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Emerging therapeutic targets for neuroblastoma

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Abstract

Introduction: Neuroblastoma (NB) is the prime cancer of infancy, and accounts for 9% of pediatric cancer deaths. While children diagnosed with clinically stable NB experience a complete cure, those with high-risk disease (HR-NB) do not recover, despite intensive therapeutic strategies. Development of novel and effective targeted therapies is needed to counter disease progression, and to benefit long-term survival of children with HR-NB.

Areas covered: Recent studies (2017–2020) pertinent to NB evolution are selectively reviewed to recognize novel and effective therapeutic targets. The prospective and promising therapeutic targets/strategies for HR-NB are categorized into (a) targeting oncogene-like and/or reinforcing tumor suppressor (TS)-like lncRNAs; (b) targeting oncogene-like microRNAs (miRs) and/or mimicking TS-miRs; (c) targets for immunotherapy; (d) targeting epithelial-to-mesenchymal transition and cancer stem cells; (e) novel and beneficial combination approaches; and (f) repurposing drugs and other strategies in development.

Expert opinion: It is highly unlikely that agents targeting a single candidate or signaling will be beneficial for an HR-NB cure. We must develop efficient drug deliverables for functional targets, which could be integrated and advance clinical therapy. Fittingly, the looming evidence indicated an aggressive evolution of promising novel and integrative targets, development of efficient drugs, and improvised strategies for HR-NB treatment.

Keywords

Emerging therapeutics; high-risk Neuroblastoma; long non-coding RNAs; micro RNAs; immunotherapy; novel combinations; novel drugs

1. Introduction

Neuroblastoma (NB) is the most common extracranial solid tumor in infants, with the highest rate of diagnosis in the first month of life [1]. Each year, 650 new cases are diagnosed in the United States; of those, ~37% are diagnosed as infants and ~90% are

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Declaration of interest

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younger than 5 years [2]. NB originates from actively dividing neural crest cells (NCC) that accumulate several mutations and molecular rearrangements [3], presented as tumor mass along the midline of the body [3,4]. The partial list of genetic bases for the disease includes germline mutations (e.g. ALK, Phox2B), gene aberrations (e.g. *HRAS*) associated with other syndromes (e.g. neurofibromatosis, Li-Fraumeni), and familial NB [5]. NB is a highly heterogeneous tumor with an array of clinical manifestations from spontaneous regression, therapy-responsive disease, clinically stable disease, and progressive disease (PD) with therapy resistance, tumor recurrence, and eventual death. Based on clinical factors (age, stage, cellular differentiation/maturation) and biological markers at the time of diagnosis, children with NB are stratified into low-risk, intermediate-risk, and high-risk (HR-NB) subsets. While low-/intermediate-risk groups display favorable prognosis with >90% overall survival (OS), the HR-NB group show poor prognosis, with <50% five-year OS and dismal long-term survival [5]. HR-NB in general is characterized with segmental chromosomal aberrations, MYCN amplification, expression of neurotrophin receptor kinases, low exonic mutations, and telomere lengthening, and is correlated with advanced stage of disease, higher risk of relapse, and poor clinical outcome [6–10]. Treatment for HR-NB is generally divided into the *induction phase* with dose-intensive cycles of chemotherapy (CT – cisplatin/carboplatin, etoposide, vincristine, doxorubicin, topotecan, cyclophosphamide) and load reduction surgery; the *consolidation phase* with myeloablative CT (busulfan/melphalan or carboplatin/etoposide/melphalan and/or cyclophosphamide/thiotepa) along with radiotherapy (external beam RT, MIBG RT) and single or tandem stem cell (SC) transplant (autologous bone marrow transplantation [ABMT]; peripheral blood SC reinfusion); and the *maintenance phase* with RT, retinoic acid treatment (RA, 13-cis-retinoic acid), immunotherapy (dinutuximab), and immune-activating cytokine (GM-CSF, IL-2) treatment. In addition to the current clinical therapy for HR-NB, a number of strategies are currently under investigation, with >500 studies in clinical evaluation (www.clinicaltrials.gov). Despite such colossal efforts to treat HR-NB, the long-term survival for young children is depressing and warrants novel and improved therapeutic schemes. Appropriately, basic, preclinical, and clinical research are focused on this task worldwide. Herein, we aim to compile the novel targets, drug candidates, and/or therapeutic strategies in development that could shift a paradigm in the cure of HR-NB. The developmental therapeutics field for HR-NB is evolving fast, and the advancements have been periodically reviewed [11]. Here, we focus our discussion on the emerging therapeutic targets, drugs, and strategies defined within the last three years.

2. Targeting long noncoding RNAs (lncRNAs)

LncRNAs lack protein-coding functions and are known to regulate gene expression and cell fate [12]. LncRNAs play crucial roles in cellular functions (proliferation, differentiation, cell death, migration, invasion) and immune response, and have been implicated in the pathogenesis of various malignant cancers [13–16], including NB [17,18]. Studies defining the roles and mechanisms of lncRNAs in NB development, progression, dissemination, and induced therapy resistance could permit more informed stratification and new/improved therapeutic strategies (Figure 1). Polymorphisms in lncRNAs, including H19, LAMC2, 00673, and HOTAIR, have been linked to increased susceptibility to NB [19–22].

Consistently, studies underscored the criticality of lncRNAs in NB progression [23–27]. For instance, independent studies demonstrated that higher levels of CAI2, ncRAN, SNHG1, SNHG7, SNHG16, pancEts-1, and NHEG1 act like oncogenes (ON-lncRNAs) and are associated with poor differentiation, advanced disease stage, and unfavorable clinical outcomes, designating these candidates as prognostic biomarkers for HR-NB [23,24,28–32]. Conversely, a group of tumor suppressor (TS) lncRNAs have been associated with NB evolution. For instance, loss of TS-lncRNA CASC15, its encoded isoforms (CASC15-S, CASC15–003, CASC15–004), and TS-lncRNA NBAT1, located at the NB risk-associated 6p22.3 locus [33,34], correlated with poor OS/EFS [27,33,34]. Further, the critical ON-lncRNAs to TS-lncRNAs balance in NB progression was recognized in a high-throughput study, where high expression of ON-lncRNAs (HCN3, lnc01105) and low expression of TS-lncRNA (MEG3) were associated with poor prognosis [35].

Researchers have also documented the function and mechanism of ON-lncRNAs/TS-lncRNAs in NB evolution. For instance, USMYCN and MYCNOS have been shown to facilitate NB progression through increased MYCN expression [24–26]. MALAT1, the lncRNA involved in post-transcriptional gene regulation and mRNA splicing, activates Axl and influences NB cell invasion/migration [36]. Conversely, MYCN binds to the promoter and directly activates histone demethylase JMJD1A, which in turn demethylates histone H3K9 at the MALAT1 gene promoter and dictates NB cells' metastatic behavior [37]. Further, the hypoxia-dependent activation of MALAT1 drives FGF2-dependent angiogenesis and contributes to NB evolution [38]. Targeting the JMJD1A/MALAT1 or MALAT1-induced Axl reverts the cellular metastatic state and prevents NB progression with metastasis [36,37]. Likewise, targeting SNHG7, which facilitates NB progression by interacting with miR-653–5p and regulating STAT2, inhibits NB cell proliferation, migration, invasion, and plasticity [28]. SNHG16 influences transcriptional/translational pathways of NB malignancy (proliferation, migration, invasion) processes [30] definitively associated with disease stage, MYCN status and poor prognosis [17,39]. Mechanistically, SNHG16 binds to mir-542–3p and activates ATG5, driving clonal expansion, migration, and invasion of NB cells [17]. Targeting SNHG16 not only suppressed clonal expansion/metastatic behavior of NB cells, but also impeded ATG5-dependent autophagy and prompted NB regression. SNHG16 also interacts with and negatively regulates miR-128–3p, which in turn activates the miR-128 direct target HOXA7, and results in activated proliferation, migration, and invasion. In parallel, SNHG16 acts as a competing endogenous RNA (ceRNA) that interacts with miR-128 and destroys its translational inhibition of HOXA7, prompting NB progression [39]. Zhao and colleagues reported that NHEG1 is a LEF1/TCF7L2-regulated lncRNA that stabilizes DDX5 through physical interaction [18]. Disrupting the LEF1/TCF7L2/NHEG1/DDX5/β-catenin positive feedback loop by targeting NHEG1 and/or DDX5 inhibits DDX5-mediated cell-cycle progression, and prompts NB regression [18].

