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BCL6 in B-cell lymphomas: old target, new tricks?

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ABSTRACT

BCL6 (B Cell Lymphoma 6) is a master regulator of humoral immunity and is required for the germinal center response. Given this role and its frequent dysregulation in germinal center-derived malignancies, it has remained an attractive target since it was first described over 30 years ago. Like other transcription factors, however, it has been difficult to inhibit due to its lack of conventional binding pockets. With the introduction of specific protein degraders, the potential to target BCL6 clinically is now within reach. In this Perspective, we summarize the roles of BCL6 in B and T cell biology as well as in lymphoma, discuss early efforts at targeting BCL6 and current approaches, and review the results of ongoing early-phase clinical trials of BCL6 degraders. We also explore potential mechanisms of resistance to these agents as well as rational combination therapies.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive lymphoma and arises through diverse genetic and transcriptional alterations that deregulate key programs controlling B cell proliferation, survival, and differentiation. Among these regulatory networks, the transcription factor B cell lymphoma 6 (BCL6) occupies a central position. BCL6 is essential for the germinal center (GC) reaction, where it enables B cells to proliferate rapidly while tolerating DNA damage associated with somatic hypermutation (SHM) and class-switch recombination (CSR). Dysregulated expression of BCL6 is a frequent event in germinal center–derived lymphomas and contributes to malignant survival by repressing pathways governing DNA damage responses, apoptosis, and differentiation. Although long recognized as a critical oncogenic driver, BCL6 has historically been considered difficult to target pharmacologically due to its function as a transcription factor. However, advances in chemical biology and targeted protein degradation have begun to challenge this paradigm, positioning BCL6 as an emerging therapeutic vulnerability in lymphoma. In this perspective, we summarize the role of BCL6 in lymphoma biology and discuss therapeutic strategies designed to disrupt BCL6 function, with particular focus on recent advances in targeted protein degradation.

BCL6 biology and function in the germinal center

Understanding how BCL6 contributes to lymphomagenesis first requires examining its physiologic role in GC biology. BCL6 is a BTB/POZ (Broad complex, Tramtrack, Bric-a-brac/Pox virus and Zinc finger) transcription factor that functions as a master regulator of the humoral immune response, playing a critical role in the initiation and maintenance of germinal centers (**Figure 1A**). *BCL6* was originally identified through recurrent chromosomal translocations involving chromosome 3q27 in diffuse large B-cell lymphoma (DLBCL), most commonly translocated to immunoglobulin heavy- or light-chain loci^{1–7}. These rearrangements, present in 30–40% of DLBCLs and 5–15% of follicular lymphomas (FLs), replace the native regulatory elements of *BCL6* with those of other promoters or enhancer elements, resulting in constitutive, high-level transcription that is uncoupled from normal developmental control. These observations implicated BCL6 as a candidate oncogenic driver and prompted further studies examining its function in normal lymphoid tissues^{5,8}.

The critical role of BCL6 in GC biology was subsequently demonstrated in murine models. Genetic loss-of-function studies in mice showed that *Bcl6*-deficient animals have profoundly impaired T cell-dependent humoral immune responses, with a complete failure to form germinal centers following antigenic challenge^{9,10}. Although naïve B cells developed normally, they were unable to enter or sustain the GC reaction, could not undergo affinity maturation or CSR, and failed to generate memory or long-lived plasma cells. Strikingly, *Bcl6*-deficient mice also lacked T follicular helper (T_{FH}) cells, revealing that BCL6 controls both B- and T-cell function of the GC microenvironment^{11–13}.

Although BCL6 functions in both GC B cells and T_{FH} cells, many of its best-characterized activities relate to its ability to coordinate the unique biological demands of the GC B cell program. A primary requirement of GCB cells is the ability to proliferate rapidly while undergoing programmed DNA damage SHM and CSR. To support this function, BCL6 represses key components of the DNA damage response - including *TP53* and *ATR* - as well as genes involved in apoptosis and cell-cycle arrest, such as *CDKN1A*, *BBC3* (also known as *PUMA*),

and *BAX*^{14–16}. Through suppression of these checkpoint and death pathways, BCL6 permits continued cell-cycle progression despite accumulating genomic lesions, a unique process that is essential for antibody diversification. At the same time, BCL6 blocks terminal differentiation by through direct repression of *PRDM1* and broader antagonism of the *IRF4-PRDM1* plasma cell differentiation program^{15–17}. In doing so, BCL6 establishes a cellular state characterized by rapid proliferation, tolerance of genomic lesions, and resistance to differentiation and apoptosis, features that mirror several hallmarks of cancer and predispose GC B cells to malignant transformation.

