2015 Joint 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	University of Oslo
	Job title and name	Professor Jason Matthews
Visiting researcher	Name	Jason Matthews
Purpose of the Research Project (approx. 250 words)		The purpose of the research project is to investigate the role of TIPARP in AHR-dependent immunosuppression following activation of the innate immune response. The AHR is a ligand-activated transcription factor that mediates the action of many environmental xenobiotics, including 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (dioxin). It also has an important role in the immune system and in T cell differentiation, but its role in the innate immune response after viral infection is incompletely understood. Dr. Takaoka's group is an expert in innate immune signaling. They have been studying that mono-ADP-ribosyltransferase play important roles in the innate immune response following viral infection. During the course of their studies they observed that TIPARP was an important mediator of AHR-dependent immunosuppression in response to viral infection. My lab recently found that TIPARP, an AHR target gene, is a critical regulator of many aspects of AHR activity and its loss increases the sensitivity of mice to dioxin toxicities. In our ongoing collaboration with Dr. Takaoka and colleagues, we have generated evidence that both endogenous and exogenous AHR ligands suppress the IFN response after infection with various types of virus, and we have identified TIPARP as the key regulator of AHR-dependent innate immune suppression. A manuscript summarizing our collaborative work with focus on the endogenous AHR activation and the innate immune response was recently accepted in Nature Immunology.
Development of the Research Project and Results (approx.. 850 words)		

	As mentioned above, our collaborative joint research project has resulted in a publication in Nature Immunology. In that study we found that constitutive AHR-signaling in the steady state modulates type-I-IFN response during infection with various types of virus. Virus-induced IFN-beta production was enhanced in AHR-deficient cells or mice, with a highly restricted viral replication. The increased response was also observed upon pharmacological inhibition with an AHR antagonist or a TDO/IDO inhibitor, which prevents the generation of potential endogenous ligands for AHR. Most interesting and relevant for our collaboration was the finding that the AHR target gene, TIPARP caused the AHR-induced downregulation of IFN response. Mechanistically, TIPARP interacted with TBK1, mono-ADP-ribosylated TBK1 resulting in a repression of its activity. Thus, our study revealed the physiological significance of endogenous activation of AHR-signaling in shaping the IFN-mediated innate response, and suggested the AHR-TIPARP axis as a potential therapeutic target for enhancing antiviral response. We are continuing this collaboration by investigating the action of exogenous AHR activation in the context of the AHR/TIPARP axis and the IFN-mediated innate immune response. These studies will include analysis of unique genetically modified mouse models of TIPARP that have been generated in my lab, which Dr. Takaoda and I will use to unravel the role of TIPARP in innate immunity. These mouse models include Tiparp whole body knockouts and a CRISPR generated catalytic mutant of Tiparp to determine the role of its enzymatic activity in mediating IFN-dependent activity. We will also investigate the cellular signals beyond the AHR axis that regulate TIPARP expression. This will involve classic promoter analysis, chromatin immunoprecipitation and reporter assays. Moreover, we will work together to identify the mono-ADP-ribosylated residues on TBK1 with the intention of using this information to develop inhibitors of TBK1. We have

	established a mass spectrometric method that effectively detects mono-ADP-ribosylation on target proteins. We have used the approach to identify 6 different mono-ADP-ribosylated peptides in TIPARP and 2 in AHR. Since no consensus ADP-ribosylation sites are known, the only way to determine which residues are mono-ADP-ribosylated is by using mass spectrometry. I look forward to continuing this fruitful and successful collaboration.
Publication *Enter the names of conference or journal and its vol. No. where the above work was presented.	【Conference, symposium, workshop etc.】
	【Journals】 **Constitutive aryl hydrocarbon receptor signaling constrains type I IFN-mediated antiviral innate defense** Taisho Yamada[1,9], Hiromasa Horimoto[1,2,9], Takeshi Kameyama[1,3], Sumio Hayakawa[1,3], Hiroaki Yamato[1,2], Masayoshi Dazai[1,2], Ayato Takada[4], Hiroshi Kida[5], Debbie Bott[6], Angela C. Zhou[7], David Hutin[6], Tania H. Watts[7], Masahiro Asaka[2], Jason Matthews[6,8], and Akinori Takaoka[1,3] Nature Immunology In press.