REVIEW

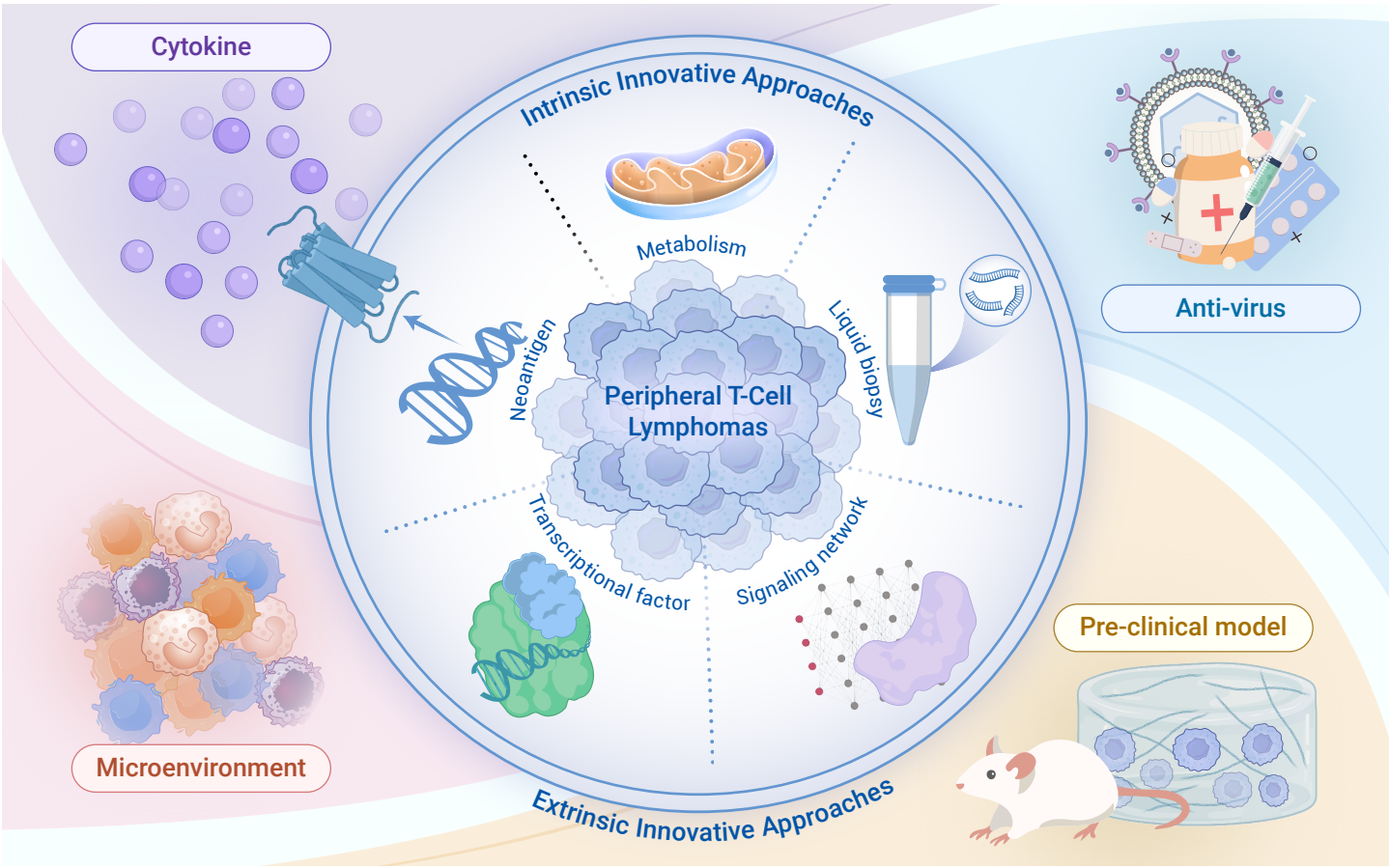
Precise diagnosis and treatment for peripheral T-cell lymphomas: From pathogenic mechanisms to innovative approaches

Yuran Qiu[1] **and Weili Zhao**[1,2,*]

*Correspondence: zhao.weili@yahoo.com

Received: September 20, 2023; Accepted: December 22, 2023; Published Online: January 2, 2024; https://doi.org/10.59717/j.xinn-med.2024.100048

GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Peripheral T-cell lymphomas (PTCLs) are clinically challenging for their heterogeneity and low chemo-sensitivity.
- Multi-omics studies reveal pathogenic mechanisms and new treatment targets for PTCLs.
- Emerging strategies bridge the research-practice gap in precise medicine for PTCLs.

REVIEW

www.the-innovation.org/medicine

Precise diagnosis and treatment for peripheral T-cell lymphomas: From pathogenic mechanisms to innovative approaches

Yuran Qiu[1] **and Weili Zhao**[1,2,*]

[1]Shanghai Institute of Hematology, State Key Laboratory of Medical Genomics, National Research Center for Translational Medicine at Shanghai, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China

[2]Pôle de Recherches Sino-Français en Science du Vivant et Génomique, Laboratory of Molecular Pathology, Shanghai 200025, China

*Correspondence: zhao.weili@yahoo.com

Received: September 20, 2023; Accepted: December 22, 2023; Published Online: January 2, 2024; https://doi.org/10.59717/j.xinn-med.2024.100048

Citation: Qiu Y. and Zhao W. (2024). Precise diagnosis and treatment for peripheral T-cell lymphomas: From pathogenic mechanisms to innovative approaches. The Innovation Medicine **2(1)**: 100048.