Another potential target, Paupar, which is transcribed upstream of Pax6 that binds to the transcriptional regulatory elements across multiple chromosomes and controls the expression of distal target genes, is known to regulate NB cell proliferation/differentiation [40]. Paupar not only regulates *Pax6* expression, but also directly interacts with KAP1, controls the expression of gene targets, and regulates proliferation and differentiation [41]. Silencing *Paupar* led to the reduction of KAP1 chromatin association and H3K9me3 at

PAX6 co-bound locations, and regulated the expression of genes involved in the cell cycle, DNA replication, mitosis, and neurite outgrowth [40].

Recognizing the oncogenic functions of lncRNAs in NB offers a series of potential target(s) that could be exploited for NB therapeutics. ON-lncRNA XIST, a lncRNA that is highly expressed in NB and corresponds to poor prognosis, interacts with EZH2 and thereby increases the level of H3K27me3 in DKK1 promoter [42]. Leveling XIST increases DKK1 and inhibits cell growth, invasion, migration, and tumor progression [42]. *PancEts-1*, a novel ON-lncRNA, endorses growth and metastatic potential of NB cells [32]. PancEts-1 binds to hnRNPK and facilitates its interaction with β-catenin, increasing the stability/transactivation of β-catenin, transcriptional regulation of downstream targets, and orchestration of disease evolution [32]. Another study showed that silencing ON-lncRNA MIAT altered genes involved in NB malignancy (growth, survival, apoptosis, oxidative stress, migration) processes [43]. High expression of another ON-lncRNA, DLX6-AS1, which blocks miR-107-targeted inhibition of BDNF and endorses NB cell proliferation and metastasis, positively correlated with poor differentiation and advanced disease [44]. Targeting DLX6-AS1 reinforced miR-107 function (targeting BDNF) and inhibited NB growth [44]. Along this line, SNHG1, which is also an ON-lncRNA that is highly expressed in NB, activated malignancy characteristics of NB cells and tumor progression through direct regulation of miR-338–3p and activation of miR-338 target PLK4 [45].

Conversely, knockdown of TS-lncRNAs CASC15 and NBAT1 prevented NB cell differentiation through increased nucleolar localization of USP36, and activated SOX9 by the regulation of CHD7 ubiquitination [33]. Loss of NBAT-1 activated neuronal-specific transcription factor NRSF/REST, thereby affecting neuronal differentiation, and contributed to NB progression [27]. Consistently, forced silencing of NBAT-1, CASC15–003, and CASC15-S has induced NB-cell proliferation, migration, and invasion [27,33,34]. Furthermore, studies indicated that high HCN3 and 01105 and loss of MEG3 are collaborative and critical for NB disease progression [35]. Silencing 01105 and HCN3 and over-expressing MEG3 led to p53 signaling (HIF-1α, Noxa, Bid) pathway-dependent cell death. Likewise, TS-lncRNA FOXD3-AS1 is downregulated in NB, and serves as an independent good prognostic marker for NB [46]. Reinforcing FOXD3-AS1 effects differentiation and reverts NB progression. Functionally, FOXD3-AS1 interacts with PARP1, represses the activation of CTCF, and activates downstream tumor-suppressive genes [46]. Differential expression of lncRNAs (ON-lncRNA/TS-lncRNA) has been causally linked to NB pathogenesis. High-throughput approaches recognized that NB is characterized by the differential expression of lncRNAs, and further noted the criticality of ON-lncRNAs↔TS-lncRNAs expressional combinations in disease evolution. Further, the mode of action and the lncRNA-driven signaling mechanism involved in NB pathogenesis were unveiled. The recognition of their significance and function, coupled with the preclinical evidence on the efficacy of their targeting, clearly designate lncRNAs as novel and potential emerging therapeutic targets for improved treatment for HR-NB. Despite such preclinical recognition, clinical validation on the potential use of lncRNAs as therapeutic targets for NB is imminent.

3. Targeting miRNAs

MicroRNAs (miRs), a group of small (19–22 nucleotides) non-coding RNAs, regulate gene expression through DNA interaction, translational repression, or by mRNA degradation. In cancer, miRs are classified as oncomiRs, metastamiRs, and Ts-miRs, and are known to impact various cellular processes (e.g. cell cycle, apoptosis, migration, invasion, angiogenesis) [47–49]. The development of therapy resistance is another complex NB issue in which the functions of miRs have been realized. Differential expression of miRs in association with NB clinicobiological physiognomies and their functions in disease pathogenesis have been noted [50,51]. For instance, a unique embryonic stem cell miR signature in NB and its association with high-risk disease and poor prognosis were reported [52]. Recently, a study compiled the present understanding of the function of miRs in NB pathogenesis, therapy resistance, and evolution [49]. Here we limit the discussion to the recently identified miR candidates that could be potential treatment targets and could deliver therapeutic benefit for HR-NB.

Numerous studies indicated the promising therapeutic benefit of targeting oncomiRs. OncomiRs (miR-221, miR-181a/b, miR-3934, miR-223) are highly expressed in NB cells/tumors and positively correlated with clinicopathological (e.g. MYCN, metastasis) characteristics and poor prognosis [48,53–55]. Functionally, miR-221 targets NLK-dependent LEF1 phosphorylation-mediated elevation of MYCN, which consequently induces proliferation, rescues cell cycle arrest, and prompts NB evolution [48]. However, MiR-181 is known to affect autophagy, apoptosis, and GTPase activity signaling pathways, and thus drives growth and dissemination destiny of NB cells. Instrumentally, miR-181 targets TS ABI1, which endorses NB pathogenesis [53]. It has been shown that TP53INP1 is a direct target of miR-3934–5p, and targeting miR-3934 prompts TP53INP1-dependent apoptosis, indicating that the miR-3934–5p/TP53INP1 axis may serve as a potential therapeutic target for NB [54]. In contrast, targeting miR-223–3p reinforces its direct target FOXO1, resulting in increased apoptosis and decreased tumor growth and invasion [55]. Recently, 11 circulating miRs (miR-513a-5p, miR-198, miR-1280, miR-1304, miR-1308, miR-1908, miR-513b, miR-548f, miR-580, miR-1261, miR-1268) were designated as prognostic markers for PD-NB [56,57]. Along the line of targeting oncomiRs, a study with nano-hybrid technology indicated that inhibition of miR-17 could fully differentiate the cancer cells into neurons and stop their growth [58].

The functional influence of TS-miRS in NB pathogenesis/evolution, mechanism of action, and the therapeutic benefit of their reinforcement has been proposed. Studies indicated critically low levels of TS-miRs (miR-324, Let7 family, miR-193b, miR-1247, miR-149, miR-323a, miR-145) in NB, and the loss of TS-miRs was significantly associated with poor clinical outcomes [59–65]. It is evident that increasing miR-324–5p inhibited its target VDAC and thus inhibited cell viability/proliferation. Preclinical evaluation of delivering (transfection/liposomes) the miR-324–5p mimic recognized the feasibility of miR-targeted chemosensitization and/or therapeutics [59]. The transcriptional regulator LMO1, a designated NB susceptibility gene, downregulated the Let-7 family (Let-7a-5p, Let-7b-5p, Let-7c, Let-7e-5p, Let-7f-5p, Let-7g-5p, Let-7i-5p) TS-miRs and dictated disease evolution

[60]. These outcomes indicate the possibility of identifying a large pool of potential therapeutic targets.

