The N-myc Oncogene: Maximizing its Targets, Regulation, and Therapeutic Potential

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Abstract
N-myc (MYCN), a member of the Myc family of basic-helix-loop-helix-zipper (bHLHZ) transcription factors, is a central regulator of many vital cellular processes. As such, N-myc is well recognized for its classic oncogenic activity and association with human neuroblastoma. Amplification and overexpression of N-myc has been described in other tumor types, particularly those of neural origin and neuroendocrine tumors. This review outlines N-myc's contribution to normal development and oncogenic progression. In addition, it highlights relevant transcriptional targets and mechanisms of regulation. Finally, N-myc's biomarker status and potential as a target using novel therapeutic approaches are discussed.

Introduction
The N-myc gene was first reported in 1983, when Schwab and Kohl discovered that there were a subset of human neuroblastoma cell lines harboring multiple copies of a DNA sequence related to the C-myc oncogene (MYC), and this region was designated N-myc (MYCN). Genomic amplification of N-myc resulted in overexpression of N-myc at the mRNA level, and rat embryo cells transfected with N-myc demonstrated oncogenic properties. These findings were first to bring attention to N-myc as a putative oncogene.

N-myc in normal development
N-myc belongs to the Myc family of proto-oncogenes, which are transcription factors of the basic-helix-loop-helix-zipper (bHLHZ) class and important for the regulation of gene expression associated with a range of cellular processes, including proliferation, growth, apoptosis, energy metabolism, and differentiation. Other Myc family transcription factors include C-myc and L-myc. While similarly diverse in their function, Myc genes are separately regulated. C-myc is ubiquitous and highly expressed in most rapidly proliferating cells during development and continues to be expressed in dividing cells of adult tissues. N-myc has a restricted expression pattern: it is expressed during embryogenesis in pre-B cells, kidney, forebrain, hindbrain and intestine, with highest expression in the developing brain. After embryonic development, N-myc is
downregulated and N-myc is not significantly expressed in adult tissues. The L-myc gene is less well characterized, demonstrates homology to N-myc and C-myc\textsuperscript{5}, and is expressed in both neonatal and adult lung tissue\textsuperscript{4}.

Because Myc proteins preferentially regulate the same sets of genes involved in differentiation and cell growth (ie, translation, ribosome biogenesis, metabolic processes), they can partially compensate for one another. For instance, mouse embryonic stem cells (ESCs) homozygous for deletion of either C-myc or N-myc genes display morphology without aberrant proliferation or differentiation compared to wild-type ESCs\textsuperscript{6,7} and N-myc can functionally replace C-myc in murine development\textsuperscript{8}. However, regional morphology of the central nervous system differs in N-myc null embryos from wild-type embryos, despite up-regulation of C-myc\textsuperscript{9}. Therefore further defining the Myc gene signatures that distinguish the targets of Myc proteins could provide insight into their tissue specific roles in normal development and oncogenesis.

N-Myc plays an essential role in normal brain development. N-myc drives proliferation of granule neuron precursors derived from neuronal progenitor cells of the developing forebrain and hindbrain\textsuperscript{10}. Constitutive deletion of N-myc is embryonic lethal\textsuperscript{6,9}, while conditional inactivation in neuronal progenitor cells leads to ataxia, behavioral abnormalities, and tremors that correlate with an overall twofold decrease in brain mass that disproportionately affects the cerebellum and the cerebral cortex, both of which show signs of disorganization. There exists severely compromised proliferation at the cellular level, including striking decrease in S phase and mitotic cells, whereas apoptosis is unaffected. In the neural crest, enhanced N-Myc expression facilitates proliferation of immature neuronal precursor cells at the expense of differentiation, and this can be stimulated by sonic hedgehog signaling\textsuperscript{11}.

Germline mutations that inactivate N-Myc cause Feingold syndrome, a rare autosomal dominant syndrome, associated with variable combinations of microcephaly, gastrointestinal atresia, limb abnormalities, and learning disability or mental retardation\textsuperscript{12}, a phenotype that may be attributable to perturbation of normal neural stem
and progenitor cell biology.

