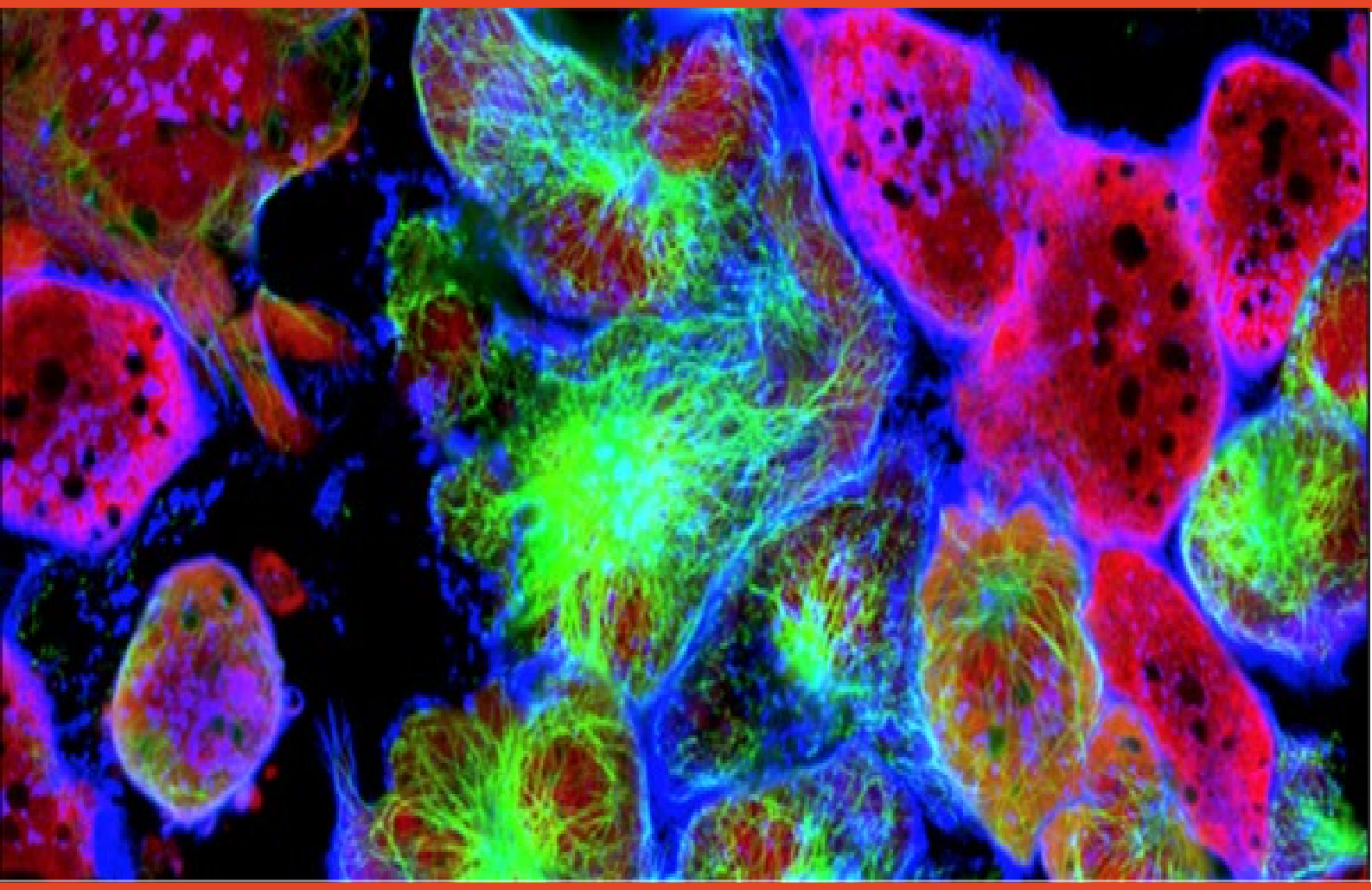
The Cancer Research Network presents the: 2023 POSTGRADUATE STUDENT CANCER RESEARCH SYMPOSIUM

16 November 2023



THE UNIVERSITY OF SYDNEY

Sydney Cancer Partners
Collaboration, Translation, Impact

2023 Postgraduate Student Cancer Research Symposium

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About the Cancer Research Network

Established in 2006, the Cancer Research Network is a cross-Faculty initiative linking cancer researchers at the University of Sydney, its teaching hospitals and its affiliated research institutes and institutions. It encompasses a wide range of researchers who share a commitment to cancer research, collaborative research, and research development. Our core values include a willingness to collaborate and share expertise, openness to multiple disciplines, and an interest in the translation of research findings into improvements in cancer control. The Network's membership has grown to over 1,000 active cancer researchers.

The Network fosters communication with and among members to facilitate multidisciplinary collaboration across research groups, with an emphasis on research translation. This builds a sense of community among cancer researchers across discipline and geographical boundaries.

The Network adapts and responds to the needs of cancer researchers, and through its activities stimulates knowledge transfer within the Network, the University and to the Government and public.

Membership is open to employees and postgraduate research students at the University of Sydney, people employed by teaching hospitals and Institutes of the University of Sydney, or people holding an academic title award from the University of Sydney, who are active in the area of cancer research.

For further information, please contact the Cancer Research Network Office

crn.cancer-research@sydney.edu.au

Organising Committee

Pranujan Pathmendra (Co-Chair)
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Ruth Allen
Gillian Reyes-Marcelino
Sooin Byeon
Tiffany Li
Xinyu Bai
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Srija Sur
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Chloe Jennett

Welcome message from the Symposium Chairs

On behalf of the Postgraduate Student Working Group (PGSWG) of the University of Sydney's Cancer Research Network, we'd like to extend a warm welcome to the 15th Annual Postgraduate Student Cancer Research Symposium. The Cancer Research Network (CRN) represents cancer research students and academics across the University of Sydney, providing opportunities for networking and collaboration with like-minded colleagues. We are delighted to collaborate with Sydney Cancer Partners again to make this symposium possible.

This year's symposium focuses on the theme of interdisciplinary partnership and careers, celebrating the diverse array of research and collaboration that is pivotal in our attempts to better understand, diagnose, and treat cancer. We are grateful to the many students who have submitted an abstract across many disciplines from genomics and molecular biology to public health– for their willingness to share their work and showcase the diverse research that is currently ongoing in cancer research. We would like to thank our wonderful keynote speakers, Dr Inês Silva and A/Prof. James Wilmott who will be sharing their interdisciplinary experiences of collaboration as a researcher and clinician. We would also like to thank Prof. Andrew Baille for organising a workshop, where we will have the opportunity to learn more about interdisciplinary partnerships and careers around cancer research. We look forward to hearing from you all and meeting you in person at the symposium and the networking event.

On behalf of the PGSWG, we would also like to extend our thanks to Catherine Barnett and Jing Wang for their continued and unwavering support for this committee and event. A huge thank you must also go to all the members of the PGSWG who have put in so much time and energy to organise this year's events which would not be possible without their tremendous contributions!

We hope that you are inspired by each other and enjoy learning about all the amazing work going on through the CRN and beyond.

Please engage with your colleagues and build new connections through Twitter by using #CRNHDRs23 and following us on @SydCancerNetwrk and @SydCancerPtnrs.

Farhana Mollah and Pranujan Pathmendra

Co-chairs, Cancer Research Network's Postgraduate Student Working Group (PGSWG)

Keynote Speakers

Dr Inês Silva

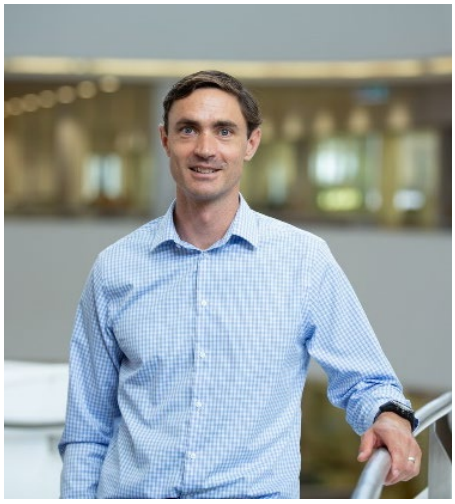
Dr Inês Silva (MD FRACP PhD) is a Medical Oncologist at Melanoma Institute Australia, Blacktown and Mater Hospitals, and Senior Lecturer at The University of Sydney.

She received her MD degree at the Universidade Nova de Lisboa (Lisbon, Portugal) and completed specialist training in Medical Oncology at Instituto Português de Oncologia (Lisbon, Portugal). She did her PhD at Bhardwaj Lab (part of Interdisciplinary Melanoma Cooperative Group and NYU Cancer Institute) in tumor immunology, describing how the dysfunction of the protective innate immune mechanisms, including NK cells, can contribute towards melanoma progression. She did two clinical fellowships in melanoma, one at NYU Cancer Institute (2014), and more recently, at Melanoma Institute Australia (2017-2019) where she was co-investigator in phase I, II and III clinical trials (neoadjuvant, adjuvant and metastatic) in melanoma.

Inês has presented her research work in several international meetings. She has received the best poster award at ESMO 2019 and Cancer Conquer merit award in 2019, 2020 and 2021, including the Bradley Stuart Beller Endowed Merit Award for the highest ranking ASCO abstract overall (2020). She has over 50 publications, including 1st author publications in Lancet Oncology, Journal of Clinical Oncology, Cancer Cell, NEJM and JITC, amongst others, senior author in JITC publication, and co-author of publications in Cancer Cell and JCI on the field of melanoma and immuno-oncology.

Her main research interests are (1) Biomarkers of response to immunotherapy and targeted therapy in melanoma; (2) Mechanisms of innate and adaptive resistance with immunotherapy; (3) Patterns of metastization and patterns of response to immunotherapy; (4) Mechanism of toxicity with immunotherapy.

A/Prof James Wilmott



Associate Prof Wilmott (BSc, PhD) is the senior scientist at the Melanoma Institute Australian's, Translational Research laboratory based at the University of Sydney. As a translational research scientist, he works closely with clinical teams and patients to identify areas of need, discover solutions and work collaboratively to implement these findings into clinical workflows. With 213 publications from multiple top-ranked journals such as Nature, Cell, Cancer Cell, Nature Cancer, and Nature Communication, he has achieved a H-index of 66. He focusses on the integration of clinicopathology, genomics, gene expression, and high-dimensional spatial pathology to develop tools that improve treatment selection and aid the understanding of drug resistance.

