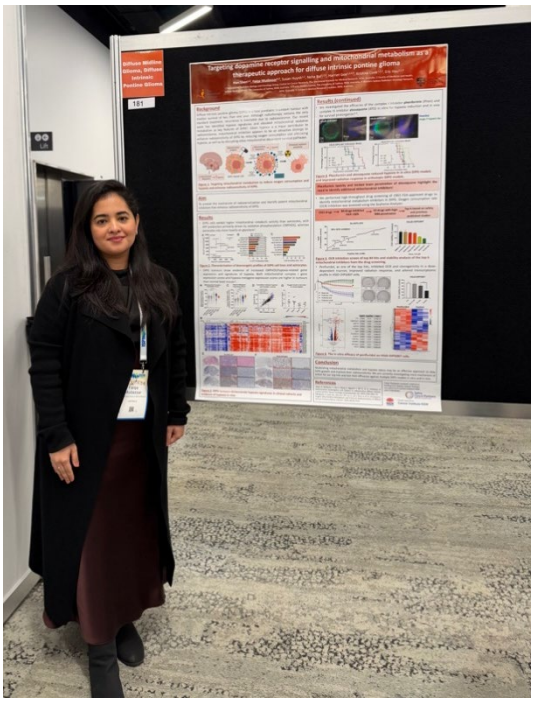
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Position & Affiliation: Research Assistant, The Westmead Institute for Medical Research
Full Reference: Shen H, **Mudassar F**, Huynh S, Bal N, Gee H, Cook K, Hau E. *Targeting dopamine receptor signalling and mitochondrial metabolism as a therapeutic approach for diffuse midline gliomas.*
Conference/Meeting Name: 22nd International Symposium on Pediatric Neuro-Oncology
Location: Sydney International Convention Centre, Sydney, NSW, Australia
Dates: 28 June – 1 July 2026
Presentation Type: Poster



ISPNO 2026 is one of the world's largest paediatric neuro-oncology conferences, bringing together more than 1,000 delegates, including clinicians, researchers and trainees from around the world. The conference covered a broad range of topics across paediatric brain tumour biology, translational research, clinical care, and emerging therapeutic approaches. Attending ISPNO 2026 provided an excellent opportunity to learn about recent advances in paediatric neuro-oncology, particularly in relation to high-risk brain tumours. The scientific program included diverse themes such as ependymoma, diffuse midline glioma, medulloblastoma, high-grade glioma, the tumour microenvironment, germ cell tumours, low-grade gliomas, precision medicine, liquid biopsies, and radiotherapy. The conference featured several outstanding invited speakers, including Dr Michelle Monje, Dr Pratiti Bandopadhayay, Dr Elizabeth Cooper, Dr Areeba Patel, Dr Roger Packer, Associate Professor Nick Vitanza, and many others. The program included Education Day sessions, tumour-specific concurrent sessions, debates, rapid-fire poster presentations, and poster viewing sessions, creating a highly engaging environment for scientific exchange and professional development.

One of my main objectives in attending ISPNO 2026 was to engage with current developments in paediatric brain tumour research and to understand how these advances relate to my own work on improving radiotherapy response in DIPG through targeting mitochondrial metabolism and tumour hypoxia. During the conference, I had the opportunity to speak with several researchers working in the paediatric brain tumour field. These discussions were highly valuable, as I learned more about DIPG xenograft models, which I have not previously used in my own research. I also received useful feedback on my project, including suggestions for additional experimental work that could further strengthen and extend my current findings. The conference also strengthened my understanding of how preclinical findings can be translated into clinically meaningful approaches. Sessions on clinical trial design, precision medicine, and drug delivery highlighted the challenges of moving promising laboratory findings into paediatric brain tumour trials, especially for tumours located behind the blood–brain barrier.

The learning outcomes from ISPNO 2026 are highly relevant to the wider Sydney Cancer Partners membership, particularly in the areas of translational cancer research, preclinical modelling, therapeutic resistance, and clinical trial development. The conference highlighted the importance of integrating tumour biology, advanced preclinical models, drug delivery strategies, biomarker discovery, and clinical trial design to improve outcomes for patients with aggressive cancers.



A personal highlight of the conference was the opportunity to engage directly with researchers working in paediatric brain tumour biology and translational neuro-oncology. I particularly valued the discussions around DIPG xenograft models and the feedback I received on my own research project. These interactions provided new ideas for future experiments and helped me better understand how my research fits within the wider international effort to improve outcomes for children with high-risk brain tumours.

