berberine is an insulin secretagogue targeting the KCNH6 potassium channel. *Nat Commun.* 2021 Sep 23;12(1):5616.
- (b) Wang Hao\*, Yuan Ying-Chao, Chang Cong, Izumi Tetsuro, Wang Hong-Hui\*, Yang Jin-Kui\*. The signaling protein GIV/Girdin mediates the Nephroin-dependent insulin secretion of pancreatic islet  $\beta$  cells in response to high glucose. *J Biol Chem.* 2023 Apr;299(4):103045.
- (c) Okunishi K, Kochi Y, Zhao M, Wang H, Nakagome K, Izumi T. Munc13-4 regulates asthma and obesity in mice by controlling functions of CD11c+ antigen-presenting cells. *Allergy.* 2024 Jul;79(7):1992-1995.

② Please list the publications that include a description that the research was supported by the Joint Research Program with IMCR and send a reprint of each publication to IMCR.

- (a) Zhao MM, Lu J, Li S, Wang H, Cao X, Li Q, Shi TT, Matsunaga K, Chen C, Huang H, Izumi T, Yang JK. Berberine is an insulin secretagogue targeting the KCNH6 potassium channel. *Nat Commun.* 2021 Sep 23;12(1):5616.
- (b) Okunishi K, Kochi Y, Zhao M, Wang H, Nakagome K, Izumi T. Munc13-4 regulates asthma and obesity in mice by controlling functions of CD11c+ antigen-presenting cells. *Allergy.* 2024 Jul;79(7):1992-1995.

③ List up to 3 conferences (name of conference, date of conference, and title of the presentation).

- (a) The 4th international symposium of endocrinology and metabolism, 12th Nov, 2022, Berberine is an insulin secretagogue targeting the KCNH6 potassium channel. Prof. Jin-Kui Yang

(b) The 83th Scientific Sessions of American Diabetes Association, 23rd-26th Jun, 2023, The role of cell-cell junction associated mediator in insulin secretion of pancreatic islets. Presenter: Prof. Hao Wang

(c) The 3<sup>rd</sup> BDI international symposium, Beijing, China, 2<sup>nd</sup> November, 2023. An essential role of GDF3-ALK7 axis in fat accumulation, Presenter: Prof. Katsuhide Okunishi.  
Identification of Ppy-lineage cells as a novel origin of pancreatic ductal adenocarcinoma. Presenter: Prof. Yoshio\_Fujitani

(d) Academic exchange between BDI and IMCR, Maebashi, Gunma, Japan, 2024. Novel mechanisms of incretin secretion and development of GLP-1 secretagogues. Presenter: Prof. Jin-Kui Yang.  
The latest research progress on the mechanism of insulin secretion in pancreatic  $\beta$  cells. Presenter: Prof. Hao Wang.

④ Exchange of information exchange with collaborating researcher from IMCR (please list main points of communication).  
Prof. Katsuhide Okunishi  
Collaborating research on novel roles of Rab27 effectors in chronic inflammatory and metabolic diseases in mice.