Interestingly, coordinated expression/function of TS-miR −193b-3p and oncomiRs' (miR92-a-3p, miR-17–5p) are reported in NB [61]. miR-193b reduces NB cell proliferation, induces caspase-dependent/-independent cell death, and prompts G1 cell cycle arrest. Studies have shown that TS-miRs (miR-193b, miR-376c) target Ccnd1/MYCN, which drives G1 cell cycle arrest and prompts cell death, targeting MCL-1 [61,66]. Interestingly, acquired loss of miR-376c-3p in progressive NB after therapy is indicated [66]. Another TS-miR target, miR-129, directly inhibits MYO10, a protein that is highly expressed in NB and correlates with poor prognosis [67], consequently regulating tumor growth and promoting sensitivity to Cytoxan [67]. A plethora of recent evidence recognized the criticality of TS-miRs' loss (and their mechanisms) in NB pathogenesis: (i) miR-146a targets the transcription/translation of BCL11a and promotes cell death [68]; (ii) miR-1247 targets ZNF346, inhibits Cyclin-D1, which dictates cell cycle progression, inhibits clonal expansion, and induces apoptosis [62]; (iii) miR-149 targets CDC42/BCL2 and inhibits proliferation, impedes colony formation, induces apoptosis, and prompts sensitization to Doxorubicin [63]; (iv) miR-323a-5p targets CCND1, CHAF1A, and INCENP, inhibits cell cycle progression, and induces apoptosis [64]; (v) miR-342–5p targets CCND1 and BCL-Xl, and thereby exerts NB regression [64]; (vi) miR-429 binds to 3′-UTR of IKKβ and inhibits clonal expansion, metastatic behavior, and tumor growth [69]; and (vii) miR-145 targets MTDH and inhibits malignancy physiognomies and tumor regression [65]. In addition, our recent studies identified a panel of 13 TS-miRs (miR-1206, miR-548–5p, miR-548f, miR-639, miR-640, miR-641, miR-647, miR-662, miR-886–3p, miR-887, miR-888, miR-576–5p, miR-600) that are completely lost in progressive disease [56,57]. Consistently, a high-throughput screening identified a large group (52 nos) of NB TS-miRs, recognizing that 7 (miR-380–5p, miR-665, miR-541–3p, miR-299–3p, miR-654–5p, miR-323–5p, miR-342–5p) shared a single locus (14q32), and the restoration of these miRs reduced NB cell viability [64]. Likewise, etoposide-resistant cells displayed monoallelic deletion of 13q14.3, where the miR-15a and miR-16–1 are located [70]. These chromosomal rearrangements corresponded to miR-15a/miR-16–1 loss-associated upregulation of BMI-1 oncoprotein and decreased TS-p16 [70].

Investigating the miR-regulatory networks for MYCN modulation, researchers showed that miR-506–3p downregulates PLAGL2, which has a dedicated binding site in the MYCN-promoter region and positively activates MYCN transcription [71]. Conversely, MYCN regulates PLAGL2 transcription through five MYCN-binding E-boxes in the PLAGL2-promoter region. PLAGL2 levels are associated with poor clinical outcomes in NB patients, and targeting PLAGL2 induces differentiation, impedes proliferation, and exerts synergism with MYCN silencing. Interestingly, RA treatment expresses miR-506 and represses MYCN and PLAGL2 [71]. Also, miR-15-a-5p, miR-15b-5p, and miR-16–5p are known to suppress MYCN mRNA by binding with the 3′UTR of MYCN, resulting in MYCN protein suppression [72]. Reinforcing these miRs inhibited proliferation, migration, and invasion of NB cells and tumor regression [72]. Moreover, the regulation of TS-miRs, at least in part, is orchestrated by the lncRNAs. LncRNAs like SNHG1, SNHG16, and DLX6-AS1 act as a ceRNA and sponge miRs, effecting negative regulation of TS-miRs (e.g. miR-107, miR-128, miR-338, miR-5423p) and destroying/depressing their target-translational inhibition

capabilities [17,39,44,45]. Interestingly, certain lncRNAs (e.g. SNHG16) are known to sponge more than one miR, activating many oncogenes and drivers that converge in NB pathogenesis.

The significance of TS-miRs in NB cell differentiation is well recognized [47]. For instance, miR-124 expression influences differentiation through transcription/translational activation of β-tubulin-III, MAP2, SYN, NF-M, and Nestin, emphasizing that reinforcement of miR-124 could serve as a potential treatment strategy for NB [73]. miR-124 is known to functionally mediate RA treatment-induced NB cell differentiation [74]. More importantly, miRs have been used for targeted delivery of oncolytic virus in NB. For example, miR-124, miR-125, and miR-134 (miRs expressed in healthy central nervous system, but not in NB) de-targeted delivery of oncolytic SFV-4 virus influenced neurovirulence reductions and increased oncolytic capacity with a NB cure rate of about 50% in a mouse model [75].

4. Targets for immunotherapy

In patients with HR-NB, human-mouse chimeric anti-GD2 antibody ch14.18 (dinutuximab) increased OS, and hence became the standard, FDA-approved therapy (2015) for this subset of patients [76–78]. The contribution of gangliosides in cell differentiation, growth, adhesion, and cellular communication has been well recognized. Such influences in cellular processes, intercellular communication, and cell-matrix interactions directly translate to the invasive/metastatic behavior of the NB cells [79]. GD2 is highly expressed in NB cells (*vs.* stroma) and serves as a strong prognostic marker for immunotherapy [80]. In the context of dose intensity limiting toxicity, unrealized biological features of constantly evolving HR-NB, identification of novel/effective markers, and adaptability/suitability of such therapeutics with the current clinical care, it is important to identify/develop new immunotherapeutic approaches for the cure of HR-NB. Dinutuximab beta (Qarziba), the mouse-human chimeric monoclonal antibody produced in mammalian cell lines, has been developed, validated, and is in clinical use [81–83]. Qarziba increases survival (OS, EFS) and led to reduced cumulative incidence of relapse/progression in HR-NB patients [84]. However, due to its side effects, including neuropathic pain, many studies are now focused on either improving GD2-immunotherapy or developing other immunotargets [79]. Along this line, a phase II trial with anti-GD2 antibody Hu14.18K322A in combination with induction CT improved early response and reduced tumor volumes in newly diagnosed HR-NB [85]. Hu14.18K322A is 98% human (hence reduces allergic reaction), displays similar binding specificity to dinutuximab, has a single point-mutation to reduce complement-associated pain, and is synthesized in a YB2/0 rat myeloma cell line that could reduce fucosylation and enhance antibody-dependent cell-mediated cytotoxicity. Conceptually, this study addressed the feasibility/efficiency of adding GD2-therapy to the induction CT (rather than salvage therapy) in improving the outcomes for HR-NB patients. Induction CT (six courses), along with hu14.18K322A and tailed with GM-CSF/IL2; consolidation therapy (busulfan/melphalan, additional course of hu14.18K322A with parent-derived NK cells); followed by Hu14.18K322A, GM-CSF, IL2, and isotretinoin showed regimen tolerance, >75% PR, primary tumor volume reductions, no progression, and, more importantly, 85% EFS [85].

Recent investigations identifying a growing list of novel molecular targets for HR-NB immunotherapy have yielded rewards. For instance, targeting c-Kit (CD117) with antibodies has been suggested for the treatment of HR-NB. The tyrosine kinase component of c-kit facilitates the binding of stem cell factor (SCF), which activates c-kit/SCF pathway-mediated tumor progression. Despite controversial claims regarding the association of c-kit with disease stage and MYCN amplification, targeting c-kit reduced NB-cell survival and clonal expansion. The encouraging clinical outcomes of c-kit immunotargeting in other tumor systems as monotherapy or in conjunction with ICIs (antiCTLA4, anti-PD1/PDL1) clearly recognize its possible use for HR-NB [86–88].

Similarly, CD133 (prominin-1), a marker for NCC and tumors derived from NCC, plays functional roles in tumorigenesis, therapy resistance, and progression. CD133 is extensively investigated in NB; higher levels of CD133 are associated with dedifferentiation, chemoresistance, and poor prognosis [3,79]. Anti-CD133 therapeutic strategies, including CD133KDEL fusion protein, polymer nanoparticles loaded with paclitaxel and targeted to CD133, anti-CD133 immunotoxin therapy, bispecific antibodies targeting CD133 and CD3 (activation of immune cells), and $CD8^+$ CAR-T cells specific to the AC133 epitope of CD133, displayed promising anti-tumor activity in a manifold of human tumors [79]. These favorable results and the documented insights into the role of CD133 in NB evolution designate CD133 as a promising target for HR-NB immunotherapy.

Likewise, higher levels of another NCC marker, the G-CSF receptor CD114, make NB cells highly tumorigenic and chemoresistant, with heightened self-renewal capacity and plasticity [89,90]. Despite its association with progression of NB and other tumors, and the defined role of G-CSFs in tumor-growth and chemoresistance, G-CSF is used to treat NB after myelosuppressive CT, underrating the undesirable consequences [79]. This complex and intertwined molecular process warrants a better understanding of the CD114-G-CSF axis for therapeutic benefit in NB. CD57, however, mediates invasion and migration of NCCs, and is associated with poor differentiation, bone marrow metastasis, and disease progression [79,91]. CD171 (L1CAM), an aberrantly expressed surface antigen in many tumors, including NB, plays a crucial role in cellular processes (growth, metastasis, angiogenesis), and is correlated with poor prognosis. Chimeric antibodies chCE7, iodine-labeled chCE7 targeting CD171, and the scFv fragments of chCE7 (CAR-T cells) exert anti-NB activity. With measurable effectiveness of autologous CE7R/HyTK+CD8+ cytolytic T-lymphocytes (Phase I trial) in HR-NB, additional trials are currently underway.