James leads the Personalised Immunotherapy Program (PIP), which aims to revolutionise the way immunotherapies are used in clinical trials and how specific treatments are selected for each patient in routine clinical care. The program generates somatic, transcriptomic and tumour immune profiles and uses this information to generate predictive biomarker reports to inform the treatment selection. The Personalised Immunotherapy Program is funded by the Cancer Institute of New South Wales (CINSW) for $3.7 million over four years (2022-2026).

Workshop Session

Chair: Prof. Andrew Baillie

Prof Andrew Baillie is a clinical psychologist and Professor of Allied Health with Sydney Local Health District. He works with Allied Health Research & Education for Translation & Innovation within SLHD to build Allied Health Research Capacity. Andrew convenes the Academic Implementation Science Network for Sydney Health Partners, and the Long-COVID Australia Collaboration. He collaborates with the Matilda Centre for Research in Substance use and Mental Health, the Edith Collins Centre (Translational Research in Alcohol Drugs and Toxicology), and the Sydney Institute of Women Children and their Families. He also works with Drug Health Services at RPA and the Psychology Team at RPAVirtual.

Panel Participants: TBA

Highlighted events

Registration, Breakfast & Welcoming Address

The symposium opens at 8:30am, where we welcome all registrants to attend early, and mingle with fellow attendees with coffee and some small breakfast items. This early registration will be a great opportunity to connect with some of your fellow HDR colleagues as well as connect with our team (Postgraduate Student Working Group (PGSWG) of the University of Sydney's Cancer Research Network).

Student presentations

We have numerous HDR and Honours students from University of Sydney sharing their important work in cancer research. We have several dedicated student sessions that we have outlined below.

Stream 1: Pre-clinical and Basic Sciences
For the present symposium, we have divided the student sessions into two streams. The first stream examines students whose work is mostly pre-clinical or use basic sciences to understand the basic processes and systems that underpin cancer and how it functions as a disease. Such knowledge is vital in our attempts to develop better ways to predict, prevent, diagnose, and treat cancer. In these sessions, students will present talks varying from 8-12 minutes, followed by answering questions from the audiences. Student presentations will be graded by judges and the top 2 best presenters will receive an award.

Stream 2: Public Health
For the present symposium, we have divided the student sessions into two streams. The second stream examines students whose work is in the domain of public health. These upcoming researchers study patients and the public with respect to their experiences around cancer to better understand how we can promote the health outcomes of cancer patients through organised efforts of the individual patients, families, organisations, and the broader public. Student presentations will be graded by judges and the top 2 best presenters will receive an award.

CRN PGSWG's 5MT Competition – "The Many Facets of Cancer Research"
The 5MT competition consists of 9 student speakers who will be sharing their research in cancer from various fields, ranging from molecular genetics to public health. Then, the students will participate in a panel discussion where the audience is invited to ask questions about their work. The aim of this panel in concordance with the conference theme is to celebrate the diverse disciplines that cancer research spans across. The audience members will vote, and the top 2 presenters with the most votes will receive an award.

Networking event

At the end of our symposium, we will be hosting an informal networking event where fellow HDRs and ECRs are invited to mingle over some drinks and snacks. This will be a great opportunity to build your interdisciplinary networks that will assist your career as a cancer researcher. Also, for HDR students, this is a great opportunity to get in touch with your fellow students and the broader CRN PGSWG team. We also have some fun networking activities organised by PGSWG members, Chloe Jennet, and Gillian Reyes-Marcelino.

PROGRAM

2023 POSTGRADUATE STUDENT CANCER RESEARCH SYMPOSIUM

Thursday, 16 November 2023
Susan Wakil Health Building, The University of Sydney

8:30	**Registration & Welcome Breakfast** *Sustain Wakil Health Building* *Level 4 Foyer*	
	PLENARY SESSION *Susan Wakil Health Building* *Level 3 Room 321, Julie Wu Lecture Theatre* **Chairs:** Farhana Mollah & Pranujan Pathmendra	
9:00	Welcome and Introductions	
CONCURRENT SESSIONS		
	Stream 1a – Pre-clinical and basic science *Susan Wakil Health Building* *Level 3 Room 322* **Chairs:** *TBA*	**Stream 2a – Public Health** *Susan Wakil Health Building* *Level 3 Room 309* **Chairs:** *TBA*
9:20	**1. The impact of telomere length on prostate cancer aggressiveness, genomic instability and health disparities** Ruotian Huang *Ancestry and Health Genomics Laboratory*	**7. Provider perspectives on the psychosocial impacts of lung cancer screening** Kathleen McFadden *Daffodil Centre*
9:35	**2. Investigation of kataegis in prostate cancer evolution and ethnic disparity** Jue Jiang *Ancestry and Health Genomics Laboratory*	**8. Risk of developing a second primary melanoma after a first primary melanoma in a population-based Australian cohort** Yuan Ni *Daffodil Centre*
9:50	**3. Pan-cancer analysis links altered RNA m7G methyltransferase expression to oncogenic pathways, immune cell infiltrations and overall survival** Anni Su *Epigenetics and RNA Biology Laboratory*	**9. Empowering Pharmacist for Early Lung Cancer Detection and Lung Health Evaluation: A Scoping Review** Simmie Chung *Sydney Pharmacy School*
10:05	**4. Atovaquone Radiosensitises Diffuse Midline Gliomas by Inhibiting Mitochondrial Metabolism and Hypoxia** Faiqa Mudassar *Translational Radiation Biology and Oncology Group*	**10. SeCoNet: A Heterosexual Contact Network Growth Model for Human Papillomavirus Disease Simulation** Weiyi Wang *School of Computer Science*
10:20	**5. Genomic Profiling and Biomarker Discovery for Predicting Early Intrahepatic Recurrence Following Resection of Colorectal Liver Metastases** Geoffrey Yuet Mun Wong *Department of Upper Gastrointestinal Surgery, Royal North Shore Hospital*	**11. Using the counterfactual framework to estimate non-intention-to-treat effects in randomised controlled trials: a methodological scoping review** Ellie Medcalf *School of Public Health*
10:35	**6. Depletion of dipeptidyl peptidase 9 (DPP9) in mouse hepatocytes elevates inflammation markers in an experimental model of hepatocellular carcinoma** Carrie Huang *Department of Liver Injury, The Centenary institute*	
10:50	**MORNING TEA**	

11:05	**Keynote speaker –** "Title TBA" *Susan Wakil Health Building, Level 3 Room 321, Julie Wu Lecture Theatre* **Chair:** Farhana Mollah **Speakers:** Dr Inês Silva & A/Prof. James Wilmott	
12:00	**LUNCH**	
1:00	**Workshop –** "Networking for Interdisciplinary Collaboration" *Susan Wakil Health Building, Level 3 Room TBA* **Chair:** Prof Andrew Baille **Panel Particpants:** TBA	
CONCURRENT SESSIONS		
	Stream 1b – Pre-clinical and basic science *Susan Wakil Health Building* *Level 3 Room 309* **Chairs:** *TBA*	**Stream 2b – Public Health** *Susan Wakil Health Building* *Level 3 Room 322* **Chairs:** *TBA*
2:05	**12. Development of 3D preclinical TNBC tumour models and investigation of novel anticancer targeted therapies** Farhana Mollah *The University of Sydney Nano Institute*	**16. The Do's and Don'ts of clinical trials interim analysis** Yu Yang Soon *NHMRC Clinical Trials Centre*
2:15	**13. Plasma Activated Liquids and their Synergy with radiation for cancer therapy** Juliette Harley Applied and Plasma Physics	**17. Risk Factors Associated with Chemotherapy-Induced Peripheral Neuropathy Persistence** Tiffany Li *Brain and Mind Centre*
2:25	**14. B-cell Maturation Antigen Antibody-Drug Conjugates (BCMA-ADCs): A Glimmer of Hope for Multiple Myeloma** Jing Shan *School of Pharmacy*	**18. Does exercise change blood flow to tumours? Acute aerobic exercise effects on liver metastases blood flow: a case series** Catherine Seet-Lee *Faculty of Medicine and Health*
2:35	**15. The molecular mechanisms underlying radiation-induced phenotypic plasticity in human oral squamous cell carcinoma cells under hyperglycaemic metabolic stress.** Thanh Dat Pham *School of Medical Sciences*	
2:45	**AFTERNOON TEA**	
3:10	**CRN PGSWG's 5MT Competition –** "The Many Facets of Cancer Research" *Susan Wakil Health building, Level 3 Room 321, Julie Wu Lecture Theatre* **Chair:** Pranujan Pathmendra **Participants:** Yibai Li, Prisca Akpabio, Nikilyn Nevins, Sali Kurtam, Celine Garrett, Natalie Smith, Danielle Chrystall, Srija Sur, Samuel Bax	
4:00	Q & A Panel of competition participants	
	AWARDS & CLOSING CEREMONY *Susan Wakil Health Building, Level 3, Room 321* **Chairs:** Farhana Mollah and Pranujan Pathmendra	
4:20	Most outstanding student presenter and runner up within each of the following streams: • Pre-clinical and basic science • Public Health Winner of the People's choice award and runner up in the 5MT Competition.	
4:40	**FINISH**	
4:45	**NETWORKING EVENT** *Susan Wakil Health Building, Level 4 Foyer* **Organisers:** Chloe Jennet and Gillian Reyes-Marcelino	

ABSTRACTS

Stream 1a: Pre-clinical and basic science

1. The impact of telomere length on prostate cancer aggressiveness, genomic instability and health disparities

Ruotian Huang* (1), M.S. Riana Bornman (2), Phillip D. Stricker (3), Ilma Simoni Brum (4), Shingai B.A. Mutambirwa (5), Weerachai Jaratlerdsiri (1), and Vanessa M. Hayes (1,2,6,7)

(1) Ancestry and Health Genomics Laboratory, Charles Perkins Centre, School of Medical Sciences, Faculty of Medicine and Health, University of Sydney, Camperdown, NSW 2006, Australia
(2) School of Health Systems and Public Health, Faculty of Health Sciences, University of Pretoria, Pretoria 0084, South Africa
(3) Department of Urology, St Vincent's Hospital, Darlinghurst, NSW 2010, Australia
(4) Endocrine and Tumor Molecular Biology Laboratory, Instituto de Ciências Básicas da Saúde, Universidade Federal do Rio Grande do Sul, Brazil
(5) Department of Urology, Sefako Makgatho Health Science University, Dr George Mukhari Academic Hospital, Medunsa 0208, South Africa
(6) Manchester Cancer Research Centre, University of Manchester, Manchester M20 4GJ, United Kingdom
(7) Faculty of Health Sciences, University of Limpopo, Turfloop Campus, Sovenga 0727, Limpopo, South Africa

Background: A human telomere consists of TTAGGG motif at the ends of chromosomes, preserving their genomic integrity and chromosomal stability. In turn, genomic instability is a hallmark of cancer - implicating telomere disturbance. Prostate cancer (PCa) shows significant ancestral disparities, with men of African ancestry at the greatest risk for aggressive or lethal disease and an elevated tumour genome instability. Yet, no study has explored the role of telomere length (TL) as it pertains to ancestrally-drive PCa health and genomic disparities, especially in the largely overlooked African PCa populations.