Peripheral T-cell lymphomas (PTCLs) encompass a diverse group of aggressive non-Hodgkin's lymphomas originating from mature T lymphocytes. Despite their relatively low prevalence compared to B-cell lymphomas, PTCLs pose significant clinical challenges due to their heterogeneity, lack of specific biomarkers, and often poor response to conventional chemotherapies. Unraveling the intricate pathogenic mechanisms underlying PTCLs is pivotal for the development of targeted therapies, which has become a major focus of PTCL research in recent years. It was previously postulated that genomic alterations play a pivotal role in T-cell transformation and lymphomagenesis. Recent multi-omics investigations and functional studies focusing on pathogenic mechanisms have unveiled that in addition to genetic abnormalities, diverse intrinsic and extrinsic mechanisms are implicated in the pathogenesis of PTCLs. In this Review, we provide an overview of the recent advances in the pathogenesis and management of PTCLs, focusing on the current and potential precise diagnosis and treatment based on intrinsic and extrinsic mechanisms. Bioengineering and drug development have enabled the effective modulation of many previously "undruggable" targets, which offers the potential to target new biomarkers associated with PTCL pathogenesis. The integration of artificial intelligence (AI) in clinical practice enables a comprehensive framework, merging diverse data sources and clinical context to discover precise biomarkers for personalized medicine. Finally, we present pressing questions and challenges that demand attention and discuss emerging solutions.

INTRODUCTION

Peripheral T-cell lymphomas (PTCLs) constitute a diverse group of aggressive non-Hodgkin's lymphomas derived from mature T lymphocytes.[1,2] Although the molecular characteristics of these hematological malignancies,[3] especially the genetic abnormalities, have been revealed, the clinical translation is still in its infancy.[4,5] While targeted therapy has dramatically improved the treatment of B-cell lymphomas,[6] PTCLs still lack precise diagnostic and therapeutic targets, leading to poor disease outcomes.

According to National Cancer Institute data, a total of 80,550 lymphoma cases are estimated to be diagnosed in 2023, resulting in about 20,180 deaths in the United States (source: https://seer.cancer.gov/statfacts/html/nhl.html). PTCLs constitute approximately 15-20% of these cases. The 5th edition WHO classification of hematological and lymphoid neoplasms identified 30 distinct entities, each with unique clinical, histopathological, and molecular traits.[7] Prognosis varies considerably among these entities, ranging from favorable outcomes in anaplastic large cell lymphoma (ALCL) to less promising prognosis in entities like follicular helper T-cell lymphoma (TFH lymphoma) and specific subtypes of PTCL, not otherwise specified (PTCL-NOS).[8] Traditional chemotherapies based on anthracycline regimens are still the primary treatment for PTCLs, which face challenges such as low response rates, frequent relapses, and treatment-related side effects.[9] Despite the advent of autologous hematopoietic stem cell transplantation, cellular therapies, and various new agents, there remains a pressing need for improving outcomes among PTCL patients.

With the development of biotechnology, multi-omics profiling has accumulated since the new millennium, revealing various molecular characteristics of PTCLs (Figure 1).[2] However, few of them have been translated into biomarkers, especially therapeutic targets.[10-12] To address this challenge, recent research has shifted its focus from large-scale sequencing to the pathogenic mechanisms of PTCLs, which facilitates better analysis of multi-omics data and identification of targetable biomarkers.[13] By modulating specific pathogenic pathways, genes, or molecules responsible, mechanism-based precision treatment aims to enhance therapeutic efficacy while minimizing harm to healthy tissues. Reported studies have illuminated the intricate interplay of genetic, transcriptomic, epigenetic, microenvironment, and pathogen factors, contributing to the development and progression of these heterogeneous malignancies (Figure 1).[14-16] These insights have set the stage for novel therapeutic targets and approaches, heralding the emergence of mechanism-based precise treatment in PTCLs.

In the last two decades, bridging the gap between bench work and clinical practice in PTCLs has been a focal point of intensive clinical research aimed at developing new strategies to improve outcomes. Since 2009, the Food and Drug Administration has approved several new drugs for PTCLs (e.g., pralatrexate,[17] romidepsin,[18] brentuximab vedotin,[19] and mogamulizumab[20]). Several promising compounds have entered clinical trials (e.g., histone deacetylase inhibitor[21], dual phosphoinositide-3-kinase (PI3K) inhibitor[22], EZH2 inhibitor[23], and immunomodulatory agent[24]). However, due to limitations in our understanding of the structural biology, protein engineering, and receptor pharmacology of biomarkers, many molecules with identified pathogenic potential lack targeted agents, such as *RHOA G17V* mutation and TCR signaling.

Here, we comprehensively explore recent advances in PTCL pathogenesis and, rooted in these mechanisms, summarize the latest achievements and potential avenues in precise diagnosis and treatment. We also discuss recent developments in other fields that may aid therapeutic targeting in PTCLs, including structure-based drug design, protein-targeting pharmacology, and AI-aided data integration. Our review aims to provide an innovative perspective on PTCLs by translating basic research into clinical practice.

DISSECTING CLINICAL HETEROGENEITY OF PTCLS

Malignant transformation occurring at various stages of T-cell maturation leads to a spectrum of malignancies characterized by diverse clinical features (Figure 2A).[25] Transformation of immature T-cells leads to T-cell acute lymphoblastic leukemia/lymphoma (T-ALL/LBL), whereas mature T-cell transformation within peripheral lymphoid organs, such as lymph nodes, extra-nodal sites, and skin, results in PTCLs. During T-cell differentiation, PTCLs rise from various types of mature T-cells and express diverse sets of transcription factors (TFs), cytokines, and surface markers (Figure 2B).[2] For instance, TFH lymphoma derived from T-follicular helper (T_{FH}) cells, which require ICOS signal co-stimulation from B-cells, and express T_{FH}-specific markers such as CXCR5 through the action of relative TFs.[26] The 5th WHO classification recognizes 30 PTCL entities with distinct clinical, morphologic, immunophenotypic, and molecular features, reflecting the intrinsic differences of tumor origin T-cells (Table S1).[7,8,27] Such diverse nature of PTCLs requires prognostic stratifications and treatment decisions for each entity.

