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REVIEW ARTICLE OPEN

Translational Therapeutics

Paediatric therapeutic development workshop on medulloblastoma

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The second Paediatric Therapeutic Development Workshop focused on medulloblastoma. Between 60–70% of patients with medulloblastoma survive, but survivors have significant long-term side effects, and the highest-risk groups have a probability of survival <10%. Thus, the unmet need is to develop therapeutics targeting specific vulnerabilities in medulloblastoma including poor prognosis disease groups (SHH-medulloblastoma, *MYCN* amplified or *TP53* mutated; and Group 3 medulloblastoma, c-*MYC* amplified) and developing less-toxic therapies for good prognosis disease (WNT-medulloblastoma). The Workshop concluded that (i) targeting SRC by a degrader is a high priority, (ii) inhibition of c-*MYC* and *MYCN* tumour-relevant functions for poor prognosis groups is a priority, (iii) targeting WNT-medulloblastoma via a radiolabelled theranostic antibody is an innovative approach for good prognosis tumours to further reduce toxicity, and (iv) B7-H3 has many advantages for CAR T-cell and ADC-based approaches. Based on currently available evidence, combinations of central nervous system penetrant selective PARP-1, CHK1/2 or CDK9 inhibitors with an ATR inhibitor could potentially be evaluated in early-phase trials for high-risk patients; however, these combinations require robust evaluation in pre-clinical models first. Early-phase clinical studies should be international, have novel designs to address small patient numbers and based on an understanding of biology with correlative biological studies. Both developing therapeutics targeting specific vulnerabilities in medulloblastoma and evaluating combinations of existing medicinal products are required to improve outcome and reduce long term sequalae.

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INTRODUCTION

The second in a series of LifeArc Paediatric Therapeutic Development Workshops [1] aimed to understand unmet treatment needs in medulloblastoma and identify priorities for therapeutic development, particularly for those subtypes with the poorest prognosis. Medulloblastoma is an embryonal tumour of the central nervous system (CNS) localised within the posterior fossa. It is the second most common malignant brain tumour in childhood, after high-grade glioma (including diffuse midline glioma), accounting for approximately 20% of all childhood tumours [2] with an annual incidence of 4–5 cases per one million children [3]. The median age of children at diagnosis is 5–7 years, with most patients presenting with the disease before the age of 16 years [3]. It is more common in males, with a male: female ratio of 1.7:1 [4].

Using a combination of surgery, radio- and chemotherapy, 60–70% of patients diagnosed with medulloblastoma survive the disease, but there are substantial differences in the outlook and relapse patterns for different subgroups [5–7]. Even in those with optimal outcomes, survival comes at the cost of life-long toxicities. Around 80% of survivors experience treatment-related morbidity with long-term neurologic, cognitive and endocrinological adverse events [8]. This presents two key challenges in medulloblastoma treatment: 1) to provide therapeutic options for all subtypes and 2) to reduce treatment's long-term impact.

To map therapeutic unmet needs and prioritise targets for drug discovery and development, detailed diligence of potential targets, including biological rationale, strength of target validation, tractability, and existing commercial development, was carried out. This was followed by a Workshop with the goals to share and discuss the scientific evidence and drug development status of the different therapeutic targets in medulloblastoma with international experts, prioritise targets based on their level of validation and tractability, and discuss potential drug combinations to progress into clinical trials.

The workshop was organised by the Childhood Cancer Translational Challenge of LifeArc (a self-funded, not-for-profit medical research organisation and charity), ITCC (a clinical trials network focused on delivering new treatments for children and adolescents) Cancer Research UK (a medical research charity), and their translational arm Cancer Research Horizons and the Cancer Grand Challenges PROTECT team. Following the workshop, future therapeutic development of any target could progress via C-Further, the LifeArc-Cancer Research Horizons Children's Cancer Therapeutics Consortium (https://www.c-further.org/) which provides funding and drug discovery laboratory support to de-risk early stage therapeutic projects. It is envisioned that this consensus would be of strategic value to academic, industry, regulatory, charity and patient advocate global communities to focus resources for development. This article summarises the prioritisation decisions and overarching recommendations from workshop participants.

BACKGROUND

Medulloblastoma is a highly heterogeneous cancer and has been classified into four principal molecular groups based primarily on gene expression and DNA methylation profiles in the current WHO classification: 1) Wingless (WNT)-activated medulloblastoma, 2) Sonic Hedgehog (SHH)-activated medulloblastoma, *TP53* wild-type, 3) SHH-activated medulloblastoma, *TP53* mutated and 4) non-WNT/non-SHH medulloblastoma (comprising classical Group 3 and Group 4) [6].

The WNT- and SHH-activated medulloblastomas respectively result from activating mutations in the WNT and SHH signalling pathways, and SHH-activated medulloblastoma can be further divided into four distinct subgroups with different clinicopathological and genetic features [9]. By contrast, the molecular origin of non-WNT/non-SHH (Group 3 and 4) medulloblastoma is less clear. These tumours can be further differentiated by DNA methylation profiling into eight molecular subtypes (Table 1) [10, 11].

Research conducted over the last 20 years has led to the identification of clinical low-risk groups, such as WNT-activated medulloblastoma and SHH-activated TP53 wild-type (WT) medulloblastoma occurring in infants (under 3–5 years at diagnosis) that can receive reduced-intensity treatments [12]. Equally, the study of the disease has helped further molecular characterisation of very high-risk groups, such as SHH-activated, TP53 mutated medulloblastoma with *MYCN* amplification and Group 3 medulloblastoma with c-*MYC* amplification, which have a low probability of overall survival (0% and 10% respectively) [13].

