Developing an Innovative Therapeutic Solution for Patients with WNT-Medulloblastoma

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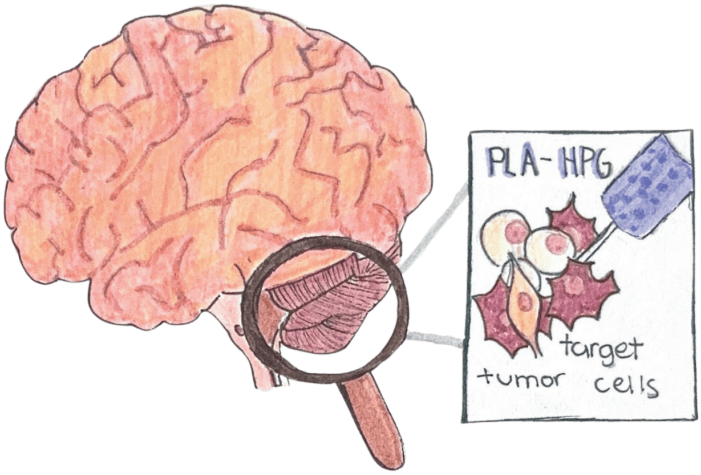

Art by Maria Delgado

Medulloblastoma (MB) is the most common malignant pediatric central nervous system (CNS) tumour, typically originating in the cerebellum and often spreading to the spinal cord via cerebrospinal fluid (CSF) (National Cancer Institute, 2023). MB primarily affects children aged 3–10 years, with a higher incidence in males and individuals of Caucasian or Hispanic heritage (Raffel, 2014). Among the four molecular subtypes, Wingless and Int (WNT)-activated MB comprises approximately 10% of cases, showing a favourable prognosis with over 95% 5-year survivorship and rare metastasis (Jackson & Packer, 2023). Despite this positive outlook, conventional treatments, especially chemotherapy and radiation, can cause significant long-term neurocognitive side effects, highlighting the need for targeted therapies that minimize these adverse outcomes.

This study proposes an innovative, two-phase therapeutic approach tailored for WNT-activated MB. In the first phase, an intratumoral microdevice (IMD) is employed to deliver microdosed WNT antagonists, such as Metformin and WIF-1, directly to the tumo-

ur site. This method, which has shown promise in glioblastoma research, enables localized drug administration, targeting the tumour while minimizing systemic exposure (Peruzzi et al., 2023; Conza et al., 2023). The approach aims to disrupt the WNT signaling pathway, a pathway crucial in WNT-activated MB due to mutations in the CTNNB1 gene, which leads to abnormal beta-catenin levels and increased tumour proliferation (Kijima et al., 2016; Maier et al., 2021).

In the second phase, biodegradable PLA-HPG nanoparticles are administered intrathecally into the CSF to bind WNT antagonists, ensuring a controlled and sustained release of therapeutic agents, which may prevent further metastasis and maintain effective drug levels (Khang et al., 2023). This delivery system aims to complement or replace traditional chemotherapy, thereby reducing neurocognitive impairments and enhancing treatment specificity. Additionally, paracrine signals from the tumour can disrupt the blood-brain barrier, making targeted delivery via IMD and nanoparticles more effective (Phoenix et al., 2016). By focusing on the molecular characteristics unique to WNT-activated MB, this dual-phase strategy offers a patient-specific treatment that minimizes harm while addressing tumour aggressiveness. This study represents a promising advancement in pediatric oncology, exemplifying how precision medicine can improve outcomes in high-risk childhood cancers (Slika et al., 2023).

References

Conza, D., Mirra, P., Fiory, F., Insabato, L., Nicolò, A., Béguinot, F., & Ulianich, L. (2023). Metformin: A new inhibitor of the WNT signaling pathway in cancer. *Cells,12*(17), 2182. https://doi.org/10.3390/cells12172182.

Cruciat, C. M., & Niehrs, C. (2013). Secreted and transmembrane WNT inhibitors and activators. *Cold Spring Harbor Perspectives in Biology, 5*(3), a015081. https://doi.org/10.1101/cshperspect.a015081.

Jackson, K., & Packer, R. J. (2023). Recent advances in pediatric medulloblastoma. *Current Neurology and Neuroscience Reports, 23*(10), 841–848. https://doi.org/10.1007/s11910-023-01316-9.

Khang, M., Lee, J. H., Lee, T., Suh, H., Lee, S., Cavaliere, A., Rushing, A., Geraldo, L. H. M., Belitzky, E., Rossano, S., De Feyter, H. M., Shin, K., Hüttner, A., Roussel, M. F., Thomas, J. L., Carson, R. E., Marquez Nostra, B., Bindra, R. S., & Saltzman, W.M. (2023). Intrathecal delivery of nanoparticle PARP inhibitor to the cerebrospinal fluid for the treatment of metastatic medulloblastoma. *Science Translational Medicine, 15*(720). https://doi.org/10.1126/scitranslmed.adi1617.

Khasawneh, A. H., Garling, R. J., & Harris, C. A. (2018). Cerebrospinal fluid circulation: What do we know and how do we know it? *Brain Circulation, 4*(1), 14-18. https://doi.org/10.4103/bc.bc_3_18.

Kijima, N., & Kanemura, Y. (2016). Molecular classification of medulloblastoma. *Neurologia Medico-Chirurgica, 56*(11), 687–697. https://doi.org/10.2176/nmc.ra.20160016.

Maier, H., Dalianis, T., & Kostopoulou, O. N. (2021). New approaches in targeted therapy for medulloblastoma in children. *Anticancer Research, 41*(4), 1715–1726. https://doi.org/10.21873/.14936.

National Cancer Institute. (2023, August 1). Medulloblastoma diagnosis and treatment. *National Cancer Institute.* https://www.cancer.gov/rare-brain spine-tumor/tumors/medulloblastoma.

Peruzzi, P., Dominas, C., Fell, G., Bernstock, J. D., Blitz, S. E., Mazzetti, D., Zdioruk, M., Dawood, H. Y., Triggs, D. V., Ahn, S., Bhagavatula, S. K., Davidson, S. M., Tatárová, Z., Pannell, M. J., Truman, K., Ball, A., Gold, M. P., Pister, V., Fraenkel, E., Chiocca, A. E., Lison, K. L., Wen, P. Y., & Jonas, O. (2023). Intratumoral drug releasing microdevices allow in situ high throughout pharmacophenotyping in patients with gliomas. *Science Translational Medicine, 15*(712). https://doi.org/10.1126/scitranslmed.adi0069.

Phoenix, T. N., Patmore, D. M., Boop, S., Boulos, N., Jacus, M. O., Patel, Y. T., Roussel, M. F., Finkelstein, D., Goumnerova, L., Perreault, S., Wadhwa, E., Cho, Y. J., Stewart, C. F., & Gilbertson, R. J. (2016). Medulloblastoma genotype dictates blood-brain barrier phenotype. *Cancer Cell, 29*(4), 508–522. https://doi.org/10.1016/j.ccell.2016.03.002.

Raffel, C. (2014, April 17). Medulloblastoma: Molecular genetics and animal models. *Neoplasia*. https://doi.org/10.1593/neo.03454.

Slika, H., Alimonti, P., Raj, D., Caraway, C. A., Alomari, S., Jackson, E. M., & Tyler, B. (2023). The neurodevelopmental and molecular landscape of medulloblastoma subgroups: Current targets and the potential for combined therapies. *Cancers, 15*(15), 3889. https://doi.org/10.3390/cancers15153889.

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