2020 Joint Usage and Research Report

<table>
<tr><td colspan="2">Title of Research Project</td><td colspan="3">Targeting PARP7 and Mono-ADP-ribosylation to Improve Cancer Immunotherapy</td></tr>
<tr><td rowspan="2">Applicant</td><td>Institution</td><td>University of Oslo</td><td>Under40
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<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>
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and Name</td><td></td><td></td><td></td></tr>
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<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
(approx. 250 words)</td><td colspan="3">Pancreatic cancer (PC) is a devastating disease with a very poor prognosis. The composition and immune status of the tumour microenvironment (TME) is central for disease progression. Cancer immunotherapy is a rapidly growing field and represents a paradigm shift in cancer treatment offering a new therapeutic approach to surgery, conventional chemotherapy, and radiation therapy. One of the most studied targets is the inhibition of programmed death ligand 1 (PDL1) and its receptor PD1, which when engaged prevents the overstimulation of the immune system by deactivating T cells. Type I interferons are central regulators of tumour immune cell infiltration and activation. Together with the Takaoka lab, we recently reported that Poly-ADP-ribose polymerase 7 (PARP7/TIPARP), a negative regulator of type I signalling. The actions of PARP7 on tumour cells allow them to “hide” from the immune system by inhibiting IFN production. Thus, restoring interferon signalling, would in essence release the “brake” that cancer uses to evade the immune system.

The purpose of this application is to determine if the loss or inhibition of PARP7 alone or in combination with immune checkpoint inhibition boosts the anti-tumour effects in intro and in vivo models of PC.
We have three research objectives: (1) Determine how genetic and pharmacologic targeting of PARP7 signalling influences PC growth; (2) Investigate the role of PARP7 in T cell mediated cancer killing (3)</td></tr>
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	Characterize how PARP7 signalling influences PC growth in syngeneic mouse studies. Our proposal will determine the role of PARP7 as a potential therapeutic target on its own or used as combination treatment with cancer immunotherapy for PC.
Development of the Research Project and Results (approx.. 850 words) *Enter the number of web meetings.	Unfortunately, like many other things during the past year, the coronavirus pandemic has reduced out research output. Because of the general travel ban in Norway and Japan, physical meetings from April 1st 2020 until March 31st 2021 were not possible. We did, however, exchange research productivity updates via email. A formal web-based meeting was not organized, but will be done in the future until other alternatives are possible. Over the past year, my lab has established the IFN type signaling analysis protocol with the help of Prof Takaoka's lab and their willingness to shar their expertise and protocols with us. We have used the platform to characterize a number of genetically modified pancreatic cancer cell lines in which we have knockout PARP7 expression using CRISPR-Cas. We have created PARP7 knockouts in human AsPC1 and Capan-1 cells and in mouse K8484 and CR704 cells. The Two mouse cell lines were generated from spontaneous pancreatic tumours from LSL-KrasG12D/+;LSL-Trp53R172H/+;Pdx-1-Cre (KPC) mouse line. As expected PARP7 knockout enhances Type I IFN signaling. We are characterizing their growth conditions and viability. We are now using various approaches (RNA-seq) to identify specific gene signatures that are changed by the loss of PARP7. These experiments are proposed under research objective 1 of our research plan. We have also generated and fully characterized and highly specific anti-PARP7 antibody that will be crucial to fully characterize PARP7's role in pancreatic cancer. The antibody works best at detecting mouse PARP7, but plans are underway to develop one that detects human PARP7 as well. The antibody is a mouse monoclonal which give us an unlimited supply by purifying it from the hybridomas. We have tested selective and specific PARP7 inhibitors in the in vitro models. We have purchased a commercially available PARP7 inhibitor that was identified by Ribon Therapeutics (https://ribontx.com), known as, RBN-2397. RNB-2397 is currently in a Phase 1 clinical trial designed to assess its

	anti-tumor activity in patients with advanced-stage solid tumors (NCT04053673). Ribon presented the anti-tumor effects of RBN-2397 at an AACR webinar in May 2020. They reported dose-dependent reduction of non-small-cell lung carcinoma (NCI-H1373) tumor growth at 30 mg/kg in a xenograft model. RBN-2397-mediated PARP7 inhibition prevented CT26 colon tumor growth in a syngeneic mouse model, which was dependent on type I IFN signaling. These are very exciting studies that will try to confirm in our PARP7 cell and mouse models. As expected, in our hands the pharmacological inhibition phenocopies what we observe in the PARP7 knockout cells. We have just recently started the preliminary studies on the co-culture experiments to investigate the role of the PARP7 in T cell mediated. Those studies are ongoing and will be one of our focus this year. Finally, we are poised to start the syngeneic cancer cell experiments using our Parp7 mutant mice and the various genetically modified Parp7 knockout mouse pancreatic cancer lines that we have generated. The project continues to develop and we expect generate interesting and significant data during the coming year.
Publication *Enter the information of conference or journal (vol. page. Year.) where the above work was presented.	The work is in progress and was not presented at a meeting or conference in 2020
	No publications this past year.