Final report form
Cancer Council ACT Research Grant

Please submit electronically to cancer.information@actcancer.org

Report due date	31/12/2024	
Project Lay Title	Testing GSTO1 inhibitors as anti-cancer therapeutics	
Grant Amount	$75,000	
Chief Investigator	Emeritus Professor Philip Board. JCSMR ANU	
Project dates	Start: 01/07/2023	End:01/03/2025

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.	There is now considerable evidence that an enzyme called glutathione transferase omega 1 (GSTO1) contributes to cancer growth and its spread to multiple areas in the body. In the case of breast cancer, GSTO1 protects breast cancer stem cells from conventional chemotherapy, and this allows the cancer to start again. We have developed to new drugs that block the activity of GSTO1 and this study will determine if they can potentially be used in cancer chemotherapy.

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.	We have worked with collaborators at the Monash Institute of Pharmaceutical Sciences (MIPS) to develop novel inhibitors of GSTO1 that could potentially be used in cancer therapy. Our initial results found that some GSTO1 inhibitors are cytotoxic to cell lines derived from colon cancer (HCT116) and breast cancer (MDA-MB-231) with an IC50 that is similar to that of cisplatin, a drug that is commonly used in cancer chemotherapy. In addition, our studies found that some GSTO1 inhibitors could decrease the capacity of these cell lines to form cancer-like colonies which is a property associated with tumour formation. To further investigate potential applications for GSTO1 inhibitors in cancer therapy we investigated possible synergistic activity with cisplatin. Cisplatin and related drugs are frequently used to treat a wide range of human cancers. Unfortunately, high doses of cisplatin can cause kidney and nerve damage which can limit the dose level needed to eliminate a patient's tumour. We have discovered that low concentrations of two GSTO1 inhibitors (C5-1 and MIPS0021445) can significantly increase the ability of cisplatin to kill MDA-MB-231 breast cancer cells. The data

	suggest that the inhibition of GSTO1 with our novel inhibitor MIPS0021445 may allow the treatment of some tumours with lower doses of cisplatin to avoid the kidney and nerve damage associated with high doses. Further work is required to determine if GSTO1 inhibitors have similar effects on other types of cancer and if the increased cytotoxicity of cisplatin occurs without an increase in the deleterious side effects. Our work so far has shown that this family of GSTO1 inhibitors is highly specific for GSTO1 and is not thioreactive in an ALARM-NMR assay. Further, the in vitro safety pharmacology of C5-1 has been profiled by screening against the Eurofins Cerep Safety Screen 44^{TM} panels to detect potential clinically relevant adverse drug reactions and was negative in an AMES test for genotoxicity. Although further studies are required, the results so far are very encouraging and suggest that these inhibitors would be safe for human therapy.

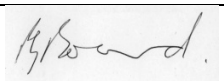
Moderating Issues Please describe any challenges that you faced and/or that have impacted upon intended activity, progress and outcomes. Please explain your strategies for any aspects of the project that are incomplete. (Limit 300 words)	The project was slow to start because Dr Padmaja Tummala was completing another project. There is of course a lot more work to do but the positive results so far will provide strong preliminary data to support a major grant application to the NHMRC.

Publications and presentations Please list any publications and/or abstracts produced as a result of the project. Include manuscripts in	One publication is in the final stages of preparation. **Development of potent glutathione transferase Omega-1 inhibitors with applications in inflammation and cancer therapy** Yiyue Xie [a], Yuji Nakano [a], Padmaja Tummala [b], Aaron J. Oakley [c], Matthew E. Cuellar [d, 1], Jessica M. Strasser [d], Jayme L. Dahlin [e, 2], MichaelA. Walters [d], Marco G. Casarotto [f], Philip G. Board [b, **], Jonathan B. Baell [a, 3, *]

preparation or in submission/under review.	[a] *Australian Translational Medicinal Chemistry Facility, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, VIC 3052, Australia* [b] *John Curtin School of Medical Research, Australian National University, Canberra, ACT 2600, Australia* [c] *Molecular Horizons and School of Chemistry and Molecular Bioscience, University of Wollongong, and Illawarra Health and Medical Research Institute, Wollongong, NSW 2522, Australia* [d] *Institute for Therapeutics Discovery and Development, 717 Delaware Street SE, University of Minnesota, Minneapolis, USA* [e] *Department of Pathology, Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115, USA* [f] *Research School of Biology, Australian National University, Canberra, ACT 2600, Australia*

Further studies and/or funding Please outline any further studies or funding which have arisen as a result of the project.	This study grew out of an earlier study to identify GSTO1 inhibitors for use in the treatment of inflammation. The Cancer Council Grant has allowed us to generate data that strongly supports the potential application of these inhibitors in cancer therapy. The provision of this additional indication makes the further development of GSTO1 inhibitors for human therapy potentially more rewarding and appealing for NHMRC and commercial translational support.

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

Signed Chief Investigator	
Date	17/03 2025