**N-myc and human cancer**

The original characterization of N-myc was soon followed by reports of its amplification in approximately 20% of cases of neuroblastoma, as well as by the observation that the degree of amplification correlated with advanced stage, unfavorable biological features, and a poor outcome\(^{13,14}\). N-myc amplification was also associated with worse prognosis in otherwise favorable patient groups\(^{13,15-17}\). Based on these observations, N-myc gene copy number is standardly assessed by fluorescence in situ hybridization (FISH) in all clinical cases of neuroblastoma, and patients with N-myc amplification are stratified for more aggressive treatment\(^{15,18}\). This is a prototypic example of how identification of a prognostic genomic biomarker can directly translate into risk stratification and change patient management.

Aberrant amplification and/or overexpression of N-myc is not only seen in neuroblastoma, but has also been described in a number of other tumor types (Table 1). Although large scale longitudinal studies assessing the prognostic value of N-myc have not yet been systematically reported for all tumor types, the presence of N-myc alterations has been associated with tumor aggressiveness and suggests a similar driving role in N-myc amplified and/or overexpressed tumors.

N-myc is implicated in a subset of medulloblastoma (5% demonstrate MYCN amplification), is found in both sonic hedgehog -driven and non- sonic hedgehog -driven disease\(^{19}\), and correlates with worse clinical outcomes\(^{20}\). Independent of amplification, activated sonic hedgehog and IGF/PI3K signaling in medulloblastoma can also upregulate N-myc through transcriptional upregulation and/or prevention of N-myc degradation\(^{21}\). N-myc is implicated as a key driver of tumor initiation and progression in medulloblastoma preclinical models\(^{19}\).

N-myc amplification also occurs in a subset of glioblastoma multiforme (GBM)\(^{22}\), is typically associated with forebrain rather than hindbrain tumors, and is rarely found in
lower grade gliomas and astrocytomas. Recently, genome wide methylation analysis of both adult and pediatric GBM identified recurrent functional mutations in the epigenetic modulator histone 3 gene (H3F3A)\textsuperscript{23}, which also results in enhanced transcription of N-myc, which, in turn, promotes proliferation and suppresses differentiation\textsuperscript{24}. Therefore, targeting H3F3A mutant tumors using therapeutic approaches to target N-myc may represent a novel therapeutic approach for a distinct subset of GBM.

The majority of cases of retinoblastoma overexpress N-myc, and a small subset of these cases also harbor significant N-myc gene amplification\textsuperscript{25,26,27} Though uncommon, N-myc amplification in retinoblastoma is mutually exclusive of germline or somatic mutation of the retinoblastoma gene (RB1), and is associated with early onset (median age 4.5 months), unilateral disease, and clinical aggressiveness\textsuperscript{28}. Therefore, N-myc amplified retinoblastomas are thought to represent a distinct molecular subclass of nonfamilial retinoblastoma. N-myc overexpression, on the other hand, occurs in the majority of retinoblastoma cases and is not a direct result of loss of regulatory control by RB1, but likely rather reflects an embryonal cell of origin\textsuperscript{29}. DNA amplification of N-myc occurs in a subset of rhabdomyosarcoma, a pediatric soft tissue sarcoma, and is predominantly found in the alveolar subset and rarely in the more common embryonal subtype\textsuperscript{30}, though N-myc mRNA and protein expression is found in the vast majority of all rhabdomyosarcoma cases regardless of histology\textsuperscript{31}.

N-myc is amplified in 15-20\% of small cell lung cancers\textsuperscript{32,33} and is associated with poor response to chemotherapy, rapid tumor growth, and shorter survival\textsuperscript{34}. N-myc amplification rarely occurs in other lung cancer histologies. N-myc amplification also occurs in approximately 40\% of neuroendocrine/small cell prostate cancers, is commonly seen concurrently with amplification of the aurora kinase A gene (AURKA), and associated with poor prognosis\textsuperscript{35,36}. In both small cell lung and prostate cancers, N-myc amplification may occur early prior to the development of metastasis. Overexpression of N-myc has also been seen in a subset of breast cancers and correlates with poor prognostic features\textsuperscript{37}.

