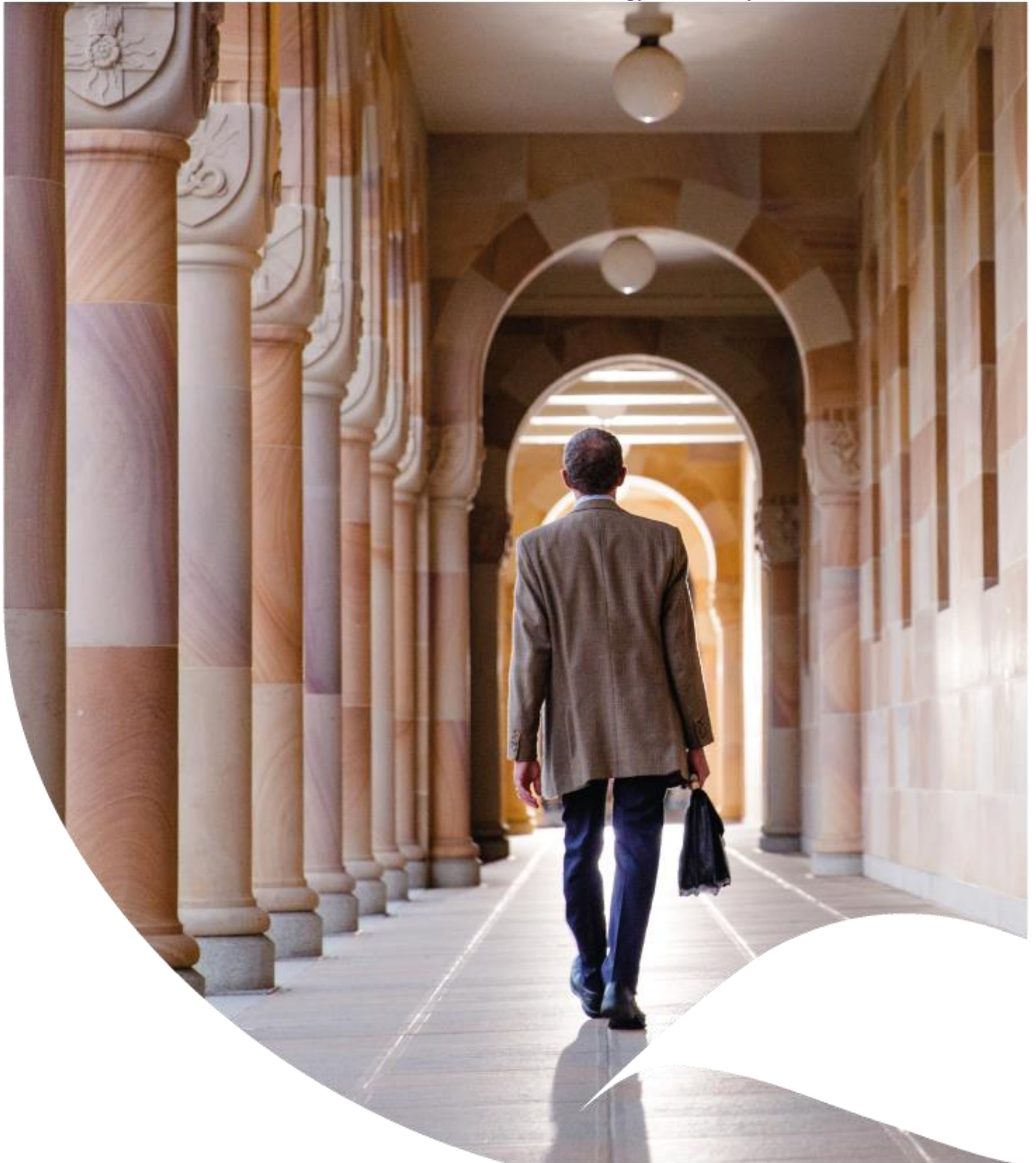


Lions Medical Research Foundation Fellowship Report

Associate Professor Carlos Salomon PhD, DMedSc, Mphil

Lions Medical Research Foundation Fellow, Head, Exosome Biology Laboratory



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Circulating Exosomes in Ovarian Cancer

Ovarian cancer (OVCA) remains one of the major causes of death for women worldwide. Survival rates depend on several factors, including tumour stage and response to chemotherapy.

