Current aplastic anemia guidelines[4] continue to suggest viral testing. However, it is less likely that this mechanistic explanation will alter current therapies as both immunosuppressive therapy[5] as well as bone marrow transplantation[6] have long had a successful therapeutic role in severe aplastic anemia, regardless of etiology. The current results also do not provide a way of predicting responders from nonresponders to immunosuppressive therapy. One could hypothesize that hematopoiesis-reactive T-cell clones should decrease in frequency or disappear upon successful immunosuppressive therapy. Whether clone frequencies correlate with disease activity and could potentially represent predictive biomarkers could be investigated in larger studies. Lastly, patients with aplastic anemia cured by successful immune system (and thus T cell) replacement via bone marrow transplant (even if the cause was viral) are often exposed again to these same viruses without relapse. Exploring the differences between the donor and the host immune responses (especially in sibling transplants) should expand our understanding of the role of mimicry.

The critical role of T cells in aplastic anemia has already been suggested by previous experimental and clinical evidence.[7,8] Ben Hamza et al elegantly furthered knowledge by systematically studying clonal expansion, associated immune phenotypes, targeted cell populations, and target antigens to demonstrate that epitopes derived from viral infections can potentially drive hematopoiesis-directed T-cell responses by molecular mimicry (see figure). Future studies should include identification of other potential target antigens, for unbiased identification of other T-cell receptor targets causing marrow failure, such as drug-induced aplastic anemia.

Conflict-of-interest disclosure: A.E.D. declares no competing financial interests. ■

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LYMPHOID NEOPLASIA

Comment on Chiba et al, page 1379

Targeting PD-L1 to treat ATLL?

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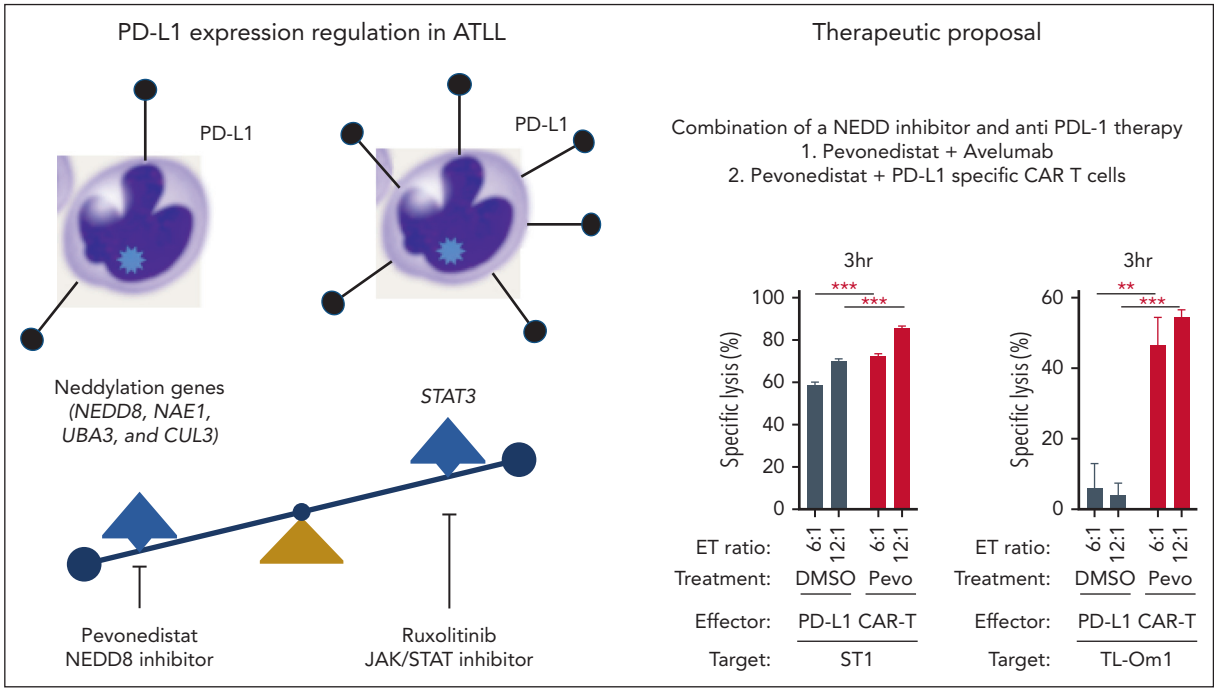
In this issue of *Blood*, Chiba et al reveal the molecular mechanisms that control the expression of programmed cell death ligand 1 (PD-L1) in adult T-cell leukemia/lymphoma (ATLL) and propose an original therapeutic approach to treat this highly aggressive T-cell malignancy.[1]