However, the biology of these high-risk tumours is not yet fully elucidated, making the identification of therapeutic targets challenging and as yet, no targeted treatments have been approved. In addition, disease models for many medulloblastoma subtypes, particularly Group 4, are scant and, in some cases, challenging to grow in the laboratory. The use of patient-derived xenograft (PDX) models may aid therapeutic discovery.

Recently, it has been found that oncogene aberrations show different levels of clonality and may not be involved in tumour initiation, yet are essential for disease progression and therapy resistance [14, 15], highlighting the need for careful target selection. Moreover, due to the inter-tumoral heterogeneity of medulloblastoma, new therapeutic agents would need to be adequately stratified to test hypotheses and maximise benefit, and the rarity of the indication means clinical trials need to be conducted at multiple geographical locations. This requires collaboration across the medulloblastoma scientific community and with drug development partners.

For patients and caregivers, increasing survival, particularly in the high-risk groups for patients with recurrent disease or metastatic foci, and reducing long-term sequelae is very important. A combination of new treatment modalities and better delivery methods to achieve CNS penetration need to be explored to achieve this, with potential late-effects and the impact of survivor quality of life taken into account when developing and testing new treatment options, both pre-clinically and clinically.

BIOLOGY OF MEDULLOBLASTOMA GROUPS AND SUBGROUPS

The different medulloblastoma subtypes display considerable biological heterogeneity and complexity. For example, expression of c-MYC is as high in WNT-activated medulloblastomas as in Group 3 tumours, but increased expression in the former is associated with good prognosis and the latter with poor prognosis, further highlighting the need to stratify treatment according to detailed molecular profiling.

WNT-activated medulloblastoma

WNT-activated medulloblastomas transcriptionally resemble normal progenitor cells from the lower rhombic lip [16, 17] and are characterised by activating mutations in the WNT pathway. WNT pathway activation increases cellular levels of β-catenin, which subsequently upregulates genes involved in cell differentiation, proliferation and migration [18]. Over 90% of WNT-activated medulloblastoma cases harbour an activating mutation in *CTNNB1*, the β-catenin gene, causing its accumulation and sustained activation of WNT target genes [19]. In most other cases, germline mutations are present in APC, which forms part of the complex that regulates β-catenin [20].

WNT-activated medulloblastomas secrete WNT antagonists that prevent blood-brain barrier formation and have an aberrant tumour blood vessel phenotype [21], which is thought to contribute to the very good prognosis of WNT-activated medulloblastomas by allowing chemotherapy to reach and

Table 1. Epidemiology, clinical features, biology, and molecular features according to molecular subgroup.

Molecular group	WNT-activated	SHH-activated					Non-WNT/non-SHH (Groups 3 and 4)							
Incidence	10% of all MB	30% of all MB					60% of all MB							
Location	Dorsal brainstem	Cerebella hemisphere					Cerebellum midline							
Presentation	Symptoms and signs of raised intracranial pressure from non-communicating hydrocephalus due to occlusion of the fourth ventricle by primary tumour													
	Rare leptomeningeal spread	Leptomeningeal spread frequent in *TP53* mut					Metastatic disease present at diagnosis in 40% of group 3 in infants and 50% of patients in non-WNT/non-SHH subgroups 2–5							
Aetiology	Mostly sporadic Turcot syndrome (APC)	Predisposed by several hereditary tumour syndromes: *TP53* WT: naevoid basal cell carcinoma syndrome (Gorlin syndrome) *TP53* mut: germline *TP53* point mutations (Li-Fraumeni syndrome)					Very little known; generally not associated with known hereditary tumour syndromes							
Molecular subgroups	n/a	SHH-1/ SHH-beta	SHH-2/ SHH-gamma	SHH-3/SHH-alpha		SHH-4/SHH-delta	1	2	3	4	5	6	7	8
		TP53 WT	*TP53* WT	*TP53* WT	*TP53* mut	*TP53* WT								
Age	Child	Infant	Infant	Child	Child	Adult	Group 3 – infant/child Group 4 – all ages (peak incidence 5-15 years)							
Sex M:F	1:2	1:1	2:3	1:1	4:1	4:3	3:2	3:1	3:1	2:1	3:1	2:1	2:1	3:1
Proportion of subgroup (%)	n/a	15–20	15–20	20–25	10–15	30–35	3–5	10–15	10–15	8–10	8–10	8–10	15–20	25-28
Prognosis	Very good	Variable	Good	Good	Poor	Intermediate	*TP53* mutated medulloblastoma with *MYCN* amplification 0% OSI Group 3 medulloblastoma with *MYC* amplification very poor outcome Distant CNS metastases are almost always present at time of recurrence. Group 3 has a poor outcome overall Chromosome 7 +, 8-, 11- and 17+ are markers of favourable outcome. Subgroups 2 and 3 are associated with poor outcomes; subgroups 4, 6 and 7 with better outcomes.							
	Very good overall, both for tumours with germline *APC* mutations and those with *CTNNB1* mutations (80% of WNT-MB). *TP53* mut does not confer poor prognosis. Metastases are rare.	Intermediate overall compared with WNT- and non-WNT/non-SHH groups. Highly variable, associated with specific clinicopathological and molecular features. Metastatic disease, TP53 mutation and MYCN amplification independently associated with poor prognosis in non-infant children and adolescents. In the absence of these high-risk features, non-infant children and adolescents have better outcomes than other age groups													
Relapse pattern	Mostly in lateral ventricle [121]	Local [122, 123]					Metastatic [122, 123]							
Five-year OS	>90%	70% *TP53* mut: 40%, *TP53* WT:80%					~75%	~55%	~45%	~85%	~60%	~80%	~85%	~75%
							TP53 mutated with *MYCN* amplification 0% OS Group 3: 50% - with *MYC* amplification 10% OS, Group 4: 75%							
References	[2–13, 121–123].													

