Form 3

# Report for Joint/Usage Research Program for Endocrine/Metabolism (Fiscal Year 2025)

Date：2026/05/31

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

| Principal Applicant | |
|---|---|
| Institution | Beijing Tongren Hospital, Capital Medical University |
| Position | Associate Professor |
| Name | Hao Wang |

We report on the results of joint research in fiscal year 2025 as below.

（Program No.　　）

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|---|---|
| 1． Research Title | Novel roles of Rab27 effectors in chronic inflammatory and metabolic diseases in mice |
| 2． Purpose and Significance of the research project | Chronic allergic disease asthma and chronic metabolic disease obesity are both associated with chronic inflammation and increasing in prevalence globally. However, the pathophysiological relationship between these two diseases is not well-known. The purpose of this study is to analyze the roles of Rab27 effectors such as melanophilin in inflammatory mechanism in cells, tissues and individuals by using knockout mice of Rab27 effectors, thus helping to clarify the patho-physiological relationship between metabolic syndrome and allergic diseases. |
| 3． Period of The Program | April 1, 2025 ～ March 31, 2026 |

4． Project Members

| Name | Age | Sex | Affiliation | Position | Role |
|---|---|---|---|---|---|
| （Principal Applicant）<br>Hao Wang | 44 | M | Beijing Diabetes Institute, Beijing Tongren Hospital, Capital Medical University | Position：Associate Professor<br>Degree：MD, PhD<br>Acquisition date：2022.1 | Project director |
| （Research Collaborators）<br>Chen-Yang Zhang | 29 | F | Beijing Diabetes Institute, Beijing Tongren Hospital, Capital Medical University | Assistant Professor | Experimental executor |
| Ze-Ju Jiang | 27 | M | Beijing Diabetes Institute, Beijing Tongren Hospital, Capital Medical University | Graduate student | Experimental executor |
| Zi-Lu Wang | 25 | F | Beijing Diabetes Institute, Beijing Tongren Hospital, Capital Medical University | Graduate student | Experimental executor |
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※If additional space is required, please attach a separate sheet.

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| 5. Collaborating Researcher of IMCR | Name of Laboratory | Endocrine and Metabolic System Regulation | Name | Katsuhide Okunishi |

6. Research Plans

(1) Check expression and localization of Rab27 effectors such as melanophilin in different immune and metabolic tissues and cells.
(2) Compare the following items between WT mice and knockout mice of each Rab27 effector;
a) Phenotypes of mouse models of asthma and HFD-induced obesity/diabetes.
b) Th2 response of different types of immune cells (e.g. hematopoietic immune cells, lung epithelial cells).
c) Inflammatory responses in white adipose tissue and in other tissues (e.g. liver).
(3) Clarify the molecular mechanisms for the findings in (2) .

7. Research results:

Please describe the details of the contribution of the joint research with IMCR in obtaining the results.
(1) Melanophilin is expressed in both lung epithelial cells and immune cells.
(2) Hypersecretion of OVA-induced Th2 cytokines in Melanophilin deficient mice in an asthma model is due to lung epithelial cells, but not due to blood immune cells.
(3) Melanophilin-deficiency exacerbates HFD-induced obesity, diabetes, and liver steatosis in mice.
(4) Melanophilin regulates obesity by controlling functions of immune cells.

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

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.
(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 3rd BDI international symposium, Beijing, China, 2nd 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 β 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.