Progress report form Cancer Council ACT Research Grant Please submit electronically to cancer.information@actcancer.org		
Report due date	13 December 2024	
Project Lay Title	Normalising the tumour microenvironment to improve treatment outcomes for triple negative breast cancer	
Grant Amount	$75,000	
Chief Investigator	Dr Teresa Bonello	
Project dates	Start: 1/06/2024	End: 32/05/2025

Project Aims/Objectives Briefly state the aims from your original application.	Immune checkpoint inhibitors have been introduced for the treatment of early-stage, high-risk triple negative breast cancer (TNBC), but biomarkers do not exist to predict response to treatment. The tumour size and nodal status of TNBC patients are the only criteria available to determine eligibility for immune checkpoint inhibitor (pembrolizumab) treatment. Thus, biomarkers are urgently needed to distinguish responders from non-responders and may also double as therapeutic targets for overcoming innate resistance in non-responders. The activity of transcriptional regulators, and well-studied oncogenes, yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ) are associated with poor prognosis in TNBC patients. YAP and TAZ are activated in both cancer cells and in the surrounding stromal compartment of the tumour microenvironment. We hypothesise that the activity of YAP and TAZ drive immunosuppression in early-stage TNBC, a feature which is unfavourable for response to immune checkpoint inhibitors. We investigate this hypothesis in both animal models and clinical samples of TNBC.
Please describe how the project is progressing against the aims. Word limit is approximately 400 words.	In collaboration with the Australian Phenomics Facility (APF), we have established an advanced breast cancer model, for which YAP and TAZ have been knocked out (KO) using CRISPR editing. KO of either YAP or TAZ strongly impaired the growth of breast cancer tumours in mice. To identify the mechanism of action, YAP and TAZ KO tumours were fixed, sectioned, and analysed for multiple markers by immunofluorescence. This has revealed an unexpected finding which we are following up with a new panel of markers. We anticipate this analysis will reveal novel mechanisms by which YAP and TAZ contribute to tumorigenesis in the context of triple negative breast cancer. Support from the CCACT has enabled the establishment of a new clinical research working group – The Canberra TNBC Research Initiative. The working group consists of Dr Teresa Bonello (Research Fellow, ANU), Dr Yada Kanjanapan (Medical Oncologist, CHS), Dr Kylie Jung (Radiation Oncologist, CHS) and A/Prof Mitali Fadia (Pathologist, CHS). The goal of the working group, with respect to our CCACT-funded research program, is to 1) improve outcomes for early-stage, TNBC patients receiving neoadjuvant immunotherapy and 2) increase the number of patients eligible for

	immunotherapy by identifying patients expected to benefit from the addition of immunotherapy to their treatment plan.

Moderating Issues Please describe any challenges that you are currently facing and/or that may have impacted upon intended activity, progress and outcomes. Please explain how you will mitigate against these circumstances. Word limit is approximately 300 words.	The formation of the Canberra TNBC Research Initiative is an essential collaboration to ensure the bidirectional flow of information between the lab and the clinic. This collaboration was only made possible once support from CCACT was awarded. Our study design and access to already collected and archived patient samples from The Canberra Hospital required approval from the ACT Health Human Research Ethics Committee. In the meantime, the working group has been optimising reagents and pipelines with the newly established Histology Facility at the John Curtin School of Medical Research.

Publications and presentations Please list any publications and/or abstracts produced as a result of the project. Include manuscripts in preparation or in submission/under review.	

Other Comments Please outline any other items of general interest which have arisen as a result of the project.	

Signed Chief Investigator	Teresa Bonello
Date	12.12.24