Targeting dopamine receptor signalling and mitochondrial metabolism as a therapeutic approach for diffuse intrinsic pontine glioma

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Background

Diffuse intrinsic pontine glioma (DIPG) is a fatal paediatric brainstem tumour with median survival of less than one year. Although radiotherapy remains the only standard treatment, recurrence is inevitable due to radioresistance. Our recent work has identified hypoxia signatures and elevated mitochondrial oxidative metabolism as key features of DIPG[1]. Given hypoxia is a major contributor to radioresistance, mitochondrial inhibition appears to be an attractive strategy to enhance radiosensitivity of DIPG by reducing oxygen consumption and alleviating hypoxia, as well as by disrupting other mitochondrial-dependent survival pathways.

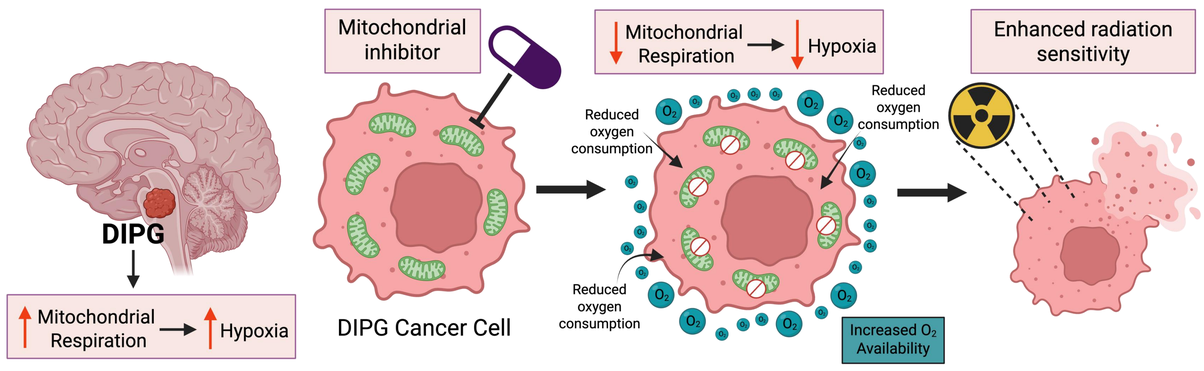


Figure 1. Targeting mitochondrial metabolism to reduce oxygen consumption and hypoxia and enhance radiosensitivity of DIPG.

Aim

To unravel the mechanism of radiosensitization and identify potent mitochondrial inhibitors that enhance radiosensitivity of DIPG.

Results

- DIPG cells exhibit higher mitochondrial metabolic activity than astrocytes, with ATP production primarily driven by oxidative phosphorylation (OXPHOS), whereas astrocytes rely more heavily on glycolysis[1].

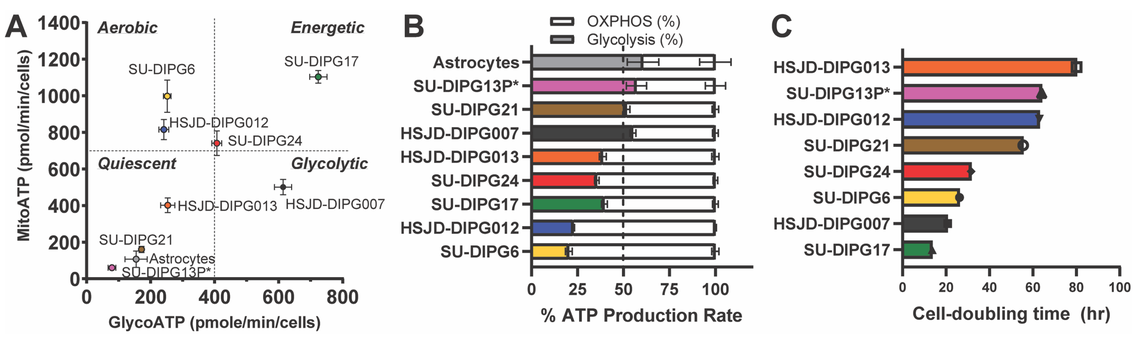


Figure 2. Characterisation of bioenergetic profiles of DIPG cell lines and astrocytes.

- DIPG tumours show evidence of increased OXPHOS/hypoxia-related gene expression and signatures of hypoxia. Both mitochondrial complex I gene expression scores and hypoxia metagene expression scores are higher in tumours than normal brain tissues[1].

