Therapeutic targeting of "undruggable" MYC

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Summary

c-MYC controls global gene expression and regulates cell proliferation, cell differentiation, cell cycle, metabolism and apoptosis. According to some estimates, MYC is dysregulated in ≈70% of human cancers and strong evidence implicates aberrantly expressed MYC in both tumor initiation and maintenance. *In vivo* studies show that MYC inhibition elicits a prominent anti-proliferative effect and sustained tumor regression while any alteration on healthy tissue remains reversible. This opens an exploitable window for treatment that makes MYC one of the most appealing therapeutic targets for cancer drug development. This review describes the main functional and structural features of the protein structure of MYC and provides a general overview of the most relevant or recently identified interactors that modulate MYC oncogenic activity. This review also summarizes the different approaches aiming to abrogate MYC oncogenic function, with a particular focus on the prototype inhibitors designed for the direct and indirect targeting of MYC.

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Introduction

The oncoprotein MYC is a pleiotropic transcription factor that modulates global gene expression and regulates critical cellular processes including proliferation, differentiation, cell cycle, metabolism and apoptosis. Strong evidence supports aberrant MYC expression as a driver of both tumor initiation and maintenance[1] and is associated with all the "hallmark" features of cancer[2,3] (Figure 1). The role of MYC as a general or specific transcription factor has been traditionally controversial, although recent studies further support the notion that MYC is a general amplifier of highly expressed genes.[4–6] The MYC oncogene family includes *c-MYC*, *MYCN* (N-MYC) and *MYCL* (L-MYC). All three paralogs have a similar function but show distinct expression timings and tissue specificities during development. c-MYC is ubiquitously expressed during tissue development and in a broad variety of tumors. N-MYC is expressed in neural tissue and early hematopoietic development and is deregulated in different cancer types including neuroblastoma, rhabdomyosarcoma, medulloblastoma, Wilms tumor or retinoblastoma although it can functionally replace c-MYC in some contexts.[7] L-MYC is expressed in lungs and particularly overexpressed in small cell lung carcinomas although it is considered to have lower transforming activity.[7,8] MYC activity is usually tightly controlled at the transcriptional and protein level, but is estimated to be aberrantly expressed in up to 70% of human cancers, many of which are highly aggressive (e.g. acute leukemia and high-grade lymphoma) and/or show poor response to treatment (e.g., small-cell lung carcinoma and neuroblastoma).[1] In support of the oncogene addiction model, it has been demonstrated that transient MYC inhibition *in vivo* results in sustained tumor regression by promoting proliferative arrest, differentiation, apoptosis and cellular senescence in cancer cells. Notably, the anti-proliferative effects on normal tissue remain minimal and reversible.[9,10] Furthermore, MYC has an unforeseen major role in enabling tumors to escape immunosurveillance through various mechanisms including decrease of MHCI expression or upregulation of inhibitory cytokines and immune checkpoint proteins such as PD-L1 and CD47, providing a compelling rational for combining MYC inhibition and immune checkpoint blockade.[11–13] Together, these data suggest small molecules targeting MYC have the potential to exploit a clinically meaningful therapeutic window making MYC one of the most enticing targets for cancer drug development.

Several approaches have attempted to inhibit MYC directly or indirectly at all levels of its regulation. Some strategies that have shown promising results *in vivo* have focused on preventing MYC gene expression using antisense oligonucleotides (ASOs) that target MYC mRNA[14] or G4-quadruplex binders that stabilize these DNA secondary structures. Other strategies are based on inhibiting MYC synthetic lethal genes required for tumorigenesis or tumor maintenance such as BUD31,[15]

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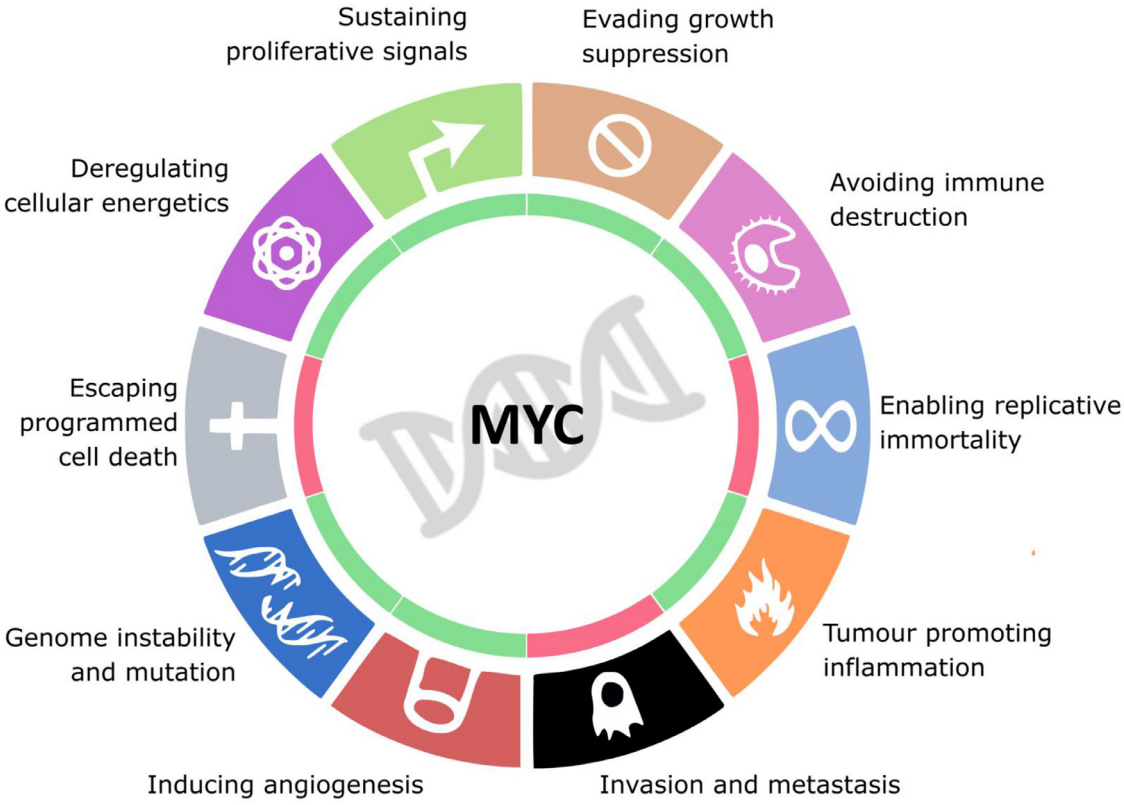

Figure 1. MYC regulates all hallmarks of cancer. Oncogenic levels of MYC promote proliferative signalling, inhibition of growth suppression, escaping immune response, tumour inflammation, angiogenesis, genome instability and changes in cellular metabolism; and inhibits cell replicative immortality, metastasis and the escape of programmed cell death.

NUAK1 (ARK5)[16] or eIF4F.[17] Other approaches receiving interest aim to reduce MYC stability and function at the protein level.[18,19] However, despite massive efforts, targeting MYC with clinical grade small molecules still represents an intractable challenge, particularly at the protein level. The fact that important functional domains of MYC are intrinsically disordered (Figure 2a) and lack an enzymatically-active site, has precluded structure-guided drug design. In addition, the high affinity interaction between MYC and its obligate partner MAX along with the partial functional redundancy of the different MYC family members and their nuclear localization pose an enduring obstacle for the design of effective MYC inhibitors.[20]

This review describes the main functional and structural features of the MYC protein, delineates the most relevant or recently identified MYC cofactors that modulate its oncogenic activity and summarizes recent advances on targeting MYC using small molecule inhibitors.

