Form 3

Report for Joint/Usage Research Program for Endocrine/Metabolism (Fiscal Year 2023)

Date：2024/4/28

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 2023 as below.

（Program No. 22005）

1． Research Title	Berberine promotes GLP-1 secretion through hERG potassium channel in en-teroendocrine 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) Jinkui Yang	60	M	Beijing Diabetes Institute, Beijing Tongren Hospital, Capital Medical University	Position：Professor Degree：MD, PhD Acquisition date：2003.10	Project director
(Research Collaborators) Hao Wang	41	M	Beijing Diabetes Institute, Beijing Tongren Hospital, Capital Medical University	Associate professor	Experimental designer and executor
Yingchao Yuan	28	F	Beijing Diabetes Institute, Beijing Tongren Hospital, Capital Medical University	Graduate student	Experimental executor

※If additional space is required, please attach a separate sheet.

5． Collaborating Researcher of IMCR	Name of Laboratory	Molecular Endocrinology and Metabolism	Name	Katsuhide Okunishi

6． Research Plans

1. Generation of hERG intestinal L-cell specific knockout mice (hERG GCG-cre).
2. Check blood glucose and serum insulin, GLP-1, GIP concentrations in control and hERG GCG-cre mice that underwent an oral glucose tolerance test after treatment with NS or BBR.
3. Detect GLP-1 secretion ability of NS or BBR treated control or KCNH6 deficient L-cells that were stimulated with glucose plus forskolin and IBMX.
4. Check blood glucose and serum insulin, GLP-1, GIP concentrations in ND and HFD mice that underwent an oral glucose tolerance test after treatment with NS or BBR.
5. Check blood glucose and serum insulin, GLP-1, GIP concentrations in control and db/db mice that underwent an oral glucose tolerance test after treatment with NS or BBR.

7． Research results:

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

1. BBR treated hERG GCG-cre mice showed no effect on glucose tolerance and serum GLP-1 level compared with those of NS treated control mice.
2. BBR promoted GLP-1 secretion in control L-cells but not KCNH6 deficient L-cells.
3. BBR treated HFD mice showed relieved glucose tolerance and increased serum GLP-1 level compared with those of NS treated HFD mice.
4. BBR treated db/db mice showed relieved glucose tolerance and increased serum GLP-1 level compared with those of NS treated db/db mice.

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@jimu.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 Nephrin-dependent insulin secretion of pancreatic islet β cells in response to high glucose. J Biol Chem. 2023 Apr;299(4):103045.

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.

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.
(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.

④ Exchange of information exchange with collaborating researcher from IMCR (please list main points of communication).

The institutional collaboration agreement between IMCR and Beijing Tongren Hospital was established in April, 2016. Applicant and Dr. Hao Wang at Prof. Izumi's laboratory have started this project and obtained promising results to support future collaboration.