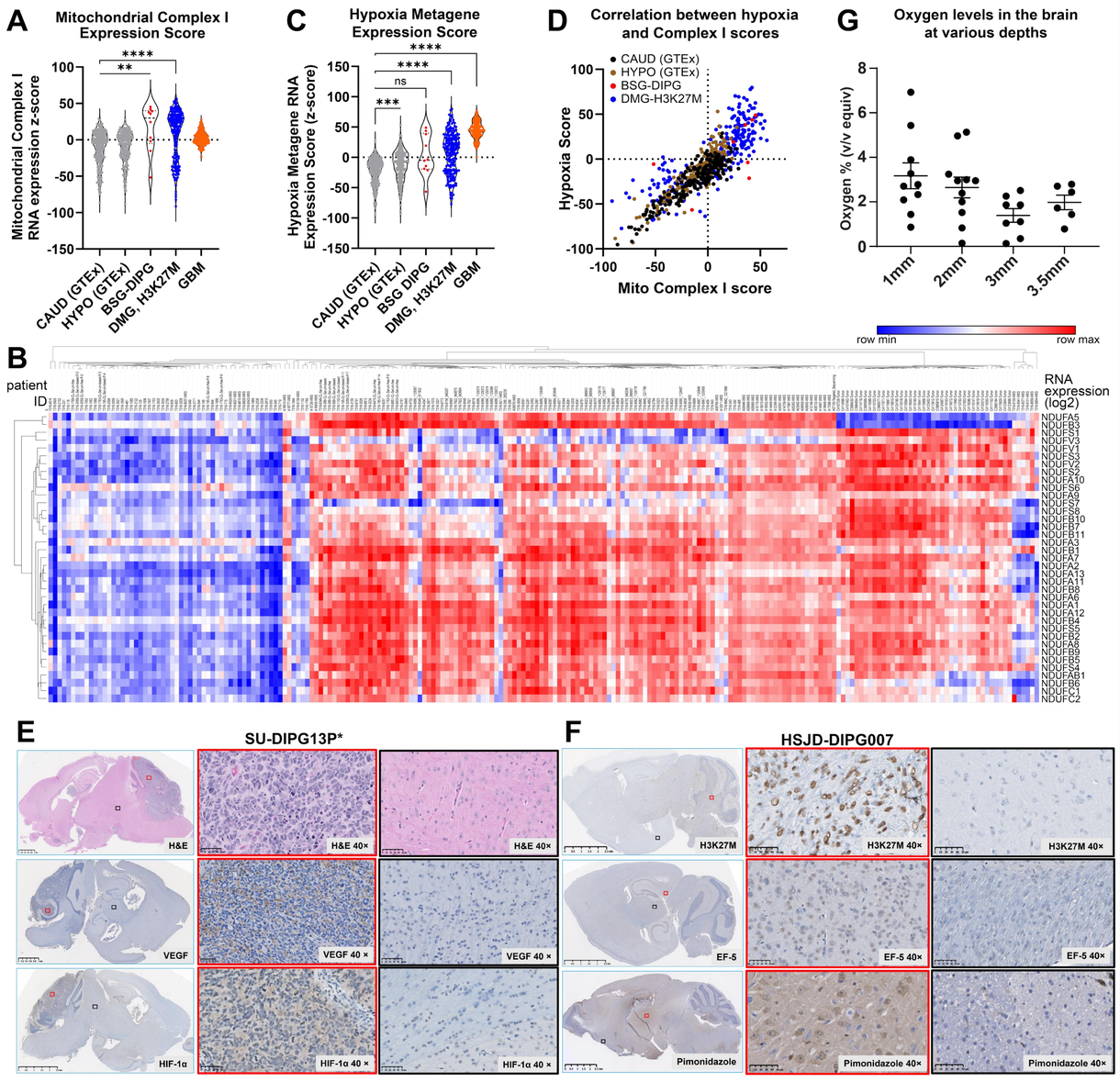


Figure 3. DIPG tumours demonstrate hypoxia signatures in clinical cohorts and evidence of hypoxia in vivo.

Results (continued)

- We investigated the efficacies of the complex I inhibitor **phenformin** (Phen) and complex III inhibitor **atovaquone** (ATO) in vitro for hypoxia reduction and in vivo for survival prolongation[1,2].

