Development of Tumour-targeted Therapy for the Treatment of Adult and Paediatric High-grade Gliomas

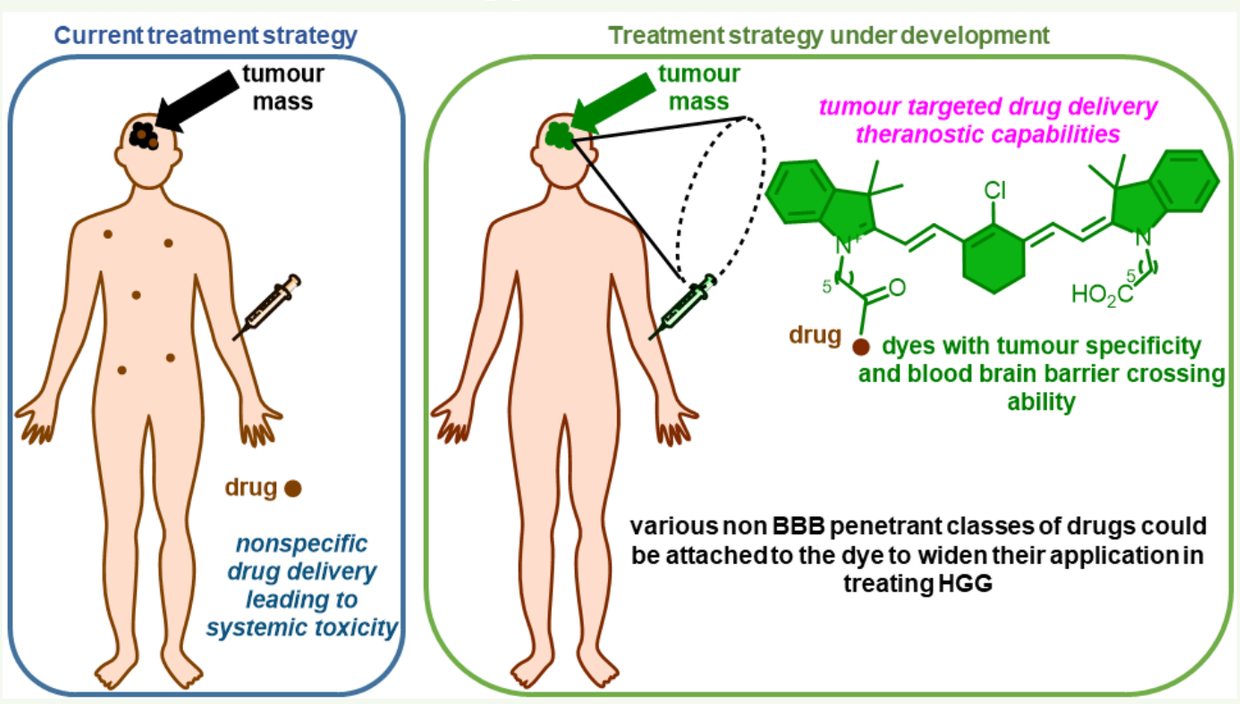
Jose, J.[1,2] , Choi, P.J.[1,2] , Lee, C.[3], Park, T. I-H. [3], Cooper, E. [3], Dragunow, M.[3], Denny, W.A.[1,2], Kim, C-Y[4], Hwang, K.[4], Nam, K. M.[4]
[1]Auckland Cancer Society Research Centre and [2] Maurice Wilkins Centre, University of Auckland.
[3]Centre for Brain Research, University of Auckland, New Zealand.
[4]Department of Neurosurgery, Seoul National University, South Korea.

Introduction

Brain cancer patients, especially those suffering from high-grade gliomas (HGG) face a bleak future with very dismal long-term disease-free survival outcomes due to the limited treatment options currently available. Therefore, there is an unmet need for new therapeutic intervention that extends patients' progress-free survival and improves their quality of life. A significant hurdle is the inability of current chemotherapy agents to cross the blood-brain barrier (BBB). BBB acts as a protective shield that filters the blood to ensure nothing harmful makes it to the brain. This protection is usually good, but it becomes a problem if you want to deliver therapeutic cancer drugs through it. This barrier blocks 98% of drugs from entering the brain. Even the ones that cross BBB are unevenly distributed in the normal brain and tumour tissue, resulting in mediocre treatment and severe side effects.

We are developing drug delivery systems that can cross the BBB and facilitate the specific accumulation of drugs in the tumour tissue.[1] This will significantly improve the efficacy of anticancer drugs in treating various brain cancers and reduce systemic toxicity. Our group has explored and developed BBB crossing and tumour targeting near infra-red cyanine dyes, which can be covalently attached to FDA-approved chemotherapy agents (drug-dye conjugates), thereby delivering it to the tumour tissue.

