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Review Article

Targeting the MYCN interaction network in neuroblastoma

Chelsea Xinyi Yow[1], Sharon Yeoh[1,2], Eoin Leen[1,2] and Richard Bayliss[1,2]

[1]School of Molecular and Cellular Biology, Faculty of Biological Sciences, University of Leeds, LS2 9JT, U.K.; [2]Astbury Centre for Structural Molecular Biology, University of Leeds, LS2 9JT, U.K.

Correspondence: Richard Bayliss (r.w.bayliss@leeds.ac.uk)

Neuroblastoma is a common solid tumour in children and accounts for a disproportionate share of childhood cancer mortality. High-risk neuroblastoma is a major clinical challenge, with survival rates below 50% despite intensive therapy. Amplification of the *MYCN* oncogene is a hallmark of high-risk disease. MYCN protein is a transcription factor that promotes proliferation and blocks differentiation. MYCN is often described as 'undruggable' due to its lack of enzymatic activity and intrinsically disordered nature that means it lacks well-defined binding pockets for small molecules. This review explores the molecular interactome of MYCN as an opportunity for therapeutic discovery. We highlight functional and structural features of the interactions with key partners, such as MAX, WDR5, TFIIIC5 and Aurora kinase A. We discuss emerging strategies to disrupt MYCN interactions and to enable its degradation through disruption of protein stabilisation mechanisms or the use of degraders such as proteolysis targeting chimeras. By integrating knowledge of MYCN biology, molecular structures and chemical biology, these approaches provide promising routes towards targeted therapies for *MYCN*-driven neuroblastoma.

Neuroblastoma

Neuroblastoma is an embryonal tumour of the sympathetic nervous system, which arises from primordial neural crest cells (NCCs) and generally results in tumours in the adrenal glands or the sympathetic ganglia [1]. It is a heterogeneous disease in which tumours can spontaneously degenerate or develop, meaning that some neuroblastomas resolve without reason while some mature and spread rapidly [2]. This heterogeneity of neuroblastoma clinical presentation—ranging from asymptomatic benign tumours to aggressive metastases—leads to different prognosis and outcomes [3].

Neuroblastoma is the most common solid extracranial tumour in infants and children, constituting 6%–10% of malignancies diagnosed in paediatric patients. However, it accounts for a disproportionately high percentage of cancer-associated deaths in children at ∼15% [4]. Around 90% of neuroblastomas were diagnosed in children younger than 5 years old, with approximately 30% of these cases reported within the first year, and nearly all cases of neuroblastoma were diagnosed before 10 years of age [5,6]. The median age of neuroblastoma diagnosis is 17–22 months; it is rarely diagnosed in adolescents and adults but, if so, clinical trajectories and prognosis are much poorer for this age group [7,8].

Considering the variability of outcomes, the International Neuroblastoma Staging System (INSS) was designed to stratify patients into groups: low-risk, intermediate-risk, or high-risk. Risk levels are dependent on the patient's INSS stage, age at diagnosis, tumour histopathology, DNA index, and *MYCN* amplification status [9]. However, the scale of surgical resection was taken into consideration in this staging system, which is problematic as it prohibits pretreatment stage classification, thereby making it complicated and non-standardised [10]. Hence, a more specific system called the International

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Neuroblastoma Risk Group Staging System was constructed to better categorise patients based on clinical presentation and tumour biology to determine further therapeutic approaches [11].

Symptoms of neuroblastoma

Neuroblastoma tumours can develop in areas where sympathetic nervous tissues are present [8]. The most common primary tumour site in children is the abdomen, which predominantly affects the adrenal glands, making abdominal mass the most typical symptom of neuroblastoma [8,12]. However, tumours can manifest anywhere along the sympathetic chain, this includes the neck, chest, and pelvis [8]. Up to 60%–70% of neuroblastoma patients exhibit metastatic disease that spreads via both lymphatic vessels and the bloodstream to sites such as the bone marrow, bone, skin, liver, and lymph nodes [13]. Metastases to these sites cause directly linked symptoms such as pancytopenia, bone pain, subcutaneous skin nodules, abdominal distention, and lymphadenopathy [10]. Other symptoms include proptosis, paralysis, diarrhoea, Horner syndrome, fever, and so forth. In rare cases (<5%), neuroblastoma metastasise to the central nervous system and lungs [14]. This illustrates the breadth of neuroblastoma clinical presentation, highlighting the difficulty of accurate diagnosis especially when patients present atypical manifestations (Figure 1).

Low- versus high-risk neuroblastoma

Low- and intermediate-risk patients have approximately 80%–95% event-free survival rate whereas high-risk patients have less than 50% chance of event-free survival, and there is a further group of refractory high-risk patients that are unresponsive to therapy [15]. Treatment is highly dependent on the risk group of the patient; low- and intermediate-risk patients require less aggressive therapy such as surgery, short-term chemotherapy, or radiation therapy [10]. Children with high-risk neuroblastoma require three phases of rigorous and intensive treatment that generally includes: surgery, chemotherapy, radiation, stem cell transplant, immunotherapy, and retinoid therapy [10].

Despite significant improvement in 5-year survival rates from 29% to 50% in the past 20 years, patients with high-risk neuroblastoma still exhibited poor prognosis and have a heightened likelihood of relapse [16,17]. Patients that suffer from relapsed neuroblastoma are rarely cured. This underscores the sharp disparity between low- and high-risk neuroblastoma in terms of treatment approaches and prognosis, emphasising the urgency for effective and long-lasting therapeutic interventions against high-risk neuroblastoma.

Among patients with high-risk neuroblastoma, *MYCN* amplification was found to be a driver of aggressive disease progression, making it one of the most powerful markers of poor prognosis [18]. This demonstrates the relationship between *MYCN* amplification and the progression to high-risk neuroblastoma. Hence, targeting and inhibiting *MYCN* amplification may provide a strategy to achieve better therapeutic outcomes for high-risk neuroblastoma [17].

MYCN and MYC

MYC proteins are a family of transcription factors comprising three paralogs *MYC*, *MYCL*, and *MYCN*. They have physiological functions in development and tissue homeostasis [19]. These proteins become oncogenic through a plethora of mechanisms, including gene amplification, chromosomal translocation, enhancer dysregulation, signalling-driven activation, protein stabilisation and, rarely, point mutations [20,21]. Of the samples investigated in the Pan-Cancer Atlas (<9000 samples covering 33 tumour types) 28% had *a MYC* paralog amplification [22]. The oncogenic functions of MYC proteins are thought to be primarily, though not exclusively via amplification of existing transcriptional programs [23–25]. This can involve activation or repression of target genes that are required for diverse biological processes, such as proliferation, metabolism, differentiation, apoptosis, resulting in aberrant dysregulation of these processes [19,26,27].

The fundamental nature of MYC function is conserved through evolution, as most clearly demonstrated through studies on the cnidarian Hydra [28]. The structure and biological functions of *MYC* and *MYCN* are similar; they are highly homologous, and encode for gene products of similar sizes that share conserved regions for DNA–protein and protein–protein interactions [29]. However, *MYC* and *MYCN* differ in their spatiotemporal expression. Studies on the three mouse *MYC* paralogs show that while *MYCN* and *MYCL* have specialised roles in restricted tissues and developmental stages, *MYC* has a more generalised role [30]. Homozygous deletion of either *MYC* or *MYCN* in mouse embryonic stem cells did not result in uncontrolled proliferation or differentiation, indicating redundant functions [29]. However, the redundancy is incomplete because although replacement of the endogenous *MYC* gene

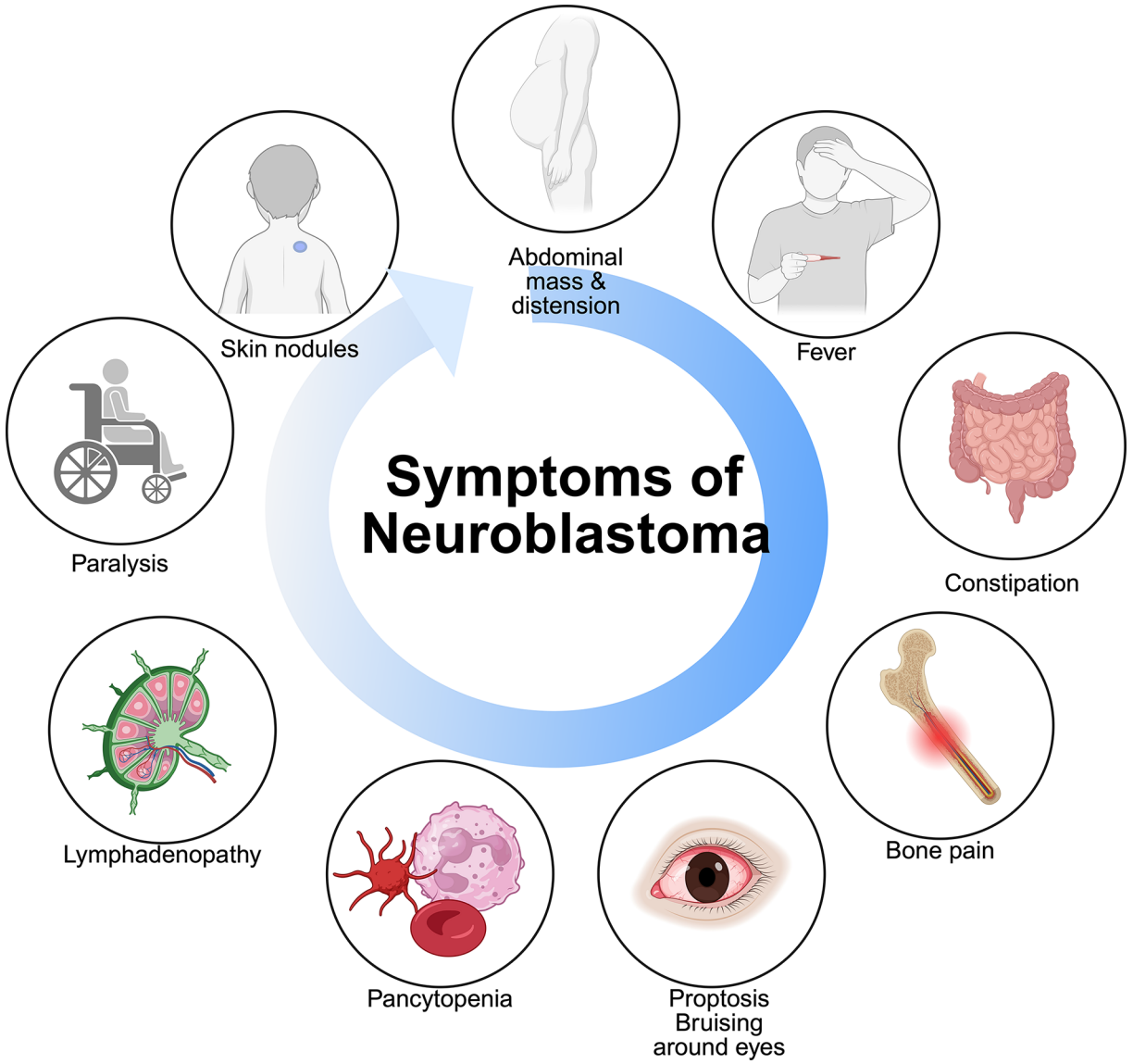

Figure 1. Overview of neuroblastoma symptoms

The symptoms of neuroblastoma are diverse and affect different parts of the body. The symptoms are illustrated in order from more common (darker blue) to less common (lighter blue). Created in BioRender; Bayliss, R. (2026) https://BioRender.com/pxrk4mi

with *MYCN* rescued embryonic lethality, and therefore most critical biological functions, the mice were smaller and had other defects [31].

