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*Mini Review*

# Pediatric Brain Tumors and Models of Pioneering

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**Abstract**

Brain and other central nervous system tumours are the second most frequent kinds of cancer among children and adolescents in the United States, after only leukaemias in incidence. Brain cancer continues to be the primary cause of mortality in children despite major advancements in detection and treatment options. It is clear that there is a need to enhance these patients' survival rates and streamline the therapy approaches. Preclinical models are essential for that goal. Pediatric brain tumour research employs a variety of models, including genetically modified mouse models, patient-derived xenografts and cell lines, and more recent models that make use of cutting-edge technologies like genome editing and organoids. Researchers from the Children's Brain Tumor Network and others have conducted significant research that has discovered multiomic landscapes. Of diverse children's brain cancers. With the use of such integrated data, these revolutionary technologies have made a number of useful models possible. Modeling's flexibility was increased via genome engineering, including CRISPR/Cas9. Through the use of models created through genome engineering, specific genetic changes might be studied in pure isogenic settings, making it easier to analyse the functional mechanisms underlying those mutations in tumour biology. Organoids have been used to examine developmental elements of carcinogenesis, which are critical in some paediatric brain cancers, as well as interactions between tumours and their microenvironments.

**Keywords:** Genome engineering, Models, Organoids, Pediatric brain tumors, Stem cells

## INTRODUCTION

Other approaches, including humanised mouse models, might be used to treat paediatric brain cancers (Wong CH 2018). These innovative models are expected to speed up the investigation of functional tumour biology and establish efficient therapies for juvenile brain cancers in addition to the current useful models (Davis C et al., 2017). Although the prognosis for children and adolescents with cancer has generally improved over the past few decades, brain and other central nervous system malignancies still have a poor outlook` (Peterson DL 1994). The most frequent types of solid cancer in children and the number one killer are paediatric brain tumours (Koestner A 1971). Brain malignancies and other CNS tumours overtake leukaemias as the most prevalent kind of cancer in teenagers (Rabotti GF 1964). The incidence of paediatric brain tumours varies by country, with the United States reporting the highest rates. The average yearly age-adjusted incidence rate of CNS malignancies among children aged was estimated by the Central Brain Tumor Registry of the United States in a study from 2020 (Cuatico W 1976). In this study, the annual age-adjusted mortality of CNS malignancies was Brain tumours were shown to be the leading cause of cancer death among children and adolescents in the age range, per 100,000 (Yoshida J 1978). The category of cancers known as paediatric brain tumours is diverse and constantly branching. Since even histologically similar tumours harbour different molecular features and, as a result, have different prognoses and therapeutic responses, extensive research and advancements over the past decades in imaging, molecular diagnostics, surgical procedures, and Tai lored therapy have shown that histological features are insufficient to define different brain tumour entities (Huszthy PC., et al 2012). In order to describe various brain and CNS malignancies, the World Health Organization began using molecular diagnosis criteria in 2016 (Simeonova I 2014). This marked the beginning of a new chapter in the overall care of this type

of disease (Neely JE 1983). This classification signalled the departure from the prevalent diagnosis from older platforms for molecular diagnosis based on tumour genomes to more recent techniques based on histologic/microscopic features and immunohistochemistry (Barbarich Marsteller NC 2013). Additionally, the first WHO Classification of Pediatric Malignancies was created in 2021 as a result of the molecular diversity and the variation in treatment response based on the genetic architecture of paediatric tumours (Aoki 2012). Morphological standards, IHC, and molecular traits are all included in the classification's multi-layered methodology (Giordano GD 2001). Pediatric brain tumours are regarded as spontaneous events, with the exception of a small number of hereditary predisposition disorders (Connan F 2006). The genes NF1 for neurofibromatosis type 1 and SMARCB1 for rhomboid tumour predisposition syndrome are linked to these familial brain tumour predisposition syndromes (Beadle JN., et al 2015). In addition to these familial tumour risk disorders, substantial research has been done on the genetic origins of sporadic juvenile brain cancers. As an illustration, medulloblastomas are molecularly divided into four groups, each driven by a different gene mutation, including. One of the most lethal juvenile brain cancers, diffuse intrinsic pontine glioma, was also genetically sub classified, with the most prevalent group being driven by the histone H3-K27M mutation. Recent studies by the Children's Brain Tumor Network and others have revealed the integrative genomic and proteomic landscapes of a variety of paediatric brain tumours, including low-grade gliomas, high-grade gliomas, ependymomas, medulloblastomas, gangliogliomas, craniopharyngiomas, and atypical ceratoid rhomboid tumours. However, many paediatric brain tumours have poor prognoses. For instance, diffuse midline gliomas with the histone H3-K27M mutation are one of the deadliest forms of cancer, with 50% of children surviving less than one year after diagnosis and only 10% surviving two years. Preclinical paediatric brain tumour models are crucial for comprehending the biology of these enormously diverse cancers and testing new treatments. Understanding cancer biology and developing more effective treatments for each tumour require integrating a vast amount of information from earlier research, including the genetic and proteomic landscape of many paediatric brain cancers.

