Form 3

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

Date：2023/5/17

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

Principal Applicant	
Institution	College of Biology, Hunan University
Position	Associate Professor
Name	Honghui Wang

We report on the results of joint research in fiscal 2022 as below.

（Program No.　　）

1． Research Title	Development of a Glucose-gated DNA-nanodevice for Glucose Control in Type I and II Diabetes
2． Purpose and Significance of the research project	This project is the continuous study following a previous project. We aim to construct an intelligent therapeutic strategy to balance glucose homeostasis in both Type I and type II diabetes. In this study, we rationally design a glucose-responsive DNA-nanodevice capable of dynamically responding to diabetic blood glucose levels and automatically promoting glucose uptake in the liver and skeletal muscle. Using this nanodevice, we have succeeded in restoring normal blood glucose levels in both Type I and Type II diabetic mouse models.
3． Period of The Program	April 1, 2022 ～ March 31, 2023

4． Project Members

Name	Age	Sex	Affiliation	Position	Role
（Principal Applicant） Hong-Hui Wang	42	M	Hunan University, College of Biology	Position：Associate Professor Degree：PhD Acquisition date：2010.3.31	Project director
（Research Collaborators） Fang He	26	F	Hunan University, College of Chemistry and Chemical Engineering	Graduate student	Cell experiment
MeiXia Wang	25	F	Hunan University, College of Biology	Graduate student	Animal experiments
Jun Zhun	27	M	Hunan University, College of Biology	Graduate student	Data analysis

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

5． Collaborating Researcher of IMCR	Name of Laboratory	IMCR	Name	Tetsuro Izumi

6． Research Plans

① Investigate the role of glucose-gated nanodevice in regulating the dynamics of c-Met dimerization on membrane and the GLUT4 translocation using TIRF microscope.

② We will study the glucose uptake using skeletal muscle organoids and liver organoids in the presence of the glucose-gated DNA nanodevice.

③ We will carry out an intraperitoneal glucose tolerance test (IPGTT) to examine if glucose-gated DNA nanodevice can regulate the hyperglycemia status in STZ mice mimicking Type I diabetes and db/db mice mimicking Type II diabetes.

7． Research results:

① We demonstrated that the glucose-gated DNA nanodevice is only activated when glucose levels rise above 7 mM, subsequently triggering the c-Met/IRS2/AKT signaling pathway.

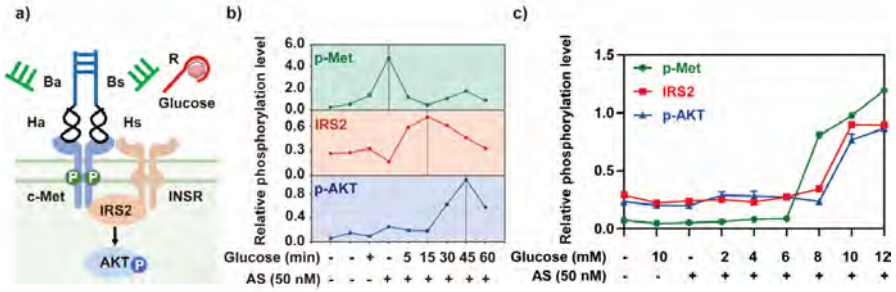

Figure 1. Distinct kinetic and phosphorylation patterns produced by insulin signaling stimulated by glucose-induced DNA-based nanodevices.

② We showed that the glucose-gated DNA nanodevice can detect high glucose levels, prompting membrane translocation of GLUT4 at the single-cell level.