The role of MYCN in neuroblastoma

While *MYC* is implicated in various cancer types, *MYCN* has a much more limited and specific role—driving paediatric malignancies originating from the central and peripheral nervous system to cause neuroblastoma, retinoblastoma, glioblastoma, and medulloblastoma [32]. *MYCN* is expressed in specific cell lineages during development with minimal expression in normal paediatric and adult tissues, hence, targeting *MYCN* may have a favourable therapeutic window [33]. However, many current approaches rely on indirect targeting of MYCN.

MYCN is located on the distal short arm of chromosome 2 (2p24) and this region is amplified in a subset of neuroblastoma patients [34]. *MYCN* amplification, which is commonly defined as greater than 10 copies of gene per cell, is observed in approximately 25% of patients with primary neuroblastoma and a substantial fraction, but

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not the majority, of high-risk cases [34]. *MYCN* amplification is a result of genomic instability and arises randomly. The additional copies of *MYCN* are located in individual circular extrachromosomal DNA molecules (ecDNA, also called double minute chromatin bodies) and self-repeating arrays on a chromosome called homogenously staining regions [35,36]. It was initially thought that other genes might be co-amplified with *MYCN*, however, only *MYCN* is consistently amplified across different tumour samples from an individual, and other genes such as ALK are occasionally co-amplified [37–39]. Crucially, however, enhancer sequences are co-amplified with the MYCN gene [40]. The enhancers are recognised by core regulatory circuit (CRC) transcription factors that drive expression of each copy of the MYCN gene, and which reinforce the expression of other CRC factors. Thus, MYCN expression is sustained at a high level in neuroblastoma cells.

MYCN plays a multifaceted role in the pathogenesis of neuroblastoma; it induces malignancy and maintains the stem-like state of NCCs, and it stimulates proliferation and prevents apoptosis of NCCs that contribute to neuroblastoma formation [41,42]. As a transcription factor, the *MYCN* oncogene fuels the survival of cancer cells by activating genes associated with cancer hallmarks such as genes that increase proliferation, metastasis, pluripotency, self-renewal [29]. Concurrently, it suppresses genes that antagonise tumorigenesis to sustain stemness, bypass cell cycle arrest, and evade immune surveillance [29].

Another key function of *MYCN* in neuroblastoma lies in its ability to suppress terminal differentiation of sympathetic neurons (neural crest-derived cells) [43]. In normal NCCs, differentiation is tightly modulated throughout embryonic development by complex gene regulatory networks. *MYCN* is expressed at high levels that drives proliferation and thus migration of NCCs from the neural plate border to the ventral region in early stages of CNS development [44]. Subsequently, *MYCN* expression levels decreases, which is critical for NCCs to undergo differentiation into other NCC-derived cell types [45]. For NCC-derived lineages that function in maintaining pluripotency and self-renewal, *MYCN* remains at high levels [46]. In neuroblastoma, dysregulated differentiation and migration is observed in neuroblasts (a type of NC-derived cells) due to *MYCN* amplification [43]. Asymmetrical cell division is a physiological process where self-renewal and differentiation is precisely balanced; but in neuroblastoma, overexpression of *MYCN* promotes symmetric cell division that increases self-renewal and expands the undifferentiated cell population [47,48]. This sheds light on the role of *MYCN* in not only tumour advancement, but also tumour initiation.

MYCN structure and interactome

Human MYCN and MYC proteins have around 45% sequence identity, consistent with a high density of conserved functional sites. Indeed, these conserved residues cluster in the key sites of protein–protein interactions, as discovered in interactome mapping studies [49,50]. MYCN comprises 464 amino acids with a molecular weight of approximately 50 kDa and contains six short sequences called MYC homology boxes (MBs): MB0, MBI, MBII, MBIIIa, MBIIIb, and MBIV that are highly conserved in MYC and MYCN (Figure 2). [51]. Each MB motif contributes to macromolecular interactions, many of which are associated with transcriptional regulation, chromatin remodelling, and phospho-regulation of stability [50].

MB0, MBI, and MBII are located within the TAD at the N-terminus of MYCN. MB0 is not necessary for tumour initiation, instead, it accelerates tumour growth and, at a molecular level, it facilitates interactions with the general transcriptional elongation factors TFIIF and TFIIIC [50,52]. MB0 also interacts with the kinase AURKA and the protein phosphatase 1-associated protein PNUTS [53,54]. Residues T58 and S62 within the phosphodegron in MBI are important phosphorylation sites for the regulation of MYCN activity and stability during the cell cycle [55,56]. MBII is crucial for transformation and transcriptional activation, mediated through the conversion of chromatin from a repressed to an active state, through the assembly of histone acetyltransferase complexes (HATs). The scaffold protein TRRAP and its associated HAT complexes are key interaction partners of MBII [50]. These include the GCN5-containing STAGA complex that contributes to the chromatin localisation and transcriptional activity of MYCN [57]. Remarkably, the co-expression of non-transforming MB0 (ΔMB0) and MBII deletion (ΔMBII) resulted in rescue of the transforming activity of *MYCN* to accelerate tumour growth. This trans-complementarity suggests that these myc boxes can act semi-autonomously with different binding partners to achieve a common goal—facilitating oncogenic *MYCN* activity [50].

The central region contains MBIIIa, MBIIIb, MBIV, and an NLS sequence (Figure 2). The NLS sequence overlaps with MBIV and is required for nuclear import of MYCN via importin-α, an interaction that has been resolved by X-ray crystallography [58]. MBIV interacts with HCF-1, a multi-domain transcriptional co-regulator that acts as a scaffold for transcription factors and chromatin-modifying enzymes [59]. The MBIIIb motif binds WDR5, a component of the COMPASS/MLL histone methyltransferase complex, which enables MYCN to bind to chromatin

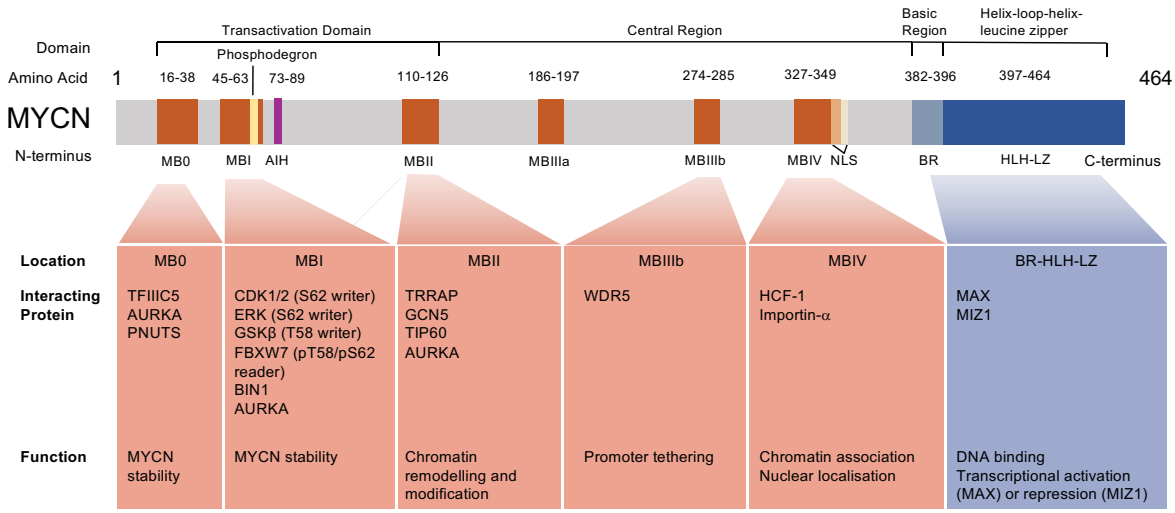

Figure 2. Structural features and functional domains of MYCN and their interactions with protein partners

The functional domains of MYCN include: the transactivation domain (TAD), central region domain, DNA binding domain, and the dimerisation domain. The orange boxes show the highly conserved MBs. Within MBI, the T58 and S62 phosphorylation sites are located within a phosphodegron (yellow box). The Aurora kinase A (AURKA)-interacting helix (AIH, purple) is specific to MYCN. The light-yellow box is the nuclear localisation signal (NLS) that overlaps with MBIV. The light blue box denotes the basic region (BR) and the dark blue denotes the helix-loop-helix-leucine-zipper (HLH-LZ) domain. The amino acids for the boundaries of structural and functional domains are indicated above. Examples of MYCN-interacting proteins, the specific regions of *MYCN* involved in these interactions, and functions are included below.

and maintain an active transcriptional state [60]. A crystal structure shows the molecular recognition of MYC MBIIIb by the β-propeller domain of WDR5, at a distinct site from its other interactors such as MLL [61].

The C-terminal region of MYCN comprises a BR for sequence-specific DNA binding tethered to an HLH-LZ domain that enables MYCN to interact with partner proteins that also contain the bHLH-LZ domain, such as MAX, to form heterodimers [62]. In the absence of DNA, the basic region can adopt a helical structure, but has greater conformational flexibility [63]. MYC can form alternative complexes with Miz1, a zinc-finger transcription factor, and thereby repress the transcription of cell cycle inhibitor genes [64]. However, MYCN interacts much more weakly with Miz1 than MYC, and this difference underlies distinct oncogenic programmes in MYC-driven versus MYCN-driven cancers [65].

MYCN is comprised of mainly intrinsically disordered regions (IDRs) with some regions of helical propensity [63,66,67]. Upon binding to partners or through post-translational modifications, these IDRs can undergo transition from disorder to order, or they can persist in a disordered state to form 'fuzzy' complexes [52,53,67,68]. MYCN may bind to its many partners in different stable conformations or in a dynamic state. Additionally, this implies that directly targeting MYCN will be challenging because of its structural dynamicity. Therefore, targeting these regions is difficult due to the lack of stability to form pockets for binding small molecules such as inhibitors or proteolysis targeting chimeras (PROTACs) [33].

In the following sections, we focus on common interactors for which structural models have been resolved, as these provide opportunities for structure-guided therapeutic discovery.

MYCN and MAX

Mammals have a single *MAX* gene that can be differentially spliced to encode MAX protein variants. The two major forms of MAX are p21 and p22, which are constitutively expressed at high levels in quiescent, growing, and differentiating cells [69–71]. MAX, like MYCN, contains a bHLH-LZ region that enables specific dimerisation to form homodimers or heterodimers [70]. Studies *in vitro* found that, at equilibrium, MYCN/MAX heterodimers predominate over MYCN or MAX homodimers, therefore establishing a quantitative association between them [71–73]. MAX can also bind to other bHLH-LZ family members, however, each heterocomplex (with MYC and bHLH-LZ family members) has a distinct set of target genes [74].