TFH lymphoma accounts for 15%-19% of PTCLs, including the angioimmunoblastic type, follicular type, and not otherwise specified.[28] Common clinical manifestations include systemic symptoms, generalized lymphadenopathy, skin lesions, immunological abnormalities, and hematological

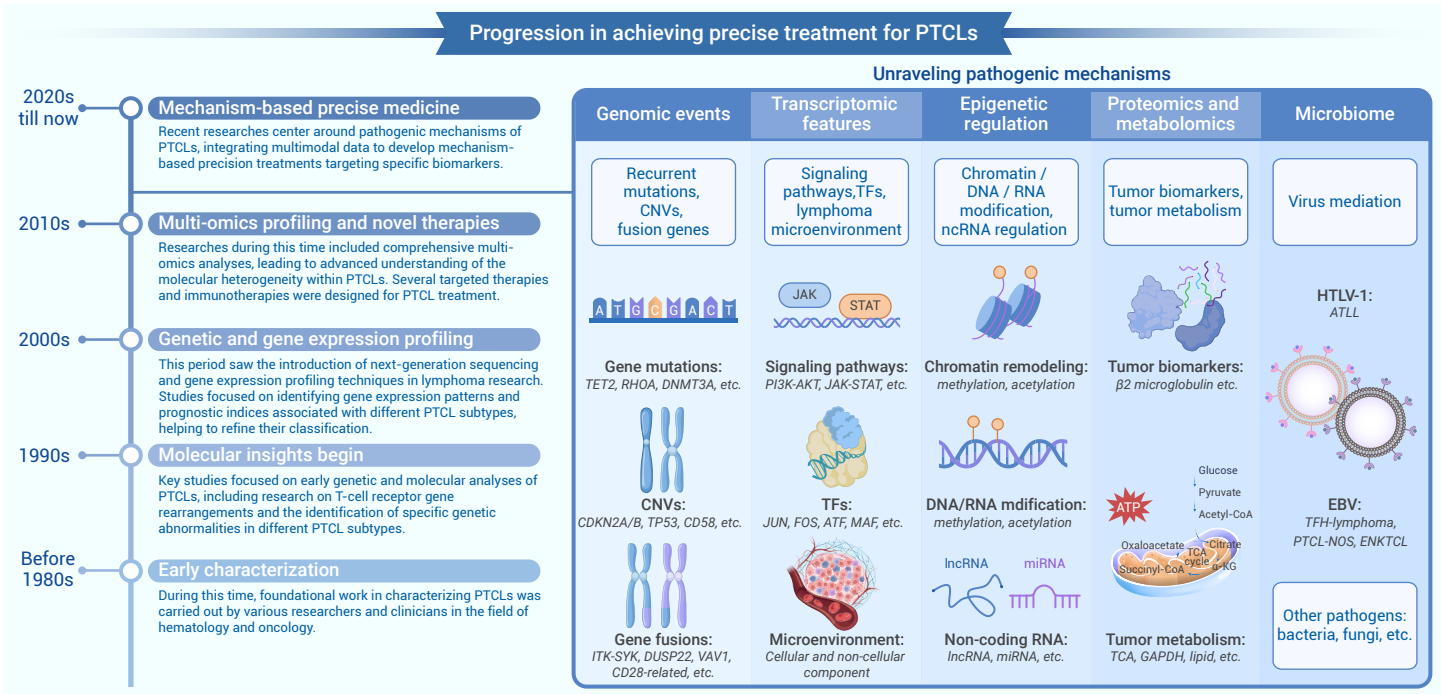


Figure 1. Progression in achieving precise management for PTCLs The timeline depicts the focus and progress of precise diagnosis and treatment of PTCLs in each decade from before 1980 to the present. The right panel highlights the specific directions of the current research on the pathogenic mechanisms of PTCLs. The figures in this review were created with BioRender.com. LncRNA, long non-coding RNA; miRNA, microRNA; TCA, tricarboxylic acid cycle; GAPDH, glyceraldehyde-3-phosphate dehydrogenase.

disorders.[29,30] The prognosis for TFH lymphoma remains dismal, with a 5-year overall survival (OS) rate not exceeding 40%.[31] These tumor cells, resembling their normal T_{FH} counterparts, are typically located in the germinal center of lymph nodes, regulating B-cell differentiation.[32] Histological features include expression of T_{FH} markers, such as CXCL13, PD-1, ICOS, BCL-6, CD10, and CXCR5,[33] alongside a prominent reactive background of B-cells, macrophages, dendritic cells, and high endothelial venules.[34] Epstein-Barr virus (EBV) infection is frequently detected in tumor cells and/or background B-cells.[35] The angioimmunoblastic type and follicular type of TFH lymphoma are distinguished based on the presence of abundant endothelial venules in biopsy samples for the angioimmunoblastic type and their absence in the follicular type.[36] Among PTCLs, TFH lymphoma displays characteristic epigenetic dysregulation, with frequent mutations in *TET2*, *RHOA*, *DNMT3A*, and *IDH2*.[3]