5. Targeting EMT and CSCs

The cellular transformation process, epithelial-to-mesenchymal transition (EMT), plays a significant role in tumor development and a conferred feature of malignancy. Upon EMT activation, cancer cells lose their epithelial characteristics (cell junctions, apical basal polarity) and acquire mesenchymal (self-renewal, migratory, invasive, sphere-forming) properties. In NB, EMT is more of an acquired process with defined molecular triggers/drivers (e.g. the WNT signaling pathway) [92]. Acquisition of EMT increases tumor-initiating capacity and confers therapy resistance. For instance, lncRNA-SNHG7 interacts with miR-653–5p, imposing STAT2 regulation, which impedes EMT and facilitates NB

progression [28]. Likewise, PLK4, a regulator for centriole replication, is highly expressed in NB (*vs.* normal tissue) and associated with poor OS/PFS [93]. PLK4 coordinates PI3K/AKT pathway-dependent EMT, and targeting PLK4 suppresses NB progression and metastasis, qualifying as a promising therapeutic target for HR-NB [93]. An independent study showed that silencing uPAR prompts nuclear translocation of uPA, which endorses EMT with suppressed epithelial (E-cadherin, Occlidin, claudin-5) and activated mesenchymal (N-Cadherin, NFκB, Snail, α-SMA) markers [94]. Consistently, pre-clinical studies targeting uPA/uPAR with inhibitors, miRs, antibodies, peptides, and gene silencing proved to be beneficial in tumors, including NB [95]. Further, the clinical evaluation (phase I, NCT00083525) of the safety, tolerability, MTD, and pharmacokinetics/dynamics of WX-UK1 (uPA inhibitor) in combination with capecitabine were assessed in patients with non-responsive advanced malignancies.

NB is characterized with a high heterogeneity (different lineage) of CSCs with self-renewing, tumor-initiating, sphere-forming capacity and that are highly resistant to current clinical therapy [96,97]. Studies recognizing the mechanisms of stemness maintenance, CSCs function in disease evolution, and their implications in cancer therapeutics [98,99] indicate the suitability of ideal targets for HR-NB treatment. For example, IGF1R is a highly expressed receptor in NB that activates EMT by expressing vimentin, Snail, and zeb1, and endorsed CSC-status through STAT3/AKT signaling [100]. Leveling IGF1R attenuated stemness behavior by suppressing Oct4, Sox2, Nanog, EpCAM, CD44, and CD133 [100]. CD44 is highly expressed in NB-cells and associated with poor prognosis in HR-NB patients, independent of MYCN status [96]. $CD44^+$ cells display NCC-mimicking stemness physiognomies, are highly tumorigenic, and produce progressive NB with metastasis [96]. Further, ALDH18A1 positivity was associated with MYCN amplification, advanced disease, NB progression/relapse, and poor OS/EFS [97]. ALDH18A1 is involved in RNA transport, ribosome biogenesis, DNA replication, and the cell cycle, and actuates proliferation and the self-renewal and tumor-initiating capacities of NB-cells [97]. ALDH18A1 increases MYCN expression through the miR-29b/SP1 autoregulatory loop and by disrupting the internal balance of the MYCN-inhibiting miRNA network(s) [97]. Targeting ALDH18A1 with YG1702 dictates MYCN suppression and inhibits NB growth [97]. CFC1, a recognized NB-CSC mobilizing factor, is known to control differentiation by targeting Activin-a. Leveling CFC1 suppresses NB aggravation via the blockade of stemness features.

Recent studies indicated that many drugs could be repur-posed/developed to target NB-CSCs and effect HR-NB control. The antipsychotic drug pimozide was shown to impede Wnt/β-catenin signaling-dependent EMT, inhibit the activation of STAT3 and STAT5 in CSCs, hinder the differentiation-inhibiting proteins (USP-1, WDR48), and thereby facilitate anti-neoplastic activity [101]. Dehydroeffusol (DHE) isolated from Chinese herbs promoted EMT suppression in NB by targeting Hedgehog and AKT/mTOR signaling, and consequently regulated the invasive phenotype [102]. Similarly, ginsenoside-Rk1 (saponin) treatment was shown to inhibit NB progression by blocking EMT with increased E-cadherin and decreased vimentin, MMP2, MMP9, and Snail [103].

In regard to induced drug resistance, studies have shown that targeting NB-CSCs could be an effective strategy to promote chemosensitization. Probenecid, a substrate for MRP,

sensitizes NB-CSCs to cisplatin by targeting MDR1, MRP2, and BCRP [104]. Researchers documented that cisplatin-/RT-resistant NB-cells exhibit CSC characteristics (CD133, ALDH, Nestin) with stemness maintenance (Sox2, Oct4, Nonog) and heightened proliferation [105]. The AKT2/mTOR and MAPK signaling pathways were essentially involved in cisplatin-/RT-resistant NB-CSCs. Targeting this axis with AKT (CCT128930) or MEK (PD98059) inhibitor reverted their malignancy characteristics [105]. Consistently, targeting the AKT/mTOR pathway in NB-CSCs with rapamycin and triciribine inhibited proliferation/migration, suggesting that AKT/mTOR is a promising target for CSC-rich HR-NB [106].

6. Novel combination strategies

Although there are many promising molecular targets for improved therapeutic options for HR-NB, conceptually out-of-box, yet effective, strategies remain a challenge. The influence of parallel and synergistic mechanisms coupled with the regulation of compromising events in disease evolution warrants a multi-target combinatorial approach for HR-NB cure. An interesting study predicted 88 targets for HR-NB, and confirmed the function of four known (PI3K, MTOR, CDK4/6, HMGCR already in clinical trials), three in-pipeline (PPARG, CDK2, ROCK in preclinical evaluation), and four novel (MAPK8, CNR2, UGCG, TSPO) targets that coordinate NB progression [107]. A preclinical combination study with serine kinase WEE1 inhibitor AZD1775 (Adavosertib) and irinotecan displayed significant synergism and therapeutic enhancement [108]. AZD1775 forced cell cycle progression without DNA damage repair, prompting mitotic catastrophe and cellular death. More importantly, a Phase I evaluation of the AZD1775-irinotecan combination for relapsed solid tumors, including NB, showed prolonged stable disease [109]. A synthetic agonist for TLR3 efficiently synergized with RA, activated the innate immune signaling and mitochondrial stress response, and consequently augmented RA-induced apoptosis [110]. Further, the TLR3-agonist-RA combination activated RAR-β and restored ATRX, resulting in induced differentiation and reduced vessel formation that dictated tumor regression [110]. Recently, a new strategy of using autologous MSCs as cargo (to metastatic disease) to evade recognition and attack from the innate/adaptive immune system proved advantageous [111,112]. To that end, a first-in-human, first-in-child study of MSC-delivered oncolytic virus (lcovir-5) conceptually recognized the use of this strategy for HR-NB, raising the possibility of reaching metastatic sites with this delivery method [111]. Alternatively, the use of allogeneic MSCs showed an NB-specific homing ability, long-term engraftment into NB, and efficient cellular delivery of anti-tumoral agents [113]. The strategy overcame limitations such as short half-life and toxicity.

Another strategy is the use of MIBG, a norepinephrine analog that is actively taken up by norepinephrine transporter receptors that are highly localized in NB. Beyond its use in NB diagnosis, MIBG is used in the treatment of relapsed/refractory HR-NB [114–116]. Studies determining the tolerated dose/toxicity in HR-NB patients reported CR/PR rates up to 66% [115]. The availability of ^{131}I-MIBG dosing (fixed, weight-based, radiation yield-based) options allowed the characterization of therapeutic ranges, requirements auto-SCR, toxicity, and patient stratification (age, previous treatments, soft-tissue/bone marrow) [115]. As with any radiotherapy, fractionation allows a high cumulative dose with maximal response.

Researchers investigated the benefit of ^{131}I-MIBG serial administrations. Retrospective review of stage-IV HR-NB cohort showed a 37% 5-Year OS; however, the review indicated the requirement for three sessions of ^{131}I-MIBG treatment for prolonged survival [114]. Beyond 131I-MIBG monotherapy, researchers have also documented the tolerance, toxicity, and response rate of ^{131}I-MIBG combination with CT (cisplatin, cyclophosphamide) and auto-SCR [115]. Coupling ^{131}I-MIBG treatment with tandem high-dose CT and auto-SCR produced a 10% increase in OS/EFS of HR-NB patients [116]. Critically, ^{131}I-MIBG treatment prior to the development of chemoresistance displayed a significant and lasting effect as part of induction treatment [115].