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The MYCN/MAX heterodimer attaches preferentially to a binding motif (5′-CACGTG-3′) called the Enhancer-box (E-box) via the basic region of *MYCN* [75,76]. This complex recruits chromatin modifying enzymes to maintain the chromatin in an uncondensed state (Figure 3A). The heterodimer is crucial for MYCN function as without MAX, the protein is inactive and cannot regulate expression of target genes that are generally involved in key processes such as cell proliferation, growth, differentiation, and apoptosis [27,77]. In neuroblastoma, unlike normal cells, *MAX* expression is variable, and this is associated with clinical outcomes: high levels of MAX correlate with better outcomes when MYCN levels are low; but in *MYCN*-amplified neuroblastoma, high levels of MAX result in aggressive tumours [78]. MAX silencing in *MYCN*-amplified cells reduces their aggressiveness through reduced cell growth, motility, and promotion of cell differentiation [78].

AURKA and MYCN stability

AURKA is a member of the mitotic serine/threonine kinase family. It is implicated in important mitotic processes such as the regulation of G2/M transition of the cell cycle, mitotic spindle assembly, and the maintenance of genetic fidelity [79]. Ordinarily, the expression of Aurora kinases is strictly cell-cycle-regulated: they are degraded in late mitosis, with only residual levels detected in the G1 phase [80]. AURKA is frequently dysregulated in cancer through gene amplification or impaired degradation, leading to elevated protein levels throughout the cell cycle [81]. Its aberrant persistence into G1 in cancer cells has been linked to increased proliferation and resistance to targeted therapies and chemotherapy [79].

In normal cells, MYCN is a short-lived protein with a half-life of approximately 30 minutes. MYCN is phosphorylated within MBI, which primes ubiquitinylation and proteolysis, thereby modulating protein stability [82]. Ser62 is first phosphorylated by kinases such as ERK or CDK1/cyclin B, and then Thr58 is phosphorylated by GSK3β (Figure 3B). Phosphorylation of these sites acts as the recognition site for SCF(FBXW7) ubiquitin ligase, which marks it for proteasomal degradation [83]. Although earlier work implicated further steps before FBXW7 binding, recent work has shown that the doubly phosphorylated form is recognised [84]. Interestingly, MYC has a second phosphodegron recognised by FBXW7, centred on phosphorylation of Thr244 and Thr248 [84]. However, this sequence is not conserved in MYCN, which is therefore dependent on the single phosphodegron in MBI.

In neuroblastoma, AURKA overexpression is associated with enhanced *MYCN* stability because it antagonises the recognition of the degradation signal by FBXW7 [85]. Consequently, MYCN is sequestered from degradation, which results in increased MYCN stability and accumulation within the cell. AURKA interacts with MYCN through an extensive interface, only part of which has been captured in a crystal structure [53]. This region of MYCN, the AIH, is C-terminal to the phosphodegron, interacts with the C-lobe of AURKA, which then competes with FBXW7. This motif lies outside an MYC box, and is not conserved in MYC, although the equivalent region has been captured in a crystal structure with the TBP/TAF1 complex, a core component of the TFIID complex that functions in RNA polymerase II initiation [86]. These equivalent motifs in MYC and MYCN both adopt helical structures when bound to their different partners, suggesting a degree of mechanistic similarity despite sequence differences. NMR studies have clarified that other regions of MYCN that interact with AURKA include MB0, MBI and MBII, and that the MB0-MBI region interacts with the kinase N-lobe [67,87]. NMR studies on MYC show a similar interaction pattern and, moreover, indicated that the interaction with AURKA is enhanced when MBI is phosphorylated [88]. Further studies are required to resolve the structural basis of AURKA interactions with MB0 and MBII at high resolution.

The AURKA–MYCN interaction is cell-cycle regulated and peaks during S-phase [49]. MYCN is also an activator of AURKA catalytic activity, and the recruitment of active AURKA to chromatin during S-phase helps to prevent transcription-replication conflicts through phosphorylation of substrates such as histone H3 [53,89]. Other binding partners of MYCN show an inverse cell-cycle dependence: they interact less strongly during S-phase. AURKA can directly displace factors from MYCN, including the TFIIIC complex.

TFIIIC and MYCN chromatin localisation

TFIIIC is a six-subunit general transcription factor that binds to internal promoter elements (A-box, B-box) within Pol III-transcribed genes, such as tRNA genes [90]. After binding to the promoter, TFIIIC recruits TFIIIB, which positions RNA polymerase III at the transcription start site. TFIIIC also interacts with cohesin and CTCF, contributing to higher-order chromatin organisation beyond its pol III-specific role. TFIIIC modulates the localisation of MYCN on chromatin, but does not affect MYCN-dependent gene expression [91]. Instead, it appears to fine-tune an RNA-related function of MYCN: depletion of TFIIIC increases the occupation of active promoter hubs by MYCN, reducing the abundance of BRCA1 and nuclear exosome at these sites, key factors in promoter-proximal RNA degradation [92]. Recent structural studies resolved that MB0 of MYCN interacts with the

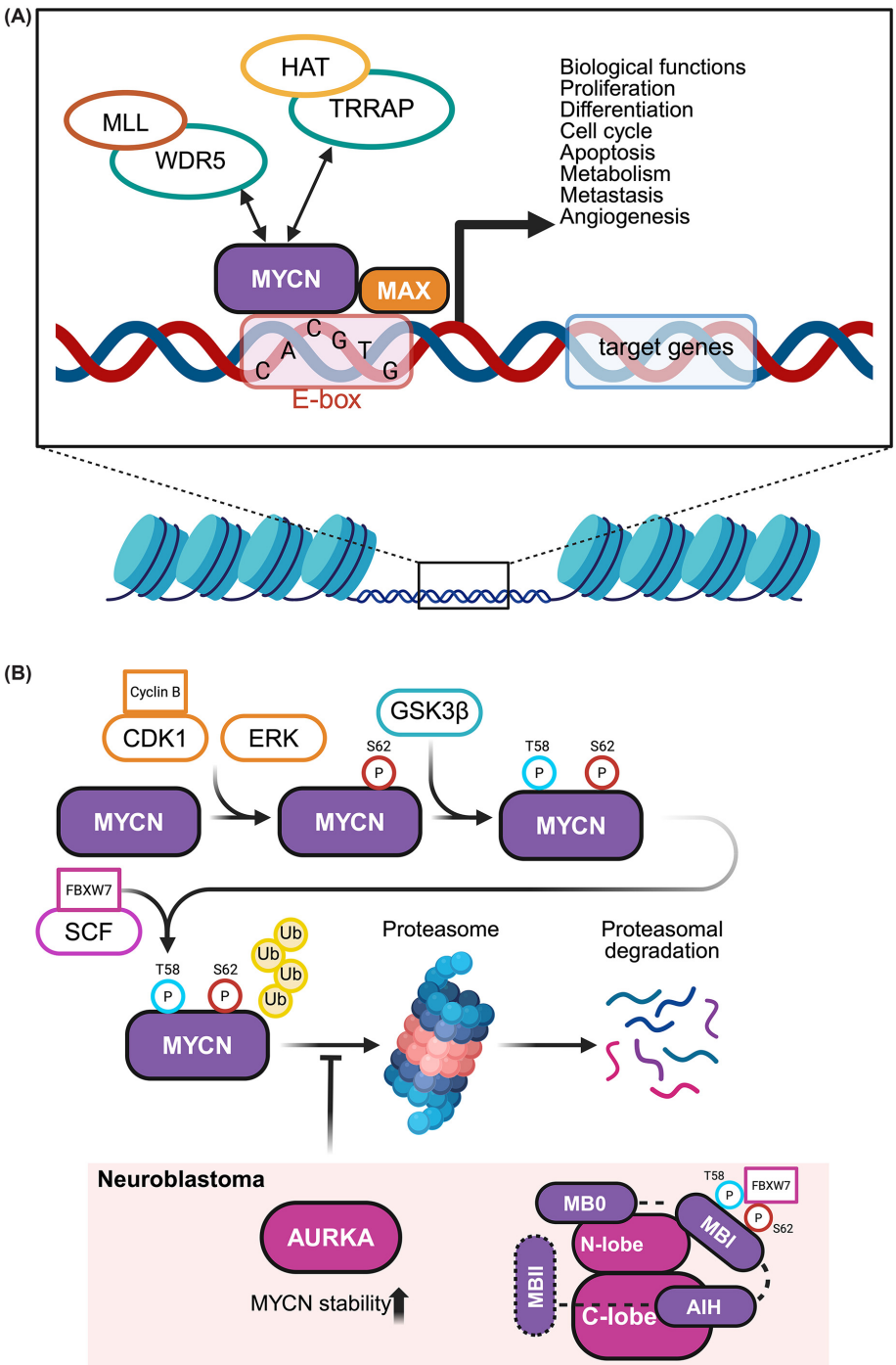

Figure 3. Molecular interactions of MYCN

(**A**) MYCN and MAX form the heterodimer MYCN/MAX that binds to the specific DNA motif 5′-CACGTG-3′ (E-box). The complex then recruits proteins such as TRRAP/TIP60 and WDR5/MLL. These complexes function in chromatin remodelling and transcriptional regulation, keeping the chromatin uncondensed such that the target genes are transcriptionally active. The target genes of the MYCN/MAX heterodimer function in many pathways. (**B**) (Top section) In normal cells, the S62 and T58 residues in MYCN are phosphorylated sequentially. The phosphodegron serves as the recognition site of the FBXW7 ubiquitin ligase. FBXW7 then ubiquitinates MYCN, marking it for proteasomal degradation. (Bottom section) In neuroblastoma, AURKA is overexpressed and forms a complex with MYCN by binding to sites that flank its phosphodegron. This inhibits FBXW7-mediated proteasomal degradation, which increases MYCN stability. Specific regions of MYCN interact with either the N-lobe or C-lobe of AURKA. Binding site of MBII is not known. Created in BioRender; Bayliss, R. (2026) https://BioRender.com/i80c1oz

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DNA binding domain of TFIIIC5 [52]. Despite its name, this domain is not critical for specific DNA recognition by the TFIIIC complex. Instead, it provides a key interface with MYCN, the regulation of which is complicated by competition with non-specific DNA sequences and an intramolecular interaction with a C-terminal, acidic plug sequence in TFIIIC5. TFIIIC has thus emerged as a modulator of MYCN chromatin localisation and RNA surveillance activity, within a complex regulatory framework that may nonetheless provide opportunities for therapeutic intervention.

Targeting MYCN as a therapeutic approach against neuroblastoma

Unlike many cancers, neuroblastoma has few mutations that restricts the number of potential targets for precision medicine. Many aspects of *MYCN* biology in neuroblastoma remain incompletely understood, including: the exact mechanisms of *MYCN* amplification, the regulation and roles of interactions between MYCN and its diverse protein partners, and which interactions underpin MYCN-driven tumour progression and poor clinical outcomes. These gaps limit the development of therapies that can specifically and effectively inhibit MYCN. Additionally, efforts to precisely target MYCN have proved to be challenging because of its dynamic, disordered nature, sparse structural data on MYCN complexes, and the difficulty of using traditional small molecules to block protein–protein or protein–DNA interactions [33]. Viewing MYCN as a network of protein complexes provides a framework for therapeutic targeting: disrupting chromatin engagement, rewriting transcriptional activity, or destabilising the protein.

