2021 Joint Usage and Research Report

<table>
<tr><td colspan="2">Title of Research Project</td><td colspan="3">Targeting PARP7 to Improve Cancer Immunotherapy</td></tr>
<tr><td rowspan="2">Applicant</td><td>Institution</td><td>University of Oslo</td><td>Under40<br>put a ○</td><td>Under35<br>put a ○</td></tr>
<tr><td>Job title<br>and Name</td><td>Professor Jason Matthews</td><td></td><td></td></tr>
<tr><td rowspan="4">Research<br>collaborators<br>(Please add lines as<br>appropriate)</td><td>Institution</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<br>(approx. 250 words)</td><td colspan="3">Cancers, such as breast and pancreatic cancer, are devastating diseases 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.<br><br>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 vitro cell line and in vivo cancer models.<br>We have three research objectives: (1) Determine how genetic and pharmacologic targeting of PARP7 signaling influences breast cancer and pancreatic cancer growth; (2) Investigate the role of PARP7 in T cell mediated cancer killing (3) Characterize how PARP7 signaling</td></tr>
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| | 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. |
| Development of the Research Project and Results<br>(approx.. 850 words)<br>*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 2021 until March 31st 2022 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.<br><br>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 SU8686 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.<br><br>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 |

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| | anti-tumor activity in patients with advanced-stage solid tumors (NCT04053673). Their data were published in Cancer Cell in 2021 (Gozgit et al Cancer Cell 2021). 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. 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 have begun our own syngeneic cancer cell experiments using our Parp7 mutant mice and the various genetically modified Parp7 knockout mouse breast cancer and pancreatic cancer lines.<br><br>In preliminary studies, injection of *Parp7*$^{WT}$ E0771 cells into *Parp7*$^{H532A}$ mice reduced, but did not prevent, tumor growth compared with *Parp7*$^{WT}$ E0771 cells injected into *Parp7*$^{+/+}$ mice. However, *Parp7*$^{ko}$ E0771 cells injected into *Parp7*$^{H532A}$ mice failed to grow into tumors. Our results so far demonstrate that loss of PARP7 in tumor cells combined with loss in the host are required to prevent mammary tumor growth. These findings further support targeting PARP7 for clinical anti-cancer therapy. |
| Publication<br>*Enter the information of conference or journal (vol. page. Year.) where the above work was presented. | 【Conference, symposium, workshop etc.】<br>The work is in progress and was not presented at a meeting or conference in 2021 and the first 3 months of 2022. The data were, however, presented during departmental meetings at the University of Oslo. In addition, this ongoing collaboration was instrumental in securing new external funding from the Norwegian Research Council to J Matthews in 2021. |
| | 【Journals】<br>No publications this past year. |