MYC structure

c-MYC (hereafter MYC) is a 439 amino acid oncoprotein that contains a well characterized C-terminal DNA-binding and an N-terminal transactivation domain (TAD). The C-terminal region ~100 residues, comprises a basic helix-loop-helix leucine zipper (bHLH-LZ) segment that regulates the heterodimerization between MYC and its bHLH-LZ partner MAX, mediating its binding to gene promoters.[21] In contrast, the TAD is comprised of residues 1-143, conforming an intrinsically disordered domain that regulates MYC's biological activity and is essential for MYC-mediated transcriptional activation.[18,22] This intrinsically disordered nature of MYC structure has been linked to the formation of transcriptional condensates at super-enhancer sites and may represent, if confirmed, a previously overlooked opportunity to tackling MYC with certain antineoplastic agents that can be preferentially partitioned into such phase-separated condensates.[23,24]

The protein sequence of MYC contains several evolutionary-conserved segments including the so called MYC homology boxes (MB), that modulate MYC function and are mostly shared amongst all MYC paralogs, L-MYC and N-MYC (Figure 2b).[25,26] Each MB shows distinct, sometimes cell dependent, contributions to MYC activity although functional redundancies have been described. MBs are often involved in highly

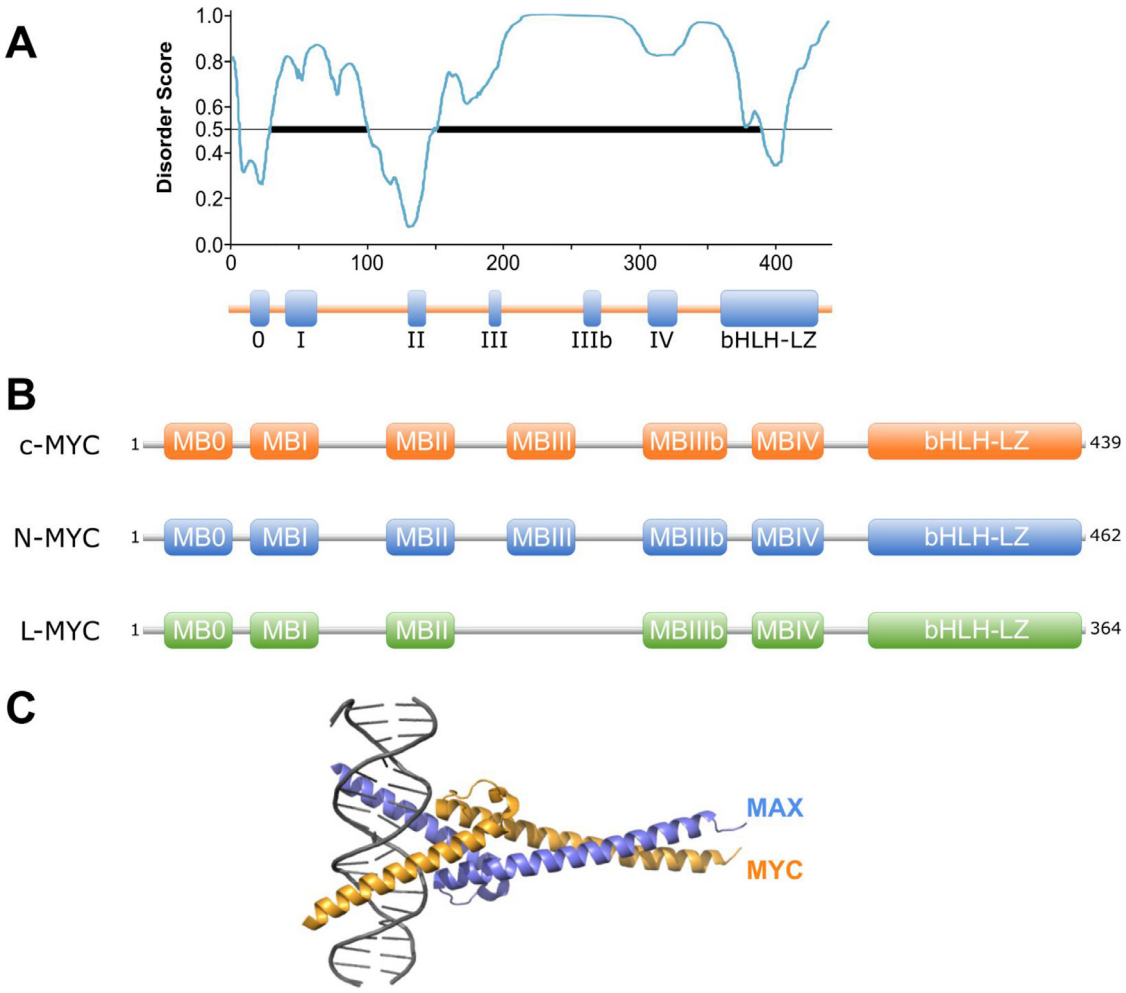

Figure 2. Structure of MYC protein. A) Intrinsically disordered region prediction for c-MYC (predictor tool PONDR). B) Organization of the main protein domains and conservation across different MYC super-family members. C) X-ray structure of MYC:MAX heterodimer binding DNA (PDB ID: 1NKP).

dynamic protein-protein interactions with a wide number of cofactors that contribute to modulate MYC's function as a master regulator (reviewed in[27]) (Figure 3). These interactions can be multivalent and occasionally involve distal binding sites outside these conserved domains. In fact, on many occasions MBs do not function as isolated regulatory entities and instead establish dynamic interactions that define complex patterns of cooperation modulating important aspects of the protein.

N-terminal Transactivation Domain

The N-terminal TAD of MYC comprises MB0, MBI and MBII subdomains involved in the regulation of the transcriptional activity and stability of the protein.[26,28-31]

MBI contains the canonical phosphodegron composed by residues S62 and T58 that regulates MYC protein stability through a sequential and hierarchical phosphorylation process. The residue S62 is first phosphorylated by RAS/MEK/ERK/CDK2 priming the subsequent phosphorylation by GSK3β at T58, followed by the dephosphorylation of S62 mediated by PIN-1 and PP2A (reviewed in[32]). Recent findings demonstrated the phosphorylation of MYC at S67, which is proximal to the S62 residue, by Aurora B Kinase counteracts GSK3β and promotes protein stability.[33] These series of post-translational modifications govern the SCF^{FBXW7}/Ub-proteasome-mediated degradation of MYC and ultimately has a prominent impact on its function. The deregulation of this pathway has strong effects on MYC stability and is frequently linked to malignant cell proliferation. For example, in Burkitt's lymphoma, in which the MYC gene is translocated (t(8:14)), T58 in MBI is recurrently mutated, leading to protein stabilization.[34] In addition, SCF^{FBXW7} is one of the most commonly

