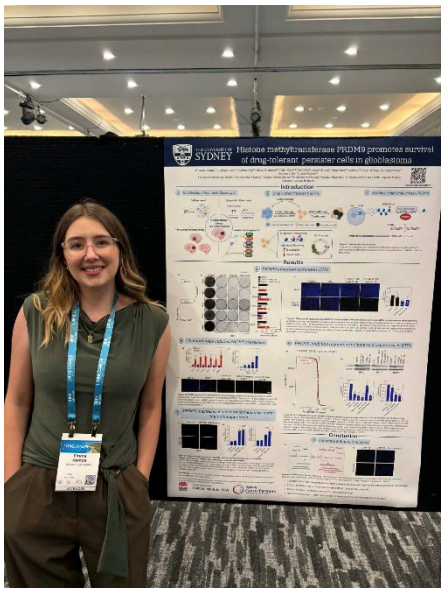
Name: Emma Kempe
Position & Affiliation: PhD Candidate, The University of Sydney
Full Reference: Kempe EG, Joun GL, Feng Y, Abbassi RH, Clark T, Du TY, Low JKK, Yang P, Loo L, Day BW, Neely GG, Don AS, Munoz L. *Histone methyltransferase PRDM9 promotes survival of drug-tolerant persister cells in glioblastoma.*
Conference/Meeting Name: Lorne Cancer 2026
Location: Lorne, VIC, Australia
Dates: 12-14/2/2026
Presentation Type (invited keynote, oral, poster): Poster



Lorne Cancer 2026 was attended by approximately 300 researchers, with a range of international and interstate speakers presenting exciting and innovative research. The keynote speaker, Dr Charles Sawyers, a researcher critical to the discovery and development of imatinib gave a fascinating talk about his current research on treatment resistant prostate cancer. Almost every single speaker was engaging and presenting exciting research, however, the other presentation that really stood out was a talk given by Professor Shalin Naik from WEHI. He is very well spoken, no doubt attributed to the fact he's previously featured on television and podcasts as a science communicator, but his research on clone tracing and haematopoietic stem cells was really interesting and inspiring. In fact, after the conference I managed to convince my supervisor we should do a similar experiment for my project- called SPLITR- that would allow me to barcode and trace my cells in response to chemotherapy treatment. We found some other presenters doing similar research in non-small cell lung cancer and ALL, however they were having some trouble isolating enough drug-tolerant persisters, so I am hoping that if I were to trial this experiment in our glioblastoma stem cells, I should get significant results.

I was also able to network with previous and new colleagues from WEHI and the Peter MacCallum Cancer Centre, and ask for advice on designing SPLITR experiments, and how to troubleshoot those experiments in a cost-effective way. There were a couple of labs that were also trialling experiments with the same compounds that I have used previously, so I was able to provide some troubleshooting suggestions to those PhD students. I am extremely grateful for the support of the Sydney Cancer Partners, as without this grant I wouldn't have been able to attend this conference.

Histone methyltransferase PRDM9 promotes survival of drug-tolerant persister cells in glioblastoma

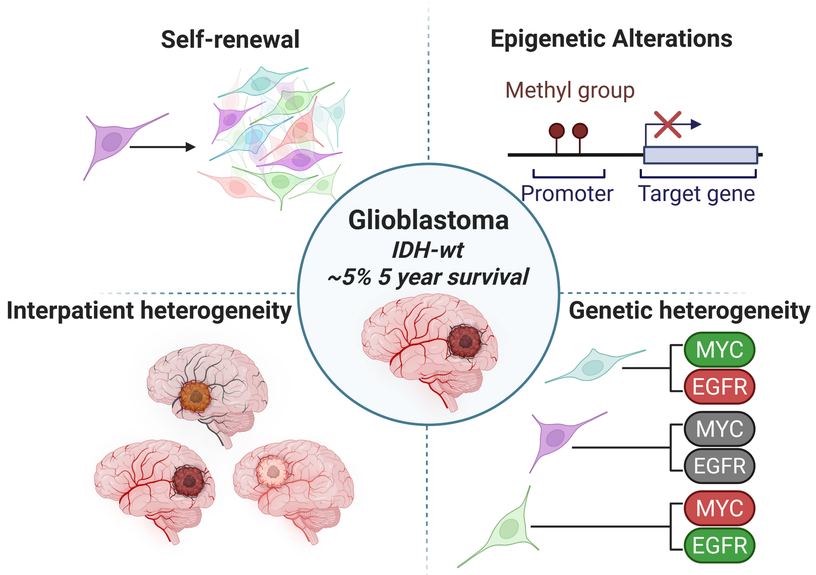
Emma G. Kempe[1,2], George L. Joun[1,2], Yuchen Feng[1,2], Ramzi H. Abbassi[1,2], Teleri Clark[2,3], Tian Y. Du[2,3], Jason K.K. Low[3], Pengyi Yang[2,3], Lipin Loo[2,3], Bryan W. Day[4], G. Gregory Neely[2,3], Anthony S. Don[1,2], Lenka Munoz[1,2]

