Form 3

Report for Joint/Usage Research Program for Endocrine/Metabolism (Fiscal Year 2021)

Date：2022/4/1

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

Principal Applicant	
Institution	Institute of Molecular and Cell Biology (IMCB), A*STAR
Position	PI; Assistant Professor
Name	Adrian Teo

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

（Program No.　　）

1．Research Title	Human stem cell-derived pancreatic beta cells for the treatment of diabetes
2．Purpose and Significance of the research project	In this proposal, we focus on the quality, efficacy and safety aspects of human pluripotent stem cell (hPSC)-derived pancreatic beta-like cells for the potential treatment of diabetes via cell therapy.
3．Period of The Program	April 1, 2021 ～ March 31, 2022

4．Project Members

Name	Age	Gender	Institution/Department	Position	Role
（Principal Applicant） Adrian Teo	39	M	Institute of Molecular and Cell Biology (IMCB), A*STAR, Singapore	PI; Assistant Professor	Project director
（Research Collaborators）					

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

5．Collaborative Researcher of IMCR	Name of the Laboratory	Diabetes and Metabolic Disorders	Name	Jun Shirakawa

6． Research Plans

We aimed to determine and improve the quality of human stem cell-derived pancreatic beta-like cells. The effects of imeglimin, a novel antidiabetes agent, on β-cell survival was assessed using mice islets, human islets, mice models , and human pluripotent stem cell-derived β-like cells.

7． Research results:

Treatment with imeglimin augmented mitochondrial function, enhanced insulin secretion, promoted β-cell proliferation, and improved β-cell survival in mouse islets. Imeglimin upregulated the expression of endoplasmic reticulum (ER)-related molecules, including Chop (Ddit3), Gadd34 (Ppp1r15a), Atf3, and Sdf2l1, and decreased eIF2α phosphorylation after treatment with thapsigargin and restored global protein synthesis in β-cells under ER stress. Imeglimin failed to protect against ER stress-induced β-cell apoptosis in CHOP-deficient islets or in the presence of GADD34 inhibitor. Treatment with imeglimin showed a significant decrease in the number of apoptotic β-cells and increased β-cell mass in Akita mice. Imeglimin also protected against β-cell apoptosis in both human islets and human pluripotent stem cell-derived β-like cells. Taken together, imeglimin modulates the ER homeostasis pathway, which results in the prevention of β-cell apoptosis both in vitro and in vivo.

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.

Li J, Inoue R, Togashi Y, Okuyama T, Satoh A, Kyohara M, Nishiyama K, Tsuno T, Miyashita D, Kin T, Shapiro AMJ, Chew RSE, **Teo AKK**, Oyadomari S, Terauchi Y, **Shirakawa J**. Imeglimin Ameliorates β-Cell Apoptosis by Modulating the Endoplasmic Reticulum Homeostasis Pathway. ***Diabetes.*** 2022 Mar 1;71(3):424-439. doi: 10.2337/db21-0123.

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.

Li J, Inoue R, Togashi Y, Okuyama T, Satoh A, Kyohara M, Nishiyama K, Tsuno T, Miyashita D, Kin T, Shapiro AMJ, Chew RSE, **Teo AKK**, Oyadomari S, Terauchi Y, **Shirakawa J**. Imeglimin Ameliorates β-Cell Apoptosis by Modulating the Endoplasmic Reticulum Homeostasis Pathway. ***Diabetes.*** 2022 Mar 1;71(3):424-439. doi: 10.2337/db21-0123.

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

N/A

④Implementation status of information exchange with faculty members in charge of joint research.

We routinely discuss the experimental results (every month).