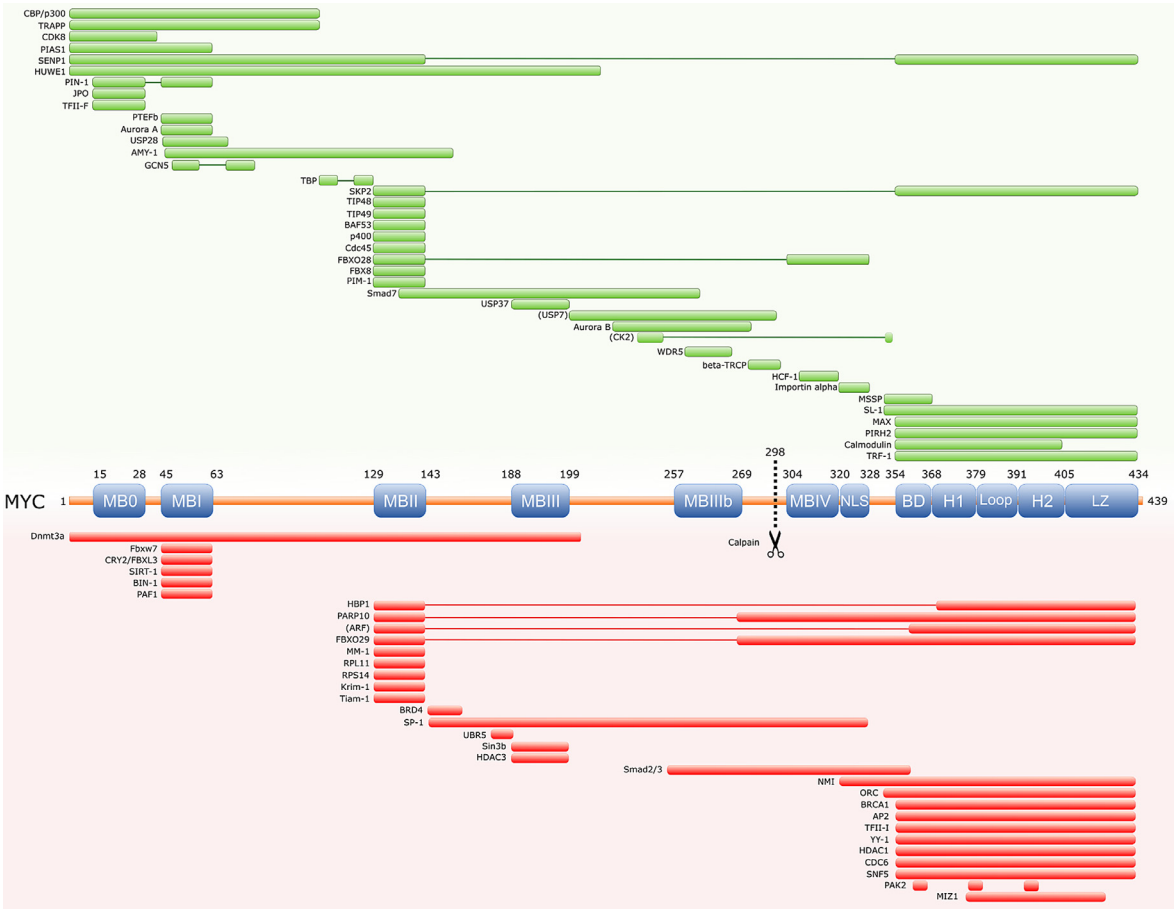

Figure 3. Schematic of MYC protein interactors. The minimal interaction region between both proteins is mapped. Green boxes represent activators of MYC function. Red boxes represent repressors of MYC activity.

mutated proteins of the ubiquitin-proteasome system in human cancer.[35]

MBII (residues 129-143) represents the most widely studied segment within the MYC TAD.[26] This domain acts as a binding hub for a myriad of critical interactors (Figure 3) and is considered fundamental for MYC biological activity.[31] *In vivo*, MBII is also indispensable for full MYC oncogenicity.[30]

Central region

The MBIII regulates protein stability and contributes to MYC cell transformation.[26,36] MBIIIb encompasses a 10-amino-acid segment that is part of a PEST domain rich in proline, glutamic acid, threonine and serine residues that expands from positions 226-270 and is involved in the regulation of MYC stability but not in ubiquitination.[37] MBIV domain may only be required for transformation in some biological contexts although there is a high *in vitro* assay variability amongst different cellular models. The main nuclear localization signal (NLS) sequence in MYC lies on residues 320-328 and, although it regulates the transport of MYC into the nucleus through the association with Importin α, it is not indispensable for MYC nuclear localization suggesting that other subdomains might be marginally involved in the process.[38,39]

C-terminal bHLH-LZ domain

The C-terminal region of the MYC protein represents the most widely studied domain. It contains the basic helix-loop-helix leucine zipper (bHLH-LZ) spanning residues 357-439 and plays a key role in DNA binding. At physiological levels, MYC preferentially binds at the canonical E box sequence 5'-CACGTG-3' of target gene promoters whereas at deregulated levels it also binds the open chromatin containing the more prevalent non-canonical 5'-CANNTG-3' E-boxes.[40] The bHLH-LZ domain also stabilizes the interaction between MYC and MAX forming an obligate heterodimer that is essential for MYC binding to DNA and regulation of gene expression.[41,42]

The structural model of the MYC-MAX heterodimer in the apo form has been recently resolved providing important structural information of the bHLH-LZ and, in contrast to older models, avoiding the conformational changes induced by DNA binding.[41,43] This new model facilitates structure-based design of drugs that could target the formation of the MYC-MAX dimer, or impede its binding to DNA, providing at the same time relevant structural information related to its interactions with other dimer-associated cofactors.

Not surprisingly, the bHLH-LZ domain is considered an attractive therapeutic target and significant efforts have been made over the last decades aiming to develop small molecule compounds that target the MYC-MAX association. Although clinical grade has not yet been achieved for such compounds, these efforts have provided important insights into MYC biology and represent the basis for the generation of improved therapeutic agents.

Targeting MYC

Direct inhibition of the MYC-MAX heterodimer and targeted degradation of MYC

The role of MAX as an obligate partner of MYC has led to significant efforts towards the development of MYC-MAX heterodimer inhibitors (Figure 2c; Table 1). Over the last decade, new chemically refined compounds such as KJ-Pyr-9[44] or SaJM589 have been identified with improved overall *in vivo* properties in comparison to the prototypic small molecules 10058-F4 and 10074-G5. SaJM589 suppressed cell proliferation in diverse cancer cell lines by disrupting MYC-MAX heterodimerization and potentially by promoting proteasome-mediated MYC degradation.[45] However, to fully realize the therapeutic potential of SaJM589, *in vivo* studies in different cancer models are still required. Another recently identified small compound, MYCMI-6, also inhibits MYC-MAX heterodimerization by binding the bHLH-LZ domain of MYC and abrogates MYC-mediated transcription [46]. *In vitro*, MYCMI-6 supresses MYC-dependent cell growth and this effect correlates with the level of MYC expression in tumor cells. The administration of MYCMI-6 in mouse bearing xenografts of SK-N-DZ neuroblastoma cells resulted in the reduction of tumor cell proliferation and microvasculature density, as well as the induction of apoptosis. In contrast to the previous small molecules that inhibit heterodimerization, the compound KSI-3716 blocks MYC-MAX binding to DNA.[47] KSI-3716 is able to inhibit tumor growth in bladder murine xenograft models and has proven effective even in xenografts resistant to Gemcitabine chemotherapy.[48,49]

The small molecule MYCi975 was recently identified following a screen of 16 million compounds using an *in silico* five-point pharmacophore model.[11] MYCi975 directly binds to the HLH domain of MYC, enhancing T58 phosphorylation, in turn reducing MYC stability, transcriptional activity and cancer cell viability. *In vivo*, MYCi975 showed reasonable pharmacokinetic properties, with the capacity to reduce tumor growth, at the same time potentiating immune cell infiltration at the site of the tumor. Most notably, when combined with anti-PD-1 immunotherapy, MYCi975 significantly reduced tumor growth suggesting combining MYC inhibition and immune checkpoint blockade is an enticing potential therapeutic strategy to test in future trials.