APC adenomatous polyposis coli gene, *CNS* central nervous system, *CTNNB1* catenin beta 1, *MYC* MYC oncogene, *MB* medulloblastoma, *OS* overall survival, *SHH* Sonic Hedgehog, *TP53* tumour protein p53, *WNT* Wingless 1.

achieve high concentrations within the tumour. However this group also has the same substantial side effects from conventional therapies as other groups.

SHH-activated medulloblastomas

SHH-activated medulloblastomas arise from granule cell progenitors and granule cells in the upper rhombic lip [22–24] and are characterised by gene mutations or copy number alterations in the SHH pathway.

The most frequent alterations in SHH-activated medulloblastoma are loss-of-function mutations or deletions in the Patched transmembrane receptor gene *PTCH1* (44-45% of cases), activating mutations in the G-protein-coupled receptor, Smoothened (*SMO*; 11-14% of cases), loss-of-function mutations in *SUFU* (8-11%, which represses the Gli family) or activating mutations in *GLI2* (8-11% of cases) [25]. *SMO* and *SUFU* mutations are rare in children and adolescents (SHH-3 subgroup) but are highly enriched in infants (SHH-1 and 2 subgroups) [6]

Other mutations occurring independently of the canonical SHH pathway include those in *GNAS* and *PRKAR1A*, found in 4.4% and 2% of cases, respectively, which both influence Gli2 activity and may indicate an alternate route for medulloblastoma formation [26].

Most efforts in developing targeted therapies for SHH-activated medulloblastomas have focused on targeting SMO but reports of skeletal growth inhibition in children prompted safety concerns, and the development of vismodegib for paediatric medulloblastoma was terminated on this basis [27, 28].

Non-WNT/non-SHH medulloblastoma

The non-WNT and non-SHH-activated medulloblastomas (Group 3 and 4) are defined by exclusion of tumours with activating mutations in the WNT or SHH pathways. While the cell of origin is unclear, it is thought that Group 3 tumours arise from undifferentiated neural progenitors and Group 4 tumours arise from unipolar brush cells [22, 29, 30].

At a transcriptional as well as epigenetic level Group 3 and 4 tumours appear akin to a continuum with intermediate phenotypes [29] rather than belonging to dichotomous groups. However, some recurrent mutations do occur at low frequencies. For example, *MYCN* amplifications occur in around 5% of cases in both Group 3 and 4, but do not share the poor prognosis of *MYCN*-amplified SHH medulloblastomas [31, 32]. The transcriptional repressor homologues *GFI1* and *GFI1B* are also activated in around 15% of Group 3 and 4 tumours [33] Chromosome 17 abnormalities are common in both groups [34] – up to 55% of group 3 tumours and 85% of Group 4. Amplifications of *c-MYC* have been reported in 17% of group 3 tumours and are associated with poor prognosis [35].

While there is no strong evidence of a genetic predisposition to Group 3 or 4 tumours, germline mutations in *CREBBP* [19], *PALB2* and *BRCA2* [36] have been reported in a small proportion of cases and may be clinically actionable.

Overall, the Group 3 and 4 tumours are poorly understood, with ~50% having no known driver other than large-scale copy-number aberrations, and there are few preclinical models and targeted therapeutics in development. Research tends to focus on *c-MYC*-driven biology, which accounts for less than a fifth of the subgroup, highlighting a need to diversify and broaden knowledge of this subgroup, an area of high unmet need within a cancer type of high unmet need.

THE MEDULLOBLASTOMA PAEDIATRIC THERAPEUTIC DEVELOPMENT WORKSHOP

To support discussions around unmet needs and research priorities in medulloblastoma, LifeArc produced a detailed diligence document covering the biology, epidemiology, clinical features, therapeutic targets, preclinical models, drug discovery pipeline and clinical development pipeline in medulloblastoma. This was circulated to participants ahead of the workshop.

A therapeutic target list was produced from screening GlobalData pipeline databases, supplemented with literature searches to identify preclinical and clinical evidence for each target's association with medulloblastoma. From an initial list of 93 targets, 64 were prioritised for which no evidence of active clinical development in medulloblastoma could be found (Supplementary Table 1). LifeArc circulated a list of targets to the workshop participants and a list of drugs currently in development for medulloblastoma (Supplementary Table 2). Participants were then asked to select the six most relevant targets that i) had some level of preclinical validation in the indication; ii) were tractable in principle; iii) for which the optimal therapeutic did not yet exist; iv) address a high unmet need within medulloblastoma and v) had the highest potential for drugs against them being effective in this indication. Submission of additional targets not identified in pipeline and literature searches by participants was encouraged, along with a supporting literature citation. To ensure broad coverage of discussion, targets were selected with differing extents of supportive validation data and existing drug development programmes (Table 2). Potential conflicts of interest were noted by the organisers of the workshop and taken into account during discussions. Moreover, all conclusions of workshop were a consensus of all participants to address this issue.