7. Drugs and strategies in development

In recent years, a manifold of promising novel targets, drugs, and strategies have been aggressively investigated in NB field. These are partially discussed below; a partial list is presented in Table 1. Third-generation ALK inhibitor repotrectinib (TPX-0005, currently in Phase I, Phase II trials) targets the active kinase conformations of ALK, ROS1, and NTRK1–3; impedes proliferation and prompts apoptosis in ALK-addicted NB cells; and inhibits ALK-driven neurite outgrowth and prompts tumor regression [117]. Vitamin K3 derivative (VK3-OH) induces apoptosis through activation of TS-p53, and downregulates Bcl-2 and Mcl-1 in MYCN-driven NB cells [118]. VK3-OH blocks MYCN transcription/translation and downregulates LIN28B in MYCN-amplified/overexpressed NB cells [118]. Sequential studies showed that therapeutic targeting (blocking peptide/sHRNA) of either MZF1-AS1 to disrupt MZF1-AS1/PAPR1/E2F1 axis-dependent proline synthesis or circ-CUX1 to deregulate circ-CUX1/EWSR1/MAZ axis-dependent glycolysis could be promising strategies for treating HR-NB [119,120]. Meriolin-1 (hybrid of meridianins/variolins) affects AKT/MAPK signaling and cell-cycle modulators (Cyclin-B1/D1, CDK1/2/4/6) that regulate cell proliferation and adhesion and prompts oxidative stress, autophagy, and death [147]. A novel antigene oligonucleotide (BGA002) that potentiates MYCN transcriptional inhibition reverts MYCN-dysregulated mitochondrial pathways in MYCN-amplified NB [148]. Likewise, the multi-kinase (RET/fusions, BRAF) inhibitor RXDX-105 targets NB cell malignancy vitals; its combination with RA produced a synergistic effect [149]. Another study showed that Isatin, an indole derivative, inhibits MAO activity and LSD1 demethylase activity, leading to increased H3K4m1 and PTEN, which negatively regulate the NB-cell metastatic state through PI3K/AKT and PTEN/p-SHC/p-FAK signaling [150]. Otsuka and colleagues demonstrated that TNIIIA2 peptide synergizes with RA treatment in increasing neuronal markers (NF-L, NF-H, GAP43) and inhibiting MYCN, dictating NB cell differentiation and tumor regression [151]. Repurposing Sildenafil for NB differentiation therapy indicated that both sildenafil and its analog IS00384 phosphorylated C3G; activated AMPK signaling; increased NeuN, NF-H, and βIII-tubulin; and induced neurite outgrowth [152]. Likewise, repurposing mefloquine for NB treatment showed that it prompts redox stress-mediated apoptosis by binding to acyl-CoA [153]. Thiopurines (small molecules, CCI52, CCI52–14) showed efficient sensitization of MYCN-spontaneous NB to 6-MP, irinotecan, and vincristine [154].

Many recent findings indicated the potential of natural phytochemicals in HR-NB treatment. As discussed above, the benefit of ginsenoside-RK1 in targeting NB EMT and malignancy/

metastatic behavior has been realized [103]. Likewise, studies have extensively documented the anti-tumor and chemo/radiosensitizing potential (and mechanisms) of curcumin and its synthetic analogues in NB [155–158]. 4-hydroxy chalcone (4HC, flavonoid) treatment induced NB cell death by increasing oxidative stress and LDH activity, and prompted chemosensitization to doxorubicin and cisplatin [159]. Conversely, a polysaccharide from *Angelica sinensis* has been shown to attenuate BCl2, activate Bax and Casp3, and promote apoptosis [160]. This polysaccharide: (i) inhibited the TGFβ1-induced EMT by targeting N-Cad, vimentin, and Zeb1 and activating E-Cad and (ii) upregulated TS-miR-205, consequently suppressing PI3K/AKT and ERK1/2 signaling [160]. Also, S-allyl-L-cysteine from aged-garlic extract prompted mitochondrial membrane depolarization and induced NB cell death [161].

The advances in nanotechnology and its significance in targeted delivery of desired anti-cancer drugs directed focus in developing strategies for HR-NB treatment [162]. Green Zn oxide nanoparticles (ZnONPs) with skeel-peel-extract generated ROS regulated autophagy (LC3-I, LC3-II, ATG4B) and induced apoptosis (↑Bax, ↑Casp3, ↓Bcl2) [163]. A study comparing delivery of hydroalcoholic extract of marine angiosperm (*Posidonia oceanica*) loaded onto two different (chitosan/PEG-soluplus) nanoparticles recognized the efficiency of the approach and the benefit of the drug candidate in NB therapy [164]. Another NP approach using a combination of semi-synthetic cytotoxic retinoid and anti-angiogenic lenalidomide displayed excellent *in vitro* cytotoxicity and *in vivo* efficacy [165]. MXD3-antisense oligonucleotide-loaded SPIONPs delivered to NB without toxicity indicated its benefit as dose-reducing agent for CT [166]. In an interesting strategy, a bismuth selenide NPs core shelled with silver was coupled with RNA 3-way junction: one leg attached to the NP, the second harbored a cell-penetrating RNA+fluorescence tag, and the third was designed to target miR-17 and RA release [58]. This strategy yielded full differentiation of NB cells into neurons and stopped their growth. Furthermore, for miR-based NB treatment, many sophisticated nano-formulations (e.g. miR-542–3p-encapsulated-NPs, TS-miR-34a +GD2Ab-SilicaNPs, amino-functionalized gold NPs complexed with miR-31, NP glazed with PEG) and novel approaches were identified for efficient delivery of miRs in passive, active, or stimuli-responsive models [162].

With an unusual strategy, researchers investigated the benefit of TCDD, a dioxin with carcinogenic properties, and a toxic industrial pollutant, hexavalent chromium (CrVI), for NB treatment [167]. TCDD prompted AhR-dependent activation of pro-adhesion genes (18S, PCDHB, PCDHG, FZD2, FLOT2, DDR2) and inhibited the spontaneous movement of NB cells [167]. CrVI involves ROS-mediated Akt/ERK/AMPK-dependent cell death. However, the usefulness of these strategies in clinics is questionable.

8. Expert opinion

Despite significant advances in NB therapy over the past three decades and achieving excellent clinical outcomes for patients with stable/intermediary-risk disease, the cure rate for HR-NB is disappointing. This gap is attributed to the ongoing acquisition of genetic and molecular rearrangements, the EMT process and CSC clonal selection/enrichment, heterogeneity of CSC populations, lack of understanding on the interplay of events and

compromising and/or alternating mechanisms, and equivocal claims of the linear response of a specific target or signaling. These gaps led to identification of pockets of signaling events and targets, with much less clinical translation and use. Since a complete understanding of NB biology is required for development of efficient therapy, researchers have focused on unveiling the disease blueprint through high-content GWAS, genomic analysis, whole-genome sequencing, transcriptomics, proteomics, and drug screening. The outcomes from these measures guided diagnosis, risk-stratification, and identification of clinicopathological features/therapy-response-specific molecular targets that may serve as candidate(s) for improved therapeutic strategies. Overall, the targets are grouped into: (i) oncotargets (oncogenes, oncomiRs, onco-lncRNAs) that activated corresponding to the mutations, amplification, modifications; (ii) inactivating tumor suppressors through deletion, epigenetic silencing, or mutation; (iii) NB- and/or cell-type-specific targets (e.g. GD2, NB-CSC markers, neuronal cell differentiation markers); and (iv) context (HR, therapy resistance, progressive/recurrent disease)-specific molecular determinants. However, a simultaneous, yet assenting (activated oncotargets and deactivated TS) interplay of events is known to drive disease pathogenesis and progression. In this regard, studies identifying novel molecular targets, and defining their functions and mechanism(s) are aggressively evolving (Figure 2). The new treatment protocols under current development are primarily directed to identify the diagnostic and/or prognostic relevance; mechanistic signaling flow-through; function in cellular processes of malignancy; drug delivery strategies; targeting efficacy in cellular and/or pre-clinical evaluation; combination strategies; or repurposing strategies. The promise of this focus is evident, as numerous clinical trials (>500) have been initiated to define novel therapeutic options for HR-NB, with an aim to evaluate new targets, drugs, a combination treatment, or repurposing strategies (Table 2).