Aims & Methods: Based on patient-matched tumour-blood whole genome sequencing data generated using a single technical an analytical pipeline, we investigated for a link between estimated TLs (blood and tumour) and PCa disease presentation, genomic instability and associated ancestral disparities, for 117 treatment naïve Africans versus 62 Europeans.

Results: We found shortened tumour TL to be associated with aggressive PCa presentation and with elevated genomic instabilities, including percentage of genome alteration and gained DNA regions, in men of African ancestry. For European PCa patients, tumour TL showed significant associations with PCa driver genes, including PTEN, TP53, MSH2, SETBP1 and DDX11L1, while shorter blood TL (< 3200 base pairs) and tumour TL (< 2861 base pairs) were correlated with higher risk of biochemical recurrence at earlier stage.

Conclusions: Concurring with previous studies suggesting TL assessment as a diagnostic and prognostic biomarker for PCa, for the first time we demonstrate differences in TL presentation associated with patient ancestry. Most notably, differences in associated tumour TL and genomic instability between the ancestries suggest not only disparities in contributing mechanisms of tumour evolution, but importantly potential implications for future treatments that target telomere dysfunction.

2. Investigation of kataegis in prostate cancer evolution and ethnic disparity

Jue Jiang*(1), Pamela X. Y. Soh (1), Shingai B. A. Mutambirwa (2), M.S. Riana Bornman (3), Vanessa M. Hayes (1,3,4) and Weerachai Jaratlerdsiri (1)

(1) Ancestry and Health Genomics Laboratory, Charles Perkins Centre, School of Medical Sciences, Faculty of Medicine and Health, University of Sydney, Camperdown, NSW, Australia
(2) Department of Urology, Sefako Makgatho Health Science University, Dr George Mukhari Academic Hospital, Ga-Rankuwa, South Africa
(3) School of Health Systems & Public Health, University of Pretoria, Pretoria, South Africa
(4) Manchester Cancer Research Centre, University of Manchester, Manchester, UK

Backgrounds: Men of African ancestry are at greatest risk for advanced prostate cancer, with tumours recently haven shown to harbour a considerably elevated level of acquired genomic variation. Kataegis has been observed in multiple types of cancer genomes with highly inflated genomic instability that has been tentatively correlated with disease aggression. However, the role of kataegis in African prostate cancer remain elusive.

Aim: If kataegis is associated with ancestral-driven prostate cancer health disparities.

Methods: We used whole genome sequencing data from 112 African and 57 European patients (obtained from Jaratlerdsiri et al., 2022) to identify kataegis with piecewise constant fitting model. Statistical analysis included Wilcoxon rank-sum test and Fisher's exact test. Multiple test results were adjusted with false discovery rate (FDR).

Results: Of the identified 247 kataegis events in 59 patients, kataegis were enriched in tumours from high-risk patients with inflated genomic instability. We observed a greater prevalence of kataegis in high-risk European derived tumours than low-risk (44% versus 0%, P-value = 0.037), and more single-nucleotide variants contributing to kataegis in African high-risk versus low-risk tumours (median, 6 versus 4, P-value = 0.014). Kataegis positive tumours, especially from high-risk African patients, demonstrated associations with factors of genomic instability (FDR = 5.9e-5 - 0.03). The aetiology analysis showed a decrease of age-related attribution and an increase of APOBEC-related signatures in kataegis in high-risk tumours (FDR = 5.1e-5 - 4e-4). Furthermore, kataegis was enriched in a subtype of European patients with worse clinical outcome (P-value = 0.007), occurring early in tumourigenesis (P-value < 3.219e-11), while in African patients kataegis appears later in cancer evolution.

Conclusion: Kataegis was linked to prostate cancer aggressiveness and genomic instability. The attribution of kataegis suggests APOBEC3A as a potential therapeutic target. The results also reveal divergence of mutational process in cancer evolution between African and European patients.

3. Pan-cancer analysis links altered RNA m7G methyltransferase expression to oncogenic pathways, immune cell infiltrations and overall survival

Anni Su* (1,2), Renhua Song (1,2), Justin Jong-Leong Wong (1,2)

(1) Epigenetics and RNA Biology Laboratory, Charles Perkins Centre, University of Sydney, Camperdown 2050, Australia
(2) Faculty of Medicine and Health, University of Sydney, Camperdown 2050, Australia

Background: N7-methylguanosine (m7G) modification is one of the most prevalent RNA modifications in humans. Dysregulated m7G modification caused by aberrant expression of m7G writers (METTL1, WDR4, RNMT, FAM103A1, WBSCR22 and TRMT112) contributes to cancer development. However, the comprehensive investigation of m7G writers in the pan-cancer cohort is limited. This study aims to systematically investigate the molecular alteration and clinical relevance of altered m7G methyltransferase expression in human cancers.

Methods: We integrated gene expression, genetic alterations, and clinical data analyses of 33 cancer types available from The Cancer Genome Atlas. Kaplan–Meier analysis was performed to determine the association between m7G writer expression and patient survival. Gene set variation analysis and Pearson correlation tests were used to define the associations between m7G writer expression and cancer-related pathways. We derived m7G scores using PCA algorithms based on the expression of m7G writers. m7G score was used to determine the association between m7G writer expression and immune cell infiltration in tumours.

Results: Copy number alterations in m7G writers were infrequent in most cancer types, except for METTL1, which showed frequent amplification in glioblastoma and sarcoma. Upregulation of m7G writers was observed across 18 types of human cancer , suggesting their roles in tumorigenesis. High expression of m7G writers correlated with overall survival in cancer patients, notably in kidney renal clear cell carcinoma (KIRC). Additionally, the expression of m7G writer is correlated with the activation or inhibition of cancer-related hallmark pathways. Furthermore, lower m7G scores correlated with increased immune cell infiltration in the KIRC tumour.

Conclusion: Our study highlights genetic alterations, expression patterns and the clinical relevance of aberrant m7G writer expression in diverse cancers. Overall, this study provides a resource to infer the role of m7G writers in cancer and presents insights into the role of m7G writers as cancer biomarkers and therapeutic targets.

4. Atovaquone Radiosensitises Diffuse Midline Gliomas by Inhibiting Mitochondrial Metabolism and Hypoxia

Faiqa Mudassar* (1,2), Prunella Ing (1), Cecilia Chang (3), Sandy Nguyen (1), Kristina M Cook (2,4), Zachary N. Warnken (5), Geraldine O'Neill (6,7), *Han Shen (1,2) and *Eric Hau (1,2,8,9)
***co-senior authors**

(1) Translational Radiation Biology and Oncology Group, Centre for Cancer Research, The Westmead Institute for Medical Research, Sydney.
(2) Sydney Medical School, The University of Sydney, Sydney.
(3) The Kinghorn Cancer Centre and Cancer Research Division, Garvan Institute of Medical Research, Sydney.
(4) Charles Perkins Centre, The University of Sydney, Sydney.
(5) Via Therapeutics LLC, Austin.
(6) Children's Cancer Research Unit, The Children's Hospital at Westmead, Sydney.
(7) Children's Hospital at Westmead Clinical School, Faculty of Medicine and Health, The University of Sydney, Sydney.
(8) Department of Radiation Oncology, Crown Princess Mary Cancer Centre, Westmead Hospital, Sydney.
(9) Blacktown Cancer and Haematology Centre, Blacktown Hospital, Sydney.

Background: Diffuse Midline Glioma (DMG) is a uniformly fatal paediatric brainstem tumour with median survival of less than 1 year. Radiotherapy has been the only effective treatment for decades, but most DMGs recur within several months due to radioresistance. The hypoxic tumour microenvironment, a main feature of solid tumours including gliomas, is a major contributor to radioresistance and impedes the efficacy of radiotherapy. Therefore, alleviating tumour hypoxia to enhance the effectiveness of radiotherapy is a therapeutic strategy to improve survival outcomes of DMG patients.

Aims: Here, we aimed to decrease the oxygen consumption rate (OCR) of DMG cells by targeting their mitochondria, which in turn will alleviate hypoxia by sparing more oxygen and subsequently improve the radiosensitivity of DMG cells.

Methods: Specifically, we performed a high-throughput screening to identify potent OCR inhibitors using a library of 1963 FDA-approved drugs. Top candidates were studied against a panel of patient-derived DMG cell lines using proliferation assays, seahorse extracellular flux assays, colony formation assays, western blots, confocal microscopy and flow cytometry.

Results and Discussion: The most promising OCR inhibitor identified was atovaquone, a drug used for treatment of pneumocystis pneumonia and malaria. We found that atovaquone inhibited mitochondrial metabolism of DMG cells by specifically targeting the mitochondrial complex III. It induced the formation of mitochondrial reactive oxygen species suggesting that it increases oxidative stress. It alleviated hypoxia, decreased the expression of hypoxia-inducible factor-1α and improved the radiosensitivity of a range of DMG cultures. The efficacy of commercially available atovaquone was compared against an improvised and a better blood-brain-penetrant version, the amorphous solid dispersion (ASD) atovaquone formulation. Both formulations inhibited OCR and hypoxia at similar doses and improved the radiosensitivity of DMG. With these promising findings, our further work is assessing the in vivo efficacies of both atovaquone formulations using orthotopic DMG models.