Chromatin association of MYCN

As MYCN functions as a transcription factor, the protein partners that mediate its interaction with chromatin represent potential targets to interrupt MYCN's transcriptional activity. Most effort has been put towards developing inhibitors of the MYCN/MAX heterodimer. Small molecule inhibitors have been reported, such as 10074-G5, 10058-F4 and MYCi361 that bind MYC/MYCN and stabilise the intrinsically disordered monomer [93–95]. However, there remain challenges in developing small molecule MYC/MYCN–MAX compounds to be potent, selective, soluble and stable. Another approach has been to design peptide-based miniproteins, notably the pioneering work on Omomyc [96]. Omomyc is derived from the bHLH-LZ region of MYC, and it forms inactive heterodimers with MYC/MYCN and MAX to prevent MYC/MAX dimerisation. Omomyc has now been developed into a cell-penetrating version (OMO-103) that has safely completed phase I clinical trials in advanced, adult solid tumours [97].

Another promising approach is to target MYCN through its interaction with WDR5. WDR5 has two druggable sites: the WBM site that interacts with MYC/MYCN, and the WIN site that interacts with MLL, the catalytic subunit of the lysine methyltransferase for histone H3. Several WIN site inhibitors have been developed, such as OICR-9429 [98]. In contrast, the discovery of WBM site inhibitors has taken more time, in part due to the more challenging nature of the pocket [99–101]. Recent work has combined a WIN and WBM site inhibitor, with synergistic effects on neuroblastoma cell viability, and there are clear opportunities to explore the optimal targeting of WDR5 in neuroblastoma through drug combinations [101]. WDR5 inhibitors establish a paradigm that MYCN chromatin localisation and function can be disrupted without targeting its DNA binding domain. This concept will surely be explored in greater breadth in the coming years, through targeting other critical interaction partners of MYCN.

Histone-modifying enzymes in MYCN transcriptional control

MYCN protein interacts functionally and physically with several histone-modifying enzymes that affect the transcriptional output of MYCN by regulating chromatin accessibility. Inhibiting these MYCN partners could indirectly inhibit the oncogenic transcriptional activity of MYCN through epigenetic modification or chromatin remodelling. These are enzymes with folded domains harbouring active sites and other pockets, and are therefore more straightforward targets for medicinal chemistry than the dynamic, disordered MYCN protein. However, this comes at the potential cost of a reduced therapeutic window due to other functions of these proteins.

There are clear functional links between MYCN and histone demethylases. MYCN recruits KDM4B to target genes, where it demethylates repressive H3K9me2/me3 marks [102]. Moreover, genetic deletion of any one of KDM4A, KDM4B, or KDM4C reduces the growth of MYCN-amplified neuroblastoma cells *in vitro* and in xenograft models [103]. Notably, the pan-KDM4 inhibitor QC6352 shows efficacy in mouse xenografts of two MYCN-amplified cell lines, and produces a durable response when combined with chemotherapy [103]. However, a

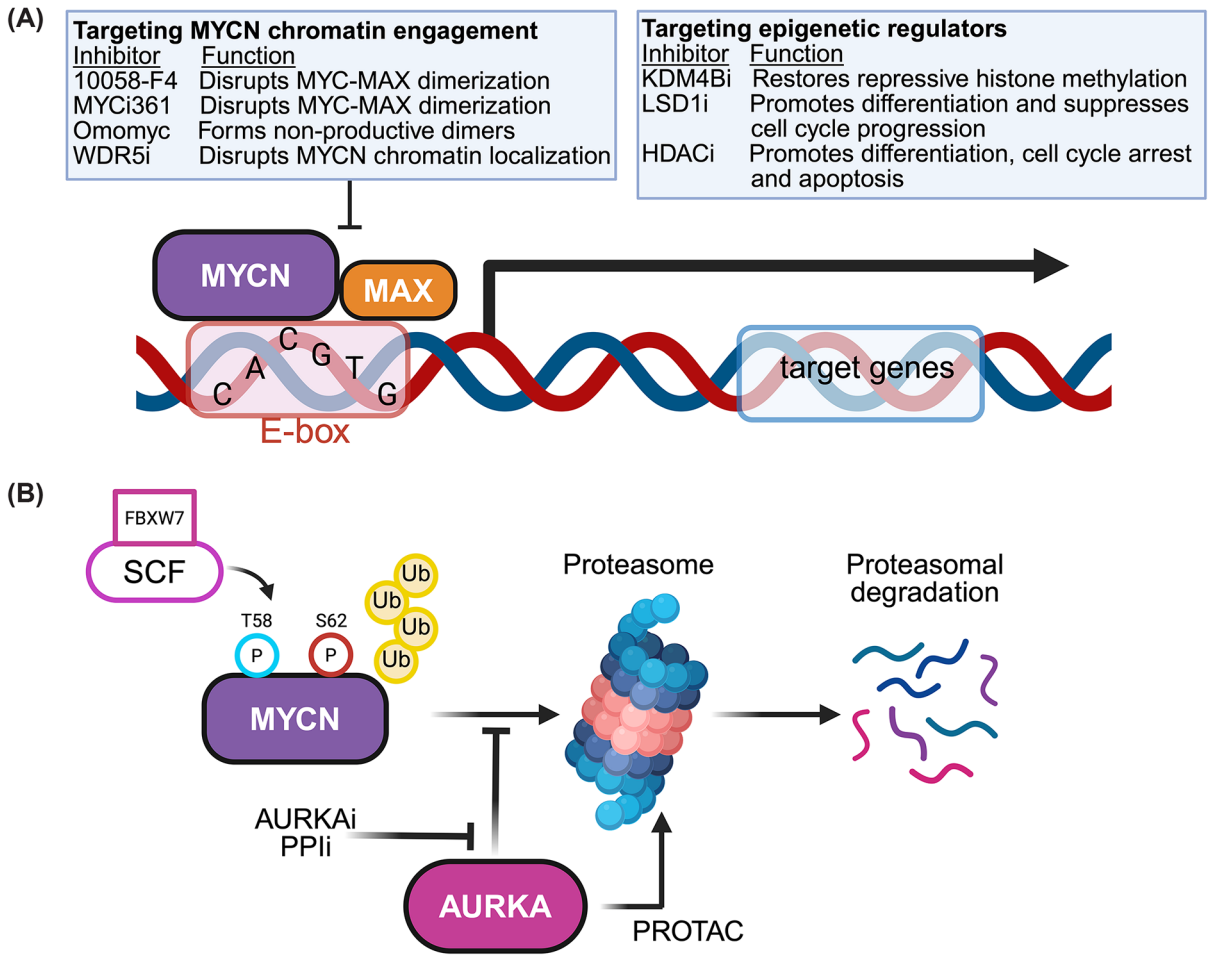

Figure 4. Potential therapeutic strategies targeting MYCN in neuroblastoma

(**A**) Disrupt MYCN transcriptional via MYCN/MAX heterodimers or other factors. (**B**) Destabilise MYCN by targetting its interaction with AURKA either directly (PPIi) or by using a PROTAC that triggers AURKA degradation. Created in BioRender; Bayliss, R. (2026) https://BioRender.com/ay7s2eg

comparable response is observed in a non-MYCN-amplified xenograft model, consistent with a broader programme of transcriptional control by KDM4 demethylases. The central region of MYCN and the PHD/Tudor domains of KDM4B are required for their association, although further work is required to map this more finely and to determine whether the interaction is direct [102].

Along similar lines, LSD1 and HDAC1 are components of the CoREST co-repressor complex and candidate target histone-modifying enzymes in MYCN-amplified cancers (Figure 4A). LSD1, also called KDM1A, is a histone H3K4 and H3K9 demethylase with a critical role in silencing genes involved in neuronal differentiation. MYCN and LSD1 can be co-immunoprecipitated from neuroblastoma cells, an association that requires MBIII of MYCN [104]. MYCN and LSD1 co-localise to the promoter of the CDKN1A gene, which encodes the p21 cell-cycle inhibitor, and LSD1 inhibition relieves the suppression of its expression by MYCN [104]. There are numerous LSD1 inhibitors in clinical development, although neuroblastoma has not been the focus of attention. LSD1 inhibitors induce cell death in two different MYCN-amplified cell-lines, and the IMR32 cell-line that has higher LSD1 expression is more sensitive [105]. There is a need for more extensive, rigorous and mechanistic testing of LSD1 inhibitors in MYCN-amplified neuroblastoma.

There is substantial evidence that histone deacetylases (HDACs) play important roles in MYCN-driven transcriptional regulation of genes controlling cell cycle control, differentiation and apoptosis [106]. HDAC-containing complexes associate with MYCN at target gene promoters, which are likely mediated by multi-protein complexes, as there is no clear evidence for direct interactions [107]. These complexes regulate the

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landscape of cellular gene expression that determines cell fate. A complex comprising MYCN, SP1, and MIZ1 localises to TRKA and p75NTR promoters where recruitment of HDAC1 establishes a repressed chromatin state and suppresses NGF-induced apoptosis [107]. HDAC inhibition induces cell-cycle arrest in neuroblastoma cell models, for example by preventing entry into S-phase by downregulation of CDK4 and upregulation of p21 [108]. Because HDACs have pleiotropic functions, the focus of preclinical and clinical investigation has been on rational combination strategies to maximise therapeutic impact while minimising toxicity. For example, combining HDAC1/2 inhibitors with 13-*cis* retinoic acid, a standard component of maintenance for high-risk neuroblastoma, enhances differentiation and reduces viability in neuroblastoma cell lines [109]. However, these preclinical observations have not translated into robust clinical reponses. Further progress will require an improved understanding of the specific roles of individual HDACs in neuroblastoma biology, as well as a broader survey of rational combination therapy targets. For example, high-throughput screening has identified ubiquitin-specific protease 5 (USP5) inhibitors as synergistic with HDAC inhibition in MYCN-amplified neuroblastoma cell lines, whilst exhibiting low toxicity in normal human fibroblasts [110]. An additional priority is to elucidate the molecular mechanisms by which MYCN recruits HDAC-containing complexes to target promoters, and to develop inhibitors that selectively disrupt these interactions without affecting broader HDAC-dependent processes.

Enabling MYCN degradation

Whilst there are many aspects of MYCN biology to be resolved, an attractive concept is to remove MYCN protein from neuroblastoma cells. This could be achieved by exploiting the mechanisms that confer stability on MYCN, such as its interaction with AURKA. Indirectly targeting MYCN through MYCN/AURKA interactions using certain AURKA inhibitors destabilises MYCN in neuroblastoma cell lines, which results in decreased MYCN protein levels and suppression of neuroblastoma tumour growth (Figure 4B). This works for certain AURKA inhibitors because they stabilise an inactive conformation of the kinase, such as MLN8054, MLN8237 (alisertib), and CD532, which are incompatible with the active kinase conformation recognised by MYCN [53,111–113]. However, clinical trials of alisertib exhibited significant haematological toxicity and an overall response rate of typically <15% [114,115]. There is clearly room for improvement, and the development of AURKA inhibitors that disrupt MYCN interaction continues, with recent examples including DBPR728 that shows activity against both MYC-high and MYCN-high cancer cell lines [116].

MYCN stimulates AURKA activity, which then phosphorylates histone H3S10 in S-phase, a function that could be exploited through combined inhibition of AURKA and ATR [89]. However, the mechanism by which AURKA stabilises MYCN degradation depends on a protein–protein interaction, and is independent of its kinase activity [53,85]. One future direction might be to develop inhibitors that block the interaction of AURKA with MYCN, without inhibiting the kinase to avoid toxicity associated with inhibiting the mitotic, kinase-dependent function of AURKA. This is challenging because the AURKA/MYCN interface has more than one site, and the only site resolved in a crystal structure overlaps with a key pocket for protein substate binding [53]. This problem might be resolved using peptidomimetic inhibitors, and tool molecules that disrupt this site directly or via an allosteric mechanism are at an early stage of development [117,118].