Although a number of targets are considered for HR-NB, mechanistically the majority of these converge on a handful of key determinants (or signaling pathways), including ALK, MYCN, RAS/MAPK, cell-cycle/apoptotic regulators, EMT/CSC drivers, and differentiation modulators. Initially, it was believed that targeting activated drivers was beneficial, but the dynamic molecular rearrangements in HR-NB indicated the acquisition of compromising and/or complementing effects, warranting the reinforcement of brake (TS) systems in parallel. For example, although it is difficult to directly target MYCN, the key player in the pathogenesis and evolution of HR-NB, it is feasible to target MYCN drivers (lncUSMYCN, lncMYCNOS) or reinforce MYCN regulators TS-miRs (miR-506–3p, miR-15-a-5p, miR-15b-5p, miR-16–5p) to treat MYCN-amplified or highly expressed progressive HR-NB. Many proposed targets and approaches independently or interactively target MYCN expression and function in NB cells, resulting in tumor regression. These new pathways identify better ways of targeting MYCN that could definitively advance therapy for HR-NB. ALK activation, which acts in synergy with MYCN expression, is an oncogenic driver for NB and could be selectively druggable. Sequential generations of small molecule ALK inhibitors are developed based on their ALK-binding affinity to all mutational variants and are in clinical evaluation for HR-NB. ALK-targeted therapy alone or in conjunction with the conventional CT is a promising possibility, particularly when a targeted population that responds to ALK inhibitors could be defined through either genomic screening for mutations in the TK domain or ALK amplification/overexpression.

Targeting EMT drivers and surface antigens that are selectively/highly expressed on NB-CSCs cells is highly beneficial, especially for progressive HR-NB. Combination and/or repurposing strategies with drugs for other medical conditions are highly effective, but warrant the evaluation of clinical benefit in HR-NB. With recent dosing advances in targeted (I^{131}MIBG) RT, this approach is exceptionally beneficial for the treatment of HR-NB. Likewise, the evolving sophistication in nanotechnology not only allows precise delivery of drugs in a safer and effective manner, but also permits a multi-target (e.g. RA, miR) approach. Beyond the betterment of strategies and drugs for the conventional targets, emerging evidence indicates a number of proteins/pathways (see Table 1) that could be promising targets for this deadly disease. These candidates fall into the categories of apoptotic, differentiation, autophagy, signal transduction, EMT, and stemness maintenance regulators. Although the functional relevance of these determinants is pre-clinically documented in HR-NB, the therapeutic benefit of targeting such candidates alongside current clinical therapy is yet to be discovered.

Taken together, the understanding of the biology of progressive HR-NB, dynamic rearrangements in response to therapy, molecular targets and mechanism(s) of action, identification/development of drug candidates, and identification of delivery tools are aggressively evolving. The continuous flow of knowledge and technical sophistication is likely to identify new, improved, and effective therapeutic strategies for specific subsets of patients with HR-NB. Though currently the progress is only halfway through, assessing the recent evolution in the field and considering the focus, the paradigm shift in HR-NB treatment could be realized in the next 5 years or so.

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Article highlights

- Novel and improved therapeutic schemes are required to counter unacceptable survival rates in children with high-risk neuroblastoma (HR-NB)
- Oncogene-like and tumor suppressor lncRNAs serves as emerging therapeutic targets for NB
- OncomiRs - TS-miRS' modulation and coordinated functions dictates NB pathogenesis
- lncRNAs sponge multiple miRs, activating oncogenes and drivers that converge in NB pathogenesis
- Novel targets for immunotherapy indicates a promising strategy for the treatment of HR-NB
- Targeting EMT and CSC stemness maintenance is highly beneficial for progressive disease
- Combination strategies and/or repurposing clinical drugs are highly effective for HR-NB.

This box summarizes key points contained in the article.

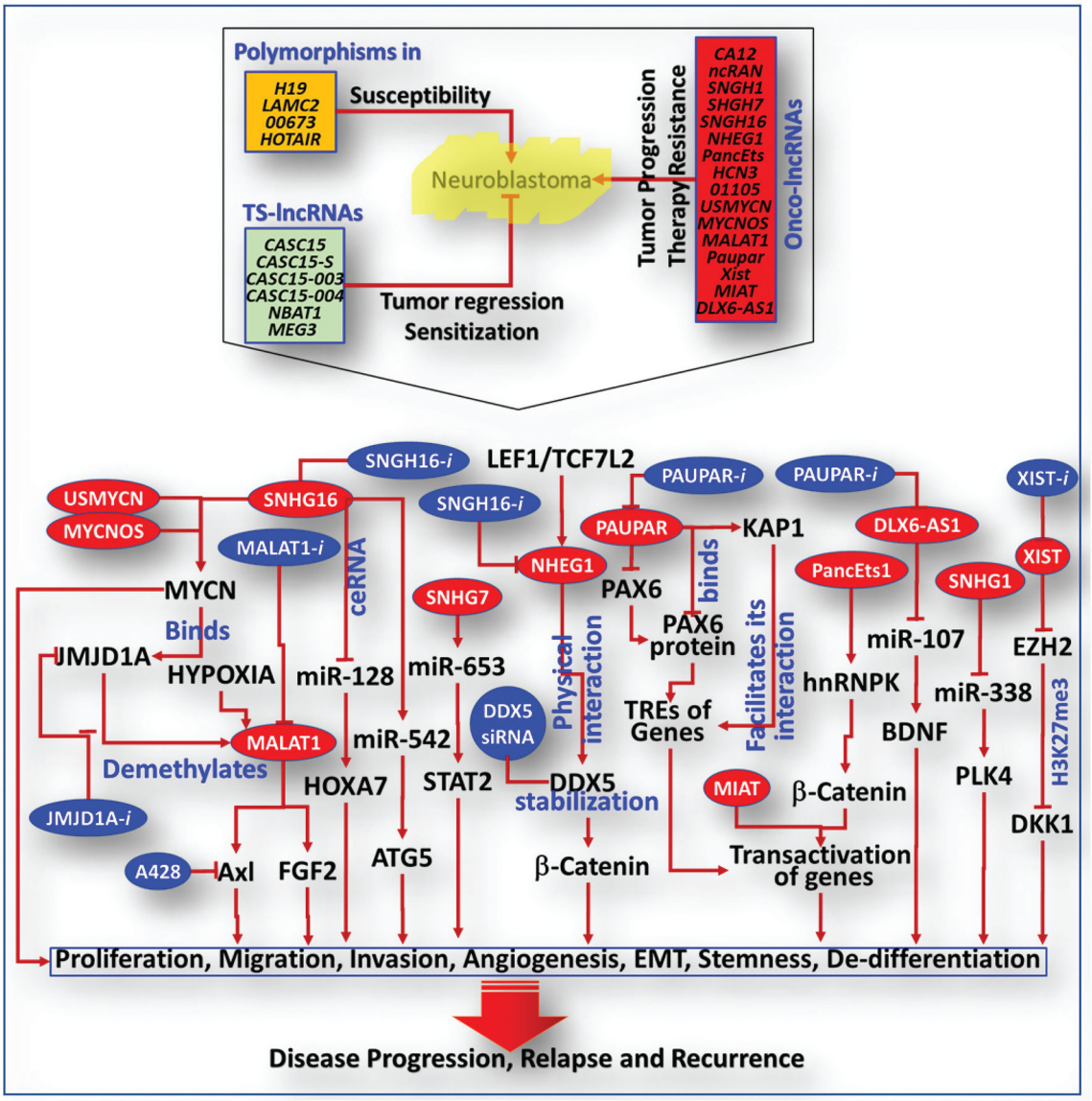

Figure 1. Schematic representation of the functional role of lncRNAs in NB pathogenesis and disease evolution.

Bottom panel: Panel of oncogene-like lncRNAs and their signaling flow-through that affects malignancy characteristics (e. g., proliferation, de-differentiation, migration, invasion, angiogenesis EMT, CSC status) in NB cells, which dictates NB pathogenesis and disease evolution. Blue circles indicates the preclinically validated targeted therapeutic strategies for HR-NB.