**Functional targets of N-myc**
Due to structural and sequence homology between the Myc family genes, the function and biochemical properties of Myc proteins are closely related. C-myc and N-myc can functionally replace one another in the appropriate context and share similar oncogenic properties\(^3\). However, their functional roles seem to be tissue specific. For instance, C-myc is causally implicated in Burkitt's lymphoma and translocation of the C-myc gene (\(MYC\), chromosome 8q24) is pathognomonic. C-myc is also overexpressed in a wide range of malignancies including the majority of breast cancers, colon cancers, gynecological cancers, hepatocellular carcinomas, and a variety of hematological tumors, making C-myc one of the most commonly altered oncogenes in human cancer. L-myc is less well characterized but is often amplified and overexpressed in small cell lung cancer\(^5\). As mentioned, N-myc is primarily implicated in high grade neuroendocrine tumors (neuroblastoma, small cell carcinomas) and those arising from the neural system (neuroblastoma, medulloblastoma, glioblastoma). Therefore despite the fact that Myc genes may share related targets, they at the same time retain other, unique ones and are exclusively overexpressed in certain tumor types, suggesting that they may have independent and tissue specific functions.

The fact that N-myc is normally not expressed in adult tissues but aberrantly expressed in tumors arising in the nervous system or de-differentiated tumors such as small cell carcinoma suggests origination or reversion to a neuronal stem cell like phenotype in these tumors (associated with or driven by reactivation of N-myc). Therefore understanding neuronal developmental pathways may help elucidate oncogenic pathways or downstream drivers of N-myc driven cancers.

N-myc is encoded by the \(MYCN\) gene on chromosome 2 (2p24). Genomic copy number gain of \(MYCN\) is consistently associated with high levels of N-myc gene and protein expression\(^3\), though overexpression can also occur in the absence of amplification. Functionally, N-myc is an oncogene; it can transform rat embryo fibroblasts\(^4\) and plays a critical role in the pathogenesis of neuroblastoma. Studies in transgenic mice show that neural crest–specific expression of N-myc causes neuroblast transformation and the development of neuroblastoma\(^4\)\. Expression of N-myc in nonamplified
neuroblastoma cell lines can induce reentry of quiescent cells into the cell cycle and correlates with growth rate, motility, and cell attachment\(^42\). The driving oncogenic role of N-myc is also enhanced by cooperating events such as RAS mutation due to Ras mediated stabilization of N-myc and/or increase in N-myc translation\(^43,40,44\). High expression of N-myc is associated with proliferation and induction of cell cycle genes\(^45,46\) and also plays a role in regulation of apoptotic cell death\(^47\).

There are a number of ways N-myc can turn on or off genes. One important mechanism is through heterodimerization with Max. N-myc is a 64 kDa nuclear protein with a N-terminus transcriptional activation domain and a C-terminus basic region helix-loop-helix leucine zipper motif (bHLH-Zip), which has DNA-binding activity and forms an obligate heterodimer with the bHLH-Zip protein Max\(^48,49\). Myc-Max complexes bind gene promoters by recognizing a DNA sequence, called E-box. N-myc preferentially binds the E-box CATGTG as well as the classic CACGTG. This in turn, activates the transcription of downstream genes involved in diverse cellular functions. Under N-myc-amplified conditions, N-myc becomes less specific and can bind additional E box motifs including CAGTTG, CATCTG, CAACTG\(^50\). Global N-myc transcription factor binding analysis in neuroblastoma has also revealed modulation of N-myc binding through E-Box methylation. N-myc may also globally regulate gene expression through influencing chromatin structure via widespread histone acetylation and methylation across the genome\(^51\). In addition, N-myc can also induce transcriptional repression of certain genes, independent of E-Box binding. This can involve recruitment of N-myc to target gene promoters by Miz-1 and disruption of the interaction between transcriptional complexes\(^52\). A complex of Myc and Miz-1 bound to the promoter leads to transcriptional silencing, at least in part by recruitment of Dnmt3a\(^53\). N-myc also directly interacts with another DNA methyltransferase EZH2\(^54\) and may repress target genes through DNA methylation. These data suggest that N-myc is also a key epigenetic regulator. In addition to binding to DNA, N-myc can also interact with several other proteins via its C-terminal domain including: N-MYC interactor (NMI), transformation/transcription associated protein (TRRAP) and TBP interacting protein 49 (TIP49)\(^18\).
There are hundreds to thousands of proposed candidate target genes of N-myc, therefore pinpointing the relevant oncogenic targets remains a significant challenge. Genome-wide gene expression analysis of forty well-characterized human neuroblastomas and twelve cell lines with and without N-myc amplification has identified candidate N-myc target genes which include genes associated with neural differentiation and those related to cellular proliferation. Expression of a subset of these genes was altered after transfection of a neuroblastoma cell line, SK-N-ER, with an N-myc expressing gene construct when protein synthesis was inhibited. Most of the genes identified have consensus N-myc binding E-box sequences in their promoter regions, suggesting they represent direct targets. Similarly, shRNA-mediated silencing of N-myc in neuroblastoma cells has identified a 157 target gene panel including those involved cell cycle, DNA repair, and neuronal differentiation genes; this panel has been associated with poor prognosis in patients with neuroblastoma. More recently, a similar set of N-myc targeted genes has been observed in neuroendocrine prostate cancer, with upregulation of cell cycle and neuroendocrine type genes. In prostate cancer, N-myc binds neuroendocrine and androgen regulated gene promoters, suggesting direct involvement in neuroendocrine transformation. These observations support that the biochemical pathways of N-myc amplified/overexpressed tumors may show overlap, regardless of tumor site of origin, and may serve a foundation for molecular classification and the development of molecular based treatment approaches.