Based on the expert opinion of the authors, five targets were selected for more detailed discussion at the workshop (see below). Whilst the focus of discussion was on the rationale and validation data for each target, it was noted that novel therapeutics were unlikely to be developed as a monotherapy, and that interplay with existing treatment modalities (such as radiotherapy) should be considered in preclinical modelling and clinical trial design.

In addition to the five shortlisted targets, the workshop participants also discussed the most promising targets for immunotherapies in medulloblastoma, opportunities to improve on WNT-activated medulloblastoma treatment, and potential new drug combinations that would merit preclinical and clinical exploration.

MEDULLOBLASTOMA TARGETS DISCUSSED IN THE WORKSHOP

The targets discussed at the workshop were *c-MYC, MYCN, SRC, OTX2 and GLI1/GLI2*.

c-MYC

c-MYC-amplified medulloblastoma is mostly subclonal at diagnosis, but is well-investigated, facilitated by an abundance of appropriate preclinical models [37], and preclinical data consistently show that growth of *c-MYC*-driven medulloblastoma models is dependent on *c-MYC* activity [38–43].

c-MYC's lack of conventional drug binding sites, ubiquitous expression and pivotal role in development have prioritised targeting indirect downstream effects of c-MYC as the preferred strategy to date [44–46]. Indirect strategies discussed at the workshop included targeting the dependency of c-MYC on the non-coding *PVT1* gene for stability, targeting replication stress present in c-*MYC*-amplified tumours and exploring c-MYC's role in the microenvironment.

As c-MYC-bound promoters can be low- or high-affinity [47], and the number of c-MYC molecules is often much higher in tumour than normal cells [48], it may still be possible to target *c-MYC*-amplified tumour cells directly.

c-MYC-targeted drugs in development include small-molecule inhibitors, transcriptional inhibitors and PROTAC/molecular glue degraders, and participants emphasised the need for preclinical studies comparing these modalities in medulloblastoma.

Table 2. Summary of prioritisation of targets.

Prioritisation	Target	Existing therapeutic programmes	Rationale/validation/tractability/commercial assessment	Recommendations	References
1.	c-MYC	4 clinical stage: • IDP-121 (NCT05908409) • OTX-2002 (NCT05497453) • ES-4000 • OMO-103 39 preclinical stage, including two dual c-MYC/MYCN inhibitors: • UNSW-SC-22 GT-19870	• Amplifications observed in ~ 17% Group 3 and less frequently in SHH and Group 4 tumours • Tumours with *c-MYC* amplification have very poor prognosis • Validated genetically in vivo and in vitro, but mostly targeted indirectly • No approved therapeutics targeting c-MYC directly • Classically "undruggable" transcription factor, but high number of development programs suggests alternative strategies are feasible	• Ongoing efforts including: small molecule inhibitors, peptides, PROTACs, oligonucleotides and genetic/epigenetic therapies should be monitored for promising activity • Blood brain barrier penetrance an important consideration	[44–48, 124–127]
2.	Src	3 marketed tyrosine kinase inhibitors • dasatinib • nintedanib • repotrectinib 2 other clinical stage: • elzovantinib • FNX-006 • MH-048 • saracatinib	• Src activation is a hallmark of Group 4 medulloblastoma, a subtype with no targeted therapeutics • Some validation in vivo and in vitro, mostly Group 4 models, pharmacological inhibition only leads to stunted cell proliferation • 15 Src inhibitors in active development. Inhibitors limited to due to broad tyrosine kinase inhibition • Next-generation inhibitors are not Src specific (all are broad tyrosine kinase inhibitors) • Development of selective inhibitors is challenging due to high sequence homology and structural similarity within this family • Side-effects of Src inhibitors include growth delay and general intolerance issues	• A Src-selective degrader should be developed and evaluated for more complete functional inhibition • Validation should be performed in Group 4 models (even if slow to grow, as this accurately reflects disease course)	[59–63, 128]
3.	OTX2	• No programmes in development targeting OTX2 - a transcription factor with no active druggable sites	• OTX2 overexpressed in WNT and non-SHH/non-WNT MB (80% of Group 3) but amplification is rare • All-trans retinoic acid (ATRA) only pharmacological agent known to reduce OTX2 expression • In vivo i) siRNA/shRNA knockdown reduces viability and proliferation, may induce cell differentiation; ii) ATRA reduces viability. In vivo shRNA knockdown in xenograft model extends survival • However, isotretinoin had no effect on event-free survival across high-risk medulloblastoma molecular groups when added to maintenance in Children's Oncology Group ACNS0332 • Structural data on human OTX2 limited to AlphaFold prediction (mouse OTX2 data available) • Potential toxicity issues as total loss is embryonic lethal but ATRA is tolerable	• Unclear if OTX2 is druggable – no tool compounds available • Evaluation of expression of OTX2 in tumour material from ACNS0332 would be valuable. however, results of ACNS0332 are not encouraging	[64–66, 129–135]