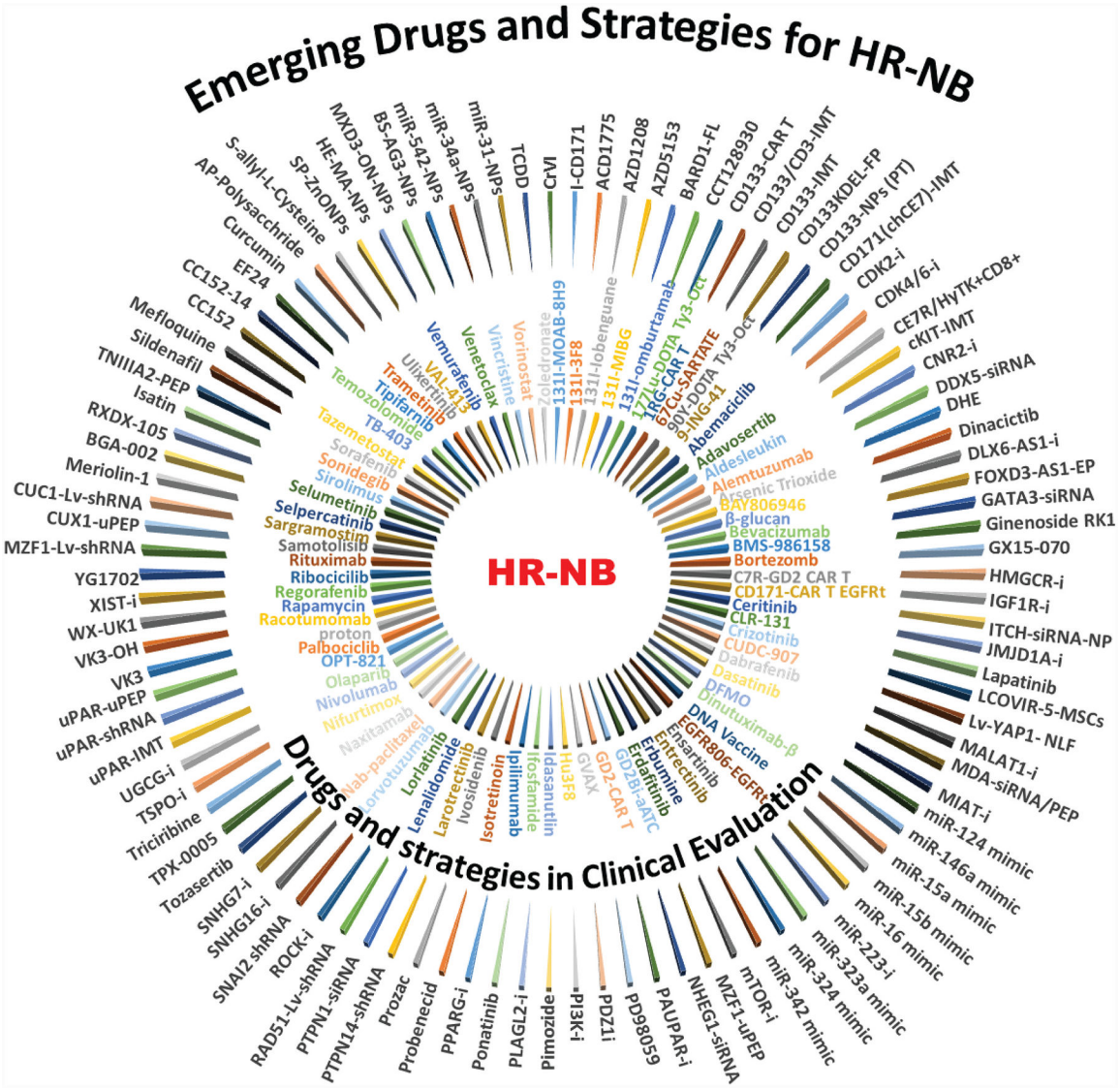

Figure 2. Concentric plot showing the recent evolution of drugs and strategies for HR-NB

Inner circle: Partial list (from 506 current clinical trials) of targeted drugs, modalities, and/or their combination in current clinical evaluation in Phase I, II, and III trials. ***Outer circle***: Partial list of potential and promising targeted (discussed in the text) developed or repurposed drugs (e. g., inhibitors, miRs, antibodies, peptides, gene silencing, clinical drugs) that were validated in preclinical settings, alone and/or in combination with conventional chemotherapy for HR-NB. Combination strategies revealed that these candidates integrated well with drugs in current clinical therapy, with a synergistic effect in the HR-NB setting.

Table 1.

Partial list of emerging targets; their functions in cellular processes (malignancy characteristics), mechanism(s) of action, and signaling flow-through; and potential drugs or strategies to improve HR-NB treatment.

Target	Function/Strategy	Targets/Signaling	Therapeutic strategy	Ref.
MDA-9/SYNTENIN	↑Metastasis, ↑EMT, ↓OS	↑Src, ↑FAK, ↑NFkB, ↑Slug, ↑MMP2, ↑MMP9. ↑integrin→SRC→RHO→RAC→CDC42	PDZ1i, MDA-siRNA, peptide	[121,122]
GLS2	↓Proliferation, ↑Cell cycle arrest	↓cMYC		[123]
$P27^{kip1}$	↓Progression	MYC→CKS1→SKP2→$P27^{kip1}$	Prozac	[124]
KLF9	↑Differentiation, ↓Proliferation, ↓Invasion	↓SHH binding to the promoter, ↓GUI,		[125]
WRD5	↑Proliferation, ↑Tumorosphere formation	↑MYC, CARM↑, ↑H3K4me3		[126]
MZF1	↑Glycolysis	↑HK2, ↑PGKI, ↑YY1	21-AA-MZF1-uPEP	[127]
SNAI2	↑Self-renewal, ↑EMT, ↑RA-resistance, ↓Differentiation	↓NRCAM, ↓CDH5	CRISPR-Cas9, shRNA	[128]
Stmn	↑Migration, ↑Invasion	↑PTPN14, miRs ↑(3935, 1281, 4682, 222, 221, 620, 488) ↓(382, 935, 4656, 132, 4492)	PTPN14-shRNA	[129]
ITCH	↓Apoptosis, ↑Radioreistance	↓TP73	siRNA-NPs	[130]
PLPR1	↓Cell-migration, ↑Adhesion	↓RAC1		[131]
TRKB	↑Entrectinib resistance	↑ERK/MAPK, ↓PTEN		[132]
BARD1	↑DNA damage after RT, ↑Apoptosis, ↑G2/M cell cycle	↑IGFIR, ↑P75	BARD1-FL	[133]
YAP1	↑Trametinib resistance, ↑Cell viability, ↑Proliferation	↑MAPK, ↑E2F, ↑MYCN, ↑$P27^{KIP1}$-NL, ↑AKT	Lv-CRISPR-YAP1-null-NLF	[134,135]
TERT	↓Prognosis, ↑Oncogenic pathway	↑BRD4, H3K27AC, H3K36me3	BRD4i (AZD5153), CDKi (dinacictib)	[136]
PNUTS	↑Proliferation	↑MYCN Protein	CDKTi (THZ1) + TKI	[137]
MYCN-LM01-ASCL1	↓Differentiation	↓NTRK/TRKA, ↓NPY	Ponatinib, Lapatinib	[138]
GX15–070→↓ BCl2	↑Prosurvival autophagy, ↓Apoptosis	↑LC3II	GX15–070 + HCQ	[139]
Hypomethylation of GATA3	↑Proliferation, ↑G2-M, ↓PARP cleavage	↑GATA3 Protein, ↑CCND1	GATA3-siRNA	[140]
PIM1	↑ALKi resistance, ↓Apoptosis		PIM1i (AZD1208) + Ceritinib	[141]
GOLPH3	↑DNA repair, ↑Therapy resistance	↑TPX2, ↑MY018A		[142]
AURKA, AURKB	↓Apoptosis, ↓G2-M	↑PGAM2, ↑ACADM	AURKi - Tozasertib (VX-680)	[143]
$PTPN1^{P}$	↑Proliferation		PTPN1-siRNA	[144]
RAD51	↑Chemoresistance		Lv-shRNA	[145]
MCPIP1	↓Proliferation, ↑G1 phase	↓Cyclins A1, b1, D1, D3, E1, E2, ↓$CDK2^{P}$, ↓$CDK4^{P}$, ↓RB		[146]

Table 2.

Partial list of investigational drugs and/or strategies (and their molecular targets) that are currently under clinical evaluation. The list is limited to represent distinct drugs and strategies.