The greatest challenge in ovarian cancer is not treatment, it is rather the lack of tools to detect the disease at a treatable stage. Unfortunately, a significant proportion of women are often diagnosed with advanced stage disease, where the 5-year survival rate is approximately 20%, compared to 90% when diagnosis is made at an early stage of disease.

Therefore, there is an urgent clinical need to develop techniques to identify OVCA, before the cancer has metastasised. The focus of my current research is to validate a biomarker assay that was developed in our lab, for the early detection of epithelial ovarian cancer through a blood test.

One of my main goals is to conduct my research in a manner that can lead to better outcomes for women and being able to communicate research outcomes to the wider community to help bridge the gap between scientists and society.

My research is primarily aimed at targeting this unmet goal through the use of small extracellular vesicles, known as exosomes (see Figure 1). Exosomes are released from multiple cells, including cancer cells, and have the

extraordinary ability to capture a snapshot of the cellular microenvironment, thus providing a magnified view of an otherwise difficult-to-access site. This capacity of exosomes makes them an ideal biomarker to detect changes in the ovary before the appearance of physical symptoms associated with advanced stage disease, proposing exosomes as “liquid biopsies”. In the last 3 years with the support of the Lions Medical Research Foundation, my group has developed a biomarker panel that can identify women with early stage ovarian cancer with over 90% accuracy (i.e. correct classification of 9 out of 10 women).

"Our biggest challenge with ovarian cancer is the lack of tools to detect the disease at an early, treatable stage."

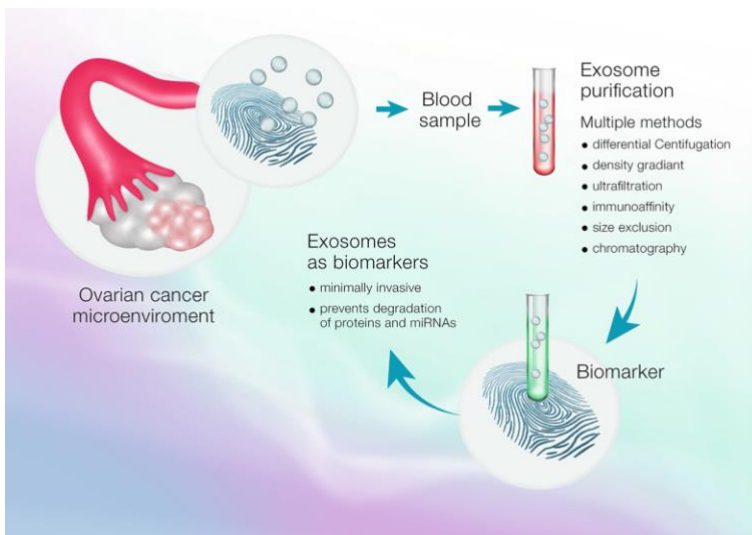


Figure 1

Recently, we published a study in the journal *Nanomedicine*, in which we identified a set of biomarkers associated with chemotherapy resistance in ovarian cancer. Interestingly, the levels of specific biomarkers within exosomes are