5. Genomic Profiling and Biomarker Discovery for Predicting Early Intrahepatic Recurrence Following Resection of Colorectal Liver Metastases

Geoffrey Yuet Mun Wong* (1,2), Jun Li (2), Nazim Bhimani (1), Connie Diakos (3), Mark P Molloy (2), Thomas J Hugh (1)

(1) Department of Upper Gastrointestinal Surgery, Royal North Shore Hospital, St Leonards, New South Wales, Australia
(2) Bowel Cancer and Biomarker Research Laboratory, Faculty of Medicine and Health, School of Medical Sciences, The University of Sydney, St Leonards, NSW, 2065
(3) Department of Medical Oncology, Royal North Shore Hospital, St Leonards, New South Wales, Australia

Introduction: The role of genomics in driving tumour biology and its influence on early recurrence in patients with colorectal liver metastases (CRLM) is inadequately understood.

Aim: This study aims to profile and discover genomic biomarkers for early intrahepatic recurrence following curative-intent resection of CRLM.

Methods: Comprehensive genomic profiling of 24 fresh frozen CRLM samples from patients with early intrahepatic recurrence after resection of CRLM was performed using the TruSight Oncology 500 assay (Illumina, San Diego, CA). Functional annotation of somatic variants and filtering was performed using open-source genomic databases (ExAc, gnomAD) and software packages (ANNOVAR). Aggregated mutation information was summarised, analysed and visualised using the maftools package (version 2.16.0). Function and interaction networks of genetic alterations were explored using GeneMANIA. Estimation of the selective advantage conferred by somatic mutations was performed using cancereffectsizeR (version 2.7.0).

Results: 117 of 523 profiled genes were altered in samples from patients with early recurrence. TP53 (88%), APC (71%), KRAS (38%), SMAD4 (21%) and PIK3CA (17%) were the top 5 frequent cancer drivers. The identified gene alterations are implicated in diverse biological processes and complex molecular interactions, including cell population proliferation, signalling response to external stimulus, DNA repair, DNA methylation, RNA binding, cell adhesion, cell cycle control, chromatin remodelling and lineage-specific transcription factors. BRAF mutation had the highest relative importance in early intrahepatic recurrence.

Conclusion: Comprehensive genomic profiling of CRLM in this cohort has identified biological characteristics associated with early recurrence and BRAF mutation as a strong prognostic biomarker relative to other cancer-related genes.

6. Depletion of dipeptidyl peptidase 9 (DPP9) in mouse hepatocytes elevates inflammation markers in an experimental model of hepatocellular carcinoma

JiaLi Carrie Huang* (1), XinLin Linda Tong (1), Michelle S. W. Xiang (1), MingChang Zhang (1), Bobby Boumelhem (1), Geoffrey W. McCaughan (1), Thomas Reinheckel (2), Hui Emma Zhang (1), Mark D. Gorrell (1)

(1) Dept. of Liver Injury, The Centenary institute
(2) Institute of Molecular Medicine and Cell research, Faculty of Freiburg, Freiburg, Germany

Background: Dipeptidyl peptidase 9 (DPP9) is an emerging cancer associated protease, which has increasingly gained scientific attentions in recent years.

Aim: A hepatocyte specific DPP9 knockout mice were generated to study the roles of DPP9 in liver cancer.

Method: Mice with hepatocyte-specific DPP9 depletion (Alb-DPP9-KO) were viable and healthy. Male hepatocyte-specific DPP9 depleted mice and their littermate control mice were treated with Diethylnitrosamine (DEN) and Thioacetamide (TAA) and provided with an atherogenic High Fat Diet (HFD) until the age of 28 weeks.

Results: The Alb-DPP9-KO mice had reduced mass of the liver and subcutaneous adipose tissue, and lower fasting plasma glucose. Upon no differences between the two genotypes in total number of macroscopic liver nodules, or in the tumour burden, inflammation score or steatosis score. The Alb-DPP9-KO mice had fewer small macroscopic liver nodules (<3 mm diameter) compared with control mice. By looking at the inflammasome, immunological and autophagy markers in these HCC bearing mouse livers. It is found that mice with hepatocyte-specific DPP9 depletion showed increased levels of active caspase-1 protein. Intrahepatic differential expression of the genes nfkbib, cxcl10 and ccl5 was observed. However, the numbers of tumour infiltrating CD8+ T cells showed no difference between genotypes.

Conclusion: Lifelong DPP9 depletion in hepatocytes affected liver cancer formation in this experimental model. Evidence for increased caspase-1 activation and a possible role in the regulation of energy metabolism was obtained in these mice.

Stream 2a: Public Health

7. Provider perspectives on the psychosocial impacts of lung cancer screening

Kathleen McFadden* (1), Nicole Rankin (2,3), Brooke Nickel (3), Nehmat Houssami (1), Rachael Dodd (1)

(1) The Daffodil Centre, a joint venture of Cancer Council NSW and the University of Sydney
(2) Melbourne School of Population and Global Health, Faculty of Medicine,Dentistry and Health Sciences, The University of Melbourne
(3) Sydney School of Public Health, Faculty of Medicine and Health, The University of Sydney

Background
Many countries are implementing lung cancer screening (LCS) programs following landmark trials demonstrating a 20-24% reduction in lung cancer mortality with screening. Psychosocial impacts are an important consideration for LCS, ranging from direct harm to individuals to downstream impacts on health beliefs, attitudes, and screening participation.

Aim
This project aimed to investigate, for the first time, providers' perspectives on psychosocial outcomes associated with LCS.

Methods
Semi-structured interviews were conducted with health professionals, experts and other key informants involved in LCS (e.g., doctors, nurses, radiographers/radiologists, and researchers). General practitioners not previously involved in LCS were also recruited, as they generally facilitate entry into LCS programs. Participants were recruited internationally to examine differences across jurisdictions, trials, and policy landscapes. Interviews were audio-recorded, transcribed, and analysed using thematic analysis.

Results
Topics explored with participants include: (a) key psychosocial impacts of LCS and downstream consequences, (b) differences in psychosocial impacts across certain groups (e.g., Aboriginal and Torres Strait Islander people), (c) unique issues for LCS populations (i.e., screening those with a significant smoking history), (d) how to design LCS programs to minimise psychosocial burden, and any barriers/enablers to this. We aim to sample 25 participants (n=5 completed as at abstract submission); preliminary results will be available and presented by November 2023.

Conclusions
This proposed work will generate critical evidence about how best to support potential LCS participants (estimated to be nearly 600,000 Australians). With a national LCS program rollout targeted by 2025, this project will provide foundational evidence for development and implementation of LCS.

8. Risk of developing a second primary melanoma after a first primary melanoma in a population-based Australian cohort

Yuan Ni*(1,2), Caroline G. Watts (1,3), Richard A. Scolyer (2,4,5,6), Christine Madronio (7), Bruce K. Armstrong (8,9), Rachael L. Morton (2,10), Scott W. Menzies (4,11), Graham J. Mann (2,12), John F. Thompson(2,4,13), Serigne N. Lo (2,4), Anne E. Cust (1,2,3)

(1) The Daffodil Centre, The University of Sydney, a joint venture with Cancer Council NSW.
(2) Melanoma Institute Australia, The University of Sydney.
(3) The Kirby Institute UNSW.
(4) Faculty of Medicine and Health, Sydney Medical School, The University of Sydney, Sydney, NSW, Australia.
(5) Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital and NSW Health Pathology.
(6) Charles Perkins Centre, The University of Sydney.
(7) Nepean Clinical School, Faculty of Medicine and Health, The University of Sydney.
(8) Sydney School of Public Health, The University of Sydney.
(9) School of Population and Global Health, The University of WA.
(10) NHMRC Clinical Trials Centre, The University of Sydney.
(11) Sydney Melanoma Diagnostic Centre, Royal Prince Alfred Hospital.
(12) The John Curtin School of Medical Research, Australian National University.
(13) Department of Melanoma and Surgical Oncology, Royal Prince Alfred Hospital.

Background
Patients with a history of melanoma have a higher risk of developing a new primary melanoma in their lifetime compared to the general population. But few studies have investigated risk factors for subsequent primary melanoma.

Aims
To identify risk factors and estimate relative and absolute risk of developing a second primary melanoma following the first primary melanoma.

Methods
3,508 patients diagnosed with first primary melanoma (3,108 invasive, 400 in situ). Patients were part of the Melanoma Patterns of Care study in NSW, diagnosed in October 2006-07 and followed up until 2018. Data were obtained from clinician surveys and linkage with NSW cancer and mortality registries. We performed Cox regression models to examine risk factors and estimated absolute risk for developing a second primary melanoma.

Results
The mean absolute risk of developing a second primary melanoma was 4.6% within 1 year, 6.6% within 2 years, 11.3% within 5 years and 16.4% within 10 years. In a multivariable model, factors associated with higher risk of developing a second primary melanoma are sex, age, high nevus count and bodysite. Factors that were not independently associated included socio-economic status, geographical location, Breslow thickness, subtype, ulceration, regression and mitotic rate.

Conclusion
Male sex, older age, family history, high nevus count, and melanoma on the trunk or upper limbs were factors associated with a higher risk of developing a second primary melanoma. Patients with these factors should be monitored with priority accordingly.

9. Empowering Pharmacist for Early Lung Cancer Detection and Lung Health Evaluation: A Scoping Review

Simmie Chung* (1), Irene Um (1), Bandana Saini (1)

(1) Sydney Pharmacy School, Faculty of Medicine and Health, The University of Sydney

Background: Lung cancer is the leading cause of cancer-related deaths, with a low 5-year survival rate of 20.5% in 2022. Early diagnosis is crucial for better outcomes. Community pharmacists, often the first point of contact for respiratory presentations, could play a critical role in assessing symptoms and referring patients to GPs for further assessment. However, there has been no active involvement for pharmacists in lung cancer screening in international concerted efforts. Utilising pharmacists as a preliminary assessment and triage step could aid in early detection of lung cancer, ultimately leading to improved patient prognosis and quality of life.

Purpose: To scope the existing literature to determine the protocols utilised and evaluate the impact of pharmacists' involvement in lung cancer awareness, screening, or triage programs.

