Fellowship ID：BR190406

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独立行政法人日本学術振興会理事長　殿
To: President, Japan Society for the Promotion of Science

研究活動報告書
Research Report

１．受入研究者/ Host researcher

受入研究機関・部局・職 Name of Host Institution, Department and Title	Professor, Faculty of Applied Biological Sciences, Gifu University
受入研究者氏名 Host Researcher's Name	Tsutomu Nakagawa

２．外国人招へい研究者/ Fellow

所属研究機関・部局・職 Name of Institution, Department and Title	Associate Professor, Texas A&M University College of Medicine
外国人招へい研究者氏名 Fellow's Printed Name	Mohammad Nasir UDDIN

３．採用期間/ Fellowship Period

2020 年 1 月 6 日 ～ 2020 年 2 月 3 日

４．研究課題/ Research Theme

Role of prorenin and (pro)renin receptor in the pathogenesis diseases, specifically in Preeclampsia.

５．研究活動報告/ Research Report

（１）研究活動の概要/ Summary of Research Results

After successful completion of the Bridge Fellowship program in my host lab and networking with other leaders in the field of the novel renin-angiotensin system associated with (pro)renin receptor [(P)RR], I am planning to pursue the following research and submit a grant proposal to NIH in collaboration with my Japanese collaborators.

Preeclampsia (preE) is a serious complication of pregnancy manifested by high blood pressure, proteinuria, and edema, sometimes with encephalopathy, seizures, and hepatic failure. PreE complicates 5 to 10% of pregnancies and is a major cause of maternal and fetal morbidity and mortality worldwide. Nevertheless, an effective therapy for this disorder does not exist. There is no known specific treatment, although palliative measures such as antihypertensive drugs, magnesium, and steroids, and early delivery improve outcomes. A growing body of evidence from my lab and my collaborators' labs supports the existence of a local, intrinsically active renin-angiotensin system (RAS) that participates in the regulation of decidual vascular remodeling and uteroplacental blood flow. Several indirect lines of evidence indicate that upregulation of the RAS in the placenta is important in the pathogenesis of preE. Prorenin can be activated in vivo both proteolytically and nonproteolytically. We discovered that a "handle" region on the receptor plays an important role in prorenin binding to (P)RR and its nonproteolytic activation. Decapeptides based on this handle-region sequence (handle-region peptides or HRP) can block binding of (pro)renin to (P)RR. We hypothesize that blockade with this decoy peptide may effectively

improve local placental perfusion and extend the duration of pregnancy, an important clinical outcome. Recently, high circulating levels of soluble (P)RR were detected at delivery in patients with preE, and both plasma and placental prorenin were found to be elevated in preE and in a rat model of preE. The overall goal of this project is to develop and characterize HRP as an innovative treatment for preE. We will confirm biological activity in vitro using markers of angiogenesis in a cytotrophoblast (CTB) assay. We will evaluate HRP and extended-half-life forms of this peptide for the first time in animal models of preE. After demonstration of the ability to normalize expression of angiogenic factors in the CTB assay and activity in the animal model. We will focus on obtaining the preclinical data necessary for submission of an IND. Pharmacokinetics and toxicity studies, as well as animal studies to demonstrate efficacy, will be performed.

I have visited lab of several Professors in Japan in addition my host Prof. Nakagawa.

Prof. Nakagawa's lab at Gifu University focuses on the basic mechanism of renin-angiotensin association with (pro)renin receptor. Prof. Nakagawa developed a novel and less expensive ELISA to measure soluble (pro)renin receptor in blood and urine samples. Moreover, one of my collaborators of same group, **Prof. Ebihara, developed an ELISA** method to measure prorenin in biological samples. During my stay, I learned the new techniques from my host researcher's lab and will standardize these techniques in my lab in Texas, USA.
In addition to pursuing my collaborative research, we initiated the exchange research program by training undergraduate and postgraduate students from Gifu University in my lab in the USA. Moreover, I delivered seminars on my translational research to the faculty and students of Gifu University, especially in the faculty of applied biological sciences. I taught the unique techniques of my translational research to junior faculty, graduate students, and undergraduate students, as eventually they may begin some patient-oriented research in collaboration with Gifu University hospital.