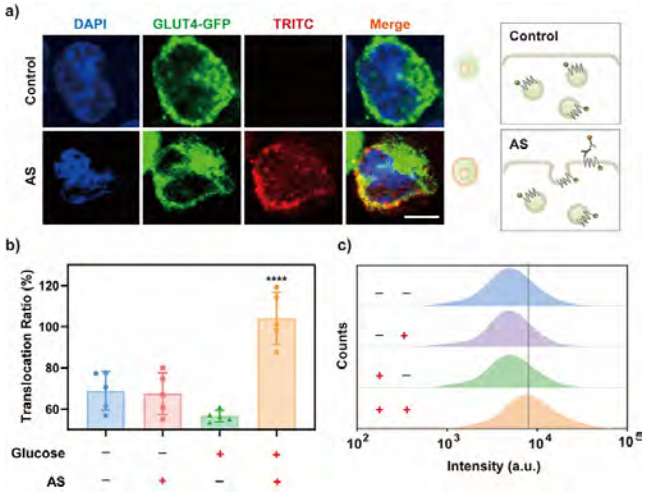

Figure 2. Glucose-responsive translocation of glucose transporter-4 (GLUT4) in hepatocytes equipped with the glucose-gated DNA nanodevice (AS).

Institute for Molecular and Cellular Regulation
Gunma University
IMCR

③ We characterized the ability of the glucose-gated DNA nanodevice to autonomously respond to high glucose levels (> 7 mM) and activate MET/AKT signaling and enhance the glucose uptake of skeletal muscle organoids.

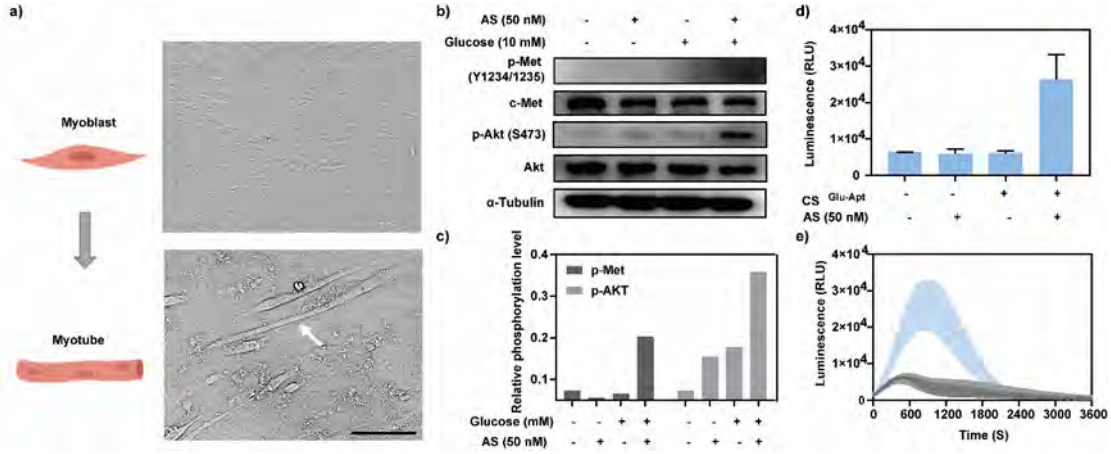

Figure 3. Autonomous glucose uptake in myotubes equipped with the glucose-gated DNA nanodevice for glucose homeostasis.

④ In our study involving STZ-induced Type I diabetic mice, we performed an intraperitoneal glucose tolerance test. The results confirmed the glucose regulation function of glucose-gated DNA nanodevices. We validated the capability of the nanodevice to significantly improve glucose tolerance and prevent hypoglycemia.