Method: A scoping review was performed to systematically explore the literature, map and summarise the evidence on the pharmacists' role in the early detection of lung cancer. The review adhered to the methodological framework for scoping reviews outlined by Arksey and O'Malley. A comprehensive search strategy was developed in consultation with academic librarian. It was then applied to interrogate Medline (PubMed), Embase, CINAHL, and Scopus databases. Studies were included if they explored pharmacist interventions in information provision, screening for, or referral of patients at risk of lung cancer. Articles published in English between January 2000 to April 2023 were considered eligible for inclusion.

Results: Of 334 articles screened, only 6 studies met the inclusion criteria. These studies included 4 qualitative studies that were conducted with a range of stakeholders (eg community pharmacists n=30, GPs, nurses, respiratory consultants, radiologist, community service leads) and lung cancer patients to gather information via focus group interviews and questionnaires. One study investigated the feasibility of a community-based pharmacy referral service that involved 17 UK community pharmacies. In this study, pharmacists invited 12 patients, all consented and 11 were found at risk and referred for a chest x-ray, but no follow-up service was provided.

Conclusion: The barriers and facilitators for the implementation of such services, including the need for workforce capacity and training, well-publicised awareness campaigns, improved communication and referral pathways between pharmacists and other health professionals as well as remuneration, were highlighted by pharmacist participants. Whilst this review provides detailed insights into the role of pharmacists in lung health assessment, especially for early detection of lung cancer, it indicated that research on this topic is, as yet, scant.

10. SeCoNet: A Heterosexual Contact Network Growth Model for Human Papillomavirus Disease Simulation

Weiyi Wang* (1), Mahrendra Piraveenan (1)

(1) School of Computer Science, Faculty of Engineering, University of Sydney

Human Papillomavirus infection is the most com- mon sexually transmitted infection, and causes serious compli- cations such as cervical cancer in vulnerable female populations in regions such as East Africa. Due to the scarcity of empirical data about sexual relationships in varying demographics, computationally modelling the underlying sexual contact networks is important to understand Human Papillomavirus infection dynamics and prevention strategies. In this work we present SeCoNet, a heterosexual contact network growth model for Human Papillomavirus disease simulation. The growth model consists of three mechanisms that closely imitate real-world relationship forming and discontinuation processes in sexual contact networks. We demonstrate that the networks grown from this model are scale-free, as are the real world sexual contact networks, and we demonstrate that the model can be calibrated to fit different demographic contexts by using a range of param- eters. We also undertake disease dynamics analysis of Human Papillomavirus infection using a compartmental epidemic model on the grown networks. The presented SeCoNet growth model is useful to computational epidemiologists who study sexually transmitted infections in general and Human Papillomavirus infection in particular.

11. Using the counterfactual framework to estimate non-intention-to-effects in randomised controlled trials: a methodological scoping review

Ellie Medcalf* (1,2), David Espinoza (2) , Robin Turner (3) , Katy Bell (1)

(1) School of Public Health, The University of Sydney, Sydney, NSW
(2) National Health and Medical Research Council (NHMRC) Clinical Trials Centre, Sydney, NSW, Australia
(3) Biostatistics Centre, University of Otago, Dunedin, Otago, New Zealand

Background: Traditionally, when treatment estimates are reported in randomised controlled trials (RCT), they are intention-to-treat (ITT) estimates. However, these estimates do not always provide information that patients and clinicians want. For example, when non-adherence occurs, ITT estimates reflect the effect of being offered the intervention, rather than adhering to the intervention. Moreover, it can often be of interest to understand what role mediators may play in facilitating the effects of an intervention. Estimating the effects of actually adhering to an intervention and of potential mediators requires non-ITT estimates that can estimated using the innovative counterfactual framework.

Aim: Conduct a methodological scoping review to identify and summarise methods that use the counterfactual framework to obtain non-ITT effects in RCTs.

Methods: We searched MEDLINE and EMBASE for articles in which authors discussed methods using the counterfactual framework in RCTs. One reviewer will undertake full-text screening and data extraction and a second reviewer will check extractions.

Results: From 745 records screened, we identified 52 eligible papers, with 39 papers focusing on non-adherence and 13 on mediation. Preliminary findings show methods using the counterfactual framework are applied in both simple scenarios (e.g., where participants either adhere or don't adhere, or where there is a single mediator) and more complex scenarios (e.g., where participants partially adhere or where there are multiple mediators). There has also been increased application of novel approaches such as combining the counterfactual framework with machine learning techniques such as random forest and stacking.

Conclusion: This scoping review will summarise evidence on methods that use the counterfactual framework and their application in RCTs. These methods allow estimation of potentially more informative estimates than ITT in RCTs, as they can assist in generating evidence that end-users are most interested in: what is the effect of an intervention if they actually adhere to it.

Stream 1b: Pre-clinical and basic science

12. Development of 3D preclinical TNBC tumour models and investigation of novel anticancer targeted therapies

Farhana Mollah* (1,2,4), Barbara Guild (4), Huimin Shao (1), Hamidreza Aboulkheyr Es (3), Majid Warkiani (3), Dinny Graham (1,4,5), Pegah Varamini1 (1,2)

(1) The University of Sydney, NSW, Australia
(2) The University of Sydney Nano Institute, NSW, Australia
(3) School of Biomedical Engineering, University of Technology, NSW, Australia
(4) The Westmead Institute for Medical Research, NSW, Australia
(5) Westmead Breast Cancer Institute, NSW, Australia

Background: Triple-negative breast cancer (TNBC) is an aggressive form of breast cancer, which accounts for 15-20% of breast cancer. There is a lack of effective targeted therapeutics for TNBC and non-specific chemotherapy is the main method of treatment, which leads to various side effects. In many TNBC cases, the disease often reoccurs or relapses after an initial successful response with future resistance to therapy. A major contributor to this survival of disease is breast cancer associated fibroblasts (BCAFs), which assist with tumour growth, progression, invasion and metastasis. Hence, TNBC is considered an unmet medical condition that urgently needs novel effective targeted therapeutics. Furthermore, to develop new therapeutics, we need preclinical models that can simulate the real situation of the tumour in humans more adequately than the conventional cell models. Multicellular three-dimensional (3D) models are excellent tools to recapitulate the spatial dimension, cellular heterogeneity, and molecular networks of the tumour microenvironment.

Aims: The aims are to develop a TNBC tumour spheroid model and determine the efficacy of a novel peptide-drug conjugate in combination with a secondary anti-BCAF agent, in TNBC spheroids and co-cultures of spheroids and BCAFs. Methods: TNBC spheroids were generated in a microwell scaffold, liquid overlay, and rotating was assessed by spheroid morphology, cell viability assays and uptake of compounds using microscopy.

Results: We have successfully developed different types of spheroids using the three methods. We demonstrated that the novel anticancer treatment showed high penetration to the spheroid structure leading to their complete disintegration.

Significance: This project could lead to the development of a more clinically relevant preclinical model of TNBC for the development of potent and selective anticancer pharmaceuticals. This will provide more accurate data in preclinical studies to improve the success rate of clinical trials in the future translation of new therapeutics for the unmet need of TNBC.

13. Plasma Activated Liquids and their Synergy with radiation for cancer therapy

Juliette Harley* (1,2), Linda Rogers (2), Caitlin Cummins (1), Natalka Suchowerska (1) David McKenzie (1,2)

(1) Applied and Plasma Physics
(2) Biomedical Innovation Hub, Chris O'Brien Life house

Radiation therapy benefits nearly 50% of cancer patients, however there are patients for whom treatment fails. The application of radiosensitising agents to boost local effects to radioresistant cancers offers the potential to improve outcomes for these patients. An emerging radiosensitising agent is a Plasma Activated Liquid (PAL) which imparts Reactive Oxygen and Nitrogen species (RONS) to the treated liquid. The ability of PAL to sensitise three different cell lines (hormone resistant prostate cancer DU 145, non-malignant prostate cells PNT1A and melanoma MM576) to ionising radiation was investigated in this work.

To determine the radiosensitising potential of the PAL, the dose response relationships of both PAL and radiation was required for each cell line. Following dose response experiments, one concentration of PAL and one dose of ionising radiation was chosen for each cell line for combination therapy experiments. The multiplicative Survival Principle was employed to assess any interactions in the combination therapy experiments and found synergistic enhancement of radiation cytotoxicity for the DU 145 and the MM576 cancerous cell lines and found antagonistic reduction in radiation cytotoxicity for the non-malignant PNT1A. When the order of PAL and radiation administration was reversed, PAL and radiation were still found to synergistically reduce cell survival regardless of the order of administration, however application of PAL prior to irradiation is significantly more cytotoxic.

Experiments were conducted to determine the relationship between PAL and its major constituents: H_2O_2 and NO_2^-. No statistical difference was found between the cytotoxicity from PAL, H_2O_2 alone and H_2O_2 with NO_2^- for either cell line. These results provide compelling evidence for future studies in the use of H_2O_2 focused therapeutics as radiosensitising agents in improving the response of radioresistant cancers.

14. B-cell Maturation Antigen Antibody-Drug Conjugates (BCMA-ADCs): A Glimmer of Hope for Multiple Myeloma

Jing Shan* (1), Catherine King (2,3), Harunor Rashid (3), Veysel Kayser* (1)

(1) School of Pharmacy, The University of Sydney, Sydney, NSW 2006, Australia
(2) Sydney School of Public Health, The University of Sydney, Sydney, NSW, 2006, Australia
(3) Sydney Infectious Diseases Institute, The University of Sydney, Westmead, NSW 2145, Australia
(4) Children's Hospital Westmead Clinical School, Faculty of Medicine and Health, The University of Sydney, Westmead, NSW 2145, Australia

Cancer claims more than 10 million of lives globally on an annual basis. Multiple myeloma (MM) has emerged as one of the most difficult to treat cancers, which is characterised by malignant plasma cells accumulating in bone marrow. In Australia, there are more than 2,000 newly diagnosed patients annually and 20,000 patients living at one any given time. Unlike other cancers, MM often evades the current treatments, leading to frequent relapses, and hence innovative therapeutic interventions are urgently needed.
B-cell Maturation Antigen (BCMA), a protein predominantly expressed on the surface of MM cells, has been primarily used for targeted therapies such as Antibody-Drug Conjugates (ADCs), aiming to destroy specifically cancer cells with minimal collateral damage to healthy tissues. For example, belantamab mafodotin, a frontrunner ADC offers a great promise; however, ocular toxicity has raised concerns in clinical trials.