I visited my following collaborators at different universities in Japan:
1. Prof. Akira Nishiyama, MD, PhD, Department of Pharmacology, Kagawa University: I visited the lab of Prof. Nishiyama during my stay in Japan. One of his research topics is to clarify the independent regulatory mechanisms of tissue renin-angiotensin-aldosterone system (RAAS) and its contribution to pathophysiology of various diseases. During my visit to his lab, I learned unique techniques—for example, novel ELISA method for measurement of prorenin in plasma and serum. I delivered a seminar in his department and interacted with other senior and junior faculty members, undergraduate and graduate students and exchange our research interests.

2. Prof. Atsuhiro Ichihara, MD, PhD, Chairman, Department of Medicine II, Tokyo Women's Medical University: I have been collaborating with Prof. Ichihara on novel renin-angiotensin system associated with (pro)renin receptor during my doctoral and JSPS postdoctoral fellowship research. I have a number of publications with him. One of the main research topics of Prof. Ichihara is to investigate the role and regulatory mechanisms of the (pro)renin receptor in endocrine and endocrine-related disease. I discussed possible future collaboration with Prof. Ichihara and delivered a seminar on my recent human patient data on (pro)renin receptor. I learned the novel techniques that he has developed in his lab to measure the soluble (pro)renin receptor in plasma and urine samples.

3. Prof. Akiyoshi Fukamizu, Life Science Center of Tsukuba Advanced Research Alliance (TARA): I visited the lab of Prof. Fukamizu and delivered a seminar talk on the pathogenesis of preeclampsia (pregnancy-induced hypertension). Prof. Fukamizu's lab showed that when human genes are injected into fertilized mouse eggs, mice with those human genes are born. Like humans, these mice also develop hypertension as they age. Prof. Fukamizu came up with the idea of using these mice to show that hypertension is caused by genes. In the process of that research, he by chance discovered that certain mice had developed hypertension during pregnancy. Most mammals do not develop increased blood pressure during pregnancy naturally. This indicates that the symptoms appeared because the mice expressed specific human genes, which he is working to identify. Prof. Fukamizu's discovery on the pathogenesis of preE is unique and new. I developed a collaboration with his lab for exchanging the technology as well as exchange junior faculties and graduate and undergraduate students between Prof. Fukamizu's lab and my lab in Texas.

（2）研究キーワード/ Keywords

Prorenin, (Pro)renin receptor, Preeclampsia and ELISA

（3）主な研究発表（雑誌論文、学会、集会、知的財産権等/ Main Research Publications

IN PROGRESS PUBLICATIONS:

1. **EXPRESSION OF PLACENTAL AND SOLUBLE (PRO)RENIN RECEPTOR IN NORMAL AND PREECLAMPTIC PREGNANCY**
   Syeda H. Afroze, PhD[1], Saiara Choudhury, BS[2], Michelle Reyes, BA,MBA[3], Nathan Drever, MD[2,3], Tsutomu Nakagawa, PhD[4], Madhava R. Beeram, MD[2,5], Thomas J. Kuehl, PhD[2,3,5], M. Nasir Uddin, PhD, FAHA[2,3,5,6]
   Departments of Medical Physiology[1], Obstetrics and Gynecology[3], Pediatrics[5], and Internal Medicine[6], Texas A&M Health Science Center College of Medicine/ Baylor Scott & White Health, Texas A&M University College of Medicine[2], Temple, Texas, [4]Department of Applied Life Science, Faculty of Applied Biological Sciences, Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan
2. **NOVEL C-TERMINAL PROCESSING MECHANISM OF SOLUBLE (PRO)RENIN RECEPTOR**
   Chiharu Suzuki-Nakagawa, et al.

（4）その他/ Remarks

It was my great experience at Prof. Nakagawa's lab under US-Japan Bridge fellowship. Both scientifically and socially it was an eventful time at Prof. Nakagawa's lab. After successful completion of Bridge Fellowship and networking with Japanese researchers, I could give a written report and an oral presentation on my fellowship networking activity in Japan to build a vibrant alumni networking in the USA. I will suggest the current leadership of JSPS US Alumni Association to arrange a yearly alumni scientific retreat for exchange in our interdisciplinary scientific fields. I will also suggest to invite the Japanese investigators to the scientific retreat, for building strong collaborations with the alumni and my host institute researchers, as well as other Japanese researchers from all over Japan.

（注）採用期間終了後 3 ヶ月以内に、電子メールで提出
(Note) Submit the form by email within 3 months after the expiration of fellowship.