[1] Faculty of Medicine and Health, The University of Sydney [2] Charles Perkins Centre, The University of Sydney [3] Faculty of Science, The University of Sydney [4] QIMR Berghofer Medical Research Institute, Brisbane

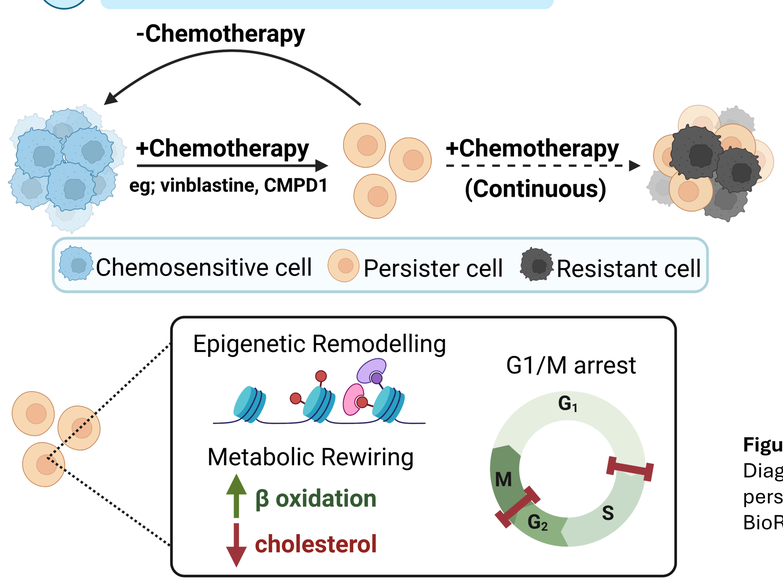
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Introduction

