

Final report form
Cancer Council ACT Research Grant

Please submit electronically to cancer.information@actcancer.org

Report due date	June 30 2023	
Project Lay Title	How do DNA receptors prevent the development of bowel cancer?	
Grant Amount	\$65,000	
Chief Investigator	Dr Anukriti Mathur	
Project dates	Start: 1 June 2022	End: 1 June 2023

<p>Project description</p> <p>Please explain the purpose of your research (including background and rationale).</p> <p>Please use language that the general public will understand. Word limit is approximately 250 words.</p>	<p>Colorectal cancer is the second leading cause of cancer-related death in Australia. According to the Cancer in Australia Report released by the Australian Institute of Health and Welfare, an estimated 20,000 Australians received a diagnosis of colorectal cancer in 2020. Treatment for bowel cancer is limited to surgery, radiation therapy, and chemotherapy. An effective immunotherapy (harnessing the power of the immune system in a therapy) against bowel cancer still eludes us due to the complex nature of this disease and our lack of understanding of the specific events that regulate its development. We have recently discovered a novel role for a DNA sensor called Ku70 in preventing bowel cancer. In this project, we will investigate how this protein provides protection against bowel cancer. Findings from this study will expand our understanding of how sensing of DNA and DNA damage in the cells can lead to a protective response against colorectal cancer. Findings from this study will also help generate new diagnostic screening tools and novel therapies for bowel cancer.</p>
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<p>Major results of this research project</p> <p>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.</p>	<p>The major results from this project show that mice and humans lacking a single allele of the DNA repair protein Ku70 had increased susceptibility to the development of intestinal cancer. We have uncovered that Ku70 induces the formation of a novel signalosome complex, composed of Ku70, Ras and Raf. This signalosome docks at the endosomal membrane and induces activation of the inflammation-inducing MEK-ERK signalling pathway during tumorigenesis, potentially attenuating the development of intestinal cancer. Mechanistically, the Ku70-Ras-Raf signalosome led to impairment in the cell cycle, reducing cell proliferation and tumorigenesis. These findings may facilitate the design of therapeutics targeting components of the Ku70 signalosome and may improve the treatment outcomes for individuals with intestinal cancer.</p>
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<p>Moderating Issues</p> <p>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.</p> <p>(Limit 300 words)</p>	<p>The challenge we faced was with respect to the Aim 2. We were not able to genotype the conditional knockout mice lacking Ku70 in intestinal epithelial cells (<i>Ku70^{fl/fl}-Vil1-Cre</i>), fibroblasts (<i>Ku70^{fl/fl}-Col1a1^{tm2.1(CAG-cre/ERT2)Dgk}</i>), haematopoietic cells (<i>Ku70^{fl/fl}-Vav1-Cre</i>), or T and B cells (<i>Ku70^{fl/fl}-CD2-cre</i>). We are collaborating with the Garvan Institute of Medical Research (Sydney) for genotyping of these mice.</p>
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<p>Publications and presentations</p> <p>Please list any publications and/or abstracts produced as a result of the project. Include manuscripts in preparation or in submission/under review.</p>	<p>The following publication is produced as result of this project:</p> <p>Pandey A., Shen C., Feng S., Tuipulotu D.E., Ngo C., Liu C., Kurera M., Mathur A., Venkataraman S., Zhang J., Talaulikar D., Song R., Wong J. J.-L., Teoh N., Kaakoush N.O., Man S.M., 2024, Ku70 senses cytosolic DNA and assembles a tumor-suppressive signalosome. <i>Science Advances</i>, Vol. 10, No. 4.</p>
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<p>Further studies and/or funding</p> <p>Please outline any further studies or funding which have arisen as a result of the project.</p>	<ol style="list-style-type: none"> 1. Development of biomarkers to identify dysregulation in the Ku70 signalling pathway in bowel cancer, which has applications in clinical medicine and diagnosis of bowel cancer, leading to more rapid detection of cancer and intellectual property rights. 2. The development for novel pathway-targeted therapeutics, such as Ku70 activators, will establish industry links and for use in patients.
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<p>Other Comments</p> <p>Please outline any other items of general interest which have arisen as a result of the project.</p>	
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<p>Signed Chief Investigator</p>	<p> Anukriti Mathur</p>
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Date	March 20 2024
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