ATLL is an aggressive mature T-cell lymphoid malignancy caused by human T-cell leukemia virus type 1 (HTLV-1) infection. The prognosis is very poor, especially in aggressive subtypes, which represent the majority of the cases at diagnosis, with an overall survival (OS) of <1 year.[2] In these subtypes, the standard of care is polychemotherapy (ie, CHOP-like regimen [cyclophosphamide, hydroxydaunorubicin, vincristine (Oncovin), prednisone] or the LSG-15 protocol in Japan that consists of a sequential combination of chemotherapies: VCAP [vincristine, cyclophosphamide, doxorubicin, prednisone], AMP [doxorubicin, ranimustine, prednisone], and VCEP [vindesine, etoposide, carboplatin, prednisone]) followed by allogeneic hematopoietic stem cell transplantation (alloSCT), when feasible. Apart from alloSCT, which proved to cure some patients and improve ATLL outcome,[3] no significant improvement in OS has been observed since the original work by Shimoyama describing different ATLL subtypes in 1991.[2] Notably, targeted therapies, such as "antiviral therapy" with the combination of zidovudine-interferon and anti–C-C chemokine receptor 4 (CCR-4) antibody (mogamulizumab), have not been able to improve significantly the outcome of ATLL.[4,5] One of the main drawbacks of ATLL treatment is the intrinsic chemoresistance of the disease, with around 40% of cases presenting with primary chemoresistance.[5]

In the past decade, the molecular understanding of ATLL has progressed. The genetic and epigenetic landscape of ATLL is now better characterized, with the identification of at least 5 key recurrent pathways, including the T-cell receptor/NF-κB pathway (~75% of cases), T-cell trafficking (~45%), immunoescape (~30%), cell-cycle regulation and tumor suppression (~25%), and Janus kinase–signal transducer and activator of transcription (JAK-STAT) signaling (~20%).[6,7] Interestingly, these alterations are not restricted to HTLV-1–related lymphomagenesis, but are shared with other peripheral B- and T-cell lymphomas. Furthermore, ethnic background does not seem to affect the genomic landscape of ATLL. Similarly, thanks to high-throughput genomic sequencing techniques, the understanding of the role of the oncovirus in lymphomagenesis has improved.[8]



Identification of molecular pathway and pharmacological compounds that regulate PD-L1 expression in ATLL and proposal for a novel combined therapy. PD-L1, programmed cell death ligand 1; NEDD8, neural precursor cell expressed, developmentally downregulated 8; NAE1, NEDD8-activating enzyme; UBA3, ubiquitin-like modifier activating enzyme 3; CUL3, cullin 3; STAT3, signal transducer and activator of transcription 3. The graphs are reproduced from Figure 7G-H in the article by Chiba et al that begins on page 1379.

In their study, Chiba and colleagues used an unbiased approach based on CRISPR whole genome technology to elegantly identify molecular pathways regulating PD-L1 expression (see figure). They demonstrated that STAT3 is a positive regulator of PD-L1 expression and identified several neddylation pathway genes (*NEDD8*, *NAE1*, *UBA3*, and *CUL3*) as negative regulators of PD-L1 expression. In vitro studies using a pharmacological inhibitor of JAK-STAT (ruxolitinib) or neddylation (pevonedistat) provided further support for these observations. Moreover, increased PD-L1 expression by the neddylation inhibitor pevonedistat alone strongly upregulated PD-L1 expression and had a cytotoxic effect on ATLL cells in vitro. The authors pursued an interesting approach by combining pevonedistat (to increase PD-L1 expression) with an anti–PD-L1 monoclonal antibody (avelumab) or with PD-L1 specific chimeric antigen receptor T cells to target ATLL cell lines. Finally, they demonstrated an increased in vitro cytotoxic effect when using combination therapy.

Chiba et al address a gap in our understanding of the biology of ATLL as well as the urgent clinical need for novel therapeutic approaches. Their observations are applicable both in the context of wild-type *PD-L1* and of somatic variants in the 3′-untranslated regions of *PD-L1* frequently observed in ATLL (~30% of cases).[9] However, from a clinical point of view, the major point of concern is that using anti–PD-L1/anti–PD-1 targeted therapy could actually stimulate growth of specific clones. Indeed, therapeutic approaches using anti–PD-1 antibodies as checkpoint inhibitors have already been reported and have led to an unexpected outcome: rapid progression in several cases of indolent ATLL.[10] Therefore, a better understanding of the biology of PD-L1/PD-1 in ATLL is essential to allow for safe use of a new class of potent drugs (immune checkpoint inhibitors), which are potentially dangerous in the context of ATLL.

In conclusion, despite the absence of an animal model to reinforce these novel results, the findings are of interest for scientists investigating ATLL molecular and cell biology, for clinicians who treat patients with ATLL, and more broadly for biologists interested in the regulation of immune checkpoint molecule expression.