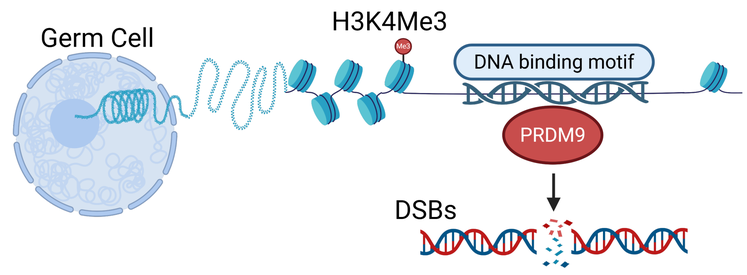
1 Glioblastoma Treatment Challenges



2 Drug Tolerant Persisters (DTPs)



3 H3K4me3 methyltransferase PRDM9

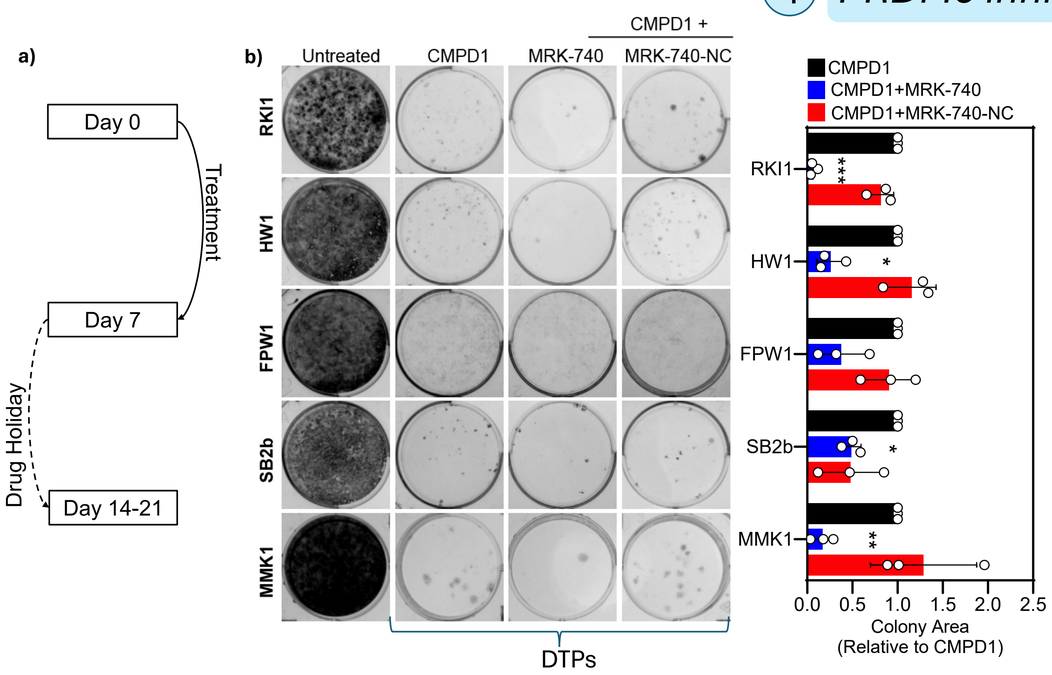


PRDM9 is aberrantly expressed in 20% of tumours[1]

Figure 1: Introductory Schematics
Diagrams of challenges with glioblastoma treatment approaches, drug tolerant persister cells and meiosis associated histone methyltransferase PRDM9. Made in BioRender.

Results

4 PRDM9 inhibition eliminates DTPs



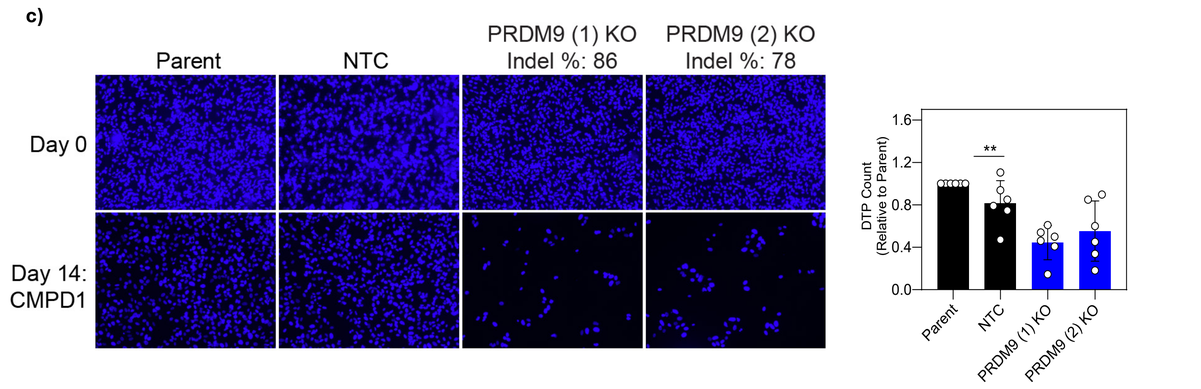


Figure 2: Microtubule targeting agent CMPD1 combined with PRMD9 inhibition eliminates DTPs in glioblastoma stem cell lines. a-b) Schematic and representative images and quantification of colony formation assay with glioblastoma stem cell lines treated with MRK-740 (3μM), MRK-740-NC (3μM) alone and in combination with CMPD1 (25μM) for 7 days, followed by a drug holiday until visible colonies formed in CMPD1-only treatments. Data are mean ± SD (n=3; one sample t-test). **d)** DAPI-stained images and quantification of RKI1 cells following PRDM9 knock-out (KO) and treated with CMPD1 (25μM, 14 days). Data are mean ± SD (n=3-6; one sample t-test). NTC: non-targeted control.