Omomyc is a 90 amino acid MYC mini-mutant that comprises the bHLH-LZ domain and competes with c-MYC, N-MYC and L-MYC for binding to DNA displacing the MYC/MAX heterodimers and inhibiting transcription of target genes.[50–52] The role of Omomyc as an effective dominant negative form able to inhibit MYC has been evidenced in several cellular models showing anti-proliferative and pro-apoptotic effects.[52,53] *In vivo*, Omomyc-mediated MYC inhibition elicited a potent anti-proliferative effect and sustained tumor regression with no detrimental effect on healthy tissue, and denoted, for the first time, MYC inhibition as a feasible anti-cancer therapeutic strategy.[10] Recently, Omomyc mini-protein showed cell-penetrating activity and partial localization to the nucleus reverting the expression of MYC-regulated genes,[54] although the MYC/Omomyc interaction is reported to occur primarily in the cytoplasm where Omomyc can bind excess MYC monomers and prevent it entering the nucleus.[51] Co-treatment with Omomyc and Paclitaxel abrogated tumor growth of human lung cancer xenografts in mice.[54] Despite its short effective half-life,[51] a dose-escalation phase I/II clinical trial started in 2021 making OMO-103 (Omomyc) the first direct MYC inhibitor to reach clinical phase studies in patients with advanced solid tumors including non-small cell lung, colorectal and triple-negative breast cancer.

Omomyc inhibits MYC in part by promoting its proteasomal degradation.[51] In recent years, the notion of directly targeting undruggable oncoproteins like MYC using Proteolysis-targeting chimeras (PROTACs) has grown in interest and the idea of enhancing the affinity

Target	Compound	Malignancy	Phase	Trial number	Main adverse effects
MYC-MAX	Omomyc	Advanced solid tumors.	Phase I/II	NCT04808362	-
	KJ-Pyr-9	Breast cancer xenografts.	Pre-clinical		
	SaJM589	B cell line P493-6, Ramos (Burkitt's lymphoma cell line), HL-60 and KG1a (acute myeloid leukemia cell lines).	Pre-clinical		
	MYCMI-6	Neuroblastoma	Pre-clinical		
	KSI-3716	Bladder cancer xenograft.	Pre-clinical		
MAX:MAX	KI-MS2-008	T-cell acute lymphoblastic leukemia and hepatocellular carcinoma mouse models.	Pre-clinical		
Aurora A kinase	MLN8237/ Alisertib	Relapsed/Refractory peripheral T-cell lymphoma, non-Hodgkin lymphoma, advanced-non hematological malignancies, lung, breast, head and neck, gastroesophageal malignancies, and advanced or metastatic sarcoma.	Phase I/II/III	NCT01482962 NCT00807495 NCT01045421 NCT01653028	Neutropenia, anemia or gastrointestinal disorders.
	CD532	Neuroblastoma xenografts.	Pre-clinical		
PLK1	BI6727 (Volasertib)	Ovarian cancer.	Phase II	NCT01121406	Anemia, neutropenia and thrombocytopenia.
PP2A	DT-061/(AZD6244)	KRAS-driven lung cancer mouse models, lung adenocarcinoma xenografts, non-small cell lung cancer xenografts.	Pre-clinical		
	FTY720	leukemia, colon cancer, non-small cell lung cancer, breast cancer, hepatocellular carcinoma, prostate cancer.	Pre-clinical		
	OP449	AML, breast cancer, and pancreatic cancer.	Pre-clinical		
	Perphenazine	Brain, breast, colon, pancreatic, liver, skin and lung cancer, ovarian and oral carcinoma and leukemia and lymphoma cell lines. T-ALL and melanoma xenografts.	Pre-clinical		
	LB-100	Myelodysplastic syndromes, extensive stage lung small-cell carcinoma and astrocytoma, glioblastoma multiforme, giant cell glioblastoma, glioma and oligodendrogliomas.	Phase I/II	NCT03886662 NCT04560972 NCT03027388	-
Pin-1	KPT-6566	Pancreatic, lung, prostate, and breast cancer cell lines. Lung cancer xenografts.	Pre-clinical		
	ATRA	Advanced adenoid cystic carcinoma, pancreatic ductal adenocarcinoma, breast cancer.	Phase I/II	NCT03999684 NCT03307148 NCT04113863	-**
	BJP-06-005-3	Pancreatic ductal adenocarcinoma.	Pre-clinical		
	Sulfopin	Neuroblastoma and pancreatic mouse model, and neuroblastoma zebrafish model.	Pre-clinical		
PIM1	AZD1208		Phase I	NCT01489722 NCT01588548	Guillain–Barré syndrome, increased blood

Table 1 *(Continued)*

Target	Compound	Malignancy	Phase	Trial number	Main adverse effects
		Acute myelogeneous leukemia and advanced solid malignancies including malignant lymphoma.			creatinine, neutropenia, anemia and gastrointestinal disorders.
	TP-3654	Advanced solid tumors.	Phase I	NCT03715504	-
	PIM447	Myelofibrosis, acute myeloid leukemia, high risk myelodysplastic syndrome, multiple myeloma.	Phase I	NCT02370706 NCT02078609 NCT01456689 NCT02160951	Thrombocytopenia, anemia or fatigue.
	SGI-1776	Refractory prostate cancer and relapsed/refractory non Hodgkin's lymphoma, relapsed/refractory leukemias,	Phase I/II	NCT00848601 NCT01239108	Cardiac toxicity.
	SEL24/MEN1703	Acute myeloid leukemia.	Phase I/II	NCT03008187	-
SKP2	SZL-P1-41	Prostate and long tumor xenografts.	Pre-clinical		
	Dioscin	Colorectal adenocarcinoma xenografts.	Pre-clinical		
	FKA	Synovial sarcoma, osteosarcoma xenografts and prostate cancer *in vivo* models.	Pre-clinical		
	SKPin C1	Uveal melanoma xenografts.	Pre-clinical		
BRD4 (and other BET proteins)	OTX015/MK-8628	Acute leukemia, solid tumors.	Phase I/II	NCT02698189 NCT02698176 NCT02296476 NCT02259114 NCT01713582	Thrombocytopenia, anemia or gastrointestinal disorders.
	GSK2820151	Solid tumors.	Phase I	NCT02630251	-*
	ZEN-3694	Metastatic castration-prostate cancer and triple-negative breast cancer.	Phase I/II	NCT02705469 NCT02711956 NCT03901469	Eye disorders, nausea or fatigue.
	CPI-0610	Lymphoma, multiple myeloma, myelofibrosis leukemia, myelocytic, acute myelodysplastic/myeloproliferative neoplasm myelodysplastic syndrome (MDS).	Phase I/II	NCT02158858 NCT01949883 NCT02157636	Gastrointestinal disorders, fatigue, anemia or thrombocytopenia.
	GSK525762/I-BET762	Hematological malignancies.	Phase I/II	NCT01943851 NCT01587703	Thrombocytopenia and gastrointestinal events.
	INCB057643	Any advanced malignancy.	Phase I/II	NCT02711137	Nausea, thrombocytopenia or fatigue.
	JQ1	Multiple myeloma, T-ALL, B-ALL, acute myeloid leukemia cell lines. Medulloblastoma, glioblastoma, neuroblastoma, colorectal carcinoma and breast cancer cells.	Pre-clinical		
USP7	P22077	Neuroblastoma and hepatocellular carcinoma xenografts.	Pre-clinical		
	XL177A	Ewing Sarcoma, acute myeloid leukemia, and multiple myeloma cell lines.	Pre-clinical		
	GNE-6640	Acute myeloid leukemia cell lines and eosinophilic leukemia xenografts.	Pre-clinical		
	GNE6776	Eosinophilic leukemia xenografts.	Pre-clinical		
	FT671	Multiple myeloma xenografts.	Pre-clinical		