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Comment on Bastian et al, page 1391

Uncovering new layers of Ph$^+$ ALL biology

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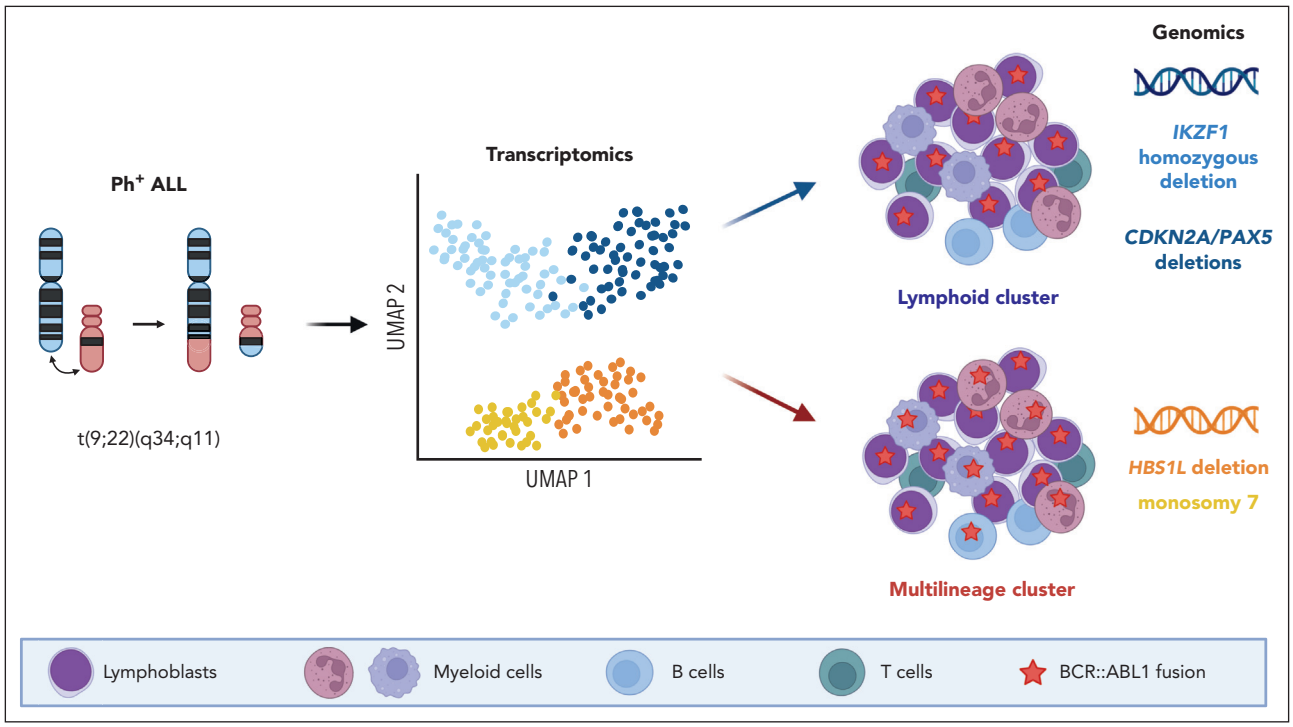
In this issue of *Blood*, Bastian et al[1] report that Philadelphia chromosome-positive acute lymphoblastic leukemias (Ph$^+$ ALLs) are more heterogeneous than previously thought. The authors identified subtypes with distinct transcriptomic and genomic profiles, which correlate with multilineage or lymphoid-only *BCR::ABL1* involvement and have distinct clinical phenotypes.

It has been 5 decades since Janet Rowley's groundbreaking discovery of the translocation t(9;22) and its association with chronic myeloid leukemia (CML) and Ph$^+$ ALL. The identification of the *BCR::ABL1* fusion gene marked a turning point in understanding these hematologic malignancies, leading to the development of targeted therapies that transformed the landscape of leukemia treatment.[2]

Since then, it has been assumed that disease heterogeneity within *BCR::ABL1*-driven malignancies, specifically CML or de novo Ph$^+$ ALL, largely depended on different types of *BCR::ABL1* fusions: the major breakpoint fusion producing the p210 isoform associated with CML occurred in an hematopoietic stem cell, and the minor fusion producing p190 was confined to the B-cell precursor compartment.[3] Although a subset of Ph$^+$ ALL presented with major fusion, there was a persistent doubt as to whether those cases represented authentic de novo Ph$^+$ ALL or CML blast crisis with an unrecognized chronic stage. Recent studies challenged this view by demonstrating *BCR::ABL1* multilineage involvement in a subset of Ph$^+$ ALL, regardless of the fusion breakpoint.[4-6] This dichotomy within Ph$^+$ ALL, namely "multilineage" or "lymphoid-only" has been recently recognized in the International Consensus Classification of acute leukemias.[7] However, little is known regarding the distinctive biology of these subtypes and their associated clinical and prognostic features. Moreover, there is



Gene expression profiling in Ph$^+$ ALL delineates 2 distinct groups that segregate cases with or without multilineage involvement, referred as multilineage or lymphoid clusters, respectively. These groups are associated with distinct genomic features including *HBS1L* deletion and monosomy 7 for the multilineage cluster and *IKZF1* homozygous deletion and *CDKN2A/PAX5* deletions for the lymphoid cluster. UMAP, uniform manifold approximation and projection.