Because N-myc expression is associated with early stages of neural differentiation pathways and tumors often display reversion to a de-differentiated developmental phenotype, it is intriguing to speculate that the N-myc amplified cell may have stem cell like characteristics. Co-expression of SOX9 with N-myc in cerebellar stem and progenitor cells has the ability to drive self-renewal, though neither SOX9 nor N-myc are able to drive self-renewal individually. N-myc can enhance the production of pluripotent and neural tumor stem cells and regulate the expression of embryonic stem cell factors including lif, klf2, klf4, and lin28b. N-myc also upregulates expression of the self-renewal protein BMI1 in neuroblastoma by directly binding to the E-Box sites.
within the promoter of BMI1. These findings suggest potential mechanisms by which N-myc may contribute to de-differentiation and maintenance of a pluripotent state.

Other implicated gene targets of N-myc include those involved in ribosome assembly and activity and several cancer associated genes/pathways including MDM2 and TP53, SKP2, NLRR1, Fyn kinase, DKK3/Wnt/beta katenin pathway signaling, and genes of the PI3k/Akt/mTOR pathway. N-myc can also inactivate Rb (through activating ID2 and also cooperating with RAS). N-Myc may also promote tumor angiogenesis through down-regulation of leukemia inhibitory factor (LIF), a modulator of endothelial cell proliferation, which leads to activation of STAT signaling.

In addition to regulation of coding gene expression, N-myc has also been implicated as an important regulator of non–protein-coding gene expression. In neuroblastoma, N-myc can activate several microRNAs (mir-17-92, mir-221, mir-9 and mir-421) and long noncoding RNAs (T-UCRs and ncRAN) and repress others (mir-184 and mir-542-5p), which can contribute to the oncogenic phenotype through regulation of downstream pathways involved in apoptosis, differentiation, epithelial mesenchymal transition, and DNA damage response. Furthermore, transcriptome profiling of N-myc associated miRNAs in human neuroblastomas has demonstrated prognostic significance.

N-myc can also indirectly upregulate the mitotic kinase Aurora kinase A through protein-protein interaction. Of a panel of 194 genes identified to be highly expressed in N-myc amplified neuroblastomas compared to non-amplified tumors, short hairpin RNA (shRNA) targeting of each gene identified 17 genes that preferentially inhibited growth of N-myc amplified versus nonamplified neuroblastoma cells. Aurora kinase A stood out amongst these genes, as it now known that Aurora A is highly expressed in N-myc amplified tumors, can also mutually regulate N-myc protein stability, and is a synthetic lethal gene to N-myc. Importantly, the Aurora A-N-myc interaction is potentially targetable using small molecule inhibitors as described below.
Regulation of N-myc