Table 1 *(*Continued*)*

Target	Compound	Malignancy	Phase	Trial number	Main adverse effects
HUWE1	BI8622/ BI8626	Multiple myeloma cell-lines and *in vivo* models.	Pre-clinical		
Aurora B kinase		Acute myeloid leukaemia and advanced solid malignancies.		NCT00497731 NCT00497991	Neutropenia, leukopenia, gastrointestinal disorders or stomatitis.
HUWE1	BI8622/ BI8626	Multiple myeloma cell-lines and *in vivo* models.	Pre-clinical		
HDAC-(PI3K)	CUDC-907	multiple myeloma, lymphoma, thyroid cancer and in solid tumors.	Phase I/II	NCT02674750 NCT01742988 NCT02909777 NCT03002623	Gastrointestinal events or thrombocytopenia, lymphopenia, leukopenia or anemia.

***Table 1*: Pre-clinical studies and clinical trials evaluating the use of compounds for the direct or indirect inhibition of MYC protein.**
* Only1/2 patients per group.

of MYC-specific ubiquitin ligases through hetero-bifunctional small molecules to promote its degradation seems plausible but remains to be shown. Some of the high-affinity molecules that target MYC could potentially be an excellent initial platform for the development of future anti-MYC PROTAC strategies. The PROTAC-mediated degradation of MYC partners, in contrast, has proven successful in pre-clinical models. The compound ARV-771 robustly degrades BET proteins in castration-resistant prostate cancer subsequently depleting the expression of c-MYC.[55] Similarly, in neuroblastoma, ARV-825 targets BET proteins resulting in inhibition of both c-MYC and N-MYC.[56] The bacterial protease Lon has also recently been described to directly degrade c-MYC in bladder and colon cancer murine models, presenting an additional potential tool to treat MYC-dependent tumors based on MYC degradation.[57]

Indirect inhibition of MYC

To date, most efforts for developing clinically applicable small molecule inhibitors of MYC have focused on targeting the MYC/MAX heterodimer, but the majority of compounds developed thus far show low cellular or *in vivo* potency, suboptimal pharmacological properties or unacceptable off-target effects.[1,11] Due to the intrinsically disordered nature of its protein structure, MYC has been traditionally considered "undruggable". However, the MYC protein presents transient secondary structure elements that become conformationally stable and can be structurally resolved when bound to other cofactors. These heterodimeric crystal models, such as those obtained for MYC-WDR5[58] or MYC-Aurora A,[59] provide a platform for the structure-based design of MYC-inhibitors potentially with a greater specificity compared to compounds that recognize disordered polypeptides.[28,60] Notably, some of these cofactors are functionally essential for MYC oncogenicity and can be potentially targeted for the indirect inhibition of MYC (Table 1; Figure 3).

Targeting MAX monomers and MAX-MAX homodimers. Apart from heterodimerizing with MYC, MAX can form homodimers or bind the proteins MGA and MXD.[61] This MAX extended network antagonizes MYC function by sequestering MAX from MYC. The compound NSC13728 stabilizes MAX/MAX homodimers, thereby decreasing MYC-mediated transcription and oncogenic transformation in chicken embryonic fibroblasts.[62] KI-MS2-008 is another compound that has been recently reported to stabilize the MAX-MAX homodimers *in vitro*.[63] KI-MS2-008 reduces the expression of MYC target genes and cancer cell growth in MYC-dependent cell lines and suppresses tumor growth in mouse models of T-cell acute lymphoblastic leukemia (T-ALL) and hepatocellular carcinoma (Table 1). These encouraging results obtained with MAX stabilizers supports the feasibility of modulating MAX dimerization as an alternative to targeting the MYC-MAX heterodimer. In addition, other interactors of the extended MAX network may provide the foundations for the development of similar therapeutic strategies.

Targeting MYC post-translational modifiers. MYC protein stability is tightly controlled by the Ub-proteasome system, a process in which the MBI phosphodegron is critically but not exclusively involved. Some of the proteins implicated in the regulation of MYC protein stability are considered as potentially exploitable therapeutic targets (Table 1).

Targeting of MYC/SCF^{FBXW7} axis through Aurora-A kinase or PLK1. The compound oridonin activates SCF^{FBXW7} leading to the degradation of MYC, inducing apoptosis in

leukemia and lymphoma cells.[64] Aurora A kinase prevents SCF^{FBXW7}-mediated MYC proteolysis by binding MBI through an interaction that relies on the phosphorylation status of T58 and S62.[60,65] The inhibition of Aurora A kinase using small molecule inhibitors has been explored as a strategy to target MYC function indirectly. Compounds such as MLN8237/alisertib and CD532 render the Aurora A-c-MYC/N-MYC complex dysfunctional and promote tumor regression in neuroblastoma and human hepatocarcinoma cells.[65,66] CD532 promotes N-MYC protein degradation in neuroblastoma xenografts,[67] while MLN8237/alisertib showed a compelling antitumor effect in various Phase I/II clinical trials including patients with non-Hodgkin lymphoma, advanced non-hematological malignancies and metastatic sarcomas, although it is associated with significant side effects, particularly hematological.[68] Unfortunately, most of the small molecule inhibitors that target this complex have not reached Phase III clinical trials, and for those that have, such as alisertib (tested in relapsed/refractory peripheral T-cell lymphoma), have not shown encouraging results.[69]

The Polo-Like Kinase-1 (PLK1) directly binds and phosphorylates FBXW7 promoting its autopolyubiquitination and degradation resulting in stabilization of N-MYC. In a feedforward loop, stabilized N-MYC activates PLK-1 transcription further supporting N-MYC oncogenicity. The selective inhibition of PLK-1 using BI6727 in combination with the BCL2 inhibitor ABT199 reduces neuroblastoma tumor volume *in vivo* supporting the clinical potential of combined PLK1/BCL2 inhibitors for MYC-over expressing malignancies.[70] In a phase II clinical trial, single agent BI6727 (Volasertib) has shown anti-tumor activity in patients with ovarian cancer.[71]