Table 2. continued

Prioritisation	Target	Existing therapeutic programmes	Rationale/validation/tractability/commercial assessment	Recommendations	References
4.	Gli1/2	1 clinical stage: • FLD-103 5 preclinical stage: • HH-201 • NP-101 • Small molecule programme at North Carolina Central University • Small molecule programme at Southern Research Institute • Small molecule programme at Lead Discovery Center GmbH	• Gli1/2 alterations (mostly amplifications) occur 9-13% of SHH-activated medulloblastoma associated with poor survival. • Smoothened (SMO) inhibitors targeting another downstream signalling molecule of the pathway are associated with skeletal growth delay in paediatric patients • Genetic/pharmacological validation of GLI1, limited validation of GLI2 • No marketed therapeutics targeting GLI1 or GLI2 • Six programmes in active development	• Gli1/2 inhibitors likely to also produce skeletal growth delay, so do not address unmet need and therefore are not a priority	[136–148]
5.	MYCN	1 clinical stage: • SACT-1 (NCT05358756) 7 preclinical stage, including two dual MYC/MYCN inhibitors: • UNSW-SC-22 • GT-19870	• SHH-medulloblastoma, *MYCN* amplified, TP53 mutated associated with a poor prognosis • Limited preclinical validation available in medulloblastoma models • No approved therapeutics. Nine therapeutics in development, mostly in preclinical stages, one compound) at clinical level, but only tested in healthy adult volunteers. Two dual MYC/MYCN inhibitors in development • Classically "undruggable" transcription factor but being explored in Cancer Grand Challenge • Indirect targeting approaches are available	Initiatives developing direct inhibitors should be monitored for promising activity	[31, 32, 35, 40, 49–58, 149–153]

c-MYC is a high-priority target, and its amplification confers a very poor prognosis. The target is well-validated in vitro and in vivo. Despite it being a classically undruggable transcription factor, there are numerous drug development programs (Table 2). Additional effort to target c-MYC for medulloblastoma would likely be fruitless in view of the substantial number of ongoing programs, unless a clear and distinctly druggable aspect of c-MYC biology is identified to be of high relevance to medulloblastoma. Existing programmes should be monitored, and if a promising therapeutic is developed, then this should be evaluated, acknowledging the importance of blood-brain barrier penetration.

MYCN

MYCN amplification is seen in SHH-activated and Group 3 and 4 medulloblastomas and associated with poor prognosis in SHH only [31, 32, 35]. Unlike c-MYC, there is a relative lack of preclinical models—only two MYCN-positive lines [49–51] and two Group 4 cell line models – and few preclinical studies. Efforts targeting MYCN to date have focused on transcriptional silencing with short interfering RNA (siRNA) [52–54] or short hairpin RNA (shRNA) [55], or indirect targeting using PI3K/mTOR inhibitors to reduce MYCN stability [56], alone or in combination with BET inhibitors [57, 58].

There are no approved therapeutics targeting MYCN; eight are in active development, mostly in preclinical stages (Table 2). One compound is at the clinical level but has only been tested in healthy adult volunteers. There are two dual c-MYC/MYCN inhibitors, one of which has been highlighted as potentially useful in Group 3 and 4 medulloblastoma. Dual targeting could offer a simplified clinical strategy, allowing pooling of c-MYC/MYCN tumours for clinical trials, and preventing one paralogue compensating for the other. However, more specific inhibitors may be desirable to avoid on-target toxicities.

SRC

Higher levels of conformationally active SRC have been suggested as a hallmark of Group 4 medulloblastoma [59], with studies showing that SRC stimulatory phosphorylation is upregulated in medulloblastoma patient samples [60, 61], and that SRC protein and mRNA levels are significantly enriched in Group 4 tumours, as well as SRC-activating enzymes, PTPN11 and PKA [59]. Constitutive activation of Src in combination with Tp53 inactivation in the murine cerebellum was also sufficient to induce tumours resembling medulloblastoma, suggesting that SRC could be a driver for the disease [59].

In vitro, pyrimidine derivatives and dasatinib induce cytotoxic effects and reduce viability of cell lines (SHH, G3, G4) and in vivo, they reduce tumour burden in xenograft and syngeneic mouse models (SHH models only) [61, 62].

SRC family kinases are known to be druggable, with several broad spectrum, not selective, small molecule inhibitors approved for oncology indications, including in paediatric populations where they are regarded as tolerable but with significant room for improvement (Table 2).

Most current SRC drug development activity is focused on expanding the current generation of inhibitors beyond oncology [63], but there are also next-generation SRC inhibitors being developed that broaden specificity to other SRC family kinases or are exploring other mechanisms such as locking SRC in an inactive conformation.

Orthodenticle homeobox 2 (OTX2)

OTX2 is a homeodomain-containing transcription factor involved in brain and sensory organ development [64]. Eighty percent of Group 3 medulloblastomas are reported to have overexpressed *OTX2* [65], and ~21% *OXT2* gain. Roles for OTX2 in SHH-dependent medulloblastoma have also been reported preclinically [66], raising the possibility that OTX2 could be a therapeutic target across all medulloblastoma subgroups.

With no OTX2-specific tool compounds available, target validation work has been limited to genetic knockdown studies, and a lack of in vivo models also means there is limited data on the toxicity effects of targeting OTX2.

OTX2 is conventionally considered undruggable because of its lack of active sites, and its nuclear localisation precludes antibody-based therapeutics. Limited structural information is available, comprising NMR assessment of mouse Otx2 and predicted or modelled structures of human OTX2, with which it may be possible to rationally design protein degraders or small-molecule DNA interaction inhibitors.

Although there are no compounds targeting OTX2 in development, a recombinant OTX2 product in preclinical development for glaucoma and retinoblastoma may provide insights into the tolerability of targeting this pathway.

