Final report form
Cancer Council ACT Research Grant

Please submit electronically to cancer.information@actcancer.org

Report due date	30th June 2023	
Project Lay Title	Exploring how a new and effective anticancer therapeutic can also help cancer patients who are at risk of hemorrhage due to chemotherapy treatments.	
Grant Amount	$60,000	
Chief Investigator	Rita Ferreira	
Project dates	Start: 1st June 2022	End:31st May 2023

Project description Please explain the purpose of your research (including background and rationale). Please use language that the general public will understand. Word limit is approximately 250 words.	Platelets are small cells that circulate by the millions in the bloodstream. Platelets are primarily responsible for sealing a blood vessel when the vessel is damaged or the tissue is infected. When platelets numbers are reduced (thrombocytopenia) excessive bleeding can occur with sometimes fatal consequences. In cancer patients, a drop in platelet production is an extremely common side effect of nearly all cancer treatments. If a therapy is causing this drop, the drug must be stopped immediately, despite the detrimental consequences to the patient. During clinical trials of the anti-cancer drug CX-5461 we observed that a proportion of the patients treated with CX-5461 showed an increase in platelets. PMR-116, a second generation anti-cancer drug built from the CX-5461 backbone, also presents this ability to increase in circulating platelets. We propose to test the ability of CX-5461 and PMR-116 to prevent or reverse the reduction in platelet numbers caused by different chemotherapy treatments. This will allow us to identify the best treatment regime for patients in the future. Other drugs, with small variations to PMR-116, have been generated but not yet tested for their ability to increase platelet numbers. This presents us with a unique and fantastic opportunity of identifying novel drugs that can potentially be used to prevent or treat the reduction of platelets caused by cancer therapies. We propose to study the effect of new untested drugs for enhanced ability to elevate platelet numbers, with reduced side effects. The identification of new drugs capable of increasing platelet numbers will have massive implication in the treatment of cancer patients by allowing continuation of their therapies as well as improve their overall quality of life.

Major results of this research project As this project is now complete, please explain the major results of your research, and what it means for advancing cancer control. Please use language that the general public will understand. Word limit is approximately 500 words.	In order to evaluate the potential of RNA polymerase I inhibitors (CX-5461, PMR-116 and new untested compounds) in the prevention or treatment of chemotherapy-induced thrombocytopenia we proposed: Aim 1: **To validate the ability of CX-5461 to counteract chemotherapy-induced thrombocytopenia.** Aim 2: **To evaluate the thrombopoietic potential of second-generation RNA Polymerase I inhibitors.** With the support of the Cancer Council ACT, we have made great progress towards these aims. **Aim 1:** We have successfully established a pre-clinical model of Carboplatin-induced thrombocytopenia. Using this model, we showed that treatment with CX-5461 did not prevent Carboplatin-induced thrombocytopenia but significantly improved the rate and extent of recovery of platelets towards normal levels. **Aim 2:** We have synthetised 8 second-generation Pol I inhibitors. We have now confirmed the RNA Polymerase I inhibitory activity of 4 of the newly-synthesised compounds. We will test a total of 6 compounds for *in vivo* for their ability to increase platelet number without significantly affecting the remaining blood cell lineages.

Moderating Issues Please describe any challenges that you faced and/or that have impacted upon intended activity, progress and outcomes. Please explain your strategies for any aspects of the project that are incomplete. (Limit 300 words)	We faced challenges that impacted the progress of both our aims. **Aim1:** The establishment of the chemotherapy-induced thrombocytopenia models took longer than anticipated. The models have now been established and the experiments using the Carboplatin-induced thrombocytopenia have been concluded. We are proceeding with experiments in the other models. **Aim2:** We originally proposed to test 20 new second-generation Pol I inhibitors for their ability to inhibit RNA Polymerase I transcription. Although you were able to synthesis all the proposed compounds, the synthesis yield of many of them was low due to the chemical properties of the molecule. We were only able to synthetise 8 compounds in quantities large enough to be used for experimental work. We are currently seeking for commercial organization that will be able to synthesise the remaining compounds in enough quantities to be used for experimental work.

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.	The data generated was presented at the International Society on Thrombosis and Haemostasis (ISTH) 2022 Conference in London (>8000 participants) by Vijay Bhoopalan, a PhD student working on this project.

Further studies and/or funding Please outline any further studies or funding which have arisen as a result of the project.	These results were included in a NHMRC grant that provided us $883,019 to support further research in this subject over the next 3 years.

Other Comments Please outline any other items of general interest which have arisen as a result of the project.	This grant allowed us to obtain addition funding to continue research in this area, which may have not have been available without the results obtain with this project. We hope that our overall research will have a direct impact on cancer patients undergoing chemotherapy as well as in other instances where low platelet numbers have serious consequences in patient's quality of life.

Signed Chief Investigator	Rita Ferreira
Date	31 August 2023