2024 Joint Usage and Research Report

<table>
<tr><td colspan="2">Title of Research Project</td><td colspan="3">Targeting AHR and PARP7 to Improve Cancer Immunotherapy</td></tr>
<tr><td colspan="2">Status</td><td colspan="3">Continued</td></tr>
<tr><td rowspan="2">Applicant</td><td>Institution</td><td>University of Oslo</td><td>Circle if under 40</td><td>Circle if under 35</td></tr>
<tr><td>Job title and Name</td><td>Professor Jason Matthews</td><td></td><td></td></tr>
<tr><td rowspan="4">Research collaborators
(Please add lines as appropriate)</td><td>Institution</td><td></td><td></td><td></td></tr>
<tr><td>Job title and Name</td><td></td><td></td><td></td></tr>
<tr><td>Institution</td><td></td><td></td><td></td></tr>
<tr><td>Job title and Name</td><td></td><td></td><td></td></tr>
<tr><td colspan="2">Host researcher at IGM</td><td colspan="3">Professor Akinori Takaoka</td></tr>
<tr><td colspan="2">Purpose of the Research Project (within 200 words)</td><td colspan="3">Type I interferons (IFNs) are cytokines and central regulators of immune cell activation, and T cell mediated tumor cell killing. The aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor that is an essential gatekeeper integrating metabolic signals to promote immunosuppression, suppress IFN signaling and enhance tumorigenesis. In cancer, AHR drives pro-survival processes that increase tumor growth. PARP7 is regulated by AHR and functions to dampen stress responses by repressing IFN signaling. Like AHR, PARP7's actions allow tumor cells to avoid immunosurveillance. Recently, small molecule inhibition of PARP7 was shown to restore IFN signaling and release the brake that cancer cells use to evade the immune system. However, PARP7 negatively regulates AHR, and its loss increases AHR signaling. Thus, when co-expressed with PARP7, the increased AHR signaling would be expected to counteract the potential therapeutic benefit of PARP7 inhibition. How ligand or genetic manipulation of the AHR-PARP7 axis affects inflammation and cancer is unknown. The purpose of this research project is to determine the role of the AHR-PARP7 axis in physiology and disease, as well as determine if this axis represents a new therapeutic target for chronic inflammatory disease cancer.</td></tr>
</table>

Results (including the number of web meetings; within 1,000 words)	Over the past year, we have exchanged emails and Professor Matthews travelled to Hokkaido University in March 2025 to meet with Professor Akinori Takaoka and his team to discuss the project and future collaborations. This was a very effective meeting in which we decided on a concrete strategy to continue to develop our ongoing research collaboration. Professor Takaoka and I also exchanged several emails during the past funding period to discuss the project. Project results: In this project, we hypothesize that loss or inhibition of PARP7 will reduce the growth of solid tumors by increasing anti-tumor immune responses in an AHR-dependent manner, and therefore AHR inhibition will improve the therapeutic benefit of PARP7 inhibition. This was tested in two research aims. In aim 1, we sought to determine how PARP7 inhibition/loss affects tumor cell growth and IFN/AHR signaling. Progress: We generated and characterized of PARP7 and AHR knockout cell lines mouse mammary cancer lines Parp7KO, and AhrKO. The Parp7KO, and AhrKO cell lines were confirmed by western blotting, gene expression analyses and other cell characterizations. Parp7KO, and AhrKO cells showed a slight reduction in proliferation compared with WT cells but were otherwise phenotypically like WT cells. We found that Py8119 but not Py230 cells were sensitive to the antiproliferative effects of PARP7 inhibition. As expected Parp7 loss increase type I IFN responses, and AHR signaling. AHR loss had minimal effect on sensitivity to PARP7 inhibition, but increased sensitivity of Py230 cells to PARP7 inhibition when combined with DMXAA treatment. In aim 2, we determined the impact of inhibition/loss of PARP7 on mammary growth *in vivo.* Injection of WT cells into Parp7H532A mice resulted in smaller tumors compared with cells injected into WT EO771 mice. However, injection of Py8119 into Parp7H532A mice (Parp7 catalytic mutant mice) developed tumors more rapidly compared with similarly

	treated WT mice. Interestingly, injection of WT cells (EO771 or Py8119) into Ahr-/- mice resulted in larger and faster growing tumors compared with WT mice. Our data highlight the importance of PARP7 in the immune cells and further support targeting PARP7 for anticancer therapy, but that these effects are cancer cell line specific. We also show that, despite *in vitro* and data suggesting that loss of Ahr leads to reduced tumor progression, tumors in Ahr-/- mice grow more rapidly compared with WT mice. We are currently doing RNA-sequencing and immunophenotyping studies to better understand the role of AHR in tumorigenesis. A manuscript summarizing the crosstalk between PARP7 and AHR in mammary cancer cell and IFN signalling will be submitted in May 2025. A second manuscript summarizing the in vivo tumor studies in Ahr-/- mice is planned for September 2025.
Publication *Provide the details of the conferences or journals where the above work was presented or published.	【Conference, symposium, workshop etc.】 Presenter(s), presentation title, meeting name, venue, date Samaneh Shabani Åhrling et al. Aryl Hydrocarbon Receptor Inhibition Enhances Checkpoint Inhibition Therapy in Triple-Negative Breast Cancer. Annual Meeting of the Norwegian Society of Pharmacology and Toxicology. Beitostølen, Norway January 23-26, 2025 Jason Matthews et al. Targeting Mono-ADP-ribosyltransferases in Breast Cancer to Enhance Antitumor Immunity. National Network for Breast Cancer Research. Oslo March 20-21, 2025
	【Journals】 Author(s), paper title, journal name, volume, pages, year, impact factor One article in preparation
	【Press release】 None.