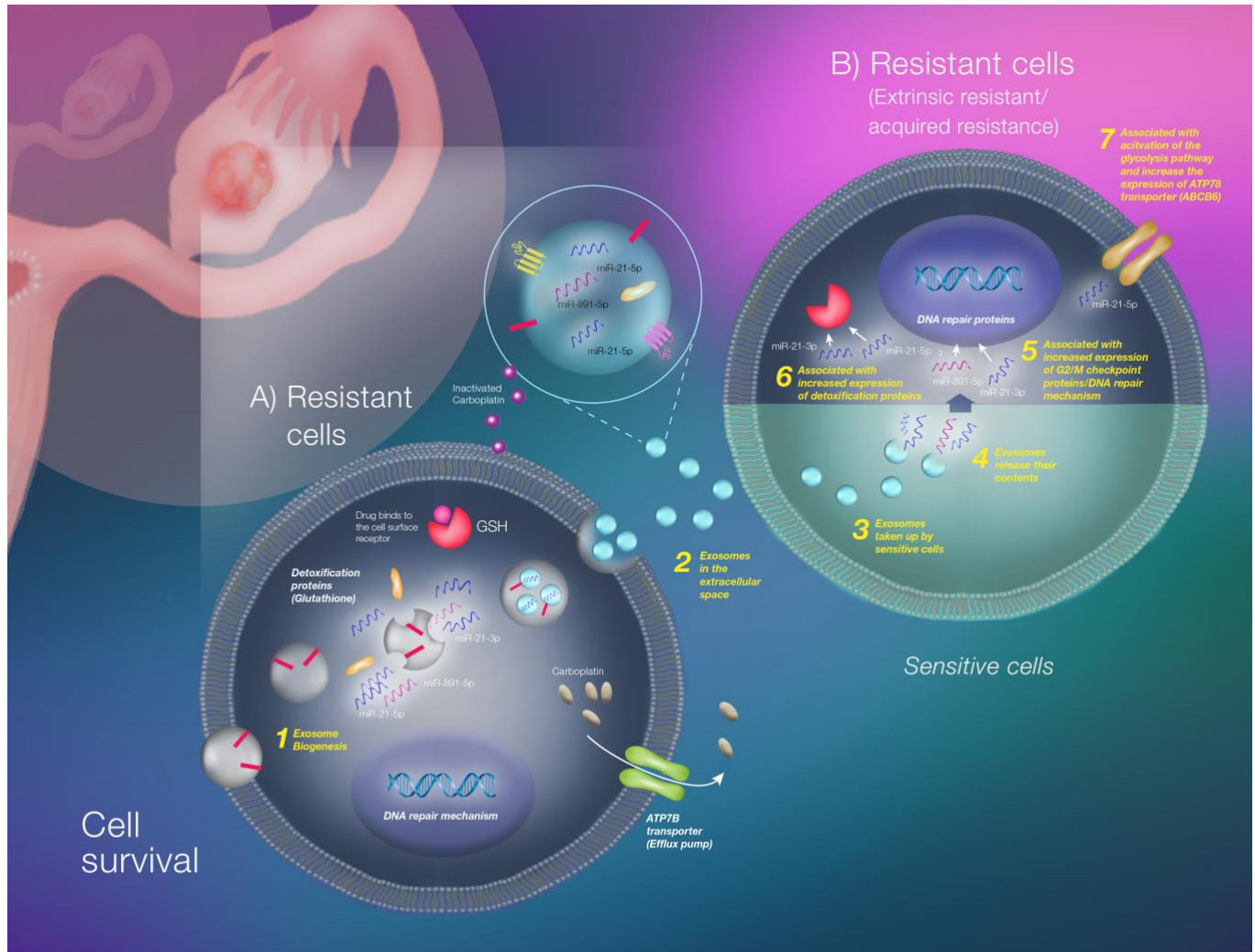


Figure 2

significantly higher in patients at risk of ovarian cancer relapse. Identification of biomarkers in small extracellular vesicles (sEVs) also provides the opportunity to track them in biological fluids to potentially determine patient response to chemotherapy. In the Figure 2, we demonstrate that we have identified the role of 3 biomarkers (miR-21-3p, miR-21-5p, and miR-891-5p) in signalling pathways associated with chemotherapy resistance in ovarian cancer. We propose that these biomarkers are enriched in circulating exosomes in patients with ovarian cancer recurrence, and might decrease chemosensitivity by transferring the resistant phenotype to recipient cells.

Research Highlights

Our research and the resulting impact for the research community has been very strong thanks to the generous support of Lions Medical Research Foundation. Details of this impact are included in the references, conferences, lecture invitations and research visits at the end of the document. I am pleased to report that I have obtained research grants from the Ovarian Cancer Research Foundation (OCRF), which will allow us to validate our biomarker panel for early detection of ovarian cancer in over 500 women in the next 2 years.

Furthermore, we have also obtained a grant from the Medical Research Future Fund (MRFF), to investigate the role of exosomes in ovarian cancer. I have received invitations to present our pilot findings in national and international meetings including lectures at Society for Reproductive investigation (SRI, Paris 2019), International Society of Extracellular Vesicles (ISEV, Japan 2019), Danish Diabetes Academy (Copenhagen, 2019), and 6th Thomas Ashworth CTC & Liquid Biopsy Symposium (Sydney, 2019).