5 Chemotherapy induces PRDM9 expression

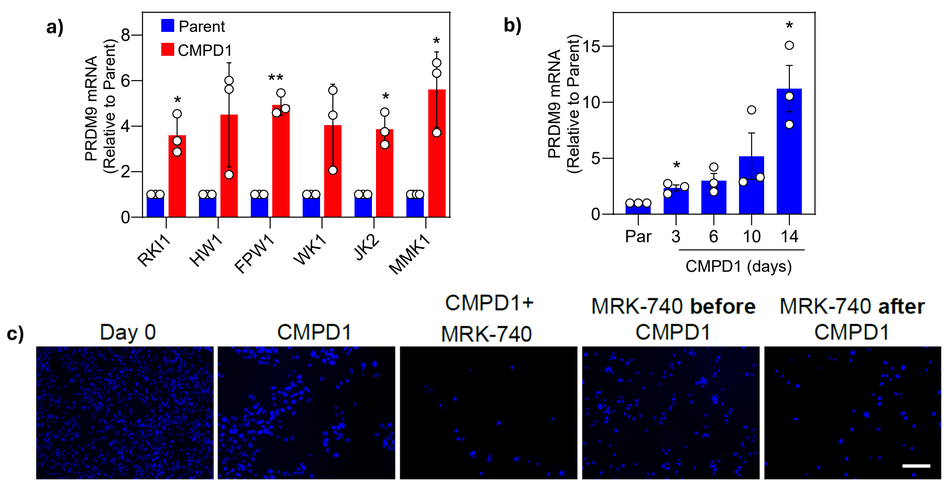


Figure 3: PRDM9 expression is increased by chemotherapy a-b) RT-qPCR analysis of PRDM9 mRNA expression in in glioblastoma stem cell lines treated with CMPD1 (25μM) for 3 – 14 days. Data are mean ± SD (n=3; one sample t-test). **c)** DAPI stained images of DTP cells surviving CMPD1 (25μM, 14 days) treatment combined simultaneously with MRK-740 (3μM) or added 3 days before or after CMPD1. Data are mean ± SD (n=3 biological replicates).

6 PRDM9 inhibition regulates cholesterol biosynthesis in DTPs

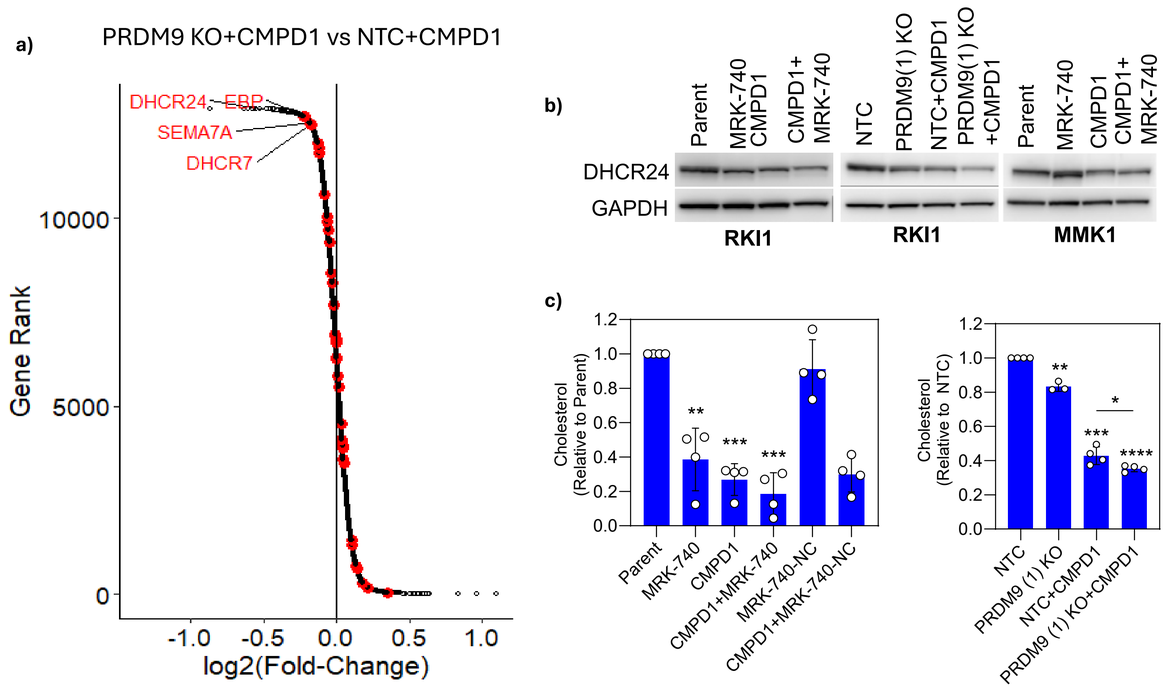


Figure 4: PRDM9 inhibition lowers cholesterol biosynthesis enzymes and products in DTPs. a) Waterfall plot of differentially expressed genes (RNA sequencing of n=3) in CMPD1 (10μM, 3 days) treated RKI1 cells transduced with NTC sgRNA (NTC) or PRDM9 sgRNA (PRMD9 KO). **b)** Immunoblots of DHCR24 of RKI1 cells with CMPD1 (10μM) ± MRK-740 (3μM) for 3 days, PRDM9 KO ± CMPD1 (10μM) for 3 days and MMK1 cells with CMPD1 (10μM) ± MRK-740 (5μM) for 3 days. Each membrane was re-probed for GAPDH. Data are mean ± SD (n=3-4; one sample t-test). **c)** Cholesterol in RKI1 cells treated with CMPD1 (10μM, 3 days) ± MRK-740 (3μM)/MRK-740-NC (3μM) and PRDM9 KO cells . Data are mean ± SD (n=4 biological replicates). One sample t-test between treatment vs. Parent or NTC., and unpaired t-test between NTC + CMPD1 and PRDM9(1) KO + CMPD1