ALCL constitutes a PTCL subtype characterized by the expression of CD30, which belongs to the tumor necrosis factor receptor (TNFR) superfamily.[37] Further classification distinguishes between ALK-positive (ALK^+) and ALK-negative (ALK^-) based on the presence or absence of ALK protein identified via immunohistochemistry.[38] ALK^+ ALCL is more prevalent in younger patients and has a better prognosis than ALK^- ALCL, featuring a 5-year OS of 79% versus 46%.[39-41] ALK^+ ALCL is marked by chromosomal translocations implicating the *ALK* gene, which encodes a tyrosine kinase, orchestrating diverse pathways pivotal in cell survival, proliferation, and differentiation.[42] The most common partner gene for *ALK* is *NPM1*, resulting in consistent activation of STAT3, NOTCH, and PI3K pathways.[37] ALK^- ALCL shares similar morphology and phenotype with ALK^+ ALCL, except for ALK expression. It accounts for about 2.6%-7.8% of all PTCL cases and is more frequent in older adults.[40] Despite the absence of *ALK* rearrangement, ALK^- ALCL harbors other genetic alterations that affect similar pathways, such as *DUSP22* or *TP63* rearrangements, JAK-STAT mutations or fusions, *NOTCH* mutations or activation, etc.[43,44] Based on these molecular features, ALK^- ALCL can be classified into three variants with widely disparate clinical outcomes: a) *DUSP22*-rearranged (30%), which has a distinctive morphology and a favorable prognosis similar to ALK^+ ALCL; b) *TP63*-rearranged (8%), which has the worst prognosis; and c) triple negative, which lacks genetic lesions of *ALK*, *DUSP22* and *TP63* and has an intermediate prognosis.[45]

PTCL-NOS is a diagnosis reached through exclusion criteria among nodal lymphomas, encompassing cases that do not conform to any other PTCL subtypes.[7,31] It stands as the most prevalent and heterogeneous entity, accounting for approximately 22%-34% of all PTCL cases, yet bears a discouraging 5-year OS rate of less than 30%.[46] PTCL-NOS displays diverse morphology and immunophenotype. Gene expression profiling (GEP) and molecular analysis have discerned two discrete subgroups characterized by the expression of TFs TBX21 and GATA3, which are associated with distinct putative cells of origin (T_H1/cytotoxic T-cells and T_H2, respectively), immunohistochemistry features, and prognosis.[47-49]

The above significant heterogeneity among PTCL entities highlights the need to consider different subtypes in terms of both pathogenic mechanisms and clinical efficacy studies.

RETHINKING PTCL PATHOGENIC MECHANISMS WITH NEW ETIOLOGY PARADIGMS

The etiology of cancers has long been attributed to stochastic errors during DNA replication in stem cells, known as driver mutations, leading to the expansion of mutant clones and subsequent oncogenesis.[50] The introduction of next-generation sequencing (NGS) in PTCLs has yielded intriguing insight into the pathogenic significance of gene mutations. Unexpectedly, PTCLs (excluding ALK^+ ALCL) exhibit a highly variable genetic landscape, where mutations independent of cell division contribute substantially to somatic alterations.[2,51,52] These malignancies lack hallmark mutations found in other cancers, such as *BCR::ABL* translocation in chronic myeloid leukemia (CML),[53] $BRAF^{V600E}$ in melanomas,[54] and *HER2* in breast cancers.[55] Moreover, in contrast to leukemia, PTCLs originate from terminally differentiated T-cells with limited stemness. These observations challenge the application of conventional mutation-centric oncogenesis theories in PTCLs.

Jassim et al. recently proposed a novel etiology paradigm 'the ground state theory', which shifts focus from a cell's 'stemness', such as stem cell or lineage-committed progenitor, to its functional state or 'ground state'.[50] Mounting evidence show that cell plasticity is a double-edged sword for developing and ageing tissues: it is essential for tissue formation and maintenance, but also risks overstepping into tumor. While the 'bad luck' theory relies on cell division,[56] the 'ground state' theory suggests that cell plasticity can be reshaped by developmental processes, ageing, injury, and other factors independent of cell division, thus increasing the risk of oncogenesis.[57,58] In the context of PTCLs, T lymphocytes are inherently susceptible to genetic alterations, given their continuous generation over the

