Form 3

# Report for Joint/Usage Research Program for Endocrine/Metabolism (Fiscal Year 2022)

Date：2022/4/20

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

| Principal Applicant | |
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| Institution | Endocrinology department, Beijing Tongren Hospital, Capital Medical University |
| Position | Professor and Director |
| Name | Jinkui Yang |

We report on the results of joint research in fiscal 2021 as below.

（Program No.　　）

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| 1． Research Title | Berberine improves insulin secretion through hERG2 potassium channel |
| 2． Purpose and Significance of the research project | In our previous studies, we found that KCNH6, as a potassium channel on plasma membrane, plays an im-portant role in insulin secretion in humans and mice (JK Yang et al, Cell Reports, 2018). Berberine (BBR), one kind of Chinese traditional medicine, has been used as a drug in treating type 2 diabetes mellitus and hyper-lipidemia for hundreds of years in China, however, the mechanism is still unknown. We found that the function that BBR promoting insulin secretion was diminished in KCNH6 knockout islets and BBR can bind with KCNH6 in beta cells. Based on these results, we speculate that BBR promoted insulin secretion might be through mediating KCNH6 potassium channel. In this study, we aim to investigate how does BBR regulate insulin exocytosis through KCNH6 pathway in pancreatic β-cells. Recent collaborative research results showed that KCNH6 is not only expressed on plasma membrane but also in cytosol and high glucose can affect the dynamic trafficking process of KCNH6 and downregulate the pro-tein expression on plasma membrane. In this study, we aim to investigate the dynamic trafficking process of KCNH6 in pancreatic β-cells under BBR stimula-tion, mainly to focus on monitoring dynamic change of KCNH6 in β-cells after administra-tion of BBR. |
| 3． Period of The Pro-gram | April 1, 2021 ～ March 31, 2022 |

4． Project Members

| Name | Age | Gender | Institution/Department | Position | Role |
|---|---|---|---|---|---|
| （Principal Applicant）<br>Jin-kui Yang | 59 | M | Endocrinology department, Beijing Tongren Hospital, Capital Medical University | Professor | Project director |
| （Research Collaborators）<br>Jing Lu | 41 | F | Endocrinology lab, Beijing Tongren Hospital, Capital Medical University | Associate pro-fessor | Experimental executor |
| Miao-miao Zhao | 29 | F | Endocrinology department, Beijing Tongren Hospital, | Graduate stu-dent | Experimental executor |

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|---|---|---|---|---|---|
| | | | Capital Medical University | | |
| Hao Wang | 40 | M | Endocrinology department, Beijing Tongren Hospital, Capital Medical University | Associate professor | Experimental executor |
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| ※If additional space is required, attach a separate sheet. | | | | | |

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| 5. Collaborative Researcher of IMCR | Name of the Laboratory | Molecular Endocrinology and Metabolism | Name | Tetsuro Izumi |

6. Research Plans

All of the research are for answering questions of reviewers from “Nature Communication”.

1. Isolation of cell fractionation: Cell fractionation will be isolated from pancreatic β-cells to detect the expression of KCNH6 using specific antibody as the marker of different subcellular organelles and plasma membrane.
2. Effect of berberine on cell viability and cytotoxicity.
3. The phenotype of HFD KCNH6 knockout mice.
4. The phenotype of KCNH6 beta-cell knockout mice.

7. Research results:

1. Short-time administration of BBR has no trafficking effect of KCNH6.
2. BBR had no cytotoxic effect on beta cells in short-time (30min) incubation.
3. BBR treated HFD-KCNH6 knockout mice showed relieved glucose tolerance and insulin secretion.
4. BBR treated KCNH6 beta-cell knockout mice showed relieved glucose tolerance and insulin secretion.

8. Publications and/or Presentations resulting from Joint Research Program with IMCR.
Exchange of information on joint research with faculty members.

①Please describe a list of publications in which the name of the collaborative researcher of IMCR appears and send one paper reprints of each publication to IMCR.
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.

②Please describe a list of publications which include the description that the research is supported by Joint Research Program with IMCR and send one copy of each publication to IMCR.
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.

③Enter the name of the conference, the date of the conference, and the title of the presentation of the conference.(up to 3 cases)

1. Jinkui Yang, Biomarkers of Diabetes and its Complications. The 2nd IMCR Symposium on Endocrine and Metabolism, 10th-11th November, 2016, Maebashi, Japan
2. Izumi Tetsuro, Insulin Regulates Lipolysis and Fat Mass by Upregulating Growth-Differentiation Factor 3 in Adipose Tissue Macrophages.The 1st Annual conference of Beijing Diabetes Institute, 30th Jan-2nd Feb, 2018, Beijing, China.
3. Izumi Tetsuro, Melanophilin Accelerates Insulin Granule Fusion without Predocking to the Plasma Membrane. The 2nd Annual conference of Beijing Diabetes Institute, 27th-30th June, 2019, Beijing, China.

④Implementation status of information exchange with faculty members in charge of joint research.
We always communicated with Professor Izumi and Dr. Wang for our joint research program.