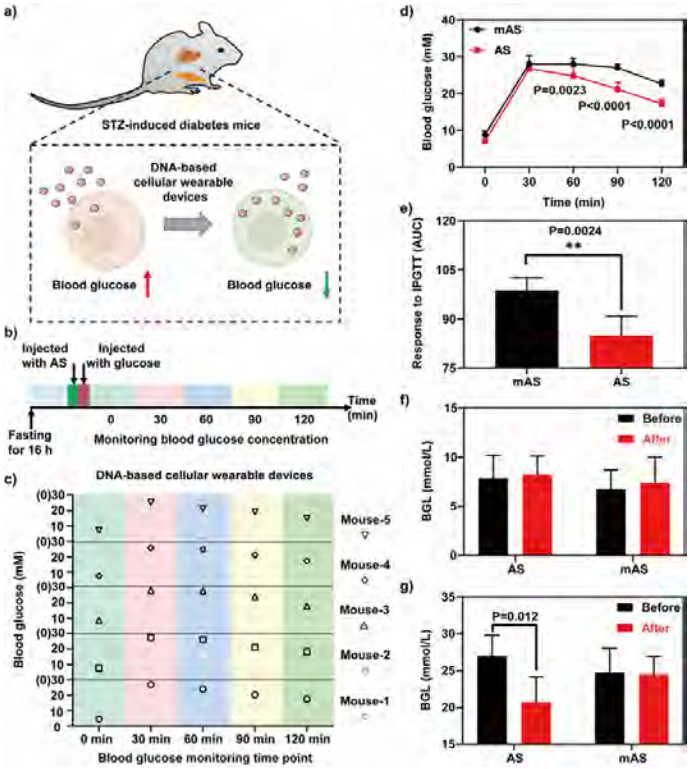

Figure 4. Functionality of the glucose-gated nanodevice in regulating blood glucose in STZ-induced mice.

Institute for Molecular and Cellular Regulation
Gunma University
IMCR

⑤ Using Type II db/db diabetic mice, we performed an intraperitoneal glucose tolerance test. The results confirmed the ability of the glucose-gated nanodevice to maintain glucose homeostasis. This approach effectively avoids hypoglycemia.

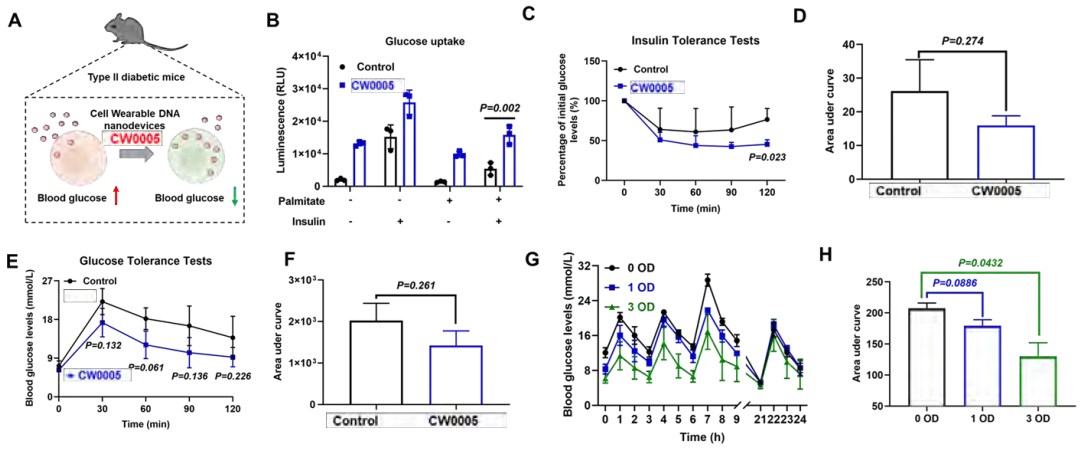

Figure 5. Efficacy of the glucose-gated nanodevice in regulating glucose in db/db diabetic mice.

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.

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. Journal of Biological Chemistry, 2023, doi: 10.1016/j.jbc.2023.103045.

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) Wu Yuchen, Huang Jin, He Hui, Wang Meixia, Yin Guanyu, Qi Lanlin, He Xiaoxiao*, Wang Hong-Hui*, Wang Kemin*. Logic Nanodevice-Mediated Receptor Assembly for Nongenetic Regulation of Cell Behavior in Tumor-like Microenvironment. Nano Letters, 2023, 23(5):1801-1809.
b) Wang Meixia, Li Xiaoxiao, He Fang, Li Juan, Wang Hong-Hui*, Nie Zhou*. Advances in Designer DNA Nanorobots Enabling Programmable Functions. Chembiochem. 2022, e202200119. doi: 10.1002/cbic.202200119

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

None

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

The institutional collaboration agreement between IMCR and College of Biology Hunan university was established in April, 2016. Applicant and Dr. Hao Wang at Dr. Izumi's laboratory have started this project and obtained promising results to support future collaboration.