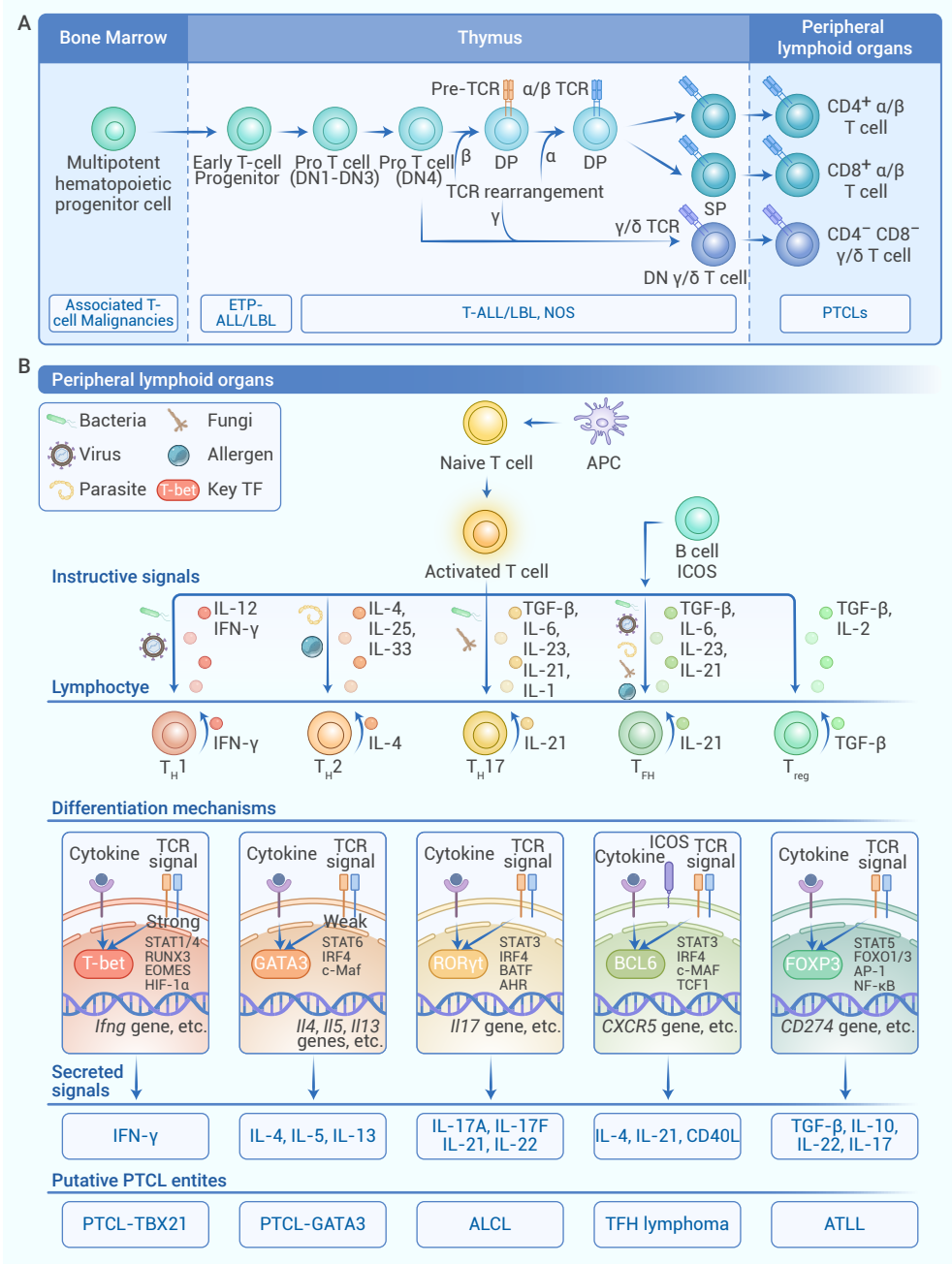


Figure 2. Overall scheme of T-cell development and differentiation The major processes of development (A) and differentiation (B) during T-cell maturation. Abnormalities at different stages of T-cell development can lead to different T-cell leukemias/lymphomas, including PTCLs occurring in peripheral lymphoid organs. Different PTCL entities are derived from different types of mature T-cells and express distinct molecular features that reflect the intrinsic differences of tumor-origin T-cells. DN, double negative; DP, double positive; SP, single positive; T_H1, T helper cell 1; T_H2, T helper cell 2; T_H17, T helper cell 17; T_{FH}, T follicular helper cell; T_{reg}, regulatory T-cell.

lifetime (producing around 50 million thymocytes daily)[59,60]. According to the 'ground state' theory, we proposed that the inherent instability, along with other intrinsic and extrinsic factors, culminates in the shifted balance of cell plasticity in T-cells, leading to pathogenesis.

The differences in pathogenesis between PTCLs and T-ALL/LBL also support this change of perspective. Despite both originating from T-cells, these diseases exhibit distinct clinical and molecular features, implying diverse pathogenic mechanisms. PTCLs arise from peripheral mature T-cells, which predominantly affect older adults (excluding ALK$^+$ ALCL) (Figure 3A).[61] T-ALL/LBL, which arises from T-cell progenitors,[62,63] primarily impacts children and young adults (Figure 3A).[64,65] T-ALL/LBL features NOTCH signaling and T-cell TF activation, with *NOTCH1* activating mutations notably discovered in 50-70% of the cases (Figure 3B).[66-68] Moreover, loss-of-function mutations of *FBXW7*, a protein that degrades activated NOTCH1, were found in 8-30% of cases (Figure 3B).[69,70] The constitutive activation of NOTCH signaling by somatic mutations in hematopoiesis stem cells (HSCs) significantly enhances cell plasticity of T-cell progenitors and simultaneously extinguishes self-renewal of long-term HSCs (Figure 3C).[71,72] As neonatal stem cells are relatively resistant to cancer, this driver mutation is capable of oncogenesis through an uphill path, without the help of other ageing or injury factors.[50] Compatible with theories of pediatric tumor etiology, a driver mutation impacts stem cells and drives lineage-restricted expansion, leading to oncogenesis.[73-75]