GLI1/GLI2

The GLI family are downstream transcription factors within the SHH signalling pathway and are known to exert the tumorigenic effects of altered upstream proteins [67–69], but they are also effectors of non-canonical SHH signalling pathways involved in medulloblastoma [70]. GLI1/2 alterations, predominantly amplifications, are observed in approximately 9-13% of SHH-activated medulloblastoma cases [26] and are associated with poor survival [71].

Target validation data is very limited and mostly relates to GLI1. Three studies demonstrated antitumour effects of targeting GLI1 in SHH-activated medulloblastoma mouse models using a small molecule inhibitor, nanoparticles containing a Gli1 antagonist, and loss-of-function mutation approaches [72, 73]. Transient knockdown of GLI2, but not GLI1, reduced cell proliferation in SHH-activated medulloblastoma cell lines [71], while a dual GLI1/2 inhibitor significantly inhibited proliferation and induced apoptosis of SHH-activated medulloblastoma cells in vitro [74]. Given that Gli2 can rescue the effects of Gli1 knockout in mice, targeting Gli1 alone may not be sufficient.

There are six active GLI-targeted programmes, including 1 clinical and 5 preclinical (Table 2). One of the main limitations is brain penetrance, but brain biodistribution has been demonstrated with some novel GLI1/2 inhibitors [75]. Overall, the consensus was that GLI1/2 inhibitors are likely to also produce skeletal growth delay due to effects on skeletally immature growth plates, as with SMO inhibitors so it may not be appropriate for development.

PRIORITISATION OF TARGETS

The participants at the workshop ranked the target priority list based on previously published methodologies [76, 77]. The greatest priority was c-MYC; followed by SRC; OTX2; GLI1; and MYCN (Table 2). Initiatives are ongoing to target c-MYC and MYCN both directly and indirectly. There is evidence suggesting that SRC could be a driver for poor prognosis Group 4 medulloblastoma [59], and the overall consensus was that the evaluation and development of an SRC degrader for high-risk medulloblastoma should be a priority.

PROMISING CELL-SURFACE TARGETS

Given the low mutational burden and variable levels of immune cell infiltration in most paediatric cancers [78, 79], the workshop discussion on immunotherapies focused on targeting cell-surface antigens. Participants were asked to consider the target expression profile in medulloblastoma subtypes, tumour expression homogeneity, normal tissue expression profile, preclinical evidence and clinical experience, resulting in a shortlist of six

potential targets to pursue. At present the relative benefits of administration of CAR T-cells ADC or bispecific antibodies to CNS tumours by intratumoral, intraventricular or intravenous routes are unclear. Despite the challenges of blood-brain barrier penetration, tumour responses can be observed after intravenous administration.

GD2

GD2 is a disialoganglioside highly expressed in multiple cancers, including all medulloblastoma subtypes, with limited expression in normal tissues [80]. A preclinical study of GD2-directed CAR T-cell therapy-controlled tumour growth and prolonged survival in orthotopic mouse models of medulloblastoma [81]. A Phase I/II clinical trial is ongoing to evaluate the safety and therapeutic efficacy of GD2 CART-cell therapy, delivered intravenously, in high-risk medulloblastoma patients [82].

B7-H3 (CD276)

B7-H3 is an immune checkpoint molecule expressed on the surface of T and B cells and non-immune cells [83]. There is limited data on subtype-specific expression, but it appears to be most frequently expressed on Group 4 medulloblastomas [84] and is found homogeneously within tumours [85]. Preclinical testing of B7-H3-directed CAR T therapy demonstrated significant antitumour activity in orthotopic xenograft models of medulloblastoma, dependent on surface antigen density [86]. Clinical experience, in solid tumours and diffuse midline gliomas, but not medulloblastoma, with B7-H3 antibodies [87] and intraventricular and intravenous CAR T-cell therapies [88, 89] suggest they are well tolerated and have shown early signals of efficacy.

Human epidermal growth factor receptor-2 (HER2/ERBB2)

A proven target for the breast cancer drug trastuzumab [90], HER2 is expressed at lower levels on medulloblastoma cells than in breast cancer but has been related to poor clinical outcome, particularly when co-expressed with HER4 (*ERBB4*) [91, 92], but may still provide a therapeutic window [93]. Moreover, in breast cancer, even very low expression of HER2 has been associated with response, so the lower level of expression in medulloblastoma may not be an issue depending on the mode of targeting [94]. HER2-directed CAR T-cells administered to orthotopic medulloblastoma xenograft mouse models via both regional and intravenous routes effectively cleared tumours, and intraventricular delivery of HER2-directed CAR T-cells to non-human primates was well tolerated [95].

HER2 CAR T-cells are also showing clinical promise in adults with glioblastoma [96] and advanced sarcoma [97]. In the paediatric context, an interim report of an ongoing Phase 1 clinical trial (BrainChild-01) evaluating repetitive locoregional dosing of HER2-specific CAR T-cells to children and young adults with recurrent/refractory CNS tumours suggests that repeated intra-CNS delivery might be well tolerated and activates a localized immune response [98].

Other strategies for HER2 include using T-cell engagers to augment tumour killing by combining the direct antitumour effects of targeting HER2 with proinflammatory effects of T-cells, as demonstrated in a humanized mouse model of breast cancer [99]. The challenge with the ADCs targeting HER2, such as trastuzumab deruxtecan and trastuzumab emstantine, which are widely used in breast cancer, is their lack of CNS penetrance, which are a general feature of ADCs.