PP2A activation and Pin-1 abrogation. PP2A is frequently inactivated in human cancers.[72] The important role played by PP2A in the SCF^{FBXW7}-mediated degradation of MYC prompted the study of either the direct or indirect therapeutic activation of PP2A to potentially enhance the dephosphorylation of MYC pS62 and its subsequent proteasomal degradation. Small molecule activators of PP2A (SMAPS) have emerged as potential therapeutic drugs for the indirect inhibition of MYC specially in kinase-inhibition resistant tumors.[72–75] In a recent study, the treatment of non-small cell lung cancer xenografts with the SMAP DT-061 suppressed tumor growth accompanied by abrogation of c-MYC protein.[76] The combined treatment of DT-061 with the MEK inhibitor AZD6244, or compounds such as FTY720 and FTY720 analogues OP449 or perphenazine, have proven effective in multiple pre-clinical models and are considered promising for cancer therapeutics.[72,77-79] Despite its role as a tumor suppressor, inhibition of PP2A-C by the small molecule inhibitor LB-100 has a potent sensitization effect for chemotherapy and radiotherapy that is currently being tested alone or in combined regimes in Phase I clinical trials including patients with myelodysplastic syndromes, small-cell lung cancer and recurrent glioblastoma.[77]

The proline isomerase PIN1 is essential in regulating MYC proteolysis via the Ub-proteasome system. *PIN1* expression is increased in most cancers and is associated with poor outcome.[80] KPT-6566 is a recently described small molecule that binds and inhibits the PIN1 active site and targets it for degradation.[81] At the same time, remnant chemical species that promote DNA damage originate from the interaction between PIN1 and KPT-6566. Through this dual mechanism of action, KPT-6566 induces cell death specifically in cancer cells *in vitro* and limits lung metastasis growth *in vivo*. The retinoid ATRA, was identified following a mechanism-based screen as a new specific binder to the PIN1 active site that inhibits PIN1 function and induces its degradation in acute promyelocytic leukemia and breast cancer cells.[82] Moreover, ATRA was recently reported to suppress Tamoxifen-resistant breast cancer cell growth *in vitro* and in tumor xenografts.[83] Recently, the highly selective compound BJP-06-005-3 was designed to probe Cys113 in the PIN1 active site and suppressed cell viability in pancreatic ductal adenocarcinoma.[84] However, despite being a promising tool, further chemical optimization may be needed to improve BJP-06-005-3 bioavailability and *in vivo* performance.[85] Similarly, the compound Sulfopin has recently been reported to target Cys113 downregulating MYC-target genes and reducing tumor progression in N-MYC driven neuroblastoma *in vivo*, as well as pancreatic cancer models. Despite the moderate effect on tumor viability *in vitro*, Sulfopin shows activity and very low toxicity *in vivo* suggesting that higher doses or combination with other treatments might be suitable for future treatments in MYC-driven malignancies.[86]

Inhibition of PIM1 kinase. PIM1 promotes T58 dephosphorylation and S62/S329 phosphorylation, stabilizing the MYC protein and increasing both its oncogenic transcriptional activity and transforming capacity.[87] PIM1 directly interacts with MBII and is recruited to MYC target genes where it phosphorylates nucleosomes at H3S10 contributing to MYC-dependent transcriptional activation and cellular transformation.[88] PIM1, along with other PIM kinases, is aberrantly expressed in several malignancies and is considered an attractive target for therapy. Accordingly, a number of small molecule PIM inhibitors have been tested in clinical trials suggesting a potential therapeutic role.[89] The small molecule AZD1208 is a pan-PIM kinase inhibitor that inhibits cell growth, induces apoptosis and sensitizes to radiation.[90] AZD1208 has been tested in phase I clinical trials including acute myeloid leukemia (AML) and advanced solid tumors;[91] however, despite showing on-target engagement, it lacked clinical efficacy as a

monotherapy, with a relatively high toxicity, particularly gastrointestinal and hematological.[92] However, the combination of AZD1208 with other agents such as immunotherapeutics, immune checkpoint blockade or synthetic lethal targets might have potential to improve functional outcomes.[93] Toxicity has also proven an issue with the PIM kinase inhibitor SGI-1776, where QT prolongation was observed on a phase I clinical trial, attributed to inhibition of the cardiac potassium channel hERG, leading to trial termination (NCT00848601). TP-3654 (SGI-9481), a second-generation pan-PIM kinase inhibitor that lacks off-target activity against hERG, has shown higher potency and lower toxicity in clinical trials for solid tumors.[94] Other examples of PIM kinase inhibitors under evaluation are PIM447 which has activity in multiple myeloma, and SEL24/MEN1703, currently tested in a Phase I/II clinical trial in patients with AML.[91,95] Targeting PIM kinases using small molecule inhibitors remains a promising anti-tumor strategy, and the outcome of ongoing clinical trials in terms of efficacy and toxicity are eagerly awaited.

Targeting SKP2. The E3 ligase SKP2 binds MBII along with the HLH-LZ domain, and targets MYC for ubiquitination and proteasome degradation. Distinct from SCF^{FBXW7}, SKP2 increases MYC turnover activating transcription of some MYC target genes.[96,97] High expression of SKP2 correlates with poor outcome in multiple malignancies[98] and its inactivation is considered a potential therapeutic strategy. Several SKP2 inhibitors, including compounds such as SZL-P1-41,[99] FKA[100,101] or Dioscin,[102] have been developed and show suppression of SKP2 oncogenic function in pre-clinical models, providing proof-of-principle for therapeutic targeting of SKP2 in human cancer therapy with associated high efficacy and safety. Further improvement on metabolic and pharmacokinetic properties of these compounds may eventually boost the development of candidates with clinical potential.

USP7 inhibition. USP7 is a multi-substrate deubiquitinating enzyme that plays a key role in proliferation and tumorigenesis, partly because it prevents the proteolysis of c-MYC and N-MYC.[103] In neuroblastoma patients, USP7 overexpression is associated with a poor outcome and its inhibition in neuroblastoma xenografts by the small molecule P22077 prevents tumor growth via N-MYC destabilization suggesting the potential of USP7 inhibition as an exploitable therapy.[104] In other malignancies such as hepatocellular carcinoma, USP7 overexpression correlates with disease progression and its inhibition by P22077 also suppresses tumor growth *in vivo*.[105] Other small molecule USP7 inhibitors such as XL177A, GNE-6640, GNE6776 or FT671 suppress the growth of different cancer cell lines and inhibit tumor growth in xenograft models.[106–108] It is also worth noting that USP7 has been shown to have an oncogenic and tumor suppressor role within different subtypes of T-ALL,[109] indicating that careful patient selection and biomarker analyses will need to be considered when USP7 inhibitors are tested in clinical trials.

Aurora B kinase. Aurora B (AURKB), a kinase that plays an important role during cell division, is frequently overexpressed in different types of cancer, including ALL and AML, and is associated with poor prognosis in patients.[110] A recent study in T-ALL shows that the direct interaction between MYC and AURKB promotes leukemogenesis and depicts a model by which AURKB increases MYC stability after the phosphorylation of S67 antagonizing the binding of GSK3β.[33] In the same study, AURKB depletion reduced MYC-induced gene expression and MYC protein levels in both primary cells and cell lines. The treatment with the highly selective Aurora B inhibitor AZD1152 combined with Vincristine suppresses tumor growth in $FBXW7^{WT}$ T-ALL xenografts suggesting a new therapeutic strategy for T-ALL.[33] In two Phase I/II clinical trials, treatment with the compound AZD1152 resulted in a hematologic response rate in 25% of patients with AML,[111] but no responses were seen in advanced solid malignancies.[112] Overall, AZD1152 showed good tolerability in both studies providing promising preliminary evidence of an exploitable therapeutic window for AURKB inhibition as a potential anticancer strategy in hematological malignancies (Table 1).

