Form 3

Report for Joint/Usage Research Program for Endocrine/Metabolism (Fiscal Year 2018)

Date: 2019/4/17

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

Principal Applicant	
Institution	The University of Texas, MD Anderson Cancer Center
Position	Assistant Professor
Name	Georgios I. Karras

We report on the results of joint research in fiscal 2018 as below.

(Program No. 18004)

1. Research Title	The modulatory effect of Hsp90 on DNA damage signaling
2. Purpose and Significance of the research project	We recently found that the molecular chaperone HSP90 modulates the Fanconi anemia DNA damage signaling pathway by affecting the folding of FANCA protein variants. In the current project, we plan to analyze more FANCA variants. Moreover, we will study the regulatory role of HSP90 on translesion synthesis polymerases. These studies will provide deep insights into the role of HSP90 in tumorigenesis and clonal evolution of cancers.
3. Period of The Program	April 1, 2018 ～ March 31, 2019

4. Project Members

Name	Age	Gender	Institution/Department	Position	Role
(Principal Applicant) Georgios I Karras	35	M	The University of Texas, MD Anderson Cancer Center	Assistant Professor	Project director
(Research Collaborators)					

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

5. Collaborative Researcher of IMCR	Name of the Laboratory	Lab of Molecular genetics	Name	Prof. Takayuki Yamashita

6 . Research Plans

1) We will stably express uncharacterized FANCA variant proteins in FANCA-null fibroblasts and analyze their functions in the following points.
- The binding capacities with HSP90 and other chaperones
- Subcellular localization (cytoplasmic vs nuclear), formation of the FA core complex (interactions with other FA proteins)
- Activation of downstream signaling (FANCD2 monoubiquitination, DNA cross-linker sensitivity)
- Effects of HSP90 inhibitors and proteotoxic stress on stability and the above functions of the FANCA variants

2) Effects of HSP90 inhibitors on the functions translesion synthesis polyemrases in oncogene-induced DNA damage signaling

7 . Research results:

We determined amounts of Hsp90 and Hsp70 bound to various FANCA mutant proteins, and found that the amounts of Hsp90-binding of the mutant FANCA proteins correlated with their capacities for nuclear targeting, downstream activation of FANCD2 monoubiquitination and cellular tolerance to DNA cross-linkers. Furthermore, we extended these analyses using FANCA mutant proteins provided by Dr. Yamashita and obtained consistent results. Together, these findings support the notion that Hsp90 assists in folding of FANCA proteins into functional protein complex, thus buffering their functional defects resulting from pathogenic mutations.

8 . Publications and/or Presentations resulting from Joint Research Program with IMCR.

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.

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.