To elucidate this complex landscape, I embarked on a systematic review, employing sophisticated tools such as ROBINS-I and SYRCLE's risk of bias tool. In my presentation, I will talk how these tools informed our data collection and interpretation, enhancing the robustness of our findings.
Initial insights suggest that while BCMA-ADCs could revolutionize treatment for multiple myeloma patients, a careful navigation is crucial. On one hand, they present a potential to reduce tumour burden, but on the other, we must remain vigilant about side effects.
MM, with its evasive nature and the limited arsenal we currently possess against it, necessitates a radical shift in our treatment paradigm. BCMA-ADCs, though still in their infancy stages, might just be the shift we are seeking. But like every promising journey, there are hurdles, learnings, and milestones. As we tread this path, it's imperative to balance hope with caution, innovation with safety.

15. The molecular mechanisms underlying radiation-induced phenotypic plasticity in human oral squamous cell carcinoma cells under hyperglycaemic metabolic stress.

Thanh Dat Pham* (1) , Rabia Zafar (1), Teana Reed (1), Sadaf Yasamin Shirazi (1), Ali Afrasiabi (2,3), Naisana Seyedasli (1,4)

(1) School of Medical Sciences, Faculty of Medicine and Health, University of Sydney, Westmead Hospital, Westmead NSW 2145, Australia
(2) Centre for Immunology and Allergy Research, Westmead Institute for Medical Research, University of Sydney, Sydney, NSW, Australia
(3) The Graduate School of Biomedical Engineering, University of New South Wales, Sydney, NSW, Australia
(4) Centre for Cancer Research, The Westmead Institute for Medical Research, Sydney, NSW 2145, Australia

Background
The phenotypic plasticity along the epithelial-mesenchymal (E-M) axis of epithelial carcinomas is one of the key aspects demonstrated to have a strong correlation with cancer progression, tumour invasion, metastasis, and the development of radioresistance. Hyperglycaemia, or chronic exposure to high glucose levels, has been shown to strongly correlate with increased risk of cancer and its involvement in different critical aspects of tumour progression, including epithelial-mesenchymal transition (EMT).

Methods
In this study, we have generated 3D tumour spheroid models from the hyperglycaemic stressed OSCC cells and performed different cellular, molecular, and high-level transcriptome analyses to investigate the cellular and molecular roles of hyperglycaemia and its downstream factors on the tumour remodelling as part of the response to ionising radiation.

Results
The hyperglycaemic-stressed cells had an enhanced post-radiation survival rate, indicating resistance to ionising radiation. An early increase in the number of E-M hybrid cells at 2hr after radiation was observed in hyperglycaemic cells, followed by a significant elevation at the 24hr time point, highlighting enhanced plasticity through induction of an E-M hybrid phenotype. In addition, the formation of IR-induced mesenchymal-phenotype cell population was found to correlate with the upregulation of EMT transcription factor ZEB1. Our initial transcriptome analysis of 3D spheroids has identified a large number of misregulated genes as a response to hyperglycaemic stress alone, indicating a glycemia-induced priming effect in cancer cells before exposure to radiation. Upon further transcriptome analysis, the radiation response in glycemia-primed cells highlighted a distinct signature in these spheroids, indicating mechanistic cues leading to the observed resistance to radiation.

Summary
So far, the study has demonstrated the enhanced phenotypic and molecular remodelling of OSCC tumour cells along the E-M axis in response to metabolic stress and radiation. These findings will contribute to a better understanding of the molecular mechanisms underlying tumour cell plasticity during metabolic and glycemic stress, hence facilitating approaches for better treatment outcomes in cancer patients with metabolism-related co-morbidities like diabetes.

Stream 2b: Public Health

16. The Do's and Don'ts of clinical trials interim analysis

Yu Yang Soon* (1), Ian Marschner (1), Martin Stockler (1), Andrew Martin (1)

(1) NHMRC Clinical Trials Centre

Background
When a randomized clinical trial (RCT) has a positive read-out from an interim analysis (IA), a conventional estimate of the treatment benefit may suffer overestimation bias. This is particularly true for read-outs that occur earlier on in an RCT, where less of the planned endpoint information sought is available. In addition, an earlier estimate of the effect on a time-to-event endpoint (e.g., overall survival (OS)) could also be different from a later estimate due to other factors relating to the treatment and/or conduct of the RCT.

Aim
To highlight the complexity of estimating a treatment effect following an early read-out and suggest strategies to improve reporting.

Method
A cohort of 142 published RCTs that read-out early was reviewed. The correlation between the reported naïve estimates of effect (OS and event-free survival (EFS)) and the timing of the IA were calculated. The ENZAMET RCT in prostate cancer was used as a case study in optimal reporting, and to illustrate how an early versus later estimate could differ due to non-proportional hazards and temporal variation in participants' characteristics over the enrolment period.

Results
Published RCTs with earlier read-outs reported greater treatment effects (rho = 0.48, P value < 0.0001 for OS and rho = 0.49, P value <0.0001 for EFS). For ENZAMET, the early naïve estimate was similar to the later estimate for the primary endpoint of OS. Both were greater than the more conservative IA result adjusted for overestimation bias. For a secondary disease progression endpoint, we found some evidence that the treatment effect was not consistent over time. There were also some systematic differences in patient characteristics over the enrolment period regarding the geographic region and use of concurrent therapy.

Conclusion
For better of reporting of IA, we suggest that IA should not be performed "too early" and the conventional estimate from IA should be reported in conjunction with the estimate adjusted for overestimation bias. It is useful to consider that non-PH is plausible, and follow-up of the participants should be continued beyond IA. It is helpful to check if baseline characteristics vary over the recruitment period.

17. Risk Factors Associated with Chemotherapy-Induced Peripheral Neuropathy Persistence

Tiffany Li* (1), Hannah C. Timmins (1), Fawaz Mayez Mahfouz (1), Terry Trinh (2), Lisa G. Horvath (3), Michelle Harrison (3), Peter Grimison (3), Michael L. Friedlander (4), Tracy King (5), Matthew C. Kiernan (1), David Goldstein (1,4), Susanna B. Park (1)

(1) Brain and Mind Centre, University of Sydney, Australia
(2) Prince of Wales Clinical School, UNSW, Australia
(3) Chris O'Brien Lifehouse, Australia
(4) Prince of Wales Hospital, Randwick, Australia
(5) Institute of Haematology, Royal Prince Alfred Hospital, Australia

Background
Chemotherapy-induced peripheral neurotoxicity (CIPN) is a common adverse effect of numerous anti-cancer treatments with symptoms often persisting for years post treatment completion and negatively affecting cancer survivors' quality of life. However, there is considerable variability in CIPN recovery and little is known about clinical profiles of patients who are more likely to experience CIPN symptom improvement. This longitudinal study aimed to identify clinical phenotypes associated with CIPN improvement.

Method
Patients commencing neurotoxic treatments (taxane, platinum, vinca-alkaloid, bortezomib, thalidomide) were assessed longitudinally. Data from two timepoints were compared for this analysis, end-of-treatment and 6-12 months post treatment. CIPN was graded by the National Cancer Institute (NCI) sensory neuropathy scale. Improvement in CIPN was defined as reduction by at least one NCI grade. Odds ratios (OR) were computed using logistic regression with results presented as mean±SD.

Results
270 patients (54.9±12.5 years, 68.1% female) were included in the study, with 207 (76.7%) patients experiencing CIPN by end-of-treatment. At second follow-up (6.9±2.6 months post treatment), 101(48.8%) experienced CIPN improvement. Each year of older age was associated with a 3.8% decrease in the odds of CIPN improvement ($P<0.005$), while there was no significant association with other clinical factors (gender, body mass index, diabetic status, baseline neuropathy, all $P>0.05$). There was no difference in CIPN improvement between patients receiving taxane or platinum therapy ($P>0.05$). Subgroup analysis in taxane-treated patients with CIPN by end-of-treatment ($n=130$) suggested older age was associated with decrease in CIPN improvement ($P<0.001$), but not other factors (all $P>0.05$).

Discussion
This series of longitudinal analyses demonstrated CIPN as a long-term toxicity. Older age was identified as a clinical risk factor for CIPN persistence. However, mechanisms underlying CIPN improvement are complex, and clinical variables alone may not be sufficient to ascertain a patient's long-term CIPN outcome. It is likely that other parameters, such as genetic risk factors also play a significant role in CIPN symptom reversibility.

18. Does exercise change blood flow to tumours? Acute aerobic exercise effects on liver metastases blood flow: a case series

Catherine Seet-Lee* (1,2), Jill Clarke (1), Kate Edwards (1,2)

(1) Faculty of Medicine and Health, University of Sydney
(2) Charles Perkins Centre, University of Sydney

Background: Effective cancer treatment relies on intravenous chemotherapy penetrating the entire tumour in sufficient concentrations, which is largely reliant on effective blood supply into and within the tumour. However, tumours contain abnormal vasculature with inefficient blood perfusion leading to the inability for chemotherapy to reach the target tumour. Pre-clinical evidence suggests acute exercise may increase blood flow by 200%. However, most pre-clinical studies investigate the effects of light-to-moderate intensity exercise and subsequently there is little evidence regarding the most effective exercise intensity for improved tumour vasculature.

Aim: Therefore, the aim of this ongoing case series is to determine whether exercise changes tumour blood flow in a clinical model using non-invasive techniques, and how exercise intensity effects degree of change in blood flow to tumours in patients with liver metastases.

Methods: Participants were eligible if they were aged over 18 years, had stage IV cancer with liver metastasis and ECOG 0-2. The study visit consisted of an aerobic fitness test (YMCA) to determine cardiorespiratory fitness and three 5-minute bouts of exercise at low, moderate and high intensities. After each exercise bout, Doppler ultrasound was used to measure a liver tumour vessel and the hepatic artery (as a control) to determine blood flow parameters.

Results: Exercise increased peak systolic velocities (PSV) to liver tumours at all intensities compared to rest. Moderate and high exercise intensities showed a marked increase in PSV within the first 2 minutes after exercise. The hepatic artery showed less variability in PSV with time compared to the liver tumour. Cardiorespiratory fitness did not affect tumour PSV.

Conclusion: The results of this case series thus far suggest that exercise increases tumour blood flow at all exercise intensities with particular emphasis on moderate and high intensities. This supports the potential for using exercise as an adjunct to standard treatment to improve chemotherapy efficacy.