An emerging strategy for MYCN-driven neuroblastoma is the use of proteolysis targeting chimeras, bifunctional small molecules that recruit a protein target to a ubiquitin E3 ligase, enabling polyubiquitination and degradation. AURKA is an attractive PROTAC target because it is readily degradable and there are a plethora of inhibitors to serve as starting points [119]. AURKA PROTACs derived from alisertib have been described and, interestingly, they do not induce the severe mitotic arrest typical of alisertib or other AURKA kinase inhibitors [120,121]. This difference likely reflects partial protection of centrosome-associated Aurora-A, allowing the cells to progress through mitosis with only minor defects [121]. It is notable that alisertib-based PROTACs have not been reported to cause degradation of MYCN. This might be because alisertib stabilises an inactive conformation of AURKA that weakens the binding of MYCN, which prefers to bind an active kinase conformation [53]. While it makes sense to based PROTAC design on an inhibitor selective for AURKA, it might not be necessary because relatively unselective inhibitor scaffolds can form the basis of highly selective degraders. Indeed, a global map of kinase degradability placed AURKA as the second most degradable kinase, with AURKB outside the top twenty [119]. Therefore several further chemotypes have been explored to generate AURKA PROTACs:HLB-0532259 is based on the CDK4/6 inhibitor ribociclib [88]; SK2188, SK4454 and SK5527 are based on the AURKA inhibitor MK-5108 [122,123]. These PROTACs trigger rapid and selective degradation of AURKA and MYCN, suppress proliferation and induce apoptosis in MYCN- amplified neuroblastoma cells preferably compared to other cell types. This selectivity is consistent with selectivity of Aurora-A PROTACs for MYCN over MYC, but this has not been formally proven. It

remains to be seen what is the optimal AURKA inhibitor from which to develop a PROTAC, but there are strong arguments in favour of Type I inhibitors that bind the active conformation of AURKA and favour ternary complex formation with MYCN [53,88].

Other MYCN interaction partners are being explored as PROTAC substrates, such as WDR5 and BET family proteins. Treatment of the human acute myeloid leukaemia cell-line MV4-11 with a WDR5-selective PROTAC MS67 reduced the chromatin association of MYC, while MYC protein levels were unaffected [124]. Although WDR5 PROTACs have not been tested in neuroblastoma cells, they can be expected to at least phenocopy, if not improve on WDR5–MYCN interaction disruptors. ARV-825, a PROTAC that induces the degradation of BET family proteins, required for high MYC/MYCN expression, shows activity in MYCN-driven neuroblastoma cells [125]. The PROTAC reduced MYCN protein levels indirectly, by reducing its expression, and was especially potent in reducing the cell viability of IMR-32, MYCN-high cells, although it is likely that factors other than MYCN contribute to this effect. There are currently no PROTACs that target MYCN itself, but a similar concept, molecular glue, has successfully been applied to MYC/MAX [126]. This compound, WBC100, glues the E3 ligase CHIP to the MYC, triggering its degradation. A similar idea could be applied to MYCN, although it would be accelerated if there was an experimental structure of MYCN that has a suitable pocket for glue or PROTAC design. Until then, computational models of MYCN/MAX could provide a starting point.

Conclusion

MYCN has a central role in neuroblastoma oncogenesis and malignancy, underscoring its value as a therapeutic target in high-risk disease. However, progress is limited by incomplete understanding of its interaction network, notably the scarcity of high-resolution structures for MYCN complexes. The set of protein interactions that have been structurally characterised only partially overlaps with those currently explored as potential drug targets. Future advances in therapies for MYCN-amplified neuroblastoma are therefore likely to focus on its network of protein complexes. Context-specific vulnerabilities will be exploited by combining disruption of selected protein–protein interactions with targeted degradation of key components within the MYCN interaction network.

Unanswered questions

What is the full spectrum of MYCN-interacting proteins and what are their respective molecular mechanisms in driving neuroblastoma malignancy? What other physiological roles do these proteins play and will targeting them cause side effects?

Can we determine the precise binding sites and binding modes of interacting proteins on MYCN? Can we resolve the composition of different MYCN complexes, and understand the basis of competition or cooperation between interacting proteins?

Given the high homology between MYCN, MYC, and MYCL, how can drugs be designed to selectivity target conserved regions such as MB0 or MBII in MYCN?

Can the IDRs of MYCN be stabilised so as to create defined pockets for drug binding? Are there any novel approaches that exploit MYCN's dynamic structure, turning a challenge into an opportunity?

What are the consequences of prolonged MYCN suppression on normal neuronal development and function? Could neurotoxicity be mitigated while maintaining therapeutic efficacy?

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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CRediT Author Contribution

Chelsea Xinyi Yow: Conceptualization, Writing—orginal draft. **Sharon Yeoh:** Figures—original draft. **Eoin Leen:** Writing—review & editing. **Richard Bayliss:** Conceptualization, Writing—orginal draft, Review & editing, Figures—orginal draft, Review & editing.

Abbreviations

AIH, AURKA interacting helix; AURKA, Aurora kinase A; BR, basic region; CRC, core regulatory circuit; E-box, enhancer-box; HAT, histone acetyltransferase complex; HDAC, histone deacetylase; HLH-LZ, helix-loop-helix-leucine-zipper; IDR, intrinsically

disordered region; INSS, International Neuroblastoma Staging System; MB, MYC homology box; NCC, neural crest cell; NLS, nuclear localisation signal; PROTAC, proteolysis targeting chimera; TAD, transactivation domain.

References

1 Davidoff, A.M. (2012) Neuroblastoma. *Semin. Pediatr. Surg.* **21**, 2–14, https://doi.org/10.1053/j.sempedsurg.2011.10.009
2 Brodeur, G.M. and Nakagawara, A. (1992) Molecular basis of clinical heterogeneity in neuroblastoma. *Am. J. Pediatr. Hematol. Oncol.* **14**, 111–116, https://doi.org/10.1097/00043426-199205000-00004
3 Matthay, K.K., Maris, J.M., Schleiermacher, G., Nakagawara, A., Mackall, C.L., Diller, L. et al. (2016) Neuroblastoma. *Nat. Rev. Dis. Primers.* **2**, 16078, https://doi.org/10.1038/nrdp.2016.78
4 Nong, J., Su, C., Li, C., Wang, C., Li, W., Li, Y. et al. (2025) Global, regional, and national epidemiology of childhood neuroblastoma (1990–2021): a statistical analysis of incidence, mortality, and DALYs. *EClinicalMedicine* **79**, 102964, https://doi.org/10.1016/j.eclinm.2024.102964
5 Colon, N.C. and Chung, D.H. (2011) Neuroblastoma. *Adv. Pediatr.* **58**, 297–311, https://doi.org/10.1016/j.yapd.2011.03.011
6 Shohet, J. and Foster, J. (2017) Neuroblastoma. *BMJ* **357**, j1863, https://doi.org/10.1136/bmj.j1863
7 Gaspar, N., Hartmann, O., Munzer, C., Bergeron, C., Millot, F., Cousin-Lafay, L. et al. (2003) Neuroblastoma in adolescents. *Cancer* **98**, 349–355, https://doi.org/10.1002/cncr.11521
8 Esiashvili, N., Anderson, C. and Katzenstein, H.M. (2009) Neuroblastoma. *Curr. Probl. Cancer.* **33**, 333–360, https://doi.org/10.1016/j.currproblcancer.2009.12.001
9 Cohn, S.L., Pearson, A.D., London, W.B., Monclair, T., Ambros, P.F., Brodeur, G.M. et al. (2009) The International Neuroblastoma Risk Group (INRG) classification system: an INRG task force report. *J. Clin. Oncol.* **27**, 289–297, https://doi.org/10.1200/JCO.2008.16.6785
10 Tolbert, V.P. and Matthay, K.K. (2018) Neuroblastoma: clinical and biological approach to risk stratification and treatment. *Cell Tissue Res.* **372**, 195–209, https://doi.org/10.1007/s00441-018-2821-2
11 Monclair, T., Brodeur, G.M., Ambros, P.F., Brisse, H.J., Cecchetto, G., Holmes, K. et al. (2009) The International Neuroblastoma Risk Group (INRG) staging system: an INRG task force report. *J. Clin. Oncol.* **27**, 298–303, https://doi.org/10.1200/JCO.2008.16.6876
12 Chu, C.M., Rasalkar, D.D., Hu, Y.J., Cheng, F.W., Li, C.K. and Chu, W.C. (2011) Clinical presentations and imaging findings of neuroblastoma beyond abdominal mass and a review of imaging algorithm. *Br. J. Radiol.* **84**, 81–91, https://doi.org/10.1259/bjr/31861984
13 Burchill, S.A. (2004) Micrometastases in neuroblastoma: are they clinically important? *J. Clin. Pathol.* **57**, 14–20, https://doi.org/10.1136/jcp.57.1.14
14 DuBois, S.G., Kalika, Y., Lukens, J.N., Brodeur, G.M., Seeger, R.C., Atkinson, J.B. et al. (1999) Metastatic sites in stage IV and IVS neuroblastoma correlate with age, tumor biology, and survival. *J. Pediatr. Hematol. Oncol.* **21**, 181–189, https://doi.org/10.1097/00043426-199905000-00005
15 Park, J.R., Eggert, A. and Caron, H. (2010) Neuroblastoma: biology, prognosis, and treatment. *Hematol. Oncol. Clin. North Am.* **24**, 65–86, https://doi.org/10.1016/j.hoc.2009.11.011
16 Irwin, M.S., Naranjo, A., Zhang, F.F., Cohn, S.L., London, W.B., Gastier-Foster, J.M. et al. (2021) Revised neuroblastoma risk classification system: a report from the children's oncology group. *J. Clin. Oncol.* **39**, 3229–3241, https://doi.org/10.1200/JCO.21.00278
17 DuBois, S.G., Macy, M.E. and Henderson, T.O. (2022) High-risk and relapsed neuroblastoma: toward more cures and better outcomes. *Am. Soc. Clin. Oncol. Educ. Book.* **42**, 1–13, https://doi.org/10.1200/EDBK˙349783
18 Yue, Z.X., Huang, C., Gao, C., Xing, T.Y., Liu, S.G., Li, X.J. et al. (2017) MYCN amplification predicts poor prognosis based on interphase fluorescence *in situ* hybridization analysis of bone marrow cells in bone marrow metastases of neuroblastoma. *Cancer Cell Int.* **17**, 43, https://doi.org/10.1186/s12935-017-0412-z
19 Jha, R.K., Kouzine, F. and Levens, D. (2023) MYC function and regulation in physiological perspective. *Front Cell Dev. Biol.* **11**, 1268275, https://doi.org/10.3389/fcell.2023.1268275
20 Dang, C.V. (2012) MYC on the path to cancer. *Cell* **149**, 22–35, https://doi.org/10.1016/j.cell.2012.03.003
21 Lancho, O. and Herranz, D. (2018) The MYC enhancer-ome: long-range transcriptional regulation of MYC in cancer. *Trends Cancer* **4**, 810–822, https://doi.org/10.1016/j.trecan.2018.10.003
22 Schaub, F.X., Dhankani, V., Berger, A.C., Trivedi, M., Richardson, A.B., Shaw, R. et al. (2018) Pan-cancer alterations of the MYC oncogene and its proximal network across the Cancer Genome Atlas. *Cell Syst.* **6**, 282.e2–300.e2
23 Nie, Z., Guo, C., Das, S.K., Chow, C.C., Batchelor, E., Simons, S.S.J. et al. (2020) Dissecting transcriptional amplification by MYC. *Elife* **9**, e52483, https://doi.org/10.7554/eLife.52483
24 Lin, C.Y., Loven, J., Rahl, P.B., Paranal, R.M., Burge, C.B., Bradner, J.E. et al. (2012) Transcriptional amplification in tumor cells with elevated c-Myc. *Cell* **151**, 56–67, https://doi.org/10.1016/j.cell.2012.08.026
25 Nie, Z., Hu, G., Wei, G., Cui, K., Yamane, A., Resch, W. et al. (2012) c-Myc is a universal amplifier of expressed genes in lymphocytes and embryonic stem cells. *Cell* **151**, 68–79, https://doi.org/10.1016/j.cell.2012.08.033
26 Lourenco, C., Resetca, D., Redel, C., Lin, P., MacDonald, A.S., Ciaccio, R. et al. (2021) MYC protein interactors in gene transcription and cancer. *Nat. Rev. Cancer* **21**, 579–591, https://doi.org/10.1038/s41568-021-00367-9
27 Ruiz-Perez, M.V., Henley, A.B. and Arsenian-Henriksson, M. (2017) The MYCN protein in health and disease. *Genes (Basel)* **8**, 113, https://doi.org/10.3390/genes8040113
28 Hartl, M., Mitterstiller, A.M., Valovka, T., Breuker, K., Hobmayer, B. and Bister, K. (2010) Stem cell-specific activation of an ancestral myc protooncogene with conserved basic functions in the early metazoan Hydra. *Proc. Natl. Acad. Sci. U.S.A.* **107**, 4051–4056, https://doi.org/10.1073/pnas.0911060107
29 Huang, M. and Weiss, W.A. (2013) Neuroblastoma and MYCN. *Cold Spring Harb. Perspect. Med.* **3**, a014415, https://doi.org/10.1101/cshperspect.a014415

