2018Joint Usage and Research Report

Title of Research Project		The ADP-Ribosyltransferase, TIPARP, is a critical mediator of AHR-mediated suppression of the innate immune response after viral infection
Applicant	Institution	Institute for Genetic Medicine
	Job title and name	Professor Akinori Takaoka
Visiting researcher	Name	Prof Jason Matthews University of Oslo
Purpose of the Research Project (approx. 250 words)		The AHR is a transcription factor that is activated by xenobiotics, dietary products and endogenous metabolites. The AHR has emerged as an important regulator of numerous physiological processes, including the immune system where it plays a role in T cell differentiation, immune tolerance and innate immunity. Through this collaboration with Dr. Takaoka's laboratory, we reported that TIPARP/PARP7 is the key regulator of AHR-dependent innate immune suppression and found that it specifically ADP-ribosylates TBK1 reducing its ability to activate type I interferon responses. (Yamada et al. Nature Immunology 2016). This suggests that pharmacological inhibition of TIPARP could be a beneficial anti-viral therapy. However, we still know very little about TIPARP's role in these processes, how it contributes to adaptive immunity, how the TIPARP-AHR axis is regulated during the innate/adaptive immune responses, and the role of TIPARP in AHR-dependent B or T cell differentiation and function. Moreover, the inhibition of TIPARP may serve as potential therapeutic strategy to boost cancer immunotherapy by reversing immunosuppression through increases in type I interferon. Our proposed project will include comprehensive studies of Tiparp knockout mice, primary and immortalize cell line models, as well as genomic and proteomic methods to characterize the importance of TIPARP in the immune system and cancer immunotherapy.
Development of the Research Project and Results (approx.. 850 words)		During the past year my lab has gained expertise in characterizing type I interferon response after treatment with synthetic pathogen-associated molecular patterns (PAMPs) like 3pRNA and cGAMP). This was done with the help and expertise of Prof. Takaoka. For these studies we have focused on mouse embyronic fibroblasts (MEFs) from our Tiparp-/- mice. We

	found that exposure to PAMPs but also LPS dramatically increases the expression of several proinflammatory cytokines in addition to type I interferons. To confirm that Tiparp catalytic activity is required for this effect, we are performing studies in MEFs isolated from our Tiparp catalytic mutant mice TiparpH532A. Our preliminary data suggest that TIPARP targets more than one component of the NFkB signaling pathway and with our improve mass spectrometric detection of mono-ADP-ribosylation, we will map the modified residues on NFkB as well as other important targets of TIPARP such as TBK1. To further understand the role of the AHR-TIPARP axis in innate immunity, Dr. Takaoka's lab has received and they are exposing the Tiparp knockout mice to various viruses and evaluating a number of relevant endpoints. These studies are still ongoing. We will complement those studies, with experiments using our catalytic mutant Tiparp mouse. This unique mouse model will be important in demonstrating the importance of Tiparp catalytic activity in mediating its role in innate immunity, as to identify cellular targets of TIPARP ribosylation. Another research focus of this work will be to investigate the role of TIPARP in T and B cell differentiation of function. We are also working closely with Dr. Takaoka for these studies. Once isolated, the cells will be differentiation and the presence of absence of AHR ligands to determine the impact of TIPARP and AHR and T and B cell differentiation and function. Together with a collaborator in the USA, we have evaluated a selective TIPARP inhibitor. We are now poised to begin in vivo studies to determine if pharmacological inhibition of TIPARP could be a beneficial anti-viral therapy. This is incredibly important and a potential breakthrough in this collaboration, since Ribon Therapeutics (https://ribontx.com/parp7/) has established a drug development program targeting TIPARP for cancer immunotherapy via its increase in type I interferon signaling. Finally, we are also creating a panel of CRISPR/Cas9 generated TIPARP knockout cell lines to determine the potential role the TIPARP in cancer. Our mouse models will be used to evaluate the role of TIPARP in cancer immunotherapy in combination with immune check point inhibitors to boost therapeutic responses. We feel that this ***novel***, research strategy to characterize the role of TIPARP in type I interferon response

	offers incredible potential for both anti-viral but also anti-cancer therapy. Our complementary expertise and access to unique animal and cell line models for studying TIPARP activity, give us an advantage over other labs pursuing this line of research. Continued support from the joint research program will ensure the success of this research.
Publication *Enter the names of conference or journal and its vol. No. where the above work was presented.	【Conference, symposium, workshop etc.】
	【Journals】 Yamada et al Nature Immunol 2016 Jun;17(6):687-94. doi: 10.1038/ni.3422. Epub 2016 Apr 18.