At the molecular level, BCL6 functions primarily as a sequence-specific transcriptional repressor that coordinates multiple cellular programs required for the GC reaction. The N-terminal BTB/POZ domain mediates homodimerization and recruits large corepressor complexes, including SMRT (silencing mediator of retinoid and thyroid hormone receptor; *NCOR2*), NCoR (nuclear receptor corepressor; *NCOR1*), and BCOR (BCL6 corepressor)^{18–22} (**Figure 1B**). These corepressors function as structural scaffolds that assemble multiprotein repression complexes containing histone deacetylase 3 (HDAC3) and other chromatin modifying enzymes to establish transcriptionally repressive chromatin marks at target loci²². Because this interaction occurs through a structurally defined interface within the BTB domain, it has emerged as a key site for pharmacological targeting of BCL6. Although BCL6 recognizes a defined motif, many target loci also contain binding sites for additional transcription factors, and BCL6 can be recruited cooperatively or indirectly through interactions with other regulatory proteins, indicating that regulation of BCL6 target genes is context dependent. Consequently, precise regulation of BCL6 expression and activity is essential for GC dynamics, and disruption of these regulatory mechanisms can contribute to the development of GC-derived lymphomas.

BCL6 in DLBCL and FL: molecular mechanisms

In DLBCL, the GC program enforced by BCL6 is frequently stabilized through genetic and epigenetic mechanisms that prevent its normal downregulation. Rather than altering the BCL6 protein itself, these mechanisms converge on maintaining aberrant BCL6 expression and/or activity.

BCL6 dysregulation in lymphoma

As described above, chromosomal rearrangements can uncouple *BCL6* transcription from its normal regulatory control(**Figure 1C**). Aberrant *BCL6* expression can also arise through somatic mutations that target the noncoding regulatory regions of BCL6. BCL6 normally contributes to negative regulation of its own transcription through binding to regulatory elements within its promoter region^{23,24}. Additionally, during normal GC exit, both BLIMP-1 and IRF4 directly bind the *BCL6* promoter to repress its transcription and facilitate plasma cell differentiation^{25,26}. Somatic mutations in these regulatory elements can disrupt both BCL6 autoregulation and post-GC silencing cues, thereby sustaining *BCL6* expression beyond its normal developmental context(**Figure 1C**)^{25,26}. BCL6 activity can also be enhanced independently of its expression. Recurrent loss-of-function mutations in *EP300* (~5%) and *CREBBP* (~20-25%) impair acetylation-dependent inactivation of BCL6^{27–29}. Acetylation of BCL6 reduces its ability to recruit corepressor complexes; thus, disruption of this regulatory axis enhances BCL6-mediated repression without altering BCL6 expression levels (**Figure 1C**). BCL6 protein stability represents another level of dysregulation. The endogenous ubiquitin ligase FBXO11, which targets BCL6 for

degradation, is recurrently inactivated in ~5% of DLBCLs and 10-20% of Burkitt lymphomas, providing an additional route to aberrant BCL6 persistence^{30–32}. As a result, lymphoma cells retain BCL6 activity even in contexts that would normally trigger differentiation or cell-cycle arrest.

Context-dependent functions of BCL6 in lymphoma

Sustained BCL6 activity may have consequences beyond persistence of the normal GC transcriptional program. An early genome-wide analysis of BCL6 binding in GC B cells versus DLBCL cell lines demonstrated substantial differences in BCL6 target genes, including altered regulation of oncogenes such as BCL2³³. Thus, malignant transformation may reshape BCL6 regulatory circuits, altering its control of pathways that contribute to lymphoma cell survival and proliferation.

The consequences of sustained BCL6 activity may also be shaped by lymphoma context. Similar mechanisms of BCL6 dysregulation are operative in FL, consistent with their shared origin in the germinal center. However, BCL6 also plays important roles in follicular retention in these contexts, and this is co-opted in FL to provide a supportive stromal niche required for maintenance of these lymphomas^{34–37}. Thus, in FL, BCL6 may not only enforce the GC transcriptional identity of the tumor cell but actively maintain its physical residence within the microenvironmental niche that sustains it, a dual dependency that distinguishes FL biology from that of DLBCL and may carry important implications for therapeutic targeting.