CRN PGSWG's 5MT Competition – "The Many Facets of Cancer Research"

19. The Geriatric Assessments and Frailty Tools in Older People with Multiple Myeloma: A Literature Review

Yibai Li* (1, 2), Bora Kim (1, 2,3), Kate White (1, 2, 3)

(1) Susan Wakil School of Nursing and Midwifery, The University of Sydney, 2050, Australia
(2) Cancer Care Research Unit, Sydney Local Health District, Sydney, 2050, Australia
(3) The Daffodil Centre, The University of Sydney, a Joint Venture with Cancer Council NSW, Sydney, Australia

Introduction: Multiple Myeloma (MM) is a rare, incurable haematological malignancy, often of long duration, that is considered a chronic illness. Given that MM is more prevalent among older patients, the development of individualised care plans that consider their comorbidities and frailty is essential. Research on geriatric and frailty assessment tools has increased in the recent years.

Aims: (1) Describe different types of geriatric and frailty assessment tools for the MM population; (2) describe the sub-domains of these tools; (3) review the clinical utility of these tools in predicting clinical outcomes; and (4) identify potential facilitators/barriers to implementing these assessments.

Method: Following PRISMA guidelines, a systematic literature search was conducted using MEDLINE, on geriatric and frailty assessments in older MM patients from January 2013 to April 2023. Data extraction was conducted systematically, and quality assessment was performed using a modified version of the Newcastle-Ottawa scale.

Findings: A total of 25 studies were included. Assessment tools fell into three categories: Comprehensive Geriatric Assessments (CGA) tools, Frailty-specific tools, and Geriatric assessments indexes that incorporate existing tools. Among seven studies focused on CGA, six found CGA was effective in predicting clinical outcomes: overall survival, treatment toxicity and performance changes. For frailty tools, the International Myeloma Working Group Frailty Index (IMWG-FI) was the most common with six studies demonstrating its effectiveness in identifying frail and non-frail patients. The common subdomains of frailty tools were physical functions, comorbidities, and functional status. Only two out of 25 papers explored potential facilitators/barriers to implementing tools and did not address clinical utilisation.

Conclusion: This review highlights the importance of geriatric and frailty assessments in older MM patients but reveals a lack of consensus on their components and a gap in clinical application. Further research on the implementation of these assessments in clinical settings is needed.

20. De novo modelling of B cell receptor modulators for synthesis and evaluation in the treatment of malignant and autoimmune B cell conditions

Prisca Akpabio* (1), Thomas Balle(1), Stephen Fuller (1)

(1) Faculty of Medicine and Health, The University of Sydney

The B cell receptor (BCR) is a transmembrane multiprotein complex that consists of membrane-bound immunoglobulins (mIg) molecules where B lymphocytes recognize the antigen and are activated, and two signal-transducing subunits Igα and Igβ. The five isotopes of mIg A, D, E, G and M each comprise two heavy chains and two light chains. Mature B cells expressing IgD and IgM, and memory B cells express IgA, IgG or IgE1. The CD79a/b is a BCR-associated heterodimer involved in the BCR transport and its functionality by providing the signalling capacity needed to regulate processes such as allelic exclusion, differentiation, anergy and apoptosis2.

In the past, it has been difficult to obtain high-resolution structural information on the intact BCR, a transmembrane receptor with a characteristically flexible hinge region in the heavy chain that links the extracellular Fab region to the Fc region3. Furthermore, critical interactions between mIg and CD79a/Cd79b are located within the plasma membrane that to date has been unable to be visualised by crystallography. However, three groups have recently determined the full-length transmembrane structures of the BCR using cryogenic electron microscopy (cryo-EM)1, 4.

The expected contribution is the reported structures of the BCR would be used as a structural platform for understanding B cell signalling and create an opportunity to address major challenges in the field of B cell receptor signalling. AS well as used as a guide in the rational design of small-molecule inhibitors, peptide drugs or antibodies for the treatment of B cell-mediated haematological malignancies and autoimmune diseases. Models are currently being created using artificial intelligence-based methods including AlphaFold2-Multimer, CHAMM-GUI and D-I-TASSER and Complexes will be validated using atomistic and coarse-grained (CG) molecular dynamics (MD) simulations. Novel peptide ligands will then be designed based on the B-cell receptor models using in-silico SBDD methods.

21. Identifying causes of apparent homologous recombination repair deficiency in ovarian cancer

Nikilyn Nevins* (1,2,3), Cristina Mapagu (1,2,3,4), Swetansu Pattanaik (5), Sivatharsny Srirangan (2), Rosemary Balleine (1,2), Anna De Fazio (1,2,3,6) for the INOVATe investigators

(1) Faculty of Medicine and Health, The University of Sydney, Sydney, NSW
(2) Center for Cancer Research, Westmead Institute for Medical Research, Sydney, NSW
(3) Department of Gynaecologic Oncology, Westmead Hospital, Sydney, NSW
(4) Illawarra and Shoalhaven Cancer Care Centre, Wollongong, NSW
(5) Garvan Institute for Medical Research, Sydney, NSW
(6) The Daffodil Centre, The University of Sydney, a joint venture with Cancer Council NSW. Sydney, NSW

Background
Homologous recombination repair deficiency (HRD) is a fault in DNA repair which leads to a large amount of structural genomic variation as well as therapeutic vulnerability to select inhibitors. HRD is a feature of ovarian cancer and the focus of several new clinical assays. These assays vary in sensitivity and specificity, and determination of an accurate HRD score threshold is challenging as the deficiency is a continuous rather than a dichotomous parameter. We assessed the underlying genomic lesions associated with HRD determined by whole-genome SNP arrays.

Aim
This study analysed causative gene alterations in ovarian cancers that have DNA copy-number changes consistent with HRD.

Methods
The HRD status by SNP array was determined for 215 cases selected from INOVATe, a real-time ovarian cancer molecular profiling study. HRD results were compared with 30-gene mutation panel and BRCA1 and RAD51C promoter methylation testing. Three cases with evidence of HRD by copy-number variation, but without an apparent fault in relevant genes, were subject to whole-genome DNA and RNA sequencing. Mutation, structural variant and fusion data were screened for potentially causative alterations, and mutation and copy-number signature analyses were performed to further examine the likelihood of HRD in these cases.

Results
In this cohort, 84% of cases with a score from SNP array result consistent with HRD also had a fault in canonical HRD-related genes. Of three cases without an apparent lesion, whole-genome analysis did not support HRD in two cases. A novel, potentially pathogenic mutation in XAB2 was found in one case with evidence of HRD on whole-genome signature analyses.

Conclusion
Some cases with copy-number variation-based scores around the threshold for HRD did not have evidence of HRD when assessed with orthogonal methods. However, one case examined had further evidence of HRD and a novel, potentially causative gene fault was identified.

22. Multifunctional Baghdadite ceramic for local chemotherapy and bone regeneration

Sally Kortam* (1) Zufu Lu (1), Pooria Lesani (1), Seyed-Iman Roohani-Esfahani (1), Ghazal Shineh (1), Leila Mamizadeh Janghour (1), Behnam Akhavan (1,2,3), Hala Zreiqat (1)

(1) School of Biomedical Engineering, The University of Sydney, Sydney, NSW 2006, Australia
(2) School of Engineering, University of Newcastle, Callaghan, NSW 2308, Australia
(3) Hunter Medical Research Institute (HMRI), New Lambton Heights, NSW 2305, Australia

Background
Osteosarcoma, a challenging bone tumor, is typically treated with surgery and systemic chemotherapy. However, systemic chemotherapy has major drawbacks. Recent research focuses on localized drug delivery through bone scaffolds but faces issues originating from both the scaffolds and the loaded drugs, including burst release and drug instability. Furthermore, currently available scaffolds lack the necessary strength required for effective bone repair.

Aims
Our study aims to overcome these challenges by integrating liposomal nanoparticles with doxorubicin (DOX) into robust ceramic. This approach seeks sustained drug release, eradicating cancer cells, reducing side effects, and enhancing bone regeneration.

Methods
We had developed a bioactive ceramic (Baghdadite, Ca3ZrSi2O9) (BAG) and demonstrated its outstanding bioactivity and mechanical properties. Here, we functionalized BAG by incorporating DOX-loaded liposomes. To facilitate enhanced binding of liposomes and prolonged DOX release, we employed an innovative ion-assisted plasma polymer (IPP) film to coat the BAG surface and examined the drug release profiles of the DOX-liposome from IPP-coated BAG. Furthermore, we assessed the cytotoxic effects of this system on osteosarcoma cells after 7 days.

Results
Analysis of confocal images of Cy5-labeled liposomes on the BAG surface reveals that IPP-coated BAG exhibits approximately double the fluorescence intensity compared to uncoated BAG. Additionally, IPP-coated BAG displays significantly higher liposome coverage than uncoated BAG. Both uncoated and coated BAG exhibit an initial burst release of liposomes/ DOX within the first few days, followed by sustained continuous release over a period of one month. IPP-coated BAG shows a higher release of liposomes/ DOX due to the increased liposome binding. Cell viability assays show that DOX released from liposomes attached to the IPP-coated BAG, exerts a potent cytotoxic effect on MG-63 cells.

Conclusion
This study demonstrates the significant potential of incorporating DOX-loaded liposomes with IPP-coated BAG system in addressing the treatment of tumor-induced bone defects.

23. The health-related quality of life of early-onset colorectal cancer patients: is it equivocal to the general Australian population?

Celine Garrett* (1,2), Daniel Steffens (1,2,3), Michael Solomon (1,2,3), Cherry Koh (1,2,3)

(1) Surgical Outcomes Research Centre (SOuRCe), Royal Prince Alfred Hospital (RPAH), Camperdown, New South Wales, Australia.
(2) Faculty of Medicine and Health, Central Clinical School, The University of Sydney, Camperdown, New South Wales, Australia.
(3) Department of Colorectal Surgery, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia.

Background
Early-onset colorectal cancer (EOCRC) patients are more likely to have advanced disease and undergo more aggressive treatment modalities. However, current literature investigating the health-related quality of life (HRQoL) of EOCRC patients is scarce.

Aim
To determine the HRQoL of an Australian cohort of EOCRC patients including a subset who underwent pelvic exenteration (PE) or cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC).