The MYC, HUWE1 and MIZ1 Trimer. The transcription factor MIZ1 binds MYC through the bHLH-LZ region and abrogates MYC transcriptional activity via two mechanisms.[113] The first involves the trimerization of MYC, MIZ1 and DNMT3A followed by DNA methylation and subsequent inhibition of MYC target genes.[114] The second mechanism is based on the competition for MYC binding between MIZ1 and the E2 ligase HUWE1.[115,116] Depending on the cellular context, HUWE1 can act as a tumor suppressor or tumor promoter by regulating the turnover of MYC/MIZ1 and balancing the ratio of both proteins at gene promoters.[115,117] Due to the profound functional implication of the MYC/MIZ1 interaction on MYC activity, fostering this association via small molecule inhibition of HUWE1 has been explored as a therapy.[113,115,116,118,119] The small compounds BI8622 and BI8626 are specific inhibitors of HUWE1 that enhance MYC proteolysis and suppress MYC-dependent transactivation resulting in inhibition of cell growth in colon carcinoma and multiple myeloma.[116,120] *In vivo*, HUWE1 knock-down clearly reduces tumor burden, but both BI8622 and BI8626 have suboptimal pharmacokinetics that prevents the assessment of their *in vivo* efficacy in MYC-driven tumor models. Nevertheless, these pre-clinical studies support the notion that it is possible to develop effective

antitumor strategies by targeting HUWE1. It is likely that other mechanisms of regulation like MIZ1-HUWE1 are involved in the interaction between MYC and other transcription factors that act as functional repressors. Extensive characterization of these mechanisms would allow the development of novel therapeutic strategies for MYC-related malignancies.

Other MYC modifiers. Apart from SCF^{FBXW7}, several other E3 ubiquitin ligases and proteases, such as CRY2-FBXL3, USP28, USP7 or USP37, SCF^{FBXO28}, FBXO29 and RNF115 (reviewed in[121]), are involved in modulation of c-MYC and/or N-MYC stability. PIAS1 is involved in SUMOylation[122] or ubiquitination of residues K51 and K52 via an SCF^{FBXW7}-independent mechanism[123,124] albeit the functional effect of these modifications on MYC are likely to be context dependent. All these MYC post-translational modifiers could be explored as potential therapeutic targets for MYC-driven malignancies.

Targeting of chromatin modifiers. BRD4. BRD4 is a transcriptional regulator involved in DNA replication and reparation that plays a key role in the maintenance of cell proliferation.[125] Apart from being a well-known transcriptional modulator of the *MYC* and *MYCN* genes, BRD4 directly interacts, phosphorylates and destabilizes MYC at the protein level through the formation of a ternary complex with ERK1 creating a regulatory network that balances MYC activity.[126] Simultaneously, MYC regulates BRD4-mediated acetylation of histones establishing a negative feedback loop that controls its own transcription. Due to its important implication in controlling MYC homeostasis, BRD4 has been intensively investigated as a therapeutic target using small compounds in MYC-driven cancers. The small molecule bromodomain inhibitor JQ1 binds BRD2/4 and blocks the association of BRD4 at acetylated histones within the MYC locus decreasing the expression of all MYC superfamily members.[127,128] As a result, anti-tumor effects are observed in diverse hematological malignancies and solid tumors.[127,129] JQ1 is the first-in-class compound that established proof-of-principle for BET inhibition as a cancer therapy, however, its poor *in vivo* pharmacokinetic properties preclude its use in clinical trials. Alternatively, numerous other improved BRD4 inhibitors such as OTX015/MK-8628, GSK2820151, ZEN-3694, CPI-0610, GSK525762/I-BET762 and INCB057643 have been developed and their safety, pharmacokinetics and activity are currently under assessment in Phase I and Phase I/II clinical trials including several cancers[130,131] (Table 1). Unfortunately, none of these inhibitors have yet received regulatory approval. More studies are necessary to optimize optimal dosing schedules and to explore potential combinations with other compounds that might improve efficacy.

HDACs and TRRAP. A myriad of components of the pre-replicative complex, including CDC6,[132] ORC1,[133] SNF5,[134,135] CBP/300 and HDACs,[36,136,137] associate with MYC through the bHLH-LZ domain, regulating DNA replication origin in response to cellular replication stress and genomic instability.[138,139] Apart from their role in gene regulation, the deacetylases HDAC1/2 also modulate MYC stability through direct Sin3b-mediated deacetylation of the MYC peptidic chain accompanied with a reduction of MYC transcriptional activity.[140] Similarly, HDAC3 attenuates MYC-mediated gene expression and MYC-associated pro-apoptotic activity through a direct protein-protein interaction.[36,137] Overexpression of HDACs is observed in different cancer types and reversing epigenetic anomalies using HDAC inhibitors is considered an enticing therapeutic strategy in cancer. Accordingly, several compounds are currently tested in clinical trials (Table 1).[141] The compound CUDC-907 is a dual inhibitor of both HDACs and PI3K that suppresses growth in MYC-dependent cancer cells[142] and demonstrates efficacy against prostate cancer mouse xenografts.[143] Results of phase I/II clinical trials reported anti-tumor activity of CUDC-907 in multiple myeloma, lymphoma, thyroid cancer and in solid tumors with MYC alterations, suggesting the therapeutic potential of CUDC-907 for the treatment of diverse MYC-driven malignancies.[75,144,145]

Transformation-transactivation domain-associated protein (TRRAP) is one of the best characterized MYC cofactors. TRRAP is the integral subunit of the GCN5-containing and the TIP60-containing histone acetyltransferase (HAT) complexes and it is crucial for their recruitment to MYC target genes, a pivotal element in regulating transcriptional activation.[146–150] TRRAP also directly acetylates MYC[136,146,151] and the association of both proteins is indispensable for MYC oncogenic activity in most contexts.[152] The recent in-depth structural characterization of the MYC-TRRAP interaction may form the basis for the development of novel MYC small molecule inhibitors.[148]

WDR5 and MYC. The WD40-repeat protein WDR5 promotes the assembly of multiple chromatin regulatory complexes responsible of the recruitment of MYC onto chromatin. The interaction between MYC and WDR5 depends on the hydrophobic residues of the highly conserved MBIIIb core EEIDVV and is important for transcription of protein synthesis-related genes, gene target recognition and for somatic cell reprogramming (Table 1).[153] However, how WDR5-MYC interaction regulates target genes is still not completely understood and the implications of MBIIIb in cell transformation remains elusive due to contradictory results from *in vitro* transformation assays using different MYC deleterious mutants.[26,153] *In vivo*, blocking the MYC-WDR5 interaction is emerging as a potential anti-tumor therapeutic strategy. In mice with stablished Burkitt's

lymphoma tumors, exchanging wild type MYC with a WDR5-binding defective MYC mutant promotes tumor regression, offering a potentially exploitable therapeutic window.[153] A series of high affinity small compounds that bind the MYC-site of WDR5 targeting the interaction between both proteins have been developed *in vitro* and are currently under optimization to improve their drug-like properties prior to cell or animal testing.[154] It is not only the MYC-binding site of WDR5 that is an enticing therapeutic target; the small molecule C6 binds the WIN-site of WDR5 and displaces it from chromatin with the subsequent eviction of MYC and downregulation of genes associated with protein synthesis.[153,155]

Outstanding Questions

Over the last decades, MYC has moved from being considered "undruggable" into one of the most appealing therapeutic targets for cancer treatment. Despite the major challenges in directly inhibiting MYC, particularly in translating promising *in vitro* results to meaningful *in vivo* efficacy, the first direct MYC inhibitors are now starting clinical trial evaluation. Omomyc, for instance, has promising *in vivo* properties in pre-clinical testing and the results of early phase trials in patients with advanced solid tumors will provide valuable insights into both the efficacy and toxicity of this approach. The complex protein structure of MYC still poses a substantial challenge for development and optimization of direct MYC inhibitors. Recent advances in the *in silico* prediction of a protein structure based on the polypeptidic sequence may represent an important breakthrough towards the refinement of incomplete crystallographic data.[156] Nevertheless, the higher demand on computational resources may present an important limitation for many research facilities and no *in silico* model is yet capable of fully deciphering the complexities of intrinsic disordered domains.