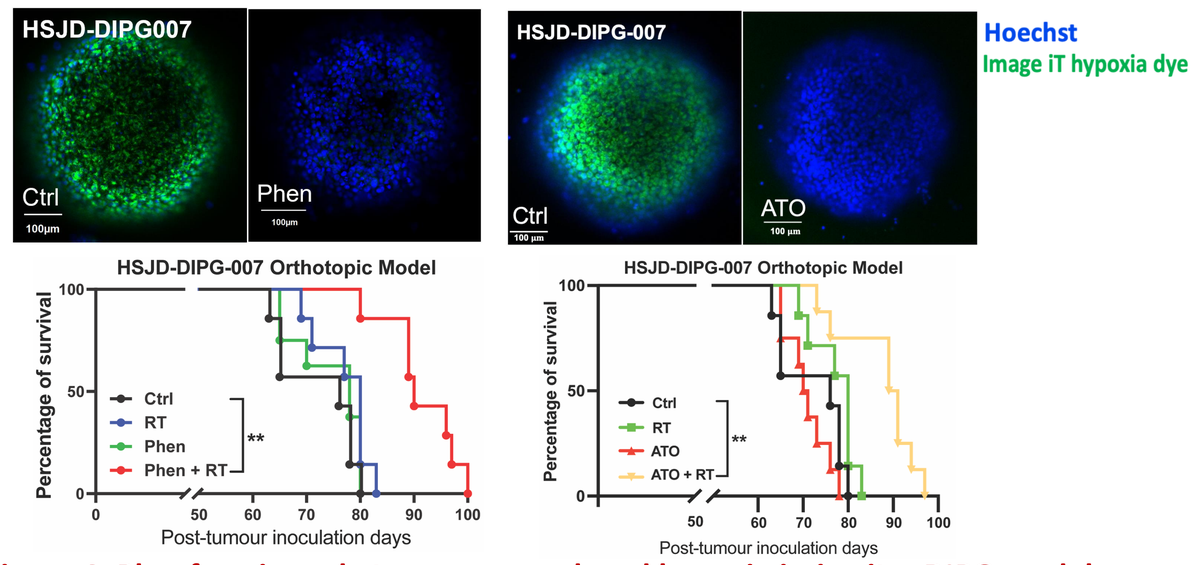


Figure 4. Phenformin and atovaquone reduced hypoxia in *in vitro* DIPG models and improved radiation response in orthotopic DIPG models.

Phenformin toxicity and limited brain penetration of atovaquone highlight the need to identify additional mitochondrial inhibitors!

- We performed high-throughput drug screening of 1963 FDA-approved drugs to identify mitochondrial metabolism inhibitors in DIPG. Oxygen consumption rate (OCR) inhibition was assessed using the Seahorse Analyzer.

1963 drugs → 84 drugs inhibited OCR >30% → 33 drugs with high BBB penetration → Top 6 based on safety and previous published studies