Recently, I was awarded the prestigious Young Tall Poppy Award for my research on exosomes, and their role in ovarian cancer. This award aims to recognise the achievements of Australia's outstanding young scientific researchers and communicators. I feel proud to represent the Lions Medical Research Foundation in all my activities and be an ambassador for the Foundation in Australia and worldwide.

Finally, I would like to express my gratitude to my PhD students developing projects on Ovarian Cancer: Miss Shayna Sharma and Mrs. Mona Alharbi; and all the members of my team including UQCCR staff and students. The Exosome Biology Laboratory Team: Katherin Scholz-Romero (Research Assistant), Soumya Nair (PhD student), Dr. Dominic Guanzon (Postdoc), Dr. Andrew Lai (Postdoc), Carlos Palma (PhD student), Suchi Dutta (PhD student), Nanthini Jayabalan (PhD student), Yohaann Jafrani and Molly Qian (Master students); and my collaborators Professor John Hooper (UQ Mater Research Institute), A/Professor Lewis Perrin (UQ Mater Research Institute), A/Professor Terry Morgan (OHSU, USA), and Professor Anna Defazio (University of Sydney).



Selected Publications 2019-2020

1. Alharbi M, Sharma S, Guanzon D, Lai A, Zuñiga F, Shiddiky MJA, et al. miRNA signature in small extracellular vesicles and their association with platinum resistance and Cancer recurrence in ovarian Cancer. *Nanomedicine: Nanotechnology, Biology and Medicine*. 2020:102207.
2. Sharma S, Salomon C. Techniques Associated with Exosome Isolation for Biomarker Development: Liquid Biopsies for Ovarian Cancer Detection. *Methods Mol Biol*. 2020;2055:181-199. doi: 10.1007/978-1-4939-9773-2_8.
3. Alharbi M, Lai A, Guanzon D, Palma C, Zuñiga F, Perrin L, He Y, Hooper JD, Salomon C. Ovarian cancer-derived exosomes promote tumour metastasis in vivo: an effect modulated by the invasiveness capacity of their originating cells. *Clin Sci (Lond)*. 2019 Jul 5;133(13):1401-1419. doi: 10.1042/CS20190082. Print 2019 Jul 15.
4. Alharbi M, Zuñiga F, Elfeky O, Guanzon D, Lai A, Rice GE, Perrin L, Hooper J, Salomon C. The potential role of miRNAs and exosomes in chemotherapy in ovarian cancer. *Endocr Relat Cancer*. 2018 Dec 1;25(12):R663-R685. doi: 10.1530/ERC-18-0019. Review.
5. Sharma S, Alharbi M, Kobayashi M, Lai A, Guanzon D, Zuñiga F, Ormazabal V, Palma C, Scholz-Romero K, Rice GE, Hooper JD, Salomon C. Proteomic analysis of exosomes reveals an association between cell invasiveness and exosomal bioactivity on endothelial and mesenchymal cell migration in vitro. *Clin Sci (Lond)*. 2018 Sep 18;132(18):2029-2044. doi: 10.1042/CS20180425. Print 2018 Sep 28.