Tight control of N-myc expression is an essential cellular mechanism for modulating N-myc function. There are a number of mechanisms for N-myc regulation; one is through control of N-myc turnover by protein degradation. N-myc protein turnover is cell cycle dependent with N-myc degradation occurring during mitosis. Although N-myc has a short half life of approximately 20-30 minutes, the extreme high steady state levels (approximately 100 times normal) in amplified tumor cells likely ensures that cell stay in cycle and do not enter G0. Notably, the proposed 157 N-myc regulated functional gene expression profile that associates with poor prognosis also associates with tumors with high nuclear N-myc protein levels, even in cases in which N-myc is not amplified or overexpressed at the mRNA level, supporting N-myc protein stability as one relevant mechanism for N-myc regulation. The ubiquitin ligase Fbxw7 normally targets N-myc for proteasomal degradation via the ubiquitin-proteasome system. This primarily occurs during the mitotic phase of the cell cycle and after phosphorylation of N-myc (S62 and T58) by the cell cycle kinase cyclin B/CDK1 and by glycogen synthase kinase-3β (GSK3β). Since GSK3β is inactivated by AKT, activation of the PI3K/AKT pathway results in stabilization of the N-myc protein, and inactivation of the pathway using a PI3K inhibitor has been shown to reduce levels of N-myc. This is one therapeutically targetable pathway that may be relevant in other N-myc driven and PI3K/AKT pathway implicated tumors as well.

Aurora kinase A is a mitotic kinase normally expressed during G2 and mitosis, which can also act to stabilize N-myc by inhibiting Fbxw7 mediated degradation of N-myc protein. Aurora kinase A is also frequently overexpressed and amplified in N-myc amplified tumors such as neuroblastoma and neuroendocrine prostate cancer, and cooperates with N-myc to promote tumor proliferation and oncogenic activity. N-myc-amplified neuroblastoma cells depend on high levels of Aurora kinase A expression for maintaining N-Myc function.

Another proposed mechanism for N-myc regulation includes translational regulation.
For instance, activation of H-Ras through an oncogeneic Ras mutation and other oncoproteins that hyperactivate the MAPK pathway can promote accumulation of N-myc by accelerating N-myc translation\textsuperscript{74}. This is mechanism that is distinct from H-Ras/MAPK regulation of C-myc, which is primarily through protein stabilization. Various microRNAs (mir-34a, mir-101, and let-7) have also been documented to regulate N-myc by targeting mRNA, resulting in reduced N-myc expression and decreased proliferation of MYCN-amplified neuroblastoma cells\textsuperscript{75, 76}.

**Detecting N-myc**

The N-myc gene, MYCN, is located on the distal short arm of chromosome 2 (2p24). In cells with amplification, the extra copies typically reside as double minute or homogenously staining region amplicons\textsuperscript{77}. Additional genes may be co-amplified with MYCN in a subset of neuroblastomas (DDX1, NAG, ALK)\textsuperscript{78}, but MYCN is the only gene that is consistently amplified from this locus. The ALK gene, which is nearby on chromosome 2p23, may also show a sporadic gain-of-function mutation in up to 8% of neuroblastomas\textsuperscript{79}. The magnitude of MYCN amplification varies, and typically ranges between 5-500+ copies per cell. Fluorescence in situ hybridization (FISH) is the standard assay to detect MYCN amplification. It is technically reliable and can discern heterogeneous gene amplification among tumor cells in the same specimen\textsuperscript{80}.

The degree of DNA amplification often correlates with N-myc mRNA and protein expression, but overexpression of N-myc can also occur in the absence of MYCN amplification\textsuperscript{64}. However, to date, there is no strong correlation between mRNA or protein levels of N-myc and prognosis in neuroblastoma. Therefore, FISH remains standard rather than assessment of gene or protein expression for neuroblastoma. To date, N-myc status is not routinely tested in other tumor types.
Targeting N-myc

Because of evidence suggesting a causal role of N-myc in the development of neuroblastoma and a potential driver of other tumor types, and the fact that it is tumor-specific and not expressed in normal tissue, the N-myc oncogene represents an attractive therapeutic target. However, similar to other transcription factors, selective inhibition of N-myc has been considered undruggable. Furthermore, the structure of N-myc is composed almost entirely of alpha helices with no surfaces for ligand binding.

There are a number of proposed approaches to indirectly target N-myc. Compounds that target the interface between Myc proteins and Max, identified through high throughput screening of chemical libraries (eg., Compound 10058-F4), have shown varied preclinical activity\(^8\) but have generally been limited due to low potencies. Omomyc is a Myc-derived bHLHZip domain compound that interferes with Myc homodimerization by substituting four amino acids in the Myc zipper. It binds C-Myc and N-Myc, Max, and Miz-1 and prevents Myc binding to promoter E-boxes and transactivation of target genes while retaining Miz-1 dependent transrepression. Anti-tumor activity with oncomyc has been seen in vivo\(^82\) and provides insight towards potentially developing clinical inhibitors that may target bHLH-ZIP proteins. Given the role of N-myc on DNA methylation, epigenetic therapies such as valproic acid and BL1521 have been tested in preclinical models and have shown promising results with induction of apoptosis, downregulation of N-myc, and changes in expression of N-myc target genes\(^83, 84\).