Methods
This was a cross-sectional study on patients <50 years old who were surgically treated for their colorectal cancer between January 2013 and December 2021 (inclusive) at the Royal Prince Alfred Hospital (RPAH) in Sydney, Australia. RPAH is also a quaternary referral centre for PE and CRS/HIPEC. Patients were divided into groups based on the time interval from their index operation: ≤2 years and >2 years. HRQoL was evaluated using the normative physical component summary (PCS) and mental component summary (MCS) scores from the SF-36v2 questionnaire. A score ± 3 of 50, was within the norm-based range of the Australian general population.

Results
A total of 50 patients were included. For patients ≤2 years from surgery, the median PCS and MCS scores were 53.3 (36.4-58.9) and 47.3 (37.5-55.7). In the >2-year group, the median PCS and MCS scores were 50.6 (43.3-57.7) and 50.2 (39.04-56.2). Stage I (vs. stage II) disease and emergency (vs. elective) surgery conferred poorer PCS scores in patients ≤2 years from surgery. No other variables impacted PCS or MCS scores in EOCRC patients in either group.

Conclusions
EOCRC patients' HRQoL was equivocal to the Australian population. Having an earlier stage of diagnosis and emergency index operation was associated with poorer levels of physical functioning in patients ≤2 years from surgery. This study was limited by its cross-sectional nature and small cohort. Thus, these findings require validation in future large-scale prospective research.

24. CD247: A Novel Determinant of Immunotherapy Response in Lung Cancer

Natalie Smith* (1), Helen McGuire (1), Michael Boyer (2), Steven Kao (2), Barbara Fazekas de St Groth (1)

(1) School of Medical Sciences, Faculty of Medicine and Health, The University of Sydney, Sydney Australia
(2) Chris O'Brien Lifehouse, Camperdown, NSW, Australia; Faculty of Medicine and Health, University of Sydney, Camperdown, NSW, Australia.

Background: Immune checkpoint inhibitors (ICIs) targeting PD-1 or its ligand PD-L1 are currently the most successful immunotherapeutic approach to treat advanced lung cancer, although only 20% of patients generate a durable response. We have previously defined a predictive immune signature of ICI non-response characterised by deficits in key adaptive immune populations, current in clinical development as a predictive test. Investigation of the mechanisms underlying the immune signature of non-response to ICIs has the potential to reveal therapeutic targets that may reverse unresponsiveness. It is well established that cancer is highly immunosuppressive, with one key mechanism being dampening of T and NK cell reactivity through downregulation of CD247. CD247 is the signalling domain of the T-cell receptor (TCR) and associates with CD16 on NK cells.

Aim: This study aimed to investigation the relationship between expression of CD247 and response to ICI therapy in lung cancer patients.

Methods: Peripheral blood mononuclear cells (PBMCs) taken prior to and during treatment with ICIs from a cohort of lung cancer patients were analysed with flow cytometry.

Results: Downregulation of T cell CD247, but not other components of the TCR including the αβ chains or CDε, was observed in ICI non-responders. Responders to ICI therapy sustained high expression of CD247 across the course of treatment. These data suggest a relationship between expression of CD247 and clinical response to ICIs.

Conclusion: Further investigation of the pathways causing downregulation of CD247 may lead us to treatable targets for neo-adjuvant therapeutics to increase responsiveness to ICIs.

25. Beam's-eye-view tracking for liver SBRT enabled by deep-learning: A multi-institutional analysis

Danielle Chrystall* (1, 2), Chandrima Sengupta (3), Emily Hewson (3), Adam Mylonas (3), Yifan Li (3), Tim Wang (4), Dominique Lee (5), Doan Trang Nguyen (3), Paul Keall (3), Jeremy Booth (1,2)

(1) Faculty of Science, The University of Sydney
(2) Northern Sydney Cancer Centre, Royal North Shore Hospital
(3) ACRF Image-X Institute, The University of Sydney
(4) Department of Radiation Oncology, Western Sydney LHD
(5) Department of Radiation Oncology, Princess Alexandra Hospital

Background
Beam's-eye-view (BEV)-based image-guidance offers an affordable and accessible motion monitoring method to enable accurate dose delivery with a standard linear accelerator (linac). Poor MV image quality and target occlusion are the primary limiting factors of accurate BEV-based image guidance.

Aim(s)
In this work, we developed and retrospectively evaluated real-time marker tracking software that employs a deep learning framework to automatically track liver-implanted markers using MV images from multi-institutionally acquired data.

Methods
MV images were acquired from 16 liver stereotactic body radiotherapy (SBRT) patients in the ethics approved TROG 17.03 LARK trial. Three institutions were involved, treating with either a TrueBeam or Elekta linac. A convolutional neural network (CNN) classifier was trained using images from 7 patients from a single institution. The performance of the classifier and tracking software were evaluated using MV images from 6 exhale-breath-hold and 4 free-breathing patients. The tracking software accuracy was quantified by the individual marker geometric error in BEV co-ordinates using manually segmented markers as the ground truth. The CNN classification performance was evaluated using the precision recall curve (PRC), sensitivity and specificity.

Results
The overall mean absolute geometric tracking error was 0.0 $\pm$ 0.8 mm and -0.1 $\pm$ 0.8 mm in the x and y-directions, respectively. The [1st, 99th] percentiles of the tracking error were [-1.6, 1.3] mm and [-0.9, 1.2] mm in the x and y-directions, respectively. The CNN classifier had an area under the PRC curve of 0.9785, sensitivity of 97.94% and specificity of 99.71%.

Conclusion
A BEV liver motion monitoring method using deep learning was developed and evaluated using multi-institutional trial data. The high classification performance of the CNN and sub-millimetre tracking accuracy suggest feasibility of the approach for real-time motion tracking during liver SBRT.

26. Complexation and characterization of Peptide-targeting nuclide molecule for the management of Triple-negative breast cancer.

Srija Sur* (1), Dale Bailey (2), Pegah Varamini (1)

(1) Sydney Pharmacy School, Faculty of Medicine and Health, The University of Sydney.
(2) Department of Nuclear Medicine, Royal North Shore Hospital, The University of Sydney

Background: Triple Negative Breast Cancer (TNBC) is the most aggressive subtype of breast cancer with a high rate of metastasis and relapse and a low survival rate than other subtypes. It represents 12–24% of all breast cancers and the limited treatment options for patients suffering from TNBC makes it as one of the most challenging types of cancer to treat in Australia and worldwide. The mainstay treatment is general chemotherapy with low efficacy and severe side effects. Hence, we need effective targeted therapeutics with combined diagnostic features (theranostics) that detect early spread to distal organs. One key approach is to use peptide-targeted radionuclide-based theranostics (radiotheranostics). The novel targeting peptide that is used to target luteinising hormone-releasing hormone (LHRH) receptors,receptor mediated a range of cancers, including TNBCs has demonstrated high stability in human plasma, excellent binding affinity and targeting potential for LHRH receptors in previously published results for effective receptor-mediated TNBC therapy.

Aim: The aim of the project is to develop a LHRH peptide-based radiotheranostic (LPThera) technology, a new peptide receptor radionuclide therapy (PRRT) for the treatment of TNBC overexpressing LHRH receptors.

Methodology: Our lab has synthesized the peptide using solid-phase peptide synthesis techniques. Peptides were synthesized using the in-situ neutralization protocol for Fmoc chemistry on Rink amide 4-methylbenzhydrylamine (MBHA) resin according to the published procedure. Thereafter, the first step of developing the novel targeting molecule was to prepare a complexation of the cold nuclide (cold non-radioactive gallium) with the LHRH targeting peptide. Later, the prepared complex was characterized to prepare the optimized formulation.

Conclusion: At the later stage of the research, the radioactive complex of the same molecule will be prepared and analyzed for theragnostic purposes in TNBC cell lines overexpressing LHRH receptors hence, proving its efficacy for targeted treatment and diagnosis.

27. Model Behaviour: 3D In Vitro Assessment of EphA2 CAR T Cell Efficacy In Paediatric Brain Cancer

Samuel Bax* (1,2), Yuyan Chen (1,2), Victoria Prior (1,2), Ken Hsu (1), Belinda Kramer (1), Teah Goodhand (1,3), Jody MacLeod (1,2), Bryce Thomas (1), Shiloh Middlemiss (1), Geoffrey McCowage (1,2), Caroline Bateman (1), Sayali Gore (1), Kavitha Gowrishankar (1,2), Geraldine O'Neill (1,2)

(1) Children's Cancer Research Unit, Kids Research, The Children's Hospital at Westmead (CHW), NSW
(2) CHW Clinical School, Faculty of Medicine and Health, University of Sydney, NSW
(3) School of Medical Sciences, University of Sydney, NSW

Aims
The membrane receptor tyrosine kinase ephrin receptor A2 (EphA2) has emerged as an important Tumour-Associated Antigen (TAA) in a range of cancers, and we have recently shown robust efficacy of EphA2 CAR T cells in childhood sarcoma. Given the association of this TAA with primary paediatric brain cancers, this work sought to conduct preclinical assessment of EphA2 CAR T cells in brain cancer.

Methods
Since many highly promising treatments tested using standard 2-dimensional (2D) preclinical assays fail to demonstrate the expected efficacy when translated to patients, we undertook to include 3D in vitro models to provide a tissue mimic of the solid tumour barrier encountered by CAR T cells trafficking in vivo as part of our preclinical workup. EphA2-induced cytotoxicity under 2D conditions was assessed by xCELLigence electrical impedance assay and ELISA-based confirmation of cytokine release. CAR T efficacy under 3D conditions was next assessed in cancer spheroids and cancer spheroid/brain organoid co-cultures using luciferase reporters and an IVIS Lumina in vivo imaging system.

Results
Our results demonstrate that brain cancer cells exhibit greater sensitivity to CAR T mediated cell death under 2D versus 3D assay conditions. In some cases, cells that were sensitive to CAR T mediated death under 2D conditions exhibited no death in 3D cultures. Notably, there was a lack of direct correlation between EphA2 cell surface expression and CAR T mediated cell death, with cells displaying very high EphA2 expression being insensitive to CAR T mediated death in 3D cultures.

Conclusion
Incorporation of tissue dimensionality into preclinical assessments results in decreased sensitivity overall, which we contend may better reflect the likely in vivo response and thus presents a better preclinical test. Moreover, transitioning this treatment to the clinic may require confirmation of biomarker expression and patient-specific CAR T cell function prior to reinfusion.