Hypothesis



Results

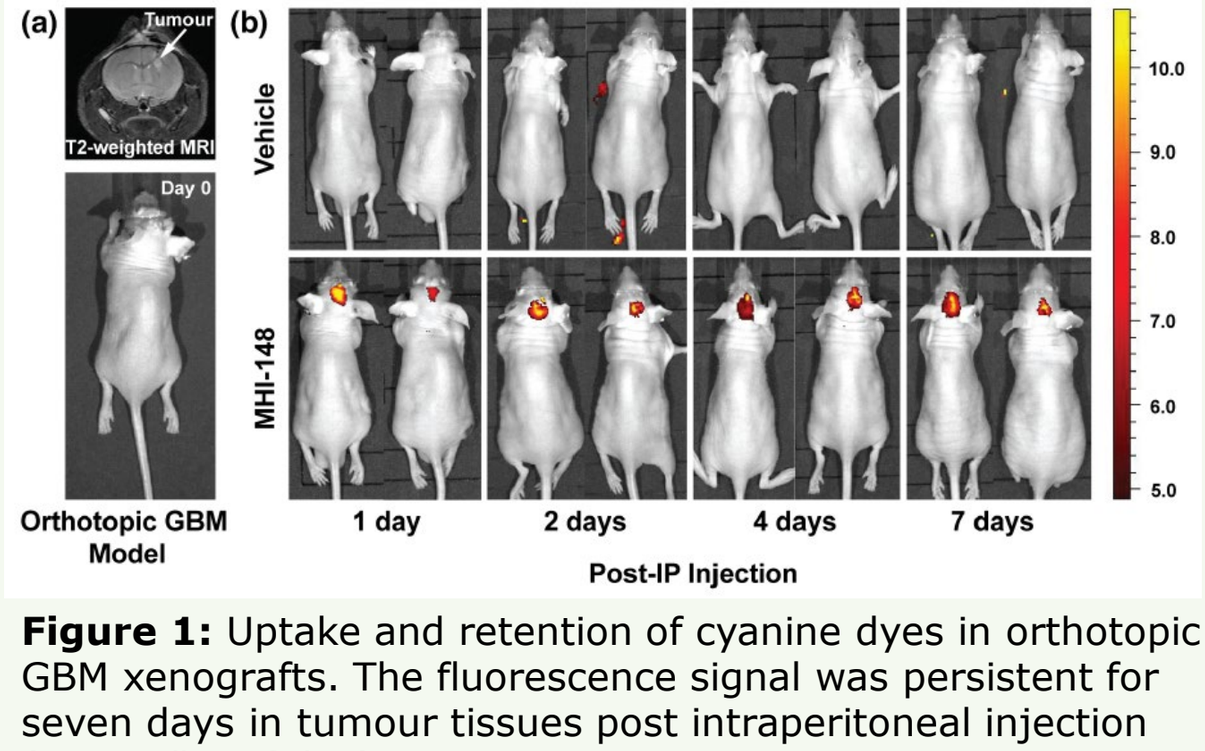


Figure 1: Uptake and retention of cyanine dyes in orthotopic GBM xenografts. The fluorescence signal was persistent for seven days in tumour tissues post intraperitoneal injection (10 mg/kg of dye).

Table 1: EC_{50} concentrations (μM) for various drug-dye conjugates derived from in vitro cytotoxicity assays performed across a panel of HGG cell lines. The corresponding drugs itself had minimal impact on the survival of these cell lines.

Anticancer Drugs	Drug-dye conjugates	U87-MG	KNS42	T115	T73	T84
Palbociclib	**SN40525**	1.1	0.33	0.11	0.63	0.041
Ceritinib	**SN40526**	0.61	0.74	0.04	0.13	0.31
Cediranib	**SN40561**	0.15	0.55	0.35	1.34	0.06
Vandetanib	**SN40532**	0.04	0.029	0.27	0.33	0.04
Brigatinib	**SN40538**	0.21	0.19	0.33	1.14	0.07
Ponatinib	**SN40555**	-	0.22	6.49	0.93	1.03