Context-dependent BCL6 biology is also evident across molecular subtypes of DLBCL. Cell of origin (COO) classification broadly groups tumors into those resembling GC B cells (GCB-DLBCL) or activated B cells (ABC-DLBCL), reflecting distinct stages of normal B cell differentiation. Unsurprisingly, BCL6 expression is highest in GCB-DLBCL, consistent with its role in enforcing a GC transcriptional program³⁸. Additionally, BCL6 expression is associated with a more favorable clinical outcome and is generally lower in ABC-DLBCLs, where post-GC differentiation programs partially antagonize BCL6 activity³⁸. Notably, *BCL6* chromosomal rearrangements show the opposite pattern, occurring more frequently in ABC-DLBCL than in GCB-DLBCL^{39,40}. This discordance suggests that the mechanisms sustaining BCL6 activity differ by COO and that BCL6 expression alone may not reflect its functional contribution to lymphoma biology. Indeed, more refined classifications of DLBCL reveal heterogeneity in *BCL6* rearrangements, activity, and oncogenic mechanisms across molecular contexts^{41–44}. Whether these differences translate into differential dependence on BCL6 and sensitivity to BCL6-directed therapies remains to be determined.

Therapeutic Targeting of BCL6

Given its role as a master regulator of the GC reaction and its frequent dysregulation in DLBCL, BCL6 quickly emerged as a therapeutic target of interest following the original studies describing its function. Transcription factors, as a class, are attractive targets due to their fundamental role in controlling cellular phenotypes and frequent dysregulation in disease. However, they have historically been considered ‘undruggable’ due to their intrinsically disordered domains, lack of conventional ligand-binding pockets, and highly dynamic interactions with DNA and co-factors. Despite these difficulties we have seen several novel strategies targeting BCL6 in the past two decades.

Disruption of co-repressor binding: peptidomimetics

The first attempts to target BCL6 were described in pioneering studies from the Melnick laboratory using peptide mimetics, which competitively occupied the lateral groove of the BTB domain, preventing co-repressor recruitment⁴⁵. In murine models, peptide inhibition of BCL6 abrogated GC formation, demonstrating effective on-target suppression of BCL6 function. In human DLBCL cell lines, disruption of corepressor binding de-repressed canonical BCL6 target genes, induced apoptosis, and triggered cell-cycle arrest. A subsequent derivative of this peptide, with enhanced stability, suppressed tumor growth in xenograft models⁴⁶. Sensitivity was independent of the genetic status of the *BCL6* locus, as peptide inhibition was effective in cell lines harboring *BCL6* point mutation or 3q27 translocation, as well as in cells with a wild-type BCL6 locus. Additionally, transcriptional programs appeared to influence response, with cell lines characterized by a B cell receptor activation signature or oxidative phosphorylation signature demonstrating relative sensitivity and resistance, respectively. These studies demonstrated the feasibility of BCL6 targeting while also highlighting potential heterogeneity in response in differing molecular contexts despite similar BCL6 expression.

Disruption of co-repressor binding: small molecule inhibitors

While peptide inhibitors provided compelling proof-of-principle that disruption of BCL6-corepressor interactions can be therapeutically effective, their clinical translation was impeded by pharmacological challenges including limited serum stability, proteolytic degradation, and difficulties achieving sustained systemic exposure. These limitations motivated efforts to develop small-molecule inhibitors capable of targeting the same BTB lateral groove but offering improved pharmacokinetics and bioavailability.

The first reported BCL6 small molecule inhibitor, 79-6, selectively bound the BTB lateral groove and disrupted interaction with SMRT and NCoR without impairing BCL6 DNA binding⁴⁷. Treatment of DLBCL cell lines with 79-6 led to derepression of canonical BCL6 target genes involved in DNA damage responses and cell-cycle arrest. Functionally, this resulted in growth suppression and apoptosis in BCL6 dependent DLBCL xenograft models, demonstrating the feasibility of this approach *in vivo*. Further refinements yielded more potent and selective inhibitors, including FX1, which more effectively displaced corepressors⁴⁸. FX1 demonstrated more potent activity both *in vitro* and *in vivo*. Notably, small-molecule BTB inhibitors demonstrated activity across both GCB and ABC DLBCL models, although the magnitude of response varied between cell lines.

In addition to 79-6 and FX1, several structurally distinct BTB groove inhibitors have been reported, including Apt48, AP-4-287, BI3812, WK500B^{49–52}. These compounds were designed to improve affinity, selectivity, and pharmacological properties while targeting the same corepressor-binding interface of the BTB domain. Many demonstrated effective displacement of corepressors, derepression of BCL6 target genes, and antitumor activity in murine xenograft models. Despite these encouraging preclinical results, however, none of these agents have advanced to clinical development, underscoring the challenges of achieving durable and complete disruption of BCL6 function *in vivo*.

Relocalization of transcriptional activators

Beyond direct inhibition of the BTB lateral groove, alternative strategies have aimed to target BCL6 function by redirecting transcriptional activators to loci normally repressed by BCL6. Early transcriptional/epigenetic inducers of proximity (TCIPs) were designed by covalently linking ligands of BCL6 to small molecules that bind transcriptional co-activators such as BRD4. These early constructs employed BET bromodomain inhibitor JQ1 as the BRD4-binding moiety⁵³. BRD4 functions primarily as a chromatin reader and scaffold protein that recruits transcriptional machinery, including transcription elongation factor b (P-TEFb), to acetylated chromatin to activate transcription. Accordingly, these bivalent compounds recruited BRD4 to BCL6-occupied promoters, increasing BRD4 occupancy at these sites and promoting RNA polymerase II elongation at pro-apoptotic target genes. The most potent BRD4-based TCIP demonstrated nanomolar toxicity in DLBCL cell lines (EC₅₀ ~1 - 10 nM), including chemotherapy resistant *TP53* mutant models, supporting the feasibility of rewiring oncogenic transcription factors to activate apoptosis pathways⁵³. However, the magnitude and durability of transcriptional activation were modest relative to later kinase-based designs.

Subsequent refinement of this approach led to the development of cyclin-dependent kinase (CDK) TCIPs. In contrast to BRD4, CDK9 is a catalytic subunit of the P-TEFb complex and directly phosphorylates RNA polymerase II to promote transcription⁵⁴. Recruitment of CDK9 to BCL6-bound chromatin therefore provided a more direct and potent mechanism for activating BCL6-repressed genes. *In vitro*, one such CDK-TCIP demonstrated potent cytotoxicity in BCL6-overexpressing DLBCL cell lines, while exhibiting markedly reduced toxicity in normal tonsillar lymphocytes⁵⁵. Additionally, mice treated with CDK-TCIP after immunization demonstrated marked depletion of BCL6-dependent GC B cells, while sparing naive and non-germinal center B cell populations. More recently, this strategy was extended to lysine acetyl transferases (KAT-TCIPs) that recruit p300/CBP to BCL6-bound chromatin⁵⁶. These compounds promoted localized acetylation and activation of BCL6-repressed apoptosis programs, resulting in potent activity in DLBCL models *in vitro* and *in vivo*. Notably, KAT-, BRD4-, and CDK9-based TCIPs produced distinct transcriptional responses, demonstrating that the recruited transcriptional regulator can shape the biological consequences of BCL6-directed transcriptional rewiring. However, because TCIPs rely on ternary complex formation, their activity is sensitive to compound concentration and can exhibit bell-shaped dose-response relationships, highlighting the need for optimization of exposure and dosing for successful clinical translation^{53,55–57}.

BCL6 degraders

While BTB groove inhibitors and transcriptional rewiring strategies demonstrated that BCL6-dependent programs can be therapeutically targeted, both approaches retain the BCL6 protein within the cell and rely on sustained target engagement to maintain suppression. Therefore, an alternative strategy has focused on eliminating BCL6 through targeted protein degradation^{58–60}. BCL6-directed proteolysis-targeting chimeras (PROTACs) and related degrader molecules are bivalent compounds that link a ligand for BCL6 to a ligand for E3 ubiquitin ligase, thereby inducing formation of a ternary complex. This proximity promotes ubiquitination of BCL6 and subsequent proteasomal degradation. In contrast to competitive BTB inhibitors or TCIPs, which modulate function, degraders eliminate BCL6 itself, thus abrogating all functional domains simultaneously. Most advanced BCL6 degraders were developed by utilizing high-affinity BTB ligands, including BI3812-based

scaffolds, and conjugating them to cereblon (CRBN)-recruiting moieties, enabling ubiquitination and proteasomal degradation of BCL6. CRBN has established clinical relevance in B cell malignancies as the molecular target of immunomodulatory drugs such as lenalidomide, providing precedent that pharmacologic engagement of this ligase can be therapeutically tolerated in hematologic cancers^{61–64}.

Two CRBN-based BCL6 degraders have advanced into clinical evaluation: BMS-986458 and ARV-393^{65–68} (**Figure 2**). Although both share canonical PROTAC architecture, they represent distinct medicinal chemistry strategies. BMS-986458 incorporates a BCL6-binding moiety derived from characterized BTB-domain ligands, consistent with targeting the BTB lateral groove. In contrast, ARV-393 employs a chemically distinct BCL6-binding scaffold; however, the precise BCL6 interface engaged by this ligand has not been publicly resolved. Both compounds recruit CRBN through thalidomide-like ligands but differ in linker architecture and overall molecular topology, suggesting potential differences in ternary complex geometry, degradation kinetics, and pharmacokinetic properties. Both compounds have demonstrated compelling preclinical data. BMS-986458 was reported to have exceptional anti-tumor activity *in vitro* and in PDX models, as well as enhancement of CD20 transcription, surface expression and clustering in cell lines, leading to potent synergy with anti-CD20 agents⁶⁷. Likewise, ARV-393 demonstrates strong anti-proliferative effects *in vitro* and was reported to synergize with glofitamab in a humanized high grade B cell lymphoma xenograft model, with transcriptomic analysis suggesting a similar upregulation of CD20 expression upon BCL6 degradation⁶⁸. While these results are intriguing, we await full publication of these findings to allow for thorough evaluation of the primary data.

A mechanistically distinct approach to BCL6 degradation has emerged from studies of BI-3802, a small molecule that binds the BCL6 BTB domain and induces degradation not through a PROTAC architecture but through drug-induced polymerization⁶⁹ (**Figure 2**). Rather than recruiting exogenous E3 ligase, BI-3802 induces highly specific, reversible polymerization of BCL6 into supramolecular filaments, followed by sequestration into cellular foci and subsequent proteasomal degradation. Cryo-EM studies revealed that BI-3802 binds at the interface between BCL6 BTB domain dimers, facilitating iterative dimer-dimer interactions through a composite ligand-protein surface, with the resulting polymerized BCL6 recognized and ubiquitinated by the endogenous E3 ligase SIAH1 via a VxP degron motif within BCL6 itself. Notably, the anti-proliferative and transcriptional effects of BI-3802 are comparable to genetic knockout of *BCL6* and exceed those of non-degrading BTB inhibitors, consistent with the notion that protein elimination may confer additional activity beyond functional blockade alone. This mechanistic framework has been directly translated to clinical development: LY4584180 is a novel oral BCL6 molecular glue that employs the same monovalent small molecule strategy employed by BI-3802, promoting selective assembly of BCL6 protein polymers to induce potent target degradation⁷⁰. LY4584180 is currently being evaluated in a first-in-human phase 1a/1b NOVA-BCL6-1 trial (NCT07226843) in patients with previously treated hematological malignancies including DLBCL and FL⁷¹.

Unlike competitive inhibitors, which require continuous occupancy to outcompete endogenous corepressors, degraders operate catalytically: a single molecule can promote multiple cycles of ubiquitination and turnover, potentially enabling more durable suppression of BCL6 with transient exposure. Molecular glue degraders offer a complementary advantage through their simpler monovalent architecture and engagement of endogenous degradation machinery, although their polymerization-dependent mechanism may impose different

pharmacological and stoichiometric constraints. However, a potential limitation of both approaches is that sustained systemic depletion of BCL6 could impair humoral immunity.

BCL6 Degraders: From bench to clinic

Early-phase clinical studies are now evaluating CRBN-based BCL6 degraders in relapsed or refractory B cell lymphomas, including DLBCL and follicular lymphoma. These trials represent the first opportunity to determine whether complete pharmacologic elimination of BCL6 translates into durable clinical responses in GC-derived malignancies.

BMS-986458 is currently being evaluated in a phase 1/2 clinical trial (NCT06090539), either as monotherapy or in combination with rituximab or bispecific antibodies. In a heavily pre-treated population of relapsed/refractory FL and DLBCL (median 4 lines of prior therapy), the ORR to monotherapy was 73% (21% CR, 52% PR) in 33 efficacy-evaluable patients⁷². Higher responses were observed in FL compared to DLBCL (ORR 79% vs. 68%). Responses were observed in two patients without BCL6 expression by IHC (defined as ≤30% positive cells), suggesting BCL6 expression may not be predictive of response. Treatment has been well-tolerated with the most common treatment-related adverse event (TRAE) being arthralgia (12%), and only 2/52 patients discontinued treatment due to TRAEs. Importantly, complete BCL6 elimination may not be required for anti-tumor efficacy; for example, responses to BMS-986458 were observed across all dose levels while pharmacodynamic analyses of tumor B cells demonstrated substantial BCL6 degradation with residual BCL6 detectable in some patients⁷³. This suggests that a therapeutic window may exist in which partial BCL6 depletion is sufficient for anti-tumor activity, although the relationship between the depth of target degradation, clinical response, and preservation of normal BCL6-dependent functions remains to be defined.

Beyond BMS-986458, two additional BCL6 degraders, ARV-393 (NCT06393738), TLN-121 (NCT07082803) are in early-stage clinical development for B and T-cell lymphomas, though neither has reported preliminary data⁶⁸. Encouragingly, despite expression of *BCL6* in T cell subsets, no depletion of peripheral T cells has been observed thus far. The concurrent development of these four BCL6 degraders, each with unique characteristics and potential different mechanisms of action, presents an opportunity to understand common and distinct therapeutic mechanisms, toxicity profiles and resistance patterns. Current trials investigating BCL6 degraders are summarized in **Table 1**.

Future perspectives

The clinical success of BCL6-directed therapies will ultimately depend not only on achieving target engagement, but on understanding determinants of sensitivity and resistance. Mechanisms of response and resistance will likely reflect tumor-intrinsic dependency, microenvironmental influences, and acquired resistance under therapeutic pressure. As we are just beginning to use these agents clinically, the following considerations remain hypothesis-generating and are informed largely by patterns of response and resistance to other targeted agents.

Primary resistance

A major future priority will be distinguishing tumors in which BCL6 is a sustained oncogenic driver from those in which its expression reflects lineage identity without ongoing functional necessity. Although BCL6 is frequently expressed in GC derived lymphomas, preliminary data suggests expression alone may not predict response. Early studies of BCL6 inhibitors demonstrated variable sensitivity across DLBCL models, including among BCL6-positive cell lines, indicating that dependency likely reflects broader molecular context rather than expression alone. Consistent with this, preliminary clinical observations have suggested that response to BCL6 degraders may not strictly correlate with baseline BCL6 expression, as responses have been observed in some tumors classified as BCL6 negative by IHC⁷². These findings raise the possibility that a subset of DLBCLs may be intrinsically less sensitive to BCL6 disruption, reflecting primary resistance due to limited reliance on BCL6-driven transcriptional programs. Together, these findings underscore the need for functional biomarkers of BCL6 dependency rather than reliance on expression alone.

An additional layer of complexity is intratumoral heterogeneity. DLBCLs often comprise subclonal populations with distinct genetic, epigenetic, and transcriptional states. It is plausible that BCL6 dependence is not uniform across all malignant cells within a given tumor. Indeed, a recent single cell analysis demonstrated that malignant subclones within individual DLBCL tumors can occupy distinct transcriptional states corresponding to GC B cell programs, memory B cell programs, or plasma cell programs⁴². Whether these malignant states represent fixed transcriptional programs or reflect transcriptional plasticity remains unresolved. Accordingly, BCL6-directed therapy could selectively deplete vulnerable fractions while allowing pre-existing or adaptive BCL6-independent states to persist, contributing to incomplete responses or relapse. This potential heterogeneity and selective pressure argue for careful consideration of combination therapies (see below).

Whether BCL6 dependency aligns with existing molecular frameworks remains an open question. While BCL6 expression is enriched in GCB DLBCLs, it is not confined to this group, and distinct mechanisms of BCL6 dysregulation may occur preferentially across different molecular subtypes⁷⁴. Therefore, it remains unclear whether therapeutic sensitivity to BCL6 degraders will map onto COO categories, specific genetic subtypes, or instead cut across existing classification systems. A more informative biomarker may therefore capture functional BCL6 activity rather than BCL6 abundance. Pretreatment tumors from patients receiving BCL6 degraders could be profiled for BCL6-regulated transcriptional programs together with genomic and epigenetic alterations that sustain BCL6 activity, and these features related to depth and durability of response. This could enable development of a composite BCL6-dependency signature that could ultimately be reduced to a targeted, clinically applicable assay.

Acquired resistance

Even in tumors that are initially sensitive to BCL6-directed therapy, resistance may emerge over time under continued treatment. As with other targeted approaches, secondary resistance could arise through adaptive changes in tumor transcriptional programs or through alterations that impair effective drug engagement. Experience with other targeted therapies provides several potential models.

Acquired resistance to targeted therapies is often mediated through mutations to genes encoding the primary drug target or those within a common regulatory pathway. Bruton tyrosine kinase (BTK) inhibitors in CLL

offer an instructive example, as recurrent C481S mutations prevent irreversible binding of the covalent BTK inhibitor ibrutinib^{75,76}. In addition, recent work has identified resistance mutations to novel BTK degraders within the binding pocket^{77,78}. Analogous mutations that interfere with degrader binding to BCL6 could provide one mechanism of resistance.

Another potential mechanism involves transcriptional upregulation of compensatory pathways. As noted above (BCL6 in FL and DLBCL: molecular mechanisms), pharmacological disruption of BCL6 has been shown to de-repress BCL2 and MYC in DLBCLs, raising the possibility that induction of these programs could attenuate responses to sustained BCL6 degradation³³. These findings may provide rationale for combination strategies pairing BCL6-degraders with BCL2 inhibitors, such as venetoclax, to constrain anti-apoptotic escape and enhance the depth of response. More broadly, transcriptional or epigenetic reprogramming could reduce reliance on GC-associated networks and enable alternative survival states under therapeutic pressure.

In the setting of PROTACs, resistance may also arise at the level of the drug-target-ligase interface. Studies of CRBN-recruiting BET degraders have shown that loss of CRBN expression, largely through chromosomal deletions, can confer resistance by preventing ternary complex formation and target ubiquitination⁷⁹. Notably, lenalidomide and other IMiDs have similarly been associated with decreased CRBN expression or acquired *CRBN* mutations, representing an analogous resistance mechanism that may be particularly relevant in the context of combination strategies utilizing CRBN-dependent degraders^{80–83}. Although resistance mechanisms have not yet been fully characterized for BCL6 degraders, these findings underscore that disruption of the E3 ligase function, or mutations affecting other components of the ubiquitin-proteasome machinery, can impair degradation without eliminating the oncogenic target itself.

Collectively, these observations suggest that resistance to BCL6 degraders may emerge through multiple, non-mutually exclusive mechanisms, including alterations in the BCL6 protein itself, disruption of the ubiquitin ligase machinery, and adaptive rewiring of downstream survival pathways. As BCL6 degraders advance in clinical development, serial circulating tumor DNA (ctDNA) profiling could enable longitudinal detection of emerging *BCL6* and *CRBN* alterations and clonal evolution, while molecular profiling of biopsies after relapse could identify transcriptional or epigenetic alterations not captured by ctDNA. Together, these approaches could distinguish true target escape from compensatory signaling adaptations. Such insights will refine patient selection and inform rational combination strategies to enhance response durability.

Combination therapies

These considerations also provide a rationale for combination strategies within DLBCL and FL. BCL6-mediated repression of DNA damage response pathways offers a mechanistic basis for pairing BCL6 degraders with contemporary anthracycline-containing regimens such as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) or Pola-R-CHP (polatuzumab vedotin). Thus, BCL6 targeting could enhance sensitivity to standard frontline therapies.

Beyond cytotoxic chemotherapy, combining BCL6 degraders with targeted therapies that disrupt complementary oncogenic programs represents a rational next step. One example is the functional cooperation between BCL6 and epigenetic regulators such as EZH2 in maintaining GC transcriptional identity, providing a

conceptual basis for combination with EZH2 inhibitors, though the clinical landscape for EZH2-targeted therapy is currently evolving. HDAC inhibitors represent a further opportunity: given the role of acetylation in negatively regulating BCL6 activity, HDAC inhibitors could synergize with BCL6 degraders through a mechanistically distinct but convergent axis. Although HDAC inhibitors are not established components of standard therapy for B cell lymphomas, their ongoing clinical evaluation in DLBCL and FL (NCT06570447⁸⁴, NCT04231448^{85,86}, NCT04231448) provides an opportunity to further define their therapeutic role and the feasibility of such combinations.

Integration of BCL6 degraders with T cell-directed immunotherapies, such as CD19-directed CAR-T cells and CD20-targeting bispecific antibodies, may offer a particularly compelling strategy. Emerging preclinical data has also demonstrated that BMS-986458 upregulates CD20 transcription and surface expression, offering a clear rationale for anti-CD20 targeting combination therapy^{66,67}. In line with this, the combination of BMS-986458 and glofitamab induced enhanced CD3+ T cell infiltration compared to either agent alone in DLBCL xenografts; similar results were reported with ARV-393^{66–68}. Therefore, BCL6 degraders could serve as both a biologically targeted debulking approach and as a modulator of tumor immunogenicity, potentially improving the efficacy of T cell-based therapies. Given that the outcomes with CAR T-cells and bispecific antibodies are influenced by antigen density, tumor burden, and the baseline immune microenvironment, careful consideration of disease bulk, immune infiltration, and treatment sequencing will likely be critical to optimizing combination strategies^{87–92}.

Conclusions

In the last 30 years, BCL6 has evolved from an “undruggable” lineage-defining transcription factor to a clinically actionable target. The next phase of development will be dependent on identifying biological contexts in which BCL6-directed strategies provide durable clinical benefit and integrating these agents thoughtfully with cytotoxic, targeted, and immunotherapeutic platforms. Continued mechanistic and translational investigation will be essential to realize the full therapeutic potential of BCL6 degradation across hematological malignancies.

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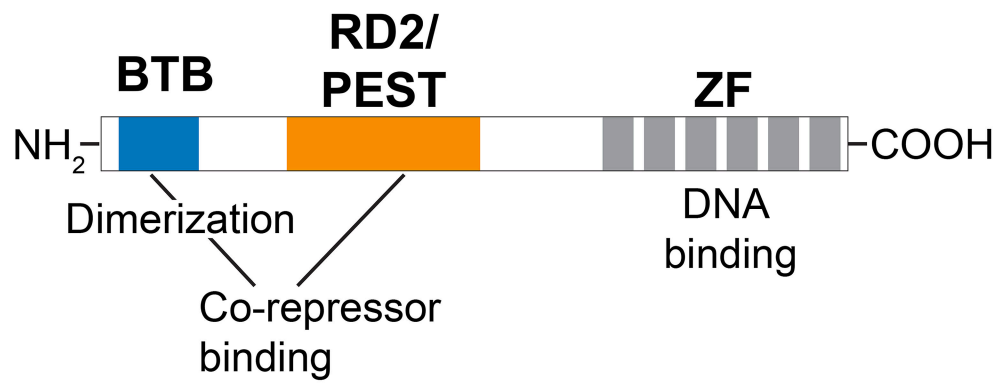
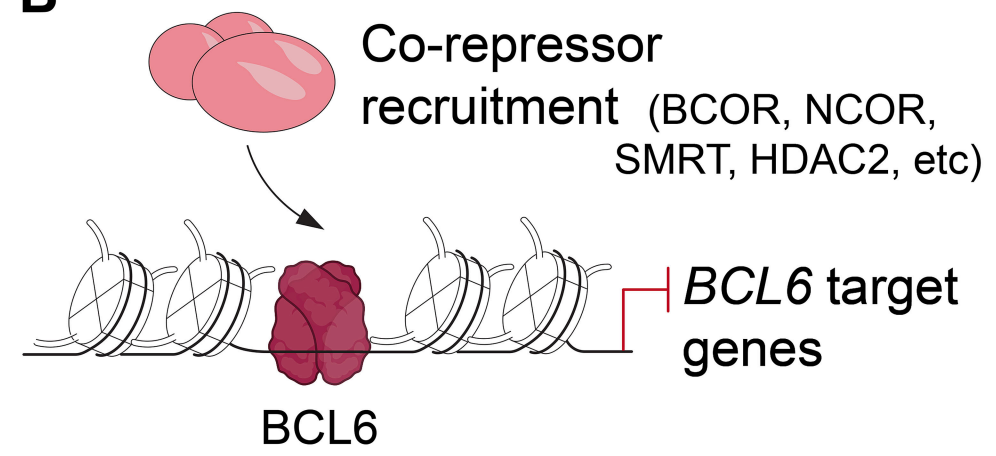
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Table 1: Current clinical trials of BCL6 degraders

Agent	Mechanism	Phase	Regimen	Prior lines of therapy	Status	NCT#
BMS-986458	Cereblon-based degrader	1/2	Monotherapy A1/B1); combination bispecific and/or anti-CD20 (A2/B2)	≥2 prior regimens	Recruiting	NCT06090539
ARV-393	PROTAC	1	Monotherapy (A/B) or glofitamab combination (C/D)	≥2 prior regimens	Recruiting	NCT06393738
TLN-121	Degrader	1	Monotherapy or combination TLN-254 (EZH2 inhibitor)	≥2 prior regimens (B cell lymphomas) or R/R T cell lymphoma	Recruiting	NCT07082803
LY4584180	Molecular glue	1a/1b	Monotherapy or rituximab combination	≥2 prior regimens	Recruiting	NCT07226843

Figure 1: BCL6 structure, function and mechanisms of lymphomagenesis. **A.** Domain structure of BCL6 protein; domain-specific functions are listed below. **B.** General mechanism of BCL6 function in transcriptional repression by the recruitment of co-repressor complexes. **C.** Mechanisms underlying BCL6 dysregulation in lymphoma and putative oncogenic effects. BTB: Broad complex, Tramtrack, Bric-a-brac; RD2/PEST: Repression Domain 2/ rich in proline [P], glutamic acid [E], serine [S], and threonine [T]; ZF: zinc finger; BCOR: BCL6 corepressor; NCOR: nuclear receptor corepressor; SMRT: silencing mediator of retinoid and thyroid hormone receptor; HDAC2: histone deacetylase complex 2; CRE: cis-regulatory element; LOF: loss-of-function.

Figure 2: Mechanisms of BCL6 degraders in clinical trials. Schematic demonstrating the mechanisms of action of BMS-986458, ARV-393, and BI-3802. The BCL6 dimer (PDB:) forms a ternary complex with cereblon and BMS-986458 (PDB: , *top*) or forms BCL6 polymers (PDB) as a result of BI-3802 binding (*bottom*). Both mechanisms lead to BCL6 ubiquitination and subsequent proteasomal degradation. Ub: ubiquitin. Note: the ternary complex induced by BMS-986458 binding is shown as there are no publicly available structures for ARV-393-BCL6-Cereblon complexes.

A**BCL6****B****C**