30 Zimmerman, K.A., Yancopoulos, G.D., Collum, R.G., Smith, R.K., Kohl, N.E., Denis, K.A. et al. (1986) Differential expression of myc family genes during murine development. *Nature* **319**, 780–783, https://doi.org/10.1038/319780a0
31 Malynn, B.A., de Alboran, I.M., O'Hagan, R.C., Bronson, R., Davidson, L., DePinho, R.A. et al. (2000) N-MYC can functionally replace c-MYC in murine development, cellular growth, and differentiation. *Genes Dev.* **14**, 1390–1399, https://doi.org/10.1101/gad.14.11.1390
32 Rickman, D.S., Schulte, J.H. and Eilers, M. (2018) The Expanding World of N-MYC-Driven Tumors. *Cancer Discov.* **8**, 150–163, https://doi.org/10.1158/2159-8290.CD-17-0273
33 Wolpaw, A.J., Bayliss, R., Buchel, G., Dang, C.V., Eilers, M., Gustafson, W.C. et al. (2021) Drugging the "undruggable" MYCN oncogenic transcription factor: overcoming previous obstacles to impact childhood cancers. *Cancer Res.* **81**, 1627–1632, https://doi.org/10.1158/0008-5472.CAN-20-3108
34 Brodeur, G.M., Seeger, R.C., Schwab, M., Varmus, H.E. and Bishop, J.M. (1984) Amplification of N-myc in untreated human neuroblastomas correlates with advanced disease stage. *Science* **224**, 1121–1124, https://doi.org/10.1126/science.6719137
35 Schwab, M., Varmus, H.E., Bishop, J.M., Grzeschik, K.H., Naylor, S.L., Sakaguchi, A.Y. et al. (1984) Chromosome localization in normal human cells and neuroblastomas of a gene related to c-myc. *Nature* **308**, 288–291, https://doi.org/10.1038/308288a0
36 Corvi, R., Amler, L.C., Savelyeva, L., Gehring, M. and Schwab, M. (1994) MYCN is retained in single copy at chromosome 2 band p23-24 during amplification in human neuroblastoma cells. *Proc. Natl. Acad. Sci. U.S.A.* **91**, 5523–5527, https://doi.org/10.1073/pnas.91.12.5523
37 Reiter, J.L. and Brodeur, G.M. (1996) High-resolution mapping of a 130-kb core region of the MYCN amplicon in neuroblastomas. *Genomics* **32**, 97–103, https://doi.org/10.1006/geno.1996.0081
38 Reiter, J.L. and Brodeur, G.M. (1998) MYCN is the only highly expressed gene from the core amplified domain in human neuroblastomas. *Genes Chromosomes Cancer* **23**, 134–140, https://doi.org/10.1002/(SICI)1098-2264(199810)23:2%3c134::AID-GCC6%3e3.0.CO;2-3
39 Tucker, E.R., Poon, E. and Chesler, L. (2019) Targeting MYCN and ALK in resistant and relapsing neuroblastoma. *Cancer Drug Resist.* **2**, 803–812, https://doi.org/10.20517/cdr.2019.009
40 Helmsauer, K., Valieva, M.E., Ali, S., Chamorro Gonzalez, R., Schopflin, R., Roefzaad, C. et al. (2020) Enhancer hijacking determines extrachromosomal circular MYCN amplicon architecture in neuroblastoma. *Nat. Commun.* **11**, 5823, https://doi.org/10.1038/s41467-020-19452-y
41 Hansford, L.M., Thomas, W.D., Keating, J.M., Burkhart, C.A., Peaston, A.E., Norris, M.D. et al. (2004) Mechanisms of embryonal tumor initiation: distinct roles for MycN expression and MYCN amplification. *Proc. Natl. Acad. Sci. U.S.A.* **101**, 12664–12669, https://doi.org/10.1073/pnas.0401083101
42 Otte, J., Dyberg, C., Pepich, A. and Johnsen, J.I. (2020) MYCN function in neuroblastoma development. *Front Oncol.* **10**, 624079, https://doi.org/10.3389/fonc.2020.624079
43 Ponzoni, M., Bachetti, T., Corrias, M.V., Brignole, C., Pastorino, F., Calarco, E. et al. (2022) Recent advances in the developmental origin of neuroblastoma: an overview. *J. Exp. Clin. Cancer Res.* **41**, 92, https://doi.org/10.1186/s13046-022-02281-w
44 Wakamatsu, Y., Watanabe, Y., Nakamura, H. and Kondoh, H. (1997) Regulation of the neural crest cell fate by N-myc: promotion of ventral migration and neuronal differentiation. *Development* **124**, 1953–1962, https://doi.org/10.1242/dev.124.10.1953
45 Knoepfler, P.S., Cheng, P.F. and Eisenman, R.N. (2002) N-myc is essential during neurogenesis for the rapid expansion of progenitor cell populations and the inhibition of neuronal differentiation. *Genes Dev.* **16**, 2699–2712, https://doi.org/10.1101/gad.1021202
46 Varlakhanova, N.V., Cotterman, R.F., deVries, W.N., Morgan, J., Donahue, L.R., Murray, S. et al. (2010) myc maintains embryonic stem cell pluripotency and self-renewal. *Differentiation* **80**, 9–19, https://doi.org/10.1016/j.diff.2010.05.001
47 Izumi, H., Kaneko, Y. and Nakagawara, A. (2020) The role of MYCN in symmetric vs. asymmetric cell division of human neuroblastoma cells. *Front Oncol.* **10**, 570815, https://doi.org/10.3389/fonc.2020.570815
48 Izumi, H. and Kaneko, Y. (2012) Evidence of asymmetric cell division and centrosome inheritance in human neuroblastoma cells. *Proc. Natl. Acad. Sci. U.S.A.* **109**, 18048–18053, https://doi.org/10.1073/pnas.1205525109
49 Buchel, G., Carstensen, A., Mak, K.Y., Roeschert, I., Leen, E., Sumara, O. et al. (2017) Association with Aurora-A controls N-MYC-dependent promoter escape and pause release of RNA polymerase II during the cell cycle. *Cell Rep.* **21**, 3483–3497, https://doi.org/10.1016/j.celrep.2017.11.090
50 Kalkat, M., Resetca, D., Lourenco, C., Chan, P.K., Wei, Y., Shiah, Y.J. et al. (2018) MYC protein interactome profiling reveals functionally distinct regions that cooperate to drive tumorigenesis. *Mol. Cell* **72**, 836–848.e7, https://doi.org/10.1016/j.molcel.2018.09.031
51 Legouy, E., DePinho, R., Zimmerman, K., Collum, R., Yancopoulos, G., Mitsock, L. et al. (1987) Structure and expression of the murine L-myc gene. *EMBO J.* **6**, 3359–3366, https://doi.org/10.1002/j.1460-2075.1987.tb02657.x
52 Leen, E., Yeoh, S., Sahak, E., Mitchell, E., Wildsmith, G., Batchelor, M. et al. (2026) Mechanism of interaction between the transactivation domain of N-MYC and the DNA-binding surface of TFIIIC5. *Nucleic. Acids. Res.* **54**, gkag181, https://doi.org/10.1093/nar/gkag181
53 Richards, M.W., Burgess, S.G., Poon, E., Carstensen, A., Eilers, M., Chesler, L. et al. (2016) Structural basis of N-Myc binding by Aurora-A and its destabilization by kinase inhibitors. *Proc. Natl. Acad. Sci. U.S.A.* **113**, 13726–13731, https://doi.org/10.1073/pnas.1610626113
54 Wei, Y., Redel, C., Ahlner, A., Lemak, A., Johansson-Akhe, I., Houliston, S. et al. (2022) The MYC oncoprotein directly interacts with its chromatin cofactor PNUTS to recruit PP1 phosphatase. *Nucleic. Acids. Res.* **50**, 3505–3522, https://doi.org/10.1093/nar/gkac138
55 Sjostrom, S.K., Finn, G., Hahn, W.C., Rowitch, D.H. and Kenney, A.M. (2005) The Cdk1 complex plays a prime role in regulating N-myc phosphorylation and turnover in neural precursors. *Dev. Cell* **9**, 327–338, https://doi.org/10.1016/j.devcel.2005.07.014
56 Kenney, A.M., Widlund, H.R. and Rowitch, D.H. (2004) Hedgehog and PI-3 kinase signaling converge on Nmyc1 to promote cell cycle progression in cerebellar neuronal precursors. *Development* **131**, 217–228, https://doi.org/10.1242/dev.00891
57 Malone, C.F., Mabe, N.W., Forman, A.B., Alexe, G., Engel, K.L., Chen, Y.C. et al. (2024) The KAT module of the SAGA complex maintains the oncogenic gene expression program in MYCN-amplified neuroblastoma. *Sci. Adv.* **10**, eadm9449, https://doi.org/10.1126/sciadv.adm9449
58 Conti, E. and Kuriyan, J. (2000) Crystallographic analysis of the specific yet versatile recognition of distinct nuclear localization signals by karyopherin alpha. *Structure* **8**, 329–338, https://doi.org/10.1016/S0969-2126(00)00107-6