Meanwhile in PTCLs, recurrent mutations are discovered in epigenetic-related genes such as *TET2* and *DNMT3A*, which occur in up to 40-50% of all cases, excluding ALK$^+$ ALCL (Figure 3B).[76-78] Other epigenetic mutations associated with histone modification are also frequently seen in PTCLs (Figure 3B).[79] However, these genomic variants have also been discovered in non-malignant disease and healthy elderlies.[80-83] Such mutations are associated with ageing-related clonal hematopoiesis (ACH), which is the expansion of HSC clones that carry somatic mutations or chromosomal alterations with increasing age.[84-87] *TET2*, *DNMT3A*, and *IDH2* mutations in HSCs or progenitor cells represent a pre-malignant event that has been extensively studied in hematologic malignancies, including lymphomas (Figure 3C).[84,88,89] These mutations cause reduced methylation of CpG sites at gene-regulatory regions, which leads to the activation of genes that promote cell plasticity.[85,90,91] Thus, initial mutations in these vital epigenetic modifiers create a favorable landscape permissive to expansion and transformation, known as clonal hematopoiesis of indeterminate potential (CHIP).[92,93] Subsequent accumulation of additional oncogenic factors, facilitated by this susceptible state, leads to further gain of cell plasticity and full lymphomagenesis.[94] Such factors include other genetic changes, ageing, microenvironment remodeling, infection, etc.[95] Moreover, a recent study reported that the germinal center B (GCB) cells found in the angioimmunoblastic form of TFH lymphoma niches carried *TET2* deficiency as well and supported tumorigenesis via the CD40-CD40LG axis.[96] This finding supports the notion that ACH occurs at an early stage of lymphoma development. Related evidence for precursor-derived tumors in children with less complex molecular pathogenesis has also been observed in B-cell malignancies. B-ALL is a common type of leukemia in children that often involves recurrent gene fusions, such as *ETV6::RUNX1*, *TCF3::PBX1*, and *BCR::ABL1*,[97] while DLBCL is a prevalent form of mature B-cell malignancy in adults with a much more complex genetic landscape and multiple molecular subtypes.[98,99]

Based on this novel etiological theory, we need to recognize that PTCLs possess a multi-step pathogenic mechanism, influenced by intrinsic and extrinsic factors. Genetic alterations are only one aspect of this multifaceted process, which poses a challenge for targeting them with the same approach as targeting *EGFR* mutants or *BCR::ABL* fusion proteins.[100,101] Instead, understanding the intrinsic and extrinsic factors that drive malignant transformation holds promise for the discovery of novel strategies in treating PTCLs.

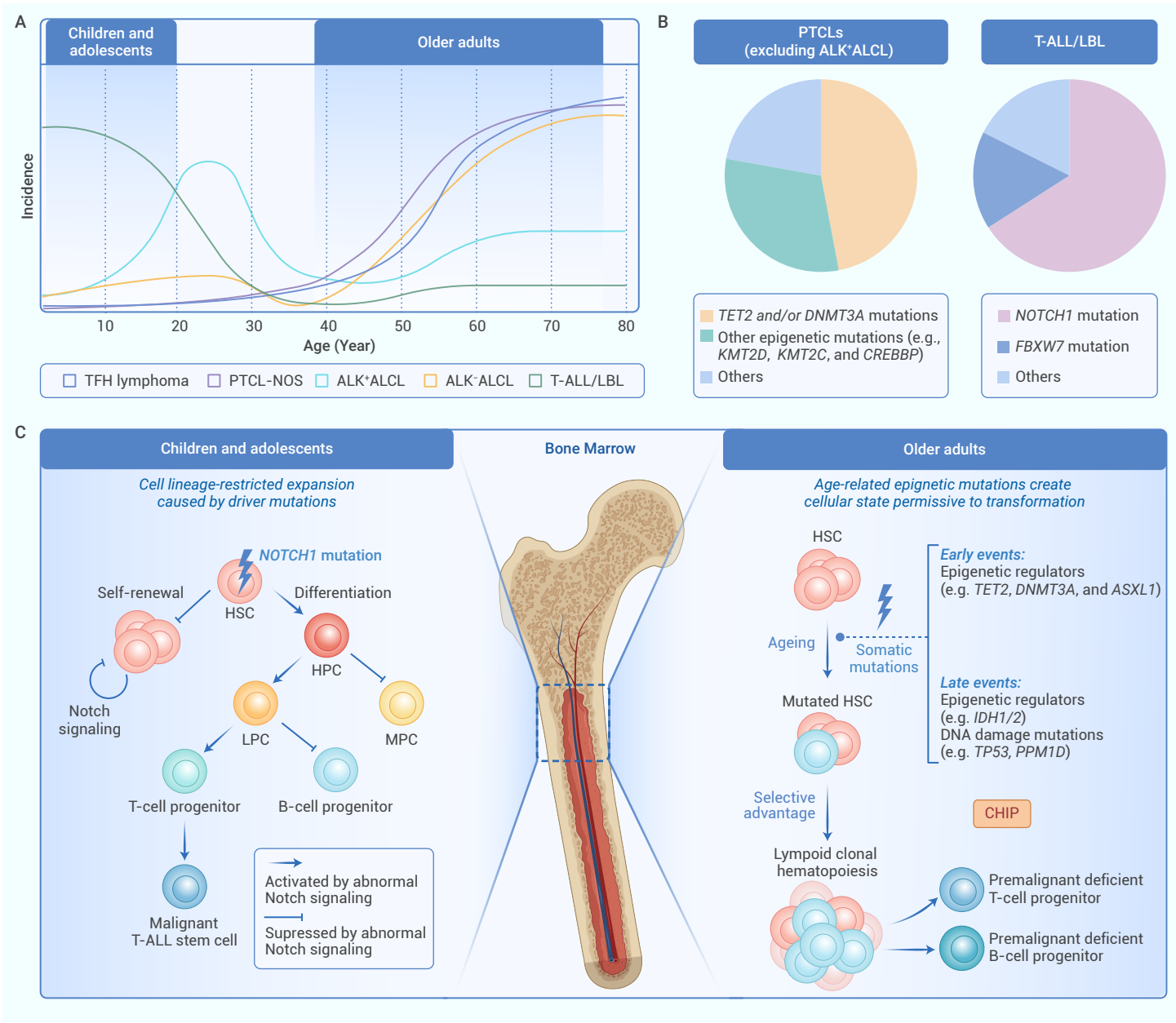


Figure 3. Comparison between PTCLs and T-ALL/LBL (A) Age distribution of disease onset of TFH lymphoma (dark blue), PTCL-NOS (purple), ALK$^+$ ALCL (cyan), ALK$^-$ ALCL (yellow), and T-ALL/LBL (green). (B) Proportion of the recurrent genomic changes in PTCLs (excluding ALK$^+$ ALCL) and T-ALL/LBL. (C) Different hematopoiesis events occurred in the bone marrow of T-ALL/LBL (left) and PTCL (right) patients. HSC, hematopoiesis stem cell; HPC, hematopoietic progenitor cell; LPC, lymphoid progenitor cell; MPC, myeloid progenitor cell; CHIP, clonal hematopoiesis of indeterminate potential.