7 PRDM9 maintains cholesterol homeostasis under chemotherapy stress

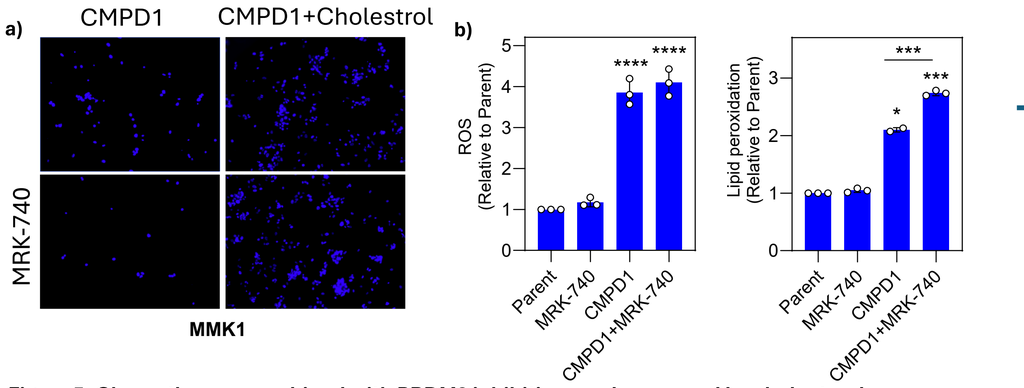


Figure 5: Chemotherapy combined with PRDM9 inhibition can be rescued by cholesterol supplementation and results in ROS generation and lipid peroxidation
a)DAPI-stained images and quantification of DTPs in MMK1 cells treated with CMPD1 (25 μM) ± MRK-740 (5 μM) ± cholesterol (100 μg/mL) for 14 days. Data are mean ± SD (n = 3; one sample t-test). **b)** Quantification of reactive oxygen species (ROS), lipid peroxidation in RKI1 cells treated with CMPD1 (10 μM, 3 days) ± MRK-740 (3 μM). Data are mean ± SD (n = 3 biological replicates). Unpaired t-test between CMPD1 vs CMPD1 + MRK-740

Conclusion

8 Summary & Future Directions

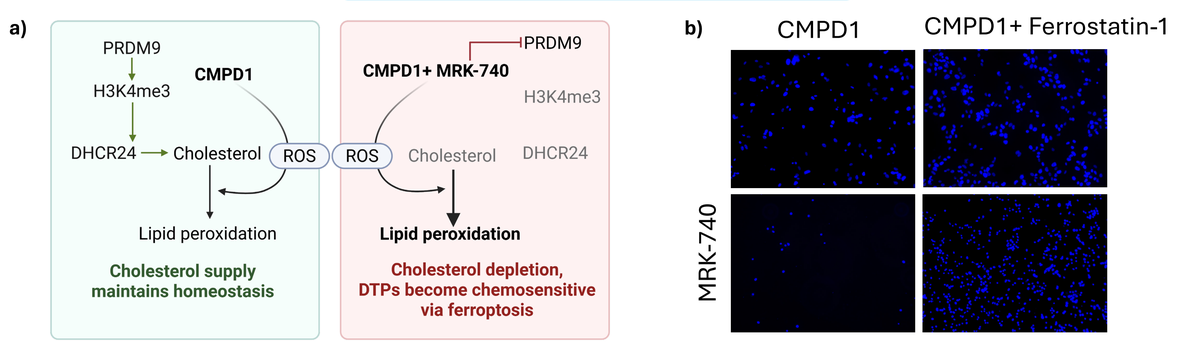


Figure 6: Summary and Future Directions. a) Schematic of PRDM9 signalling pathway in the context of chemotherapy treatment. Diagram made in BioRender **b**) DAPI-stained images of DTPs surviving CMPD1 ± MRK-740 (5μM) ± ferrostatin-1 (10μM)

- This study identifies how glioblastoma DTPs utilise a non-essential enzyme, PRDM9, to promote their survival.
- PRDM9-inhibition has a cholesterol lowering effect that is tumour-specific.
- This encourages the development of PRDM9-targeting drugs
- Future research aims to determine the role of ferroptosis in MRK-740 combination therapy

References: 1. Houle, A. A. et al. Aberrant PRDM9 expression impacts the pan-cancer genomic landscape. Genome Res 28, 1611–1620 (2018).

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