# DISCUSSION

We will summarise and talk about the existing approaches utilised to Using cutting-edge tools like genome engineering and organoids, we simulate numerous forms of paediatric brain cancers, including the canonical and frequently used models, as well as investigate the more recently generated models. We'll go into more detail on how these models can help close the gap between preclinical and clinical research on juvenile brain tumours. Resembling the structure of internal organs and cell arrangement. Ogawa showed that clustered regularly interspaced short palindromic repeats in a brain organoid might simulate the growth of glioblastoma. Bian used transposon and CRISPR/Cas9 to introduce various combinations of genetic changes to simulate different malignancies, such as paediatric glioblastoma, medulloblastomas, atypical teratoid rhabdoid tumour, and CNS primitive neuroectodermal tumour. The primary platforms for medication safety and efficacy research are still in vivo models. To support testing on humans the mouse is by far the most commonly employed organism for juvenile brain research among the many models that are used in many domains. In vivo systems, like in vitro models, have benefits and drawbacks that must all be taken into account when planning preclinical studies. Patient-derived xenografts and GEMMs are the two main types of murine models employed in paediatric brain tumour studies, as was already mentioned. We will discuss these several platforms of models for other children brain malignancies as well as the well-studied paediatric medulloblastomas and gliomas. The most typical type of paediatric brain tumour is a glioma. Astrocytoma, brain stem, ependymomas, and optic nerve gliomas are the subtypes of gliomas that are frequently detected in children. Pediatric Gliomas are a diverse group of tumours that present a significant therapeutic challenge. Gliomas can be divided into low-grade and high-grade subtypes according to their histological grade; the latter tumours include the distinctive Diffuse Midline Glioma H3-K27 altered subtype, which is typically treated as a separate category due to its molecular characteristics, clinical presentation, and prognosis. The most recent WHO Categorization of Tumors of the CNS included information on integrated diagnostics with a focus on molecular criteria for brain tumour classification. Cell proliferation, mitosis, and neo angiogenic pathways, such as MAPK, EGFR, and VEGF pathways, are frequently impacted in juvenile gliomas. Children's gliomas most frequently have BRAF, TP53, histone H3, FGFR, and MYB/MYBL1 changed. In vitro models are still essential for examining the molecular processes that underlie tumour development, for detecting genetic and epigenetic alterations in cancer cells, and for predicting how well malignancies will respond to various treatments. Basic in vitro models used to study paediatric brain malignancies include cell lines derived from mice or humans as well as primary cells such neutrosphere cultures or tumour stem cells. The capacity of the individual cell lines to mimic the genetic properties of the primary tumours from which they were derived or which they are intended to imitate is the most important component for accurate in vitro models. These well-established glioma cell lines' main benefit is that they have well-defined molecular features, providing Information on drug sensitivity that is trustworthy, subtype-specific, extensive, and simple to replicate is helpful in locating new therapeutic targets. The main drawbacks of these models, however, are that they are unable to account for tumour heterogeneity and the tumour microenvironment, which is a crucial component of tumour biology. Gliomas and other tumour forms have historically been studied using chemically produced brain

tumours. N-nitro urea and cancer-causing viruses like RSV-1 and human adenovirus are the most common ways to cause brain tumours. A lot of the cell lines obtained from brain tumours produced in mice and rats include In general, these cell lines have undergone numerous passages. From the initial malignancies' genetic deviation the main flaws of these models are their degrees of phenotypic homogeneity. Patient-derived cell lines serve as the overcoming models.

# CONCLUSION

The PLWH whose statements were chosen to represent the entire group were identified by the writers. The commonality of the patients' most frequent responses is used to make this determination. The replies are their presumptions regarding the physical/behavioral, social/ emotional, cultural/historical, and spiritual components of the body, life, and power of clinical participants. This is done in order to guarantee the subjectivity of writers in directing research results connected to the legitimacy and accuracy of the findings. The Indonesian Psychological Association's Code of Professional Ethics for Psychologists and Psychology Scientists, as well as the institutional and/or national research committee's ethical guidelines, were followed in all procedures involving human subjects in this study.

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