59 Thomas, L.R., Foshage, A.M., Weissmiller, A.M., Popay, T.M., Grieb, B.C., Qualls, S.J. et al. (2016) Interaction of MYC with host cell factor-1 is mediated by the evolutionarily conserved Myc box IV motif. *Oncogene* **35**, 3613–3618, https://doi.org/10.1038/onc.2015.416
60 Liu, Z., Zhang, X., Xu, M., Hong, J.J., Ciardiello, A., Lei, H. et al. (2024) MYCN drives oncogenesis by cooperating with the histone methyltransferase G9a and the WDR5 adaptor to orchestrate global gene transcription. *PLoS Biol.* **22**, e3002240, https://doi.org/10.1371/journal.pbio.3002240
61 Thomas, L.R., Wang, Q., Grieb, B.C., Phan, J., Foshage, A.M., Sun, Q. et al. (2015) Interaction with WDR5 promotes target gene recognition and tumorigenesis by MYC. *Mol. Cell* **58**, 440–452, https://doi.org/10.1016/j.molcel.2015.02.028
62 Nair, S.K. and Burley, S.K. (2003) X-ray structures of Myc-Max and Mad-Max recognizing DNA. Molecular bases of regulation by proto-oncogenic transcription factors. *Cell* **112**, 193–205, https://doi.org/10.1016/S0092-8674(02)01284-9
63 Sammak, S., Hamdani, N., Gorrec, F., Allen, M.D., Freund, S.M.V., Bycroft, M. et al. (2019) Crystal structures and nuclear magnetic resonance studies of the Apo form of the c-MYC:MAX bHLHZip complex reveal a helical basic region in the absence of DNA. *Biochemistry* **58**, 3144–3154, https://doi.org/10.1021/acs.biochem.9b00296
64 Staller, P., Peukert, K., Kiermaier, A., Seoane, J., Lukas, J., Karsunky, H. et al. (2001) Repression of p15INK4b expression by Myc through association with Miz-1. *Nat. Cell Biol.* **3**, 392–399, https://doi.org/10.1038/35070076
65 Vo, B.T., Wolf, E., Kawauchi, D., Gebhardt, A., Rehg, J.E., Finkelstein, D. et al. (2016) The interaction of Myc with Miz1 defines medulloblastoma subgroup identity. *Cancer Cell* **29**, 5–16, https://doi.org/10.1016/j.ccell.2015.12.003
66 Andresen, C., Helander, S., Lemak, A., Fares, C., Csizmok, V., Carlsson, J. et al. (2012) Transient structure and dynamics in the disordered c-Myc transactivation domain affect Bin1 binding. *Nucleic. Acids. Res.* **40**, 6353–6366, https://doi.org/10.1093/nar/gks263
67 Rejnowicz, E., Batchelor, M., Leen, E., Ahangar, M.S., Burgess, S.G., Richards, M.W. et al. (2024) Exploring the dynamics and interactions of the N-myc transactivation domain through solution nuclear magnetic resonance spectroscopy. *Biochem. J.* **481**, 1535–1556, https://doi.org/10.1042/BCJ20240248
68 Helander, S., Montecchio, M., Pilstal, R., Su, Y., Kuruvilla, J., Elven, M. et al. (2015) Pre-anchoring of Pin1 to unphosphorylated c-Myc in a fuzzy complex regulates c-Myc activity. *Structure* **23**, 2267–2279, https://doi.org/10.1016/j.str.2015.10.010
69 Prendergast, G.C., Lawe, D. and Ziff, E.B. (1991) Association of Myn, the murine homolog of max, with c-Myc stimulates methylation-sensitive DNA binding and ras cotransformation. *Cell* **65**, 395–407, https://doi.org/10.1016/0092-8674(91)90457-A
70 Blackwood, E.M. and Eisenman, R.N. (1991) Max: a helix-loop-helix zipper protein that forms a sequence-specific DNA-binding complex with Myc. *Science* **251**, 1211–1217, https://doi.org/10.1126/science.2006410
71 Amati, B. and Land, H. (1994) Myc-Max-Mad: a transcription factor network controlling cell cycle progression, differentiation and death. *Curr. Opin. Genet. Dev.* **4**, 102–108, https://doi.org/10.1016/0959-437X(94)90098-1
72 Littlewood, T.D., Amati, B., Land, H. and Evan, G.I. (1992) Max and c-Myc/Max DNA-binding activities in cell extracts. *Oncogene* **7**, 1783–1792
73 Amati, B., Dalton, S., Brooks, M.W., Littlewood, T.D., Evan, G.I. and Land, H. (1992) Transcriptional activation by the human c-Myc oncoprotein in yeast requires interaction with Max. *Nature* **359**, 423–426, https://doi.org/10.1038/359423a0
74 Wilde, B.R. and Ayer, D.E. (2015) Interactions between Myc and MondoA transcription factors in metabolism and tumourigenesis. *Br. J. Cancer* **113**, 1529–1533, https://doi.org/10.1038/bjc.2015.360
75 Kerkhoff, E., Bister, K. and Klempnauer, K.H. (1991) Sequence-specific DNA binding by Myc proteins. *Proc. Natl. Acad. Sci. U.S.A.* **88**, 4323–4327, https://doi.org/10.1073/pnas.88.10.4323
76 Park, S., Chung, S., Kim, K.M., Jung, K.C., Park, C., Hahm, E.R. et al. (2004) Determination of binding constant of transcription factor myc-max/max-max and E-box DNA: the effect of inhibitors on the binding. *Biochim. Biophys. Acta* **1670**, 217–228, https://doi.org/10.1016/j.bbagen.2003.12.007
77 Jiang, M., Stanke, J. and Lahti, J.M. (2011) The connections between neural crest development and neuroblastoma. *Curr. Top. Dev. Biol.* **94**, 77–127, https://doi.org/10.1016/B978-0-12-380916-2.00004-8
78 Ferrucci, F., Ciaccio, R., Monticelli, S., Pigini, P., di Giacomo, S., Purgato, S. et al. (2018) MAX to MYCN intracellular ratio drives the aggressive phenotype and clinical outcome of high risk neuroblastoma. *Biochim. Biophys. Acta Gene Regul. Mech.* **1861**, 235–245, https://doi.org/10.1016/j.bbagrm.2018.01.007
79 Nikonova, A.S., Astsaturov, I., Serebriiskii, I.G., Dunbrack, Jr., R.L. and Golemis, E.A. (2013) Aurora A kinase (AURKA) in normal and pathological cell division. *Cell. Mol. Life Sci.* **70**, 661–687, https://doi.org/10.1007/s00018-012-1073-7
80 Lindon, C., Grant, R. and Min, M. (2015) Ubiquitin-mediated degradation of Aurora kinases. *Front Oncol.* **5**, 307
81 Asteriti, I.A., Rensen, W.M., Lindon, C., Lavia, P. and Guarguaglini, G. (2010) The Aurora-A/TPX2 complex: a novel oncogenic holoenzyme? *Biochim. Biophys. Acta* **1806**, 230–239, https://doi.org/10.1016/j.bbcan.2010.08.001
82 Ramsay, G., Stanton, L., Schwab, M. and Bishop, J.M. (1986) Human proto-oncogene N-myc encodes nuclear proteins that bind DNA. *Mol. Cell. Biol.* **6**, 4450–4457
83 Welcker, M., Orian, A., Jin, J., Grim, J.E., Harper, J.W., Eisenman, R.N. et al. (2004) The Fbw7 tumor suppressor regulates glycogen synthase kinase 3 phosphorylation-dependent c-Myc protein degradation. *Proc. Natl. Acad. Sci. U.S.A.* **101**, 9085–9090, https://doi.org/10.1073/pnas.0402770101
84 Welcker, M., Wang, B., Rusnac, D.V., Hussaini, Y., Swanger, J., Zheng, N. et al. (2022) Two diphosphorylated degrons control c-Myc degradation by the Fbw7 tumor suppressor. *Sci. Adv.* **8**, eabl7872, https://doi.org/10.1126/sciadv.abl7872
85 Otto, T., Horn, S., Brockmann, M., Eilers, U., Schuttrumpf, L., Popov, N. et al. (2009) Stabilization of N-Myc is a critical function of Aurora A in human neuroblastoma. *Cancer Cell* **15**, 67–78, https://doi.org/10.1016/j.ccr.2008.12.005
86 Wei, Y., Resetca, D., Li, Z., Johansson-Akhe, I., Ahlner, A., Helander, S. et al. (2019) Multiple direct interactions of TBP with the MYC oncoprotein. *Nat. Struct. Mol. Biol.* **26**, 1035–1043, https://doi.org/10.1038/s41594-019-0321-z
87 Hultman, J., Morad, V., Tanner, E., Kenney, T.M.G., Pietras, Z., Khare, L.P. et al. (2026) The N-Myc MB0-MBI region interacts specifically and dynamically with the N-lobe of Aurora kinase A. *Nat. Commun.* **17**, 2016, https://doi.org/10.1038/s41467-026-69725-1