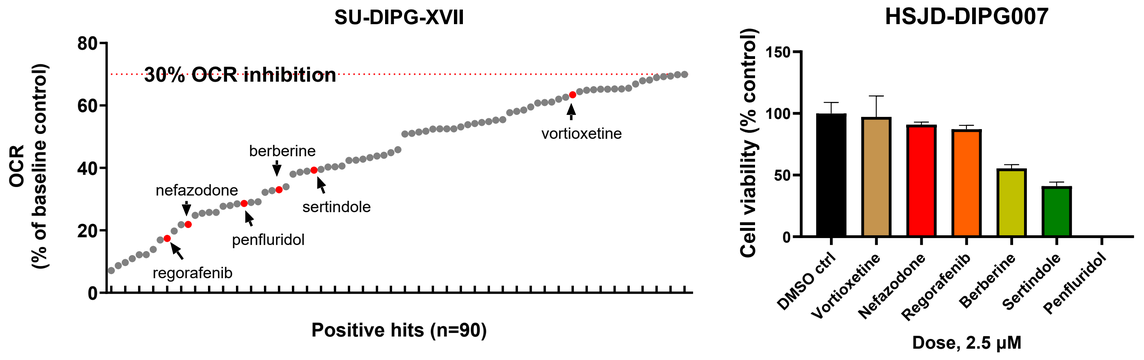
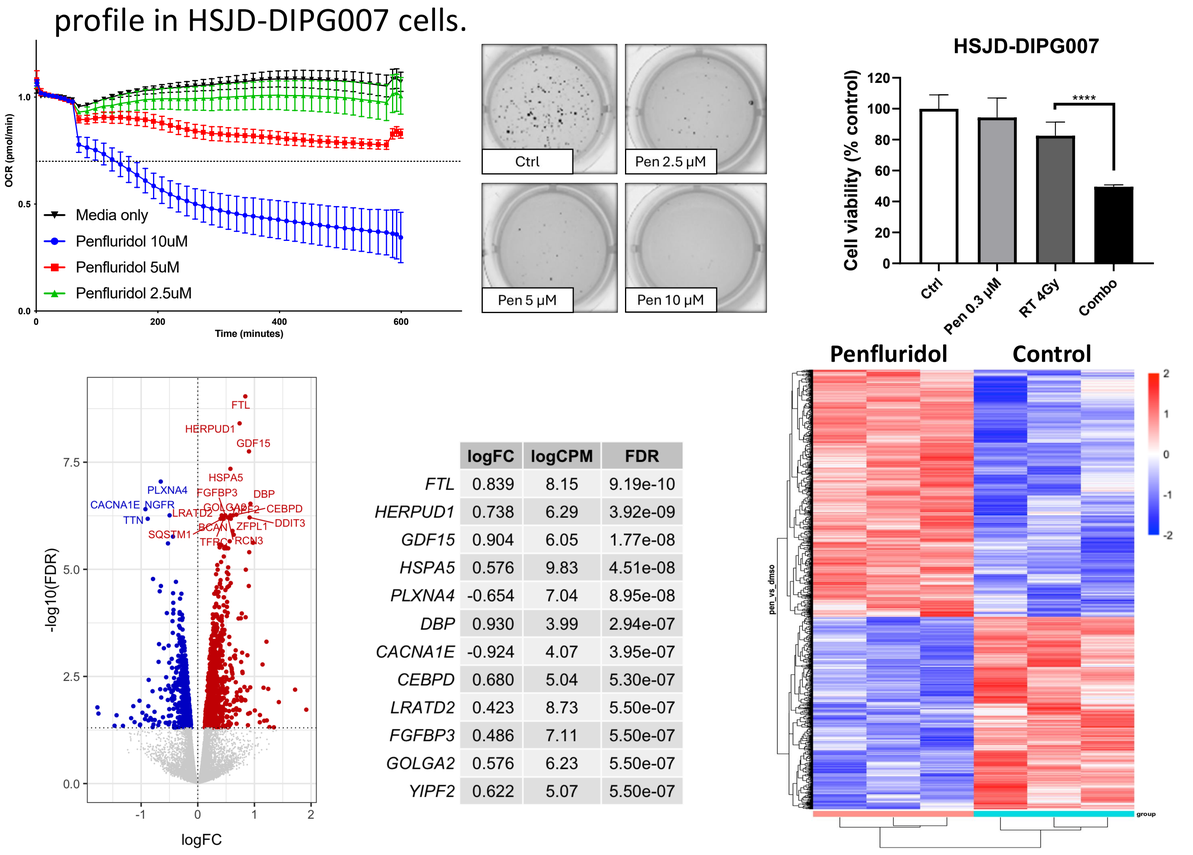


Figure 5. OCR inhibition screen of top 84 hits and viability analysis of the top 6 mitochondrial inhibitors from the drug screening.

- Penfluridol, as one of the top hits, inhibited OCR and clonogenicity in a dose-dependent manner, improved radiation response, and altered transcriptomic profile in HSJD-DIPG007 cells.



	logFC	logCPM	FDR
FTL	0.839	8.15	9.19e-10
HERPUD1	0.738	6.29	3.92e-09
GDF15	0.904	6.05	1.77e-08
HSPA5	0.576	9.83	4.51e-08
PLXNA4	-0.654	7.04	8.95e-08
DBP	0.930	3.99	2.94e-07
CACNA1E	-0.924	4.07	3.95e-07
CEBPD	0.680	5.04	5.30e-07
LRATD2	0.423	8.73	5.50e-07
FGFBP3	0.486	7.11	5.50e-07
GOLGA2	0.576	6.23	5.50e-07
YIPF2	0.622	5.07	5.50e-07

Figure 6. The in vitro efficacy of penfluridol on HSJD-DIPG007 cells.

Conclusion

Modulating mitochondrial metabolism and hypoxia status may be an effective approach to slow DIPG growth and improve their radiosensitivity. We are currently investigating more mechanism of action for our top hits and test their efficacies against multiple DIPG models in vitro and in vivo.

References

[1]Shen H, Mudassar F, Ma S, Wang X, Nguyen S, Bal N, et al. Inhibition of mitochondrial bioenergetics and hypoxia to radiosensitize diffuse intrinsic pontine glioma. Neuro-oncology (Charlottesville, Va). 2025;27(4):1061-75.
[2]Mudassar F, Cook KM, Warnken ZN, Bal N, Lai J, Gloss B, et al. Atovaquone Targets Mitochondrial Metabolism and Enhances Radiosensitivity of Diffuse Intrinsic Pontine Glioma. Cancers. 2026;18(10):1553.

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