INTRINSIC PATHOGENIC MECHANISMS AND RELEVANT TARGETED THERAPIES

Cell identity and targeted therapies

Under physiological conditions, T lymphocytes possess certain cell plasticity and can differentiate into various types or interconvert with each other depending on the instructive signals they receive (Figure 2B).[102] Malignant transformation causes T-cells to acquire genetic and regulatory defects that make them express specific TFs and differentiate into a particular T-cell lineage.[103,104] These cells mimic their normal counterparts in their phenotype, including surface markers and microenvironmental interactions. This similarity serves as the basis for predicting the PTCL cell identity through immunophenotypic resemblance (Table S1).[47,48,105-108] However, progenitor cells with abnormal differentiation may lead to differences from their cell of origin, as revealed by GEP comparing tumor and normal T-cells.[109,110] Some PTCL entities have ambiguous cell identities, and bulk tissue sequencing may introduce a confounding mixture of other normal cellular components, including reactive T cells, which impede data analysis and interpretation.

Functional biomarkers are needed to capture the diverse transcriptional networks that differentiate malignant T-cells. Stained tissue specimens can reveal the morphometric features of these processes, which are essential for the diagnosis and classification of PTCLs.[111] For example, the diagnostic criteria of TFH lymphoma require simultaneous detection of at least three TFH-related antigens: CXCL13, PD-1, BCL6, CD10, ICOS, SAP, and CCR5.[107] While within PTCL-NOS, two gene expression-based subgroups have been identified: one characterized by high GATA3 expression, and the other marked by elevated expression of TBX21 and eomesodermin, along with their downstream targets.[48,112,113] GATA3 is a master regulator for T_H2 cells, while TBX21 is a master regulator for T_H1 cells and cytotoxic T-cells, supporting different cell identities for these subgroups.[114,115] The GATA3 subgroup exhibits a less favorable prognosis, marked by reduced stromal reliance, elevated MYC, and proliferation gene signatures, while the TBX21 subgroup generally has a more favorable prognosis, except for a cytotoxic subset with CD8 expression and poor outcome.[116] A novel transcriptomic approach has been developed for accurate and reproducible subclassification of PTCL-NOS using formalin-