Small molecule inhibitors of acetyl-lysine recognition domain (ie., bromodomain)-containing proteins can also target Myc transcription factors\(^85\) by interfering with chromatin-dependent signal transduction and inhibiting Myc transcription. Recently, the bromodomain inhibitor, JQ1, was shown to target N-myc amplified tumors by blocking N-myc dependent transcription, impairing growth, and inducing apoptosis\(^86\). Knockdown of the bromodomain protein BRD4 phenocopied these effects. Bromodomain inhibition also conferred a survival advantage in preclinical models of N-myc amplified...
neuroblastoma, providing preclinical rationale for developing bromodomain inhibitors for patients with N-myc driven tumors. Clinical investigation of bromodomain inhibitors for relapsed or refractory neuroblastoma is underway.

Identifying and targeting essential co-factors (such as aurora kinase A) as a mechanism to destabilize N-myc or targeting upstream pathways of N-myc (such as PI3K) may represent alternative mechanisms to indirectly target N-myc. Some of the available inhibitors of Aurora kinase A induce an unusually distorted conformation of its kinase domain, thus impairing its interaction with N-myc. Aurora kinase A inhibitors have shown preclinical activity in N-myc amplified neuroblastoma and neuroendocrine prostate cancer, are now undergoing Phase 2 evaluation for these diseases. Recently, Bjerke and colleagues carried out a synthetic lethal screen to identify kinases that could represent a therapeutic target in N-myc amplified pediatric glioblastoma multiforme. Out of 714 kinases tested, knockdown of CHK1 (checkpoint kinase 1) or AURKA (aurora kinase A) promoted N-myc stability and reduced viability in N-myc amplified cells. In a dose-dependent manner, the aurora kinase A inhibitor VX-689 decreased levels of N-myc protein and cell viability; therefore targeting Aurora kinase A or the Aurora-A-N-myc interaction may be an effective approach for other N-myc driven tumors as well. The CHK1 inhibitor CCT244747 has shown anti-tumor activity in neuroblastoma in vivo and several CDK inhibitors are in various stages of clinical development.

Since phosphorylation of N-myc is directly regulated by Gsk3β, and indirectly by upstream signaling through PI3K/Akt/mTOR pathway, targeting PI3K/Akt/mTOR may be an effective therapeutic approach. Furthermore, mTORC1 also downregulates PP2A, which normally dephosphorylates N-myc, targeting it for ubiquitination and promoting stabilization of N-myc. Akt is also commonly activated in N-myc driven tumors. The PI3K/mTOR inhibitor LY294002 has shown preclinical activity in neuroblastoma which is rescued when cells are engineered to express T58/S62 phosphorylation site-deficient N-myc mutants. The PI3K inhibitor NVP-BEZ235 has
been shown preclinically to decrease angiogenesis and improve survival in N-myc neuroblastoma models (both in vitro and in vivo)\textsuperscript{91} N-myc expression was reduced in treated tumors, and evidence for both PI3K and mTOR inhibition was demonstrated, supporting the notion that PI3K inhibition can lead to inhibition or de-stabilization of N-myc. Various inhibitors of PI3K, AKT, and TORC1/2 are in clinical development.

**Conclusions**

N-myc is an oncogenic transcription factor and a well recognized, clinically relevant prognostic biomarker for neuroblastoma. We now know that a subset of other solid tumors, especially small cell carcinomas and neural derived tumors, are also driven by N-myc and associated with poor prognosis, yet systematic evaluation of N-myc status is not standard practice for other tumor types. Due to the diverse range of targets of N-Myc, functional overlap with other Myc family proteins, and complex regulation, it remains challenging to elucidate which distinct targets of N-myc are driving tissue specific oncogenesis and how regulation of these genes coordinate to promote tumorigenesis. However, continued investigation and developing mechanisms to directly or indirectly target N-myc are important steps towards improving outcomes for patients with N-myc driven tumors.
References:


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Molecular Cancer Research

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