The indirect inhibition of MYC through targeting binding proteins that are critical for its oncogenicity have emerged as a promising alternative. The identification of novel key cofactors for MYC function in promoting cancer opens new exploitable ways for the indirect inhibition of MYC (Figure 4). In addition, the

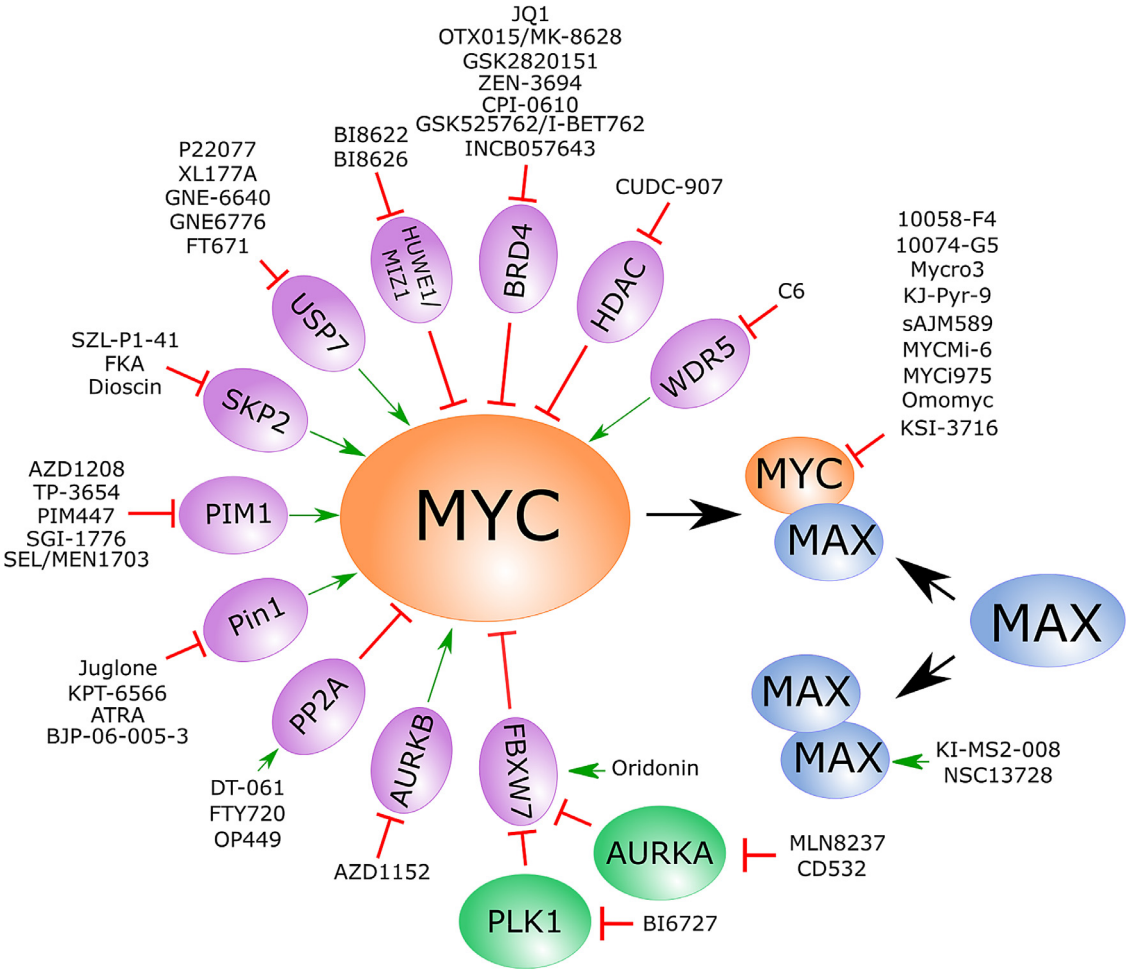

Figure 4. Strategies for direct and indirect small-molecule inhibition of MYC protein.

identification of novel critical binding partners may facilitate our understanding of the molecular mechanisms by which MYC promotes oncogenesis and tumor maintenance providing at the same time useful information for the development of future successful therapies. However, MYC interacts with a plethora of different proteins and these interactions are usually context dependent thus the effects of indirect MYC inhibition are likely to be tumor specific.

Given the importance of MYC to tumor maintenance, it is possible that a variety of resistance mechanisms might be engaged by tumor cells to escape therapeutic targeting. For instance, mutations interfering with drug engagement might be selected for with certain small molecule inhibitors, or genomic alterations of the E3 ligase complex might occur on chronic exposure to PROTACs, as recently described for BET-PROTACs.[157] Moreover, indirect targeting of MYC may induce highly adaptive signaling pathways, potentially associated with therapeutic resistance. In contrast, direct targeting of MYC with compounds such as Omomyc might be less likely to promote drug resistance since MYC acts as a central regulatory node of gene expression without obvious bypass pathways.[158] The fact that c-MYC, N-MYC and L-MYC can functionally replace each other in some contexts adds an additional layer of complexity to the development of specific MYC-inhibitors, particularly as their interactomes vary. Although some small molecules have shown the ability to inhibit different MYC family members, the future development of new pan-MYC inhibitors will increase the chances of success when translating the results from bench-to-bedside. Finally, combination strategies with small molecule MYC inhibitors and immunomodulators or indirect MYC inhibitors along with other antitumoral agents should be included in future studies. However, the fact that MYC inactivation can induce cellular senescence[159] needs to be considered when designing such combination trials, particularly those that include chemotherapeutic drugs whose efficacy is cell cycle dependent. Significant progress has been achieved to date, but further research is still required to better understand the regulation mechanism of several MYC interactors, and to bring MYC inhibitors to daily clinical practice.

Search strategy and selection criteria

Data for this Review were identified by searches of PubMed, and references from relevant articles using the search terms "MYC small molecule inhibitor", "MYC binding protein OR MYC interactor" and "(MYC-binding protein) small molecule inhibitor". All relevant information and reference code for clinical trials was retrieved from Clinicaltrials.gov. Abstracts and reports from meetings were excluded. Only articles published in English were included and original reports published after 2016 were prioritized highlighting more novel findings. Nevertheless, references back to 1988 have been included for contextualization.

Contributors

V. Llombart contributed on the conceptualization, data curation, funding acquisition, investigation, project administration, resources, writing of original draft and editing. M. R. Mansour contributed on the conceptualization, funding acquisition, resources, supervision, validation, and review of the manuscript.

Declaration of interests

No conflicts of interest.

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