88 Tang, J., Moorthy, R., Hirsch, L.E., Demir, O., Baker, Z.D., Naumann, J.A. et al. (2025) Targeting N-Myc in neuroblastoma with selective Aurora kinase A degraders. *Cell. Chem. Biol.* **32**, 352.e10–362.e10, https://doi.org/10.1016/j.chembiol.2024.12.006
89 Roeschert, I., Poon, E., Henssen, A.G., Garcia, H.D., Gatti, M., Giansanti, C. et al. (2021) Combined inhibition of Aurora-A and ATR kinase results in regression of MYCN-amplified neuroblastoma. *Nat. Cancer.* **2**, 312–326, https://doi.org/10.1038/s43018-020-00171-8
90 Seifert-Davila, W., van Breugel, M.E., van Leeuwen, F. and Muller, C.W. (2025) Should I stay or should I go: TFIIIC as assembly factor and barrier in RNA polymerase III transcription. *Biochem. Soc. Trans.* **53**, 925–934, https://doi.org/10.1042/BST20253058
91 Vidal, R., Leen, E., Herold, S., Muller, M., Fleischhauer, D., Schulein-Volk, C. et al. (2024) Association with TFIIIC limits MYCN localisation in hubs of active promoters and chromatin accumulation of non-phosphorylated RNA polymerase II. *Elife* **13**, RP94407, https://doi.org/10.7554/eLife.94407
92 Papadopoulos, D., Solvie, D., Baluapuri, A., Endres, T., Ha, S.A., Herold, S. et al. (2022) MYCN recruits the nuclear exosome complex to RNA polymerase II to prevent transcription-replication conflicts. *Mol. Cell* **82**, 159.e12–176.e12, https://doi.org/10.1016/j.molcel.2021.11.002
93 Muller, I., Larsson, K., Frenzel, A., Oliynyk, G., Zirath, H., Prochownik, E.V. et al. (2014) Targeting of the MYCN protein with small molecule c-MYC inhibitors. *PloS ONE* **9**, e97285, https://doi.org/10.1371/journal.pone.0097285
94 Follis, A.V., Hammoudeh, D.I., Wang, H., Prochownik, E.V. and Metallo, S.J. (2008) Structural rationale for the coupled binding and unfolding of the c-Myc oncoprotein by small molecules. *Chem. Biol.* **15**, 1149–1155, https://doi.org/10.1016/j.chembiol.2008.09.011
95 Han, H., Jain, A.D., Truica, M.I., Izquierdo-Ferrer, J., Anker, J.F., Lysy, B. et al. (2019) Small-molecule MYC inhibitors suppress tumor growth and enhance immunotherapy. *Cancer Cell* **36**, 483.e15–497.e15, https://doi.org/10.1016/j.ccell.2019.10.001
96 Soucek, L., Helmer-Citterich, M., Sacco, A., Jucker, R., Cesareni, G. and Nasi, S. (1998) Design and properties of a Myc derivative that efficiently homodimerizes. *Oncogene* **17**, 2463–2472, https://doi.org/10.1038/sj.onc.1202199
97 Garralda, E., Beaulieu, M.E., Moreno, V., Casacuberta-Serra, S., Martinez-Martin, S., Foradada, L. et al. (2024) MYC targeting by OMO-103 in solid tumors: a phase 1 trial. *Nat. Med.* **30**, 762–771, https://doi.org/10.1038/s41591-024-02805-1
98 Grebien, F., Vedadi, M., Getlik, M., Giambruno, R., Grover, A., Avellino, R. et al. (2015) Pharmacological targeting of the Wdr5-MLL interaction in C/EBPalpha N-terminal leukemia. *Nat. Chem. Biol.* **11**, 571–578, https://doi.org/10.1038/nchembio.1859
99 Ding, J., Li, G., Liu, H., Liu, L., Lin, Y., Gao, J. et al. (2023) Discovery of potent small-molecule inhibitors of WDR5-MYC interaction. *ACS Chem. Biol.* **18**, 34–40, https://doi.org/10.1021/acschembio.2c00843
100 Ding, J., Liu, L., Chiang, Y.L., Zhao, M., Liu, H., Yang, F. et al. (2023) Discovery and structure-based design of inhibitors of the WD repeat-containing protein 5 (WDR5)-MYC interaction. *J. Med. Chem.* **66**, 8310–8323, https://doi.org/10.1021/acs.jmedchem.3c00787
101 Han, Q.L., Zhang, X.L., Ren, P.X., Mei, L.H., Lin, W.H., Wang, L. et al. (2023) Discovery, evaluation and mechanism study of WDR5-targeted small molecular inhibitors for neuroblastoma. *Acta Pharmacol. Sin.* **44**, 877–887, https://doi.org/10.1038/s41401-022-00999-z
102 Yang, J., AlTahan, A.M., Hu, D., Wang, Y., Cheng, P.H., Morton, C.L. et al. (2015) The role of histone demethylase KDM4B in Myc signaling in neuroblastoma. *J. Natl. Cancer Inst.* **107**, djv080, https://doi.org/10.1093/jnci/djv080
103 Abu-Zaid, A., Fang, J., Jin, H., Singh, S., Pichavaram, P., Wu, Q. et al. (2024) Histone lysine demethylase 4 family proteins maintain the transcriptional program and adrenergic cellular state of MYCN-amplified neuroblastoma. *Cell Rep. Med.* **5**, 101468, https://doi.org/10.1016/j.xcrm.2024.101468
104 Amente, S., Milazzo, G., Sorrentino, M.C., Ambrosio, S., Di Palo, G., Lania, L. et al. (2015) Lysine-specific demethylase (LSD1/KDM1A) and MYCN cooperatively repress tumor suppressor genes in neuroblastoma. *Oncotarget* **6**, 14572–14583, https://doi.org/10.18632/oncotarget.3990
105 Mills, C.M., Turner, J., Pina, I.C., Garrabrant, K.A., Geerts, D., Bachmann, A.S. et al. (2022) Synthesis and evaluation of small molecule inhibitors of LSD1 for use against MYCN-expressing neuroblastoma. *Eur. J. Med. Chem.* **244**, 114818, https://doi.org/10.1016/j.ejmech.2022.114818
106 Phimmachanh, M., Han, J.Z.R., O'Donnell, Y.E.I., Latham, S.L. and Croucher, D.R. (2020) Histone deacetylases and histone deacetylase inhibitors in neuroblastoma. *Front. Cell. Dev. Biol.* **8**, 578770, https://doi.org/10.3389/fcell.2020.578770
107 Iraci, N., Diolaiti, D., Papa, A., Porro, A., Valli, E., Gherardi, S. et al. (2011) A SP1/MIZ1/MYCN repression complex recruits HDAC1 at the TRKA and p75NTR promoters and affects neuroblastoma malignancy by inhibiting the cell response to NGF. *Cancer Res.* **71**, 404–412, https://doi.org/10.1158/0008-5472.CAN-10-2627
108 Ouwehand, K., de Ruijter, A.J., van Bree, C., Caron, H.N. and van Kuilenburg, A.B. (2005) Histone deacetylase inhibitor BL1521 induces a G1-phase arrest in neuroblastoma cells through altered expression of cell cycle proteins. *FEBS Lett.* **579**, 1523–1528, https://doi.org/10.1016/j.febslet.2005.01.058
109 Frumm, S.M., Fan, Z.P., Ross, K.N., Duvall, J.R., Gupta, S., VerPlank, L. et al. (2013) Selective HDAC1/HDAC2 inhibitors induce neuroblastoma differentiation. *Chem. Biol.* **20**, 713–725, https://doi.org/10.1016/j.chembiol.2013.03.020
110 Cheung, B.B., Kleynhans, A., Mittra, R., Kim, P.Y., Holien, J.K., Nagy, Z. et al. (2021) A novel combination therapy targeting ubiquitin-specific protease 5 in MYCN-driven neuroblastoma. *Oncogene* **40**, 2367–2381, https://doi.org/10.1038/s41388-021-01712-w
111 Dodson, C.A., Kosmopoulou, M., Richards, M.W., Atrash, B., Bavetsias, V., Blagg, J. et al. (2010) Crystal structure of an Aurora-A mutant that mimics Aurora-B bound to MLN8054: insights into selectivity and drug design. *Biochem. J.* **427**, 19–28, https://doi.org/10.1042/BJ20091530
112 Brockmann, M., Poon, E., Berry, T., Carstensen, A., Deubzer, H.E., Rycak, L. et al. (2013) Small molecule inhibitors of Aurora-a induce proteasomal degradation of N-myc in childhood neuroblastoma. *Cancer Cell* **24**, 75–89, https://doi.org/10.1016/j.ccr.2013.05.005
113 Gustafson, W.C., Meyerowitz, J.G., Nekritz, E.A., Chen, J., Benes, C., Charron, E. et al. (2014) Drugging MYCN through an allosteric transition in Aurora kinase A. *Cancer Cell* **26**, 414–427, https://doi.org/10.1016/j.ccr.2014.07.015
114 Mosse, Y.P., Fox, E., Teachey, D.T., Reid, J.M., Safgren, S.L., Carol, H. et al. (2019) A phase II atudy of alisertib in children with recurrent/refractory solid tumors or leukemia: children's oncology group Phase I and Pilot Consortium (ADVL0921). *Clin. Cancer Res.* **25**, 3229–3238, https://doi.org/10.1158/1078-0432.CCR-18-2675
115 DuBois, S.G., Mosse, Y.P., Fox, E., Kudgus, R.A., Reid, J.M., McGovern, R. et al. (2018) Phase II trial of alisertib in combination with irinotecan and temozolomide for patients with relapsed or refractory neuroblastoma. *Clin. Cancer Res.* **24**, 6142–6149, https://doi.org/10.1158/1078-0432.CCR-18-1381

116 Chang, C.P., Yeh, T.K., Chen, C.T., Wang, W.P., Chen, Y.T., Tsai, C.H. et al. (2024) Discovery of a long half-life AURKA inhibitor to treat MYC-amplified solid tumors as a monotherapy and in combination with everolimus. *Mol. Cancer Ther.* **23**, 766–779, https://doi.org/10.1158/1535-7163.MCT-23-0602

117 Dawber, R.S., Gimenez, D., Batchelor, M., Miles, J.A., Wright, M.H., Bayliss, R. et al. (2024) Inhibition of Aurora-A/N-Myc protein–protein interaction using peptidomimetics: understanding the role of peptide cyclization. *ChemBioChem* **25**, e202300649, https://doi.org/10.1002/cbic.202300649

118 Gimenez, D., Walko, M., Miles, J.A., Bayliss, R., Wright, M.H. and Wilson, A.J. (2024) Constrained TACC3 peptidomimetics for a non-canonical protein–protein interface elucidate allosteric communication in Aurora-A kinase. *Chem. Sci.* **16**, 354–363, https://doi.org/10.1039/D4SC06100D

119 Donovan, K.A., Ferguson, F.M., Bushman, J.W., Eleuteri, N.A., Bhunia, D., Ryu, S. et al. (2020) Mapping the degradable kinome provides a resource for expedited degrader development. *Cell* **183**, 1714.e10–1731.e10, https://doi.org/10.1016/j.cell.2020.10.038

120 Adhikari, B., Bozilovic, J., Diebold, M., Schwarz, J.D., Hofstetter, J., Schroder, M. et al. (2020) PROTAC-mediated degradation reveals a non-catalytic function of AURORA-A kinase. *Nat. Chem. Biol.* **16**, 1179–1188, https://doi.org/10.1038/s41589-020-00652-y

121 Wang, R., Ascanelli, C., Abdelbaki, A., Fung, A., Rasmusson, T., Michaelides, I. et al. (2021) Selective targeting of non-centrosomal AURKA functions through use of a targeted protein degradation tool. *Commun. Biol.* **4**, 640, https://doi.org/10.1038/s42003-021-02158-2

122 Rishfi, M., Krols, S., Martens, F., Bekaert, S.L., Sanders, E., Eggermont, A. et al. (2023) Targeted AURKA degradation: towards new therapeutic agents for neuroblastoma. *Eur. J. Med. Chem.* **247**, 115033, https://doi.org/10.1016/j.ejmech.2022.115033

123 Krols, S., Rishfi, M., Martens, F., Van Hauwermeiren, A., Sanders, E., De Sutter, P.J. et al. (2025) Second-generation AURKA-targeting PROTACs: structural optimization toward *in vivo* degradation in neuroblastoma. *J. Med. Chem.* **68**, 23962–23976, https://doi.org/10.1021/acs.jmedchem.5c01271

124 Yu, X., Li, D., Kottur, J., Shen, Y., Kim, H.S., Park, K.S. et al. (2021) A selective WDR5 degrader inhibits acute myeloid leukemia in patient-derived mouse models. *Sci. Transl. Med.* **13**, eabj1578, https://doi.org/10.1126/scitranslmed.abj1578

125 Li, Z., Lim, S.L., Tao, Y., Li, X., Xie, Y., Yang, C. et al. (2020) PROTAC bromodomain inhibitor ARV-825 displays anti-tumor activity in neuroblastoma by repressing expression of MYCN or c-Myc. *Front Oncol.* **10**, 574525, https://doi.org/10.3389/fonc.2020.574525

126 Xu, Y., Yu, Q., Wang, P., Wu, Z., Zhang, L., Wu, S. et al. (2022) A selective small-molecule c-Myc degrader potently regresses lethal c-Myc overexpressing tumors. *Adv. Sci. (Weinh)* **9**, e2104344, https://doi.org/10.1002/advs.202104344