Phase	NCT ID	Drugs / Strategy	Target
Phase 1	NCT04049864	DNA Vaccine	Phox2B, Survivin, MAGEA1/3, PRAME
Phase 1	NCT00790413	^{131}I-MIBG+CT+T-Cell^{-}+Lymp^{+} +HSC+MSC+Rituximab	CD20
Phase 1	NCT02573896	Auto-NKCs + Dinutuximab +/− Lenalidomide	GD2, TNFa, VEGF, bFGF
Phase 1	NCT03294954	GD2-CAR + IL15- Auto-NKTs + CT	GD2
Phase 1	NCT04106219	LY3295668 Erbumine +/− CT	AURA
Phase 1	NCT02298348	Sorafenib + Topotecan, Cyclophosphamide	Tyrosine Kinase
Phase 1	NCT04023331	67Cu-SARTATE PR-RT	SSTR
Phase 1	NCT03966651	177Lu-DOTA0-Tyr3-Octreotate PR-RT	SSTR
Phase 1	NCT02914405	Nivolumab +Ch14.18/CHO	PD-1, GD2
Phase 1	NCT00492167	beta-glucan + 3F8	
Phase 1	NCT04239040	GVAX + Nivolumab, Ipilimumab	PD-1, CTLA-4
Phase 1	NCT01711554	Lenalidomide +Dinutuximab +/− Isotretinoin	angiogenesis inhibitor
Phase 1	NCT02311621	CD171-CAR T cells expressing EGFRt	CD171, EGFR
Phase 1	NCT03332667	131I-MIBG With Dinutuximab	GD2
Phase 1	NCT03107988	Lorlatinib	ALK, ROS-1
Phase 1	NCT01953900	iC9-GD2-CAR-VZV-CTLs	GD2
Phase 1	NCT02030964	DFMO + Celecoxib + CT	ODC
Phase 1	NCT02761915	1RG-CART	GD2
Phase 1	NCT02748135	TB-403	PLGF
Phase 1	NCT03635632	C7R-GD2.CART cells + CT	GD2
Phase 1	NCT00089245	I131 MOAB 8H9	glycoprotein 4Ig-B7-H3
Phase 1	NCT03478462	CLR 131	
Phase 1	NCT02909777	CUDC-907	HDAC
Phase 1	NCT04239092	9-ING-41 + Irinotecan	GSK-3β
Phase 1	NCT03709680	Palbociclib + Temozolomide + Irinotecan	CDK4, CDK6, DNA replication
Phase 1	NCT03236857	venetoclax + CT	BCl2
Phase 1	NCT04337177	VAL-413 + Temozolomide	DNA Replication

Phase	NCT ID	Drugs / Strategy	Target
Phase 1	NCT04308330	Vorinostat + Chemotherapy	HDAC
Phase 1	NCT02536183	Lyso-thermosensitive liposomal dox + MR-HIFU	
Phase 1	NCT03618381	EGFR806-EGFRt + CD19-Her2tG	EGFR
Phase 1	NCT02508038	Zoledronate + TCRαβ+/CD19+ depleted H-HSCT	
Phase 1	NCT01331135	Sirolimus	mTOR
Phase 1	NCT01625351	Sirolimus, Alemtuzumab	mTOR, CD52,
Phase 1	NCT02644460	Abemaciclib	CDK4, CDK6
Phase 1	NCT03434262	Gemcitabine, Ribocicilib, Sonidegib, Trametinib	CyclinD1, CDK4/6, HH, MEK1, MEK2
Phase 1	NCT01121588	Crizotinib (PF-02341066)	ALK, ROS1
Phase 1	NCT02085148	Regorafenib + Vincristine + Irinotecan	RTK, VEGFR2-TIE2
Phase 1	NCT03936465	BMS-986158	BET
Phase 1	NCT03507491	Nab-paclitaxel + Gemcitabine	
Phase 1	NCT04238819	Abemaciclib + Temozolomide, Irinotecan	CDK4, CDK6
Phase 1	NCT02650401	Entrectinib (Rxdx-101)	Trk, Ros1, Alk Fusions
Phase 1/2	NCT00703222	SNJB-JF-IL2 and SJNB-JF-Lptn + Dose Level 1 SKNLP	
Phase 1/2	NCT02173093	GD2Bi-aATC	GD2
Phase 1/2	NCT02139397	DFMO + Bortezomib	ODC, proteasome inhibitor
Phase 1/2	NCT00911560	OPT-821 vaccine with GD2L and GD3L	GD2, GD3
Phase 1/2	NCT03860207	Hu3F8-BsAb	GD2
Phase 1/2	NCT03923257	PRRT-177Lu-DOTA tyr3-Octreotide	SSTR
Phase 1/2	NCT04029688	Idasanutlin + Venetoclax + CT	MDM2, BCl2
Phase 1/2	NCT02095132	Adavosertib + Irinotecan	WEE1
Phase 1/2	NCT02124772	Dabrafenib, Trametinib	B-RAF, MEK1, MEK2
Phase 1/2	NCT00788125	Dasatinib + Ifosfamide + CT + surgery + RT	Bcr-ABL, Src
Phase 2	NCT03363373	GM-CSF + Naxitamab	GD2
Phase 2	NCT03503864	Arsenic Trioxide + induction CT	
Phase 2	NCT03373097	GD2-CAR-T Cells +/− CT & lymphodepletion	GD2
Phase 2	NCT04301843	DFMO + Etoposide	ODC,
Phase 2	NCT02679144	DFMO	ODC
Phase 2	NCT04023331	67Cu-SARTATE PR-RT (Cohort expansion)	SSTR
Phase 2	NCT02998983	Racotumomab	anti-N-glycolyl GM3 Ab inducer

Phase	NCT ID	Drugs / Strategy	Target
Phase 2	NCT03033303	Hu3F8/GM-CSF + Isotretinoin	GD2
Phase 2	NCT02559778	Ceritinib + Dasatinib + Sorafenib + Vorinostat + DFMO	ODC, HDAC, ALK, VEGFR, PDGFR, RAF
Phase 2	NCT02308527	Bevacizumab + Temozolomide ± Irinotecan	VEGF-A, DNA replication
Phase 2	NCT01467986	Dasatinib + Rapamycin + Irinotecan + Temozolomide	Bcr-ABL, Src, mTOR, DNA replication
Phase 2	NCT00107289	lobenguane I 131	
Phase 2	NCT00601003	Nifurtimox	
Phase 2	NCT02035137	131I-MIBG +/− Viscristine, Irinotecan / Vorinostat	HDAC
Phase 2	NCT02452554	Lorvotuzumab Mertansine	CD56 binding
Phase 2	NCT03273712	PRRT-90Y-DOTA tyr3-Octreotide	SSTR
Phase 2	NCT04320888	Selpercatinib	RET
Phase 2	NCT04195555	Ivosidenib	IDH1
Phase 2	NCT04284774	Tipifarnib	FTase
Phase 2	NCT03698994	Ulixertinib	ERK1/2
Phase 2	NCT03526250	Palbociclib	CDK4, CDK6
Phase 2	NCT03220035	Vemurafenib	B-RAF
Phase 2	NCT03233204	Olaparib	PARP
Phase 2	NCT03213704	Larotrectinib	TrkA, TrkB, TrkC
Phase 2	NCT03213678	Samotolisib	PI3K, mTOR, DNA-PK
Phase 2	NCT03210714	Erdafitinib	FGFR
Phase 2	NCT03155620	Ensartinib, Erdafitinib, Larotrectinib, Olaparib, Palbociclib, Samotolisib, Selpercatinib, Selumetinib Sulfate, Tazemetostat, Tipifarnib, Ulixertinib, Vemurafenib	ALK, FGFR, TrkA, TrkB, TrkC, PARP, CDK4/6, PI3K, mTOR, RET, MEK1, MEK2, EZH2, Ftase, ERK1/2, B-RAF
Phase 2	NCT03213665	Tazemetostat	EZH2
Phase 2	NCT02378428	MIBG	NET Receptors
Phase 2	NCT03458728	BAY806946	PI3K
Phase 2	NCT02574728	Sirolimus + Metronomic CT	mTOR
Phase 2/3	NCT03275402	131I-omburtamab	B7-H3
Phase 3	NCT03126916	Crizotinib/Iobenguane I^{131} + Auto-HSC, CT, Dinutuximab, EBRT, Isotretinoin, Sargramostim, Surgery, Vincristine	ALK, ROS-1, NET receptors
Phase 4	NCT03975829	Dabrafenib, Trametinib	B-RAF, MEK1, MEK2