Abstracts

1. Alharbi M, Lai A, Guanzon D, Zuñiga F, Perrin L, He Y, Hooper J, Salomon C. Ovarian cancer cell invasiveness regulates their exosomes which induces oncogenic potential and cancer progression in vivo. 66th Annual Meeting of the Society for Reproductive Investigation, Paris, 2019
2. Shayna Sharma, Andrew Lai, Dominic Guanzon, Terry Morgan, Lewis C. Perrin, John D. Hooper, Carlos Salomon. Circulating Exosomal miRNAs from Women with Ovarian Cancer for Early Detection and Real-Time Monitoring of Cancer Progression. 2019 66th Annual Meeting of the Society for Reproductive Investigation, Paris (Oral Presentation)
3. Shayna Sharma, Andrew Lai, Dominic Guanzon, Terry Morgan, Lewis Perrin, John Hooper, Carlos Salomon. Exosomal miRNAs and Proteins Signature as Prognostic Biomarkers for Early Stage Epithelial Ovarian Cancer. 2019 ISEV's 7th Annual Meeting, Kyoto
4. Shayna Sharma, Andrew Lai, Dominic Guanzon, Terry Morgan, Lewis Perrin, John Hooper, Carlos Salomon. Profiling of circulating exosomal content across epithelial ovarian cancer and the role of exosomes in tumour progression. 2019 ISEV's 7th Annual Meeting, Kyoto
5. Shayna Sharma, Dominic Guanzon, Andrew Lai, Terry Morgan, Lewis Perrin, John Hooper, Carlos Salomon. Exosomes-Big Information in Small Packages. 2019 BLiSS-Brisbane Life Science ECR Symposium, Brisbane
6. Shayna Sharma, Andrew Lai, Dominic Guanzon, Terry Morgan, Lewis Perrin, John Hooper, Carlos Salomon. Exosomes as Tools for Early Detection of Epithelial Ovarian Cancer. 2019 Tissue Engineering & Regenerative Medicine International Society-AP Chapter and the 7th Asian Biomaterials Congress. Brisbane
7. Shayna Sharma, Andrew Lai, Dominic Guanzon, Terry Morgan, Lewis Perrin, John Hooper, Carlos Salomon. Utilisation of Exosomal miRNAs and Proteins for Identification of Early Stage Epithelial Ovarian Cancer. 2019 7th Annual TRI Translational Poster Symposium, Brisbane
8. Shayna Sharma, Andrew Lai, Dominic Guanzon, Terry Morgan, Lewis Perrin, John Hooper, Carlos Salomon. Utilisation of Exosomal miRNAs and Proteins for Identification of Early Stage Epithelial Ovarian Cancer. 2019 Faculty of Medicine HDR Symposium, Brisbane (Oral Presentation)
9. Shayna Sharma, Andrew Lai, Dominic Guanzon, Terry Morgan, Lewis Perrin, John Hooper, Carlos Salomon. Exosomal miRNAs and Proteins as Biomarkers for Identification of Early Stage Epithelial Ovarian Cancer. 2019 6th Thomas Ashworth CTC & Liquid Biopsy Symposium, Sydney (Oral Presentation)
10. Shayna Sharma, Andrew Lai, Dominic Guanzon, Terry Morgan, Lewis Perrin, John Hooper, Carlos Salomon. Ovarian Cancer Exosomal miRNAs are Associated with the Epithelial to Mesenchymal Transition. 2019 6th Thomas Ashworth CTC & Liquid Biopsy Symposium, Sydney

11. Xiaoqi Qian, Shayna Sharma, Andrew Lai, Carlos Salomon. Profile of the protein content within circulating exosomes in ovarian cancer reveals an association with disease progression. 2019 6th Thomas Ashworth CTC & Liquid Biopsy Symposium, Sydney
12. Xiaoqi Qian, Shayna Sharma, Andrew Lai, Carlos Salomon. Profile of the protein content within circulating exosomes in ovarian cancer reveals an association with disease progression. 2019 Faculty of Medicine HDR Symposium, Brisbane
13. Xiaoqi Qian, Yohaann Jafrani, Shayna Sharma, Andrew Lai, Carlos Salomon. Circulating exosomal protein profiling indicates an association with ovarian cancer progression. SCMB 15th Annual Student Research Symposium, Brisbane
14. Yohaann Jafrani, Xiaoqi Qian, Shayna Sharma, Andrew Lai, Carlos Salomon. Differentially expressed exosomal miRNAs in Epithelial Ovarian Cancer Progression. 2019 6th Thomas Ashworth CTC & Liquid Biopsy Symposium, Sydney
15. Yohaann Jafrani, Xiaoqi Qian, Shayna Sharma, Andrew Lai, Carlos Salomon. Potential role of exosomal miRNA in early detection of ovarian cancer. 2019 Faculty of Medicine HDR Symposium, Brisbane
16. Yohaann Jafrani, Xiaoqi Qian, Shayna Sharma, Andrew Lai, Carlos Salomon. Role and association of exosomal miRNAs in aiding ovarian cancer progression. SCMB 15th Annual Student Research Symposium, Brisbane

Contact us

Nicole Zanyat
Faculty of Medicine Advancement
0448 413 157
n.zanyat@uq.edu.au