Ephrin receptor A2 (EphA2)

EphA2 is a protein tyrosine kinase expressed in primary and recurrent WNT-activated and Group 3 medulloblastomas [100]. Preclinical studies have demonstrated efficacy of intrathecal delivery of EphA2 CAR T-cells in primary, metastatic and recurrent Group 3 medulloblastoma PDX mouse models [101] and of intracranial delivery to glioma xenografts in severe combined immunodeficiency (SCID) mice [102]. In the clinic, EphA2-directed ADCs, given intravenously, and peptide conjugates have had mixed results; an ADC study closed following haemorrhagic events [103] and it is unknown if these adverse events were due to target-intrinsic effects of EphA2 or due to the ADC payload, while a peptide conjugate (given intravenously) appears to have a better safety profile [104].

Interleukin-13 receptor subunit alpha-2 (IL13RA2)

IL-13Rα2 is a membrane receptor for the anti-inflammatory cytokine IL-13 that is overexpressed in Group 3 and 4 medulloblastomas [101]. Intrathecally delivered IL-13Rα2-directed CAR T-cell therapy showed efficacy in a Group 3 medulloblastoma patient-derived xenograft model [101]. Intratumoral and/or intraventricular delivery of IL-13Rα2-directed CAR T-cell therapy in adults with relapsed high-grade glioma was shown to be tolerable and positively associated with survival [105].

GPC2

Glypicans are cell-surface glycoproteins functioning as coreceptors for signalling molecules involved in regulating cell growth, motility and differentiation [106]. mRNA analysis has shown that *GPC2* is expressed in all medulloblastoma subgroups, with slightly higher expression in Group 4 [107]. One preclinical study has shown efficacy of intra-tumoral GPC2-targeted CAR T-cell therapy in a medulloblastoma PDX model [107], and an open-label Phase I study (NCT05650749) evaluating GPC2 CAR T-cells, given intravenously, is currently recruiting children and adults with high-risk neuroblastoma.

Table 3 summarizes the expression profile of these cell-surface targets in medulloblastoma and normal tissues.

IMPROVING TREATMENT OF WNT-ACTIVATED MEDULLOBLASTOMA

Patients with WNT-activated medulloblastoma consistently show a favourable prognosis (>90% survival) to standard treatment strategies but are left with long-term secondary effects that impact quality of life, and there is a need to explore treatment reduction or less toxic alternatives.

Several WNT inhibitors are already in development but pursuing this pathway in children carries the risk of long-term toxicities, particularly neurodevelopment disorders [108]. Moreover, the majority of WNT medulloblastomas are driven by activating mutations in molecules downstream from WNT itself – *CTNNB1*, *APC* and *CDH1* [19] – so inhibitors developed upstream in the WNT pathway would have no effect.

A unique opportunity in WNT-activated medulloblastoma is that the blood-brain barrier is disrupted [21], making it amenable to systemic infusion of large molecules that would not otherwise traverse the barrier. One study has used plasma proteome profiling to identify cell-surface antigens in WNT-activated medulloblastoma with the aim of developing a theranostic antibody with the potential to avoid or reduce surgery and chemoradiotherapy [109]. However, the blood-brain barrier penetration of the antibody and the tolerability of local toxicity (such as necrosis and oedema) need to be determined. Other approaches discussed in the workshop included testing the gamma secretase inhibitor nirogacestat in WNT-medulloblastoma models, which targets the Notch signalling pathway and in turn may influence WNT/β-catenin activity [110]. The consensus was that targeting WNT-medulloblastoma via a radiolabelled theranostic antibody is an innovative approach for good prognosis tumours to reduce toxicity and should be developed.

Table 3. Immunotherapy expression profiles.

	GD2	B7-H3	HER2	EphA2	IL13Rα2	GPC2
Medulloblastoma subtype	100% SHH-MB 64% WNT-MB 77% Group 3 89% Group 4	All MB subtypes Limited data on subtype expression levels	30-40% all MB Limited data on subtype expression levels	WNT-MB Group 3	Group 3 (protein level) Group 4 (mRNA level)	All MB Slightly higher in Group 4
Homogeneity	Intratumoral heterogeneity	Homogeneous	Lower than in breast cancer	Difference in expression level dependent on Group 3 subclass ($\alpha > \gamma > \beta$)	Good level of expression across samples	Variable between samples
Profile in normal tissue	Peripheral nerve tissues Low levels in the brain	Basal squamous epithelium of the skin Inducible in antigen-presenting cells	Low expression in epithelial cells Cardiomyocytes	Vascular endothelium	Testes	Low levels in skin and oesophagus
Reference	[80]	[84–86]	[91, 92]	[100]	[101]	[107]

DRUG COMBINATION STRATEGIES

Biological rationale and published experience indicate that combination approaches will be more efficacious than the same agents used alone. Therefore, there is an increasing need to evaluate innovative drugs for medulloblastoma using combinatorial approaches. A deep understanding of biology is required for the selection of the optimal combination of approaches. However, one barrier is the lack of early-phase clinical trials in medulloblastoma in Europe, particularly for the high-risk groups (SHH-activated, *TP53* mutant medulloblastoma with *MYCN* amplification and Group 3 medulloblastoma, c-*MYC* amplified). Cognisant of this, therapeutics that could feasibly move into clinical trials for medulloblastoma in the short term and have mechanisms of action linked to medulloblastoma biology were considered. Taking into account these principles, targeting replication stress, which is a known vulnerability in high-risk medulloblastoma [111], and indirectly targeting c-MYC and MYCN is the most pragmatic approach in the immediate future.