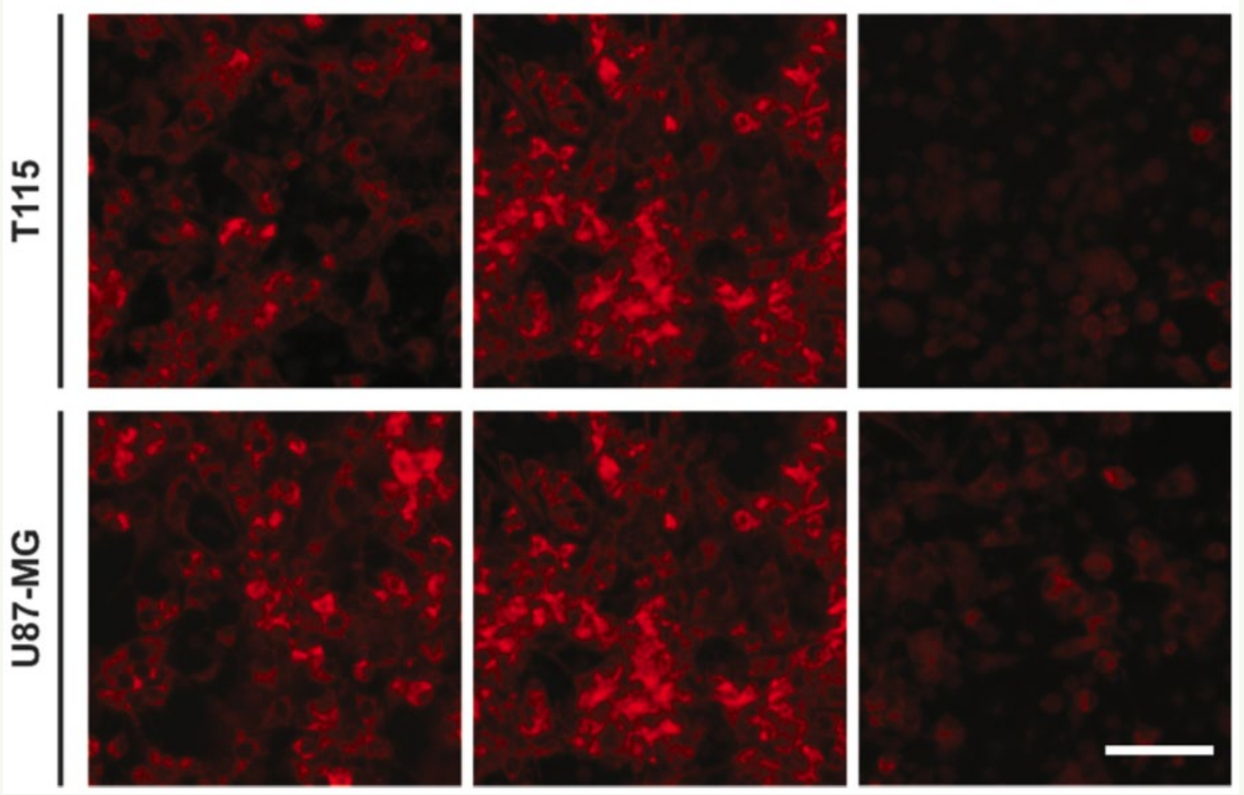


Figure 2: The elucidation of the role played by organic anion transporting polypeptides (OATP) in uptake of drug-dye conjugate by HGG cell lines.

The synthesized drug-dye conjugates targeted various aberrant pathways in HGG and elicited potent cytotoxicity in multiple patient-derived HGG cell lines (Table 1). The corresponding drugs itself did not show appreciable cell killing ability. The dye itself is nontoxic and only facilitates the uptake of the drugs into cancer cells and tumour tissues (Figure 1). The uptake of such drug-dye conjugates is facilitated by certain isoforms of OATP (OATP1A2, 2B1, 1C1 and 4A1) which is expressed in relative abundance in brain tumour tissues (Figure 2).[2] The retention of these conjugates in tumour cells is attributed to it's covalent interaction with albumin.

Conclusions and outlook

The results obtained from this work serve as proof of principle that enables tumour-specific drug delivery to treat HGG. This work also paves the way for treating other brain cancers and CNS disorders like Parkinson's and Alzheimer's disease, for which no adequate therapy exists.

References

1. Choi, P. J.; Park, T. I. H.; Cooper, E.; Dragunow, M.; Denny, W. A.; Jose, J., Heptamethine Cyanine Dye Mediated Drug Delivery: Hype or Hope. *Bioconjug Chem* **2020,** *31*, 1724-1739.
2. Cooper, E.; Woolf, Z.;….Choi, P. J.; Dragunow, M.; Jose, J.; Park, T. I.-H., Single-cell image analysis reveals over-expression of organic anion transporting polypeptides (OATPs) in human glioblastoma tissue. *Neuro-Oncology Advances* **2022,** *4*, vdac166.
3. Usama, S. M.;….. Burgess, K., Role of Albumin in Accumulation and Persistence of Tumor-Seeking Cyanine Dyes. *Bioconjug Chem* **2020,** *31*, 248-259.

Acknowledgement: