small series of patients with treatment-naive nodal PTCL treated with a combination of azacitidine, romidepsin, and durvalumab exhibited very high CR rate (3 out of 5 patients treated). Lastly, multiple trials exploring the role of different ICIs used alone and in combination with epigenetic agents in the relapsed, refractory setting are showing encouraging results with no evidence of hyperprogression, suggesting that these agents could be incorporated into earlier lines of treatment.[9,10]

In summary, the scientific community dedicated to advancing the care of rare diseases such PTCL should collaborate to answer fundamental questions that as of today remain open. For example, what is the role of ASCT in CR1? Are there different consolidation approaches with less toxicity profiles that can be tailored to disease subtype-specific sensitivity?

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LYMPHOID NEOPLASIA

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CELMoD for ALL: an exciting prospect

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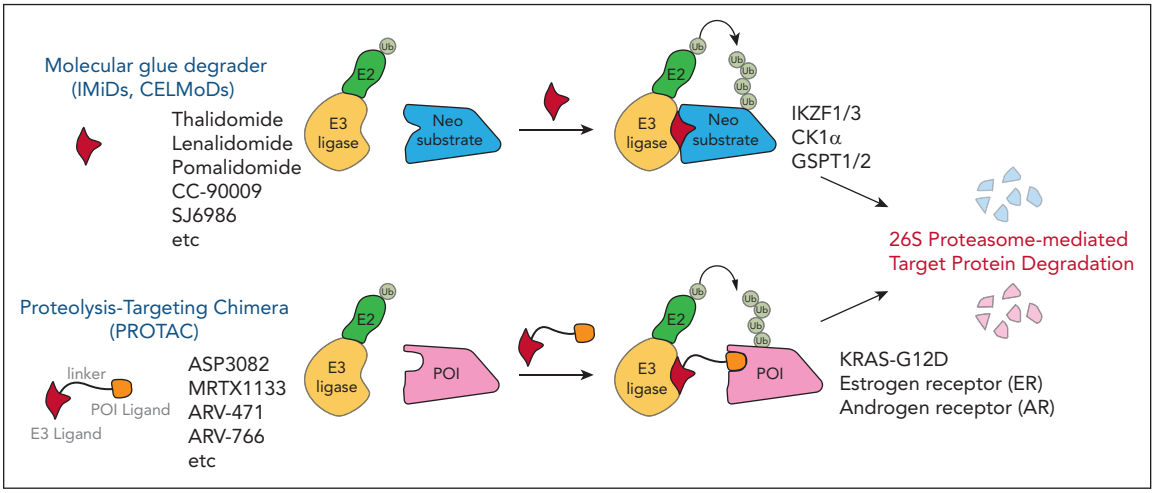
In this issue of *Blood*, Chang et al describe SJ6986, a novel molecular glue degrader that exhibits anti–acute lymphoblastic leukemia (ALL) activity in vitro and in vivo.[1]

Immunomodulatory imide drugs (IMiDs), such as thalidomide, lenalidomide, and pomalidomide, are key components of multiple myeloma and follicular lymphoma therapies. Their mechanism of action has been progressively uncovered, based on the groundbreaking study by Ito et al, which identified cereblon (CRBN)—part of an E3 ubiquitin ligase complex—as a thalidomide target relevant to its teratogenicity.[2] It was later discovered that lenalidomide acts as a "molecular glue" holding CRBN and either transcription factor IKZF1 (Ikaros) or IKZF3 (Aiolos) together, thereby promoting their ubiquitination and subsequent proteasome-mediated degradation by the E3 ubiquitin ligase CUL4-RBX1-DDB1-CRBN ($CRL4^{CRBN}$).[3] These IMiD target proteins are referred to as neo substrates (see figure).

The therapeutic concept of a proteolysis-targeting chimera (PROTAC), which forcibly recruits a protein of interest (POI) to a ubiquitin ligase complex, resulting in its proteasome-mediated degradation, was proposed before the CRBN/molecular glue discoveries.[4] This concept was further refined by using IMiD as an E3 ligand.[5] This approach sparked drug development initiatives in both pharmaceutical and academic settings, as, theoretically, PROTACs targeting POIs can be developed if POI ligands are available. In fact, several PROTACs targeting key molecules associated with cancer, such as mutant Ras, androgen receptor, and estrogen receptor, are currently undergoing clinical trials (see figure).[6,7]

Recently, next-generation IMiDs, termed cereblon E3 ligase modulators (CELMoDs), have been developed. They exhibit enhanced CRBN binding affinity, superior half maximal inhibitory concentration, and distinct neo substrate profiles.[8] CC-90009 (eragidomide) is a novel CELMoD that specifically targets G_1 to S phase transition 1 (GSPT1), a small GTPase that regulates translation termination in collaboration with the eukaryotic translation termination factor 1.[9] CC-90009 induces an integrated stress response and subsequent apoptosis in acute myeloid leukemia (AML) blasts,[9] and the drug is currently being tested in clinical trials as monotherapy (NCT02848001) or in combination with azacitidine, venetoclax, or gilteritinib (NCT04336982), for AML and/or myelodysplastic syndrome.

Initially identified as an orally bioavailable CELMoD targeting GSPT 1/2, SJ6986 has



Molecular glue degraders and proteolysis-targeting chimeras (PROTACs). The figure illustrates the distinct mechanisms by which molecular glue degraders and PROTACs mediate targeted protein degradation. Specific examples of each compound and their respective targets are provided. SJ6986 represents a molecular glue degrader (cereblon E3 ligase modulator [CELMoD]) that selectively degrades G_1 to S phase transition 1 (GSPT1) and GSPT2. CK1a, casein kinase 1 alpha; IKZF1/3, Ikaros zinc finger 1/3; POI, protein of interest.

shown anti-leukemic activity in human leukemia lines.[10] Chang et al comprehensively analyze the anti-ALL properties of SJ6986 using various ALL lines and xenograft mouse models. Significantly, SJ6986 monotherapy proved highly effective against patient-derived xenograft (PDX) models of high-risk ALL, including Ph-like ALL, hypodiploid ALL, and *ZNF384*-rearranged mixed phenotype acute leukemia. SJ6986 inhibits S to G_2/M cell cycle transition, inducing cellular apoptosis and exhibits anti-ALL activity superior to that of CC-90009 in vivo. These effects are likely attributed to its favorable pharmacokinetic profile. Notably, SJ6986 has minimal effects on normal hematopoiesis, as evidenced by colony-forming unit assay using human $CD34^+$ cells derived from human cord blood.

To elucidate the mechanisms of action of SJ6986, the authors conducted genome-wide CRISPR/Cas9 dropout screens and identified genes relevant to drug resistance. These genes include components of the $CRL4^{CRBN}$ E3 ubiquitin ligase complex, protein neddylation mediators, neddylation/constitutive photomorphogenesis 9 (COP9) signalosome regulators, and proteasomes. Furthermore, interleukin enhancer-binding factor 2/3, which regulates the splicing of *CRBN* transcripts and thereby its expression, were also identified as regulators of SJ6986 sensitivity, as reported in CC-90009.[9] More important, although mammalian target of rapamycin (mTOR) activation is known to confer resistance to CC-90009 in the U937 AML cell line,[9] SJ6986 sensitivity remained unaffected on depletion of either tuberous sclerosis complex 1 (TSC1) or tuberous sclerosis complex 2 (TSC2), both of which act as suppressors of mTOR activity. This is promising for a drug targeting ALL blasts, as the phosphatidylinositol 3-kinase–AKT–mTOR pathway is often activated in these cells.

The work by Chang et al is compelling, as SJ6986 is among the first orally bioavailable CELMoDs with potential application in ALL therapy. The safety and efficacy evaluation in clinical trials is highly awaited. Considering the dynamic changes in B-cell ALL therapy from the introduction of new therapeutic approaches, such as blinatumomab, future studies will also have to explore the optimal integration of these new agents.

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