Although in vitro studies with cell lines and mouse PDX models showed promise [112, 113] where cyclin-dependent kinase (CDK) 4 and 6 inhibitors emerged as potential drug candidates for medulloblastoma, clinical experience has not been promising to date [114].

Histone deacetylase (HDAC) inhibitors that target DNA replication regulators and replication stress are a potential treatment option for medulloblastoma and results are awaited from the PNOC016 trial (NCT03893487) which tested fimepinostat, a dual HDAC and PI3K inhibitor, in patients with recurrent medulloblastoma. Drug combinations including fimepinostat could be explored.

To target replication stress, WEE1 inhibitors have been evaluated in medulloblastoma, but high-risk patient groups were not selected, and responses were equivocal (one of nine patients demonstrated stable disease, and one patient experienced unconfirmed partial response [115, 116].

Small-molecule screening in six human medulloblastoma cell lines has shown that cell cycle checkpoint kinase 1 and 2 (CHK1/2) inhibition synergistically enhances the cytotoxic activity of several chemotherapy drugs and chemoradiotherapy [117] and, based on this work, CHK1/2 inhibition in combination with radiation is a potential frontline therapeutic strategy for patients with SHH-medulloblastoma $TP53^{mut}$ subtype tumours requiring clinical validation. A strategy combining the CHK1/2 inhibitor prexasertib with established DNA-damaging agents is currently being evaluated in the SJELIOT phase 1 trial (NCT04023669) in recurrent or refractory medulloblastoma.

Another approach is to use poly-ADP ribose polymerase (PARP) inhibitors to sensitise tumours to radiation, which has been demonstrated in human medulloblastoma cells and in mouse xenograft models [118], either alone or in combination with ATR inhibitors. CNS-penetrant PARP1-selective inhibitors have recently been developed and are being explored in combination with temozolomide or ADCs for brain tumours [119].

CDK7 and CDK9 inhibitors have also been tested in medulloblastoma and can suppress c-MYC and cell growth [120]. Zotiraciclib, a brain-penetrant CDK inhibitor currently in a clinical trial in adults with glioblastoma (NCT03224104), could also be explored for medulloblastoma, however CDK9 inhibitors with a greater therapeutic index are required [109]. CDK7 and CDK9 inhibitors could potentially be combined with radiotherapy. In summary, there are several potential combination approaches that now require pre-clinical evaluation in medulloblastoma models.

CONCLUSION

Although 60–70% of patients with medulloblastoma survive, survivors have significant long-term side effects, and the highest-risk groups have a probability of survival <10%. Thus, the unmet

need is to develop therapeutics targeting the drivers of medulloblastoma including poor prognosis (SHH-activated, *TP53*^{mut} medulloblastoma with *MYCN* amplification and Group 3 medulloblastoma, *c-MYC* amplified) and developing less-toxic therapies for good prognosis disease (WNT-medulloblastoma).

High-priority targets for poor prognosis disease are c-MYC (although mostly subclonal at diagnosis), SRC and MYCN. Direct targeting of c-MYC and MYCN would be preferred, and multiple drug development programmes are ongoing. The PROTECT and KOODAC Cancer Grand Challenge programmes are focusing on developing degraders against a range of childhood cancer targets, including MYCN. Developing SRC degraders is a high-priority approach for further development and testing in Group 4 medulloblastoma models, as SRC inhibition alone, by small molecule tyrosine kinase inhibitors, is unlikely to be sufficiently active. CAR T-cell therapy and ADCs are the most promising antigen-directed therapies for medulloblastoma, and a series of tumour-specific epitopes for the basis of these approaches have been identified. B7-H3 has advantages including homogeneous tumour expression, limited normal tissue expression and promising clinical data.

Targeting WNT-activated medulloblastoma via a radiolabelled theranostic antibody is an innovative approach in early development to reduce late toxicity in this very good prognosis subpopulation.

Systematic or hypothesis-driven preclinical evidence is required to support the clinical development of specific therapeutic combinations. Based on the mechanism of action and currently available evidence from single-agent studies and other diseases, combinations of either a PARP1-selective CNS-penetrant inhibitor with a CHK1/2 or CDK9 inhibitor or ATR inhibitor require preclinical evaluation in medulloblastoma models and if positive progression to early-phase trials in relapsed poor prognosis patients. Early-phase studies in medulloblastoma need to be designed based on a deep understanding of biology and run with integrated patient group selection and biological studies. Progress in the field will require international studies using novel trial designs to address critical groups with small patient numbers,

Improved understanding of biology, collaboration between international stakeholders and research groups is mandatory to address the challenge in improving outcomes for poor prognosis medulloblastoma.

DATA AVAILABILITY

No new scientific data were generated or analysed for this commentary and all data are within the paper.

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AUTHOR CONTRIBUTIONS

Conception and design: CME, JSB, JJM, IA, SD, LD, and PK, Sheena Patel, ADJP, DJ, FD, and SCC. Collection and assembly of data: JSB, JJM, and ADJP. Data analysis and interpretation: all authors. Drafting manuscript: JSB, ADJP, FD, and SCC. Revising Manuscript: all authors. Manuscript writing: all authors. Final approval of manuscript: all authors. Accountable for all aspects of the work: all authors.

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Claudia Montiel Equihua, Joseph Baxter, Itziar Areso, Geffen Lass and David Jenkinson, are employees of LifeArc. Andrew DJ Pearson is a consultant for LifeArc. All other authors have no conflicts of interest to declare.

ADDITIONAL INFORMATION

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