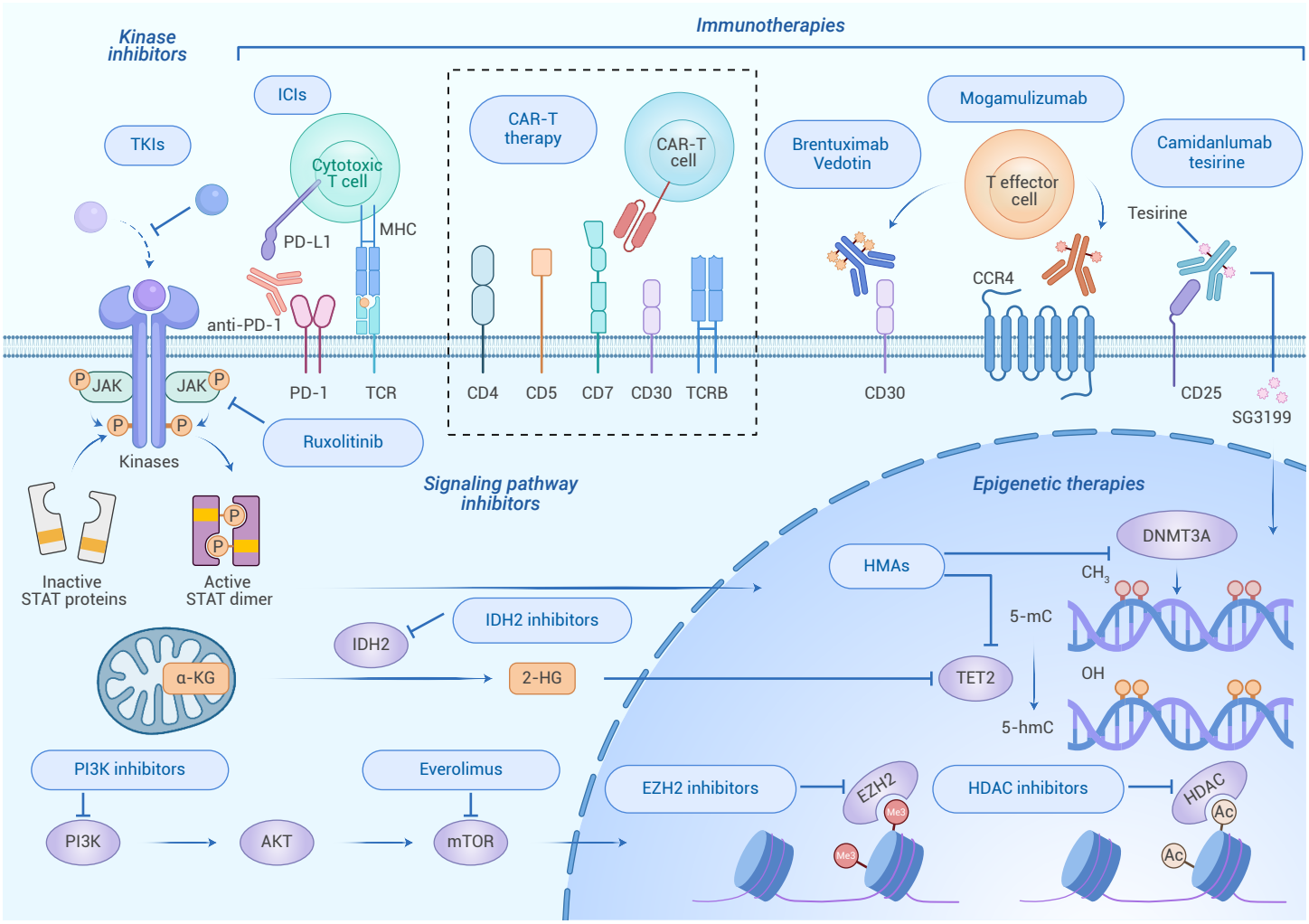


Figure 4. Cellular targets for precise medicine in PTCLs The successful development of precision medicine approaches for patients with PTCLs. Monoclonal antibodies targeting CD30 (Brentuximab vedotin), CCR4 (Mogamulizumab), and CD25 (Camidanlumab tesirine). The major targets for CAR-T cell therapies undergoing clinical trials include CD4, CD5, CD7, CD30, and TCRB. Among the immune checkpoint inhibitors, anti-PD-1 (Pembrolizumab and Nivolumab) has been approved; other inhibitors are currently in clinical development. Epigenetic regulators that have entered clinical practice include HMAs (Azacitidine and Decitabine) and HDAC inhibitors (Vorinostat, Romidepsin, Belinostat, and Chidamide). Agents in clinical trials include EZH2 inhibitors (Valemetostat tosilate and SHR2554) and IDH2 inhibitor (Enasidenib). Available signaling pathway inhibitors include JAK inhibitor (Ruxolitinib), PI3K inhibitors (Duvelisib and Copanlisib), and mTOR inhibitor (Everolimus). Among tyrosine kinase inhibitors, Dasatinib is a multi-kinase inhibitor approved for PTCLs, and NMP1-ALK inhibitor Crizotinib is undergoing clinical trials. ICI, immune checkpoint inhibitor; CAR-T, chimeric antigen receptor T-cell; TKI, tyrosine kinase inhibitor; HMA, hypomethylating agent; HDAC, histone deacetylase; α-KG, α-ketoglutarate; 2-HG, 2-hydroxyglutarate; 5-hmC, 5-hydroxymethylcytosine; 5-mC, 5-methylcytosine; -CH_3, methyl; -OH, hydroxy.

fixed, paraffin-embedded tissue samples.[117] Despite these advances, the pathological diagnosis of PTCLs remains a challenge due to their rarity, heterogeneity, similarity to other lymphoproliferative disorders, and limited tissue samples from core needle biopsies. AI-driven digital pathology technologies, based on whole-slide digital scanning and deep learning neural networks, can improve PTCL diagnosis by increasing accuracy and speed, supporting clinical decisions, and reporting prognostic or predictive variables.[118] Building a reliable reference database with manual annotations is an important direction for future research. Two major targeting strategies based on surface markers related to cell identity include humoral immunotherapy with monoclonal antibodies and cell-based therapy with target-specific chimeric antigen receptor T (CAR-T) cells (Figure 4).

Monoclonal antibodies. CD30, a TNFR superfamily member, serves as a diagnostic and prognostic marker, as well as a therapeutic target, in PTCLs.[119] In 1985, *Stein* et al. first reported the restricted expression of the Ki-1 antigen (CD30) in Hodgkin's lymphoma cases and specific histiocytic malignancies originating from activated lymphoid cells, now recognized as ALCL.[120] While CD30 expression is a distinctive biomarker for ALCL, it's noteworthy that other PTCL entities also exhibit surface and/or cytoplasmic CD30 expression, encompassing TFH lymphoma (46-80%)[109], PTCL-NOS (32-64%)[109], enteropathy-associated T-cell lymphoma (EATL) (50-100%)[121], and subcutaneous panniculitis-like T-cell lymphoma (SPTCL)[122]. However, its role in lymphoma remains unclear. Brentuximab vedotin (BV) is an antibody-drug conjugate that targets CD30-positive cells (Figure 4) and stands out as one of the most successful targeted therapies for PTCLs.[123,124] A recent phase III trial (ECHELON-2) compared BV plus cyclophosphamide, doxorubicin, and prednisone (BV+CHP) with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) for patients with CD30-positive PTCLs.[125] BV+CHP significantly improved progression-free survival (PFS) and OS over CHOP, with a 30% reduction in progression events and a 28% reduction in the risk of mortality (Table 2).[125] Consequently, the NCCN Guidelines® recommend BV+CHP as the preferred first-line therapeutic option for ALCL (category 1) or other CD30-positive entities (category 2A).[126]

Other antibody drugs include mogamulizumab targeting chemokine receptor 4 (CCR4)[127] and camidanlumab tesirine targeting CD25[128] (Figure 4). CCR4 is mainly expressed on the surface of T_H2 cells, T_{reg} cells, and skin lymphocyte antigen-positive homing T-cells.[129] Together with its ligands CCL17 and CCL22, CCR4 mediates T-cell accumulation in skin, which is an important pathogenic mechanism of CTCL.[130,131] Its expression is also upregulated in tumor cells of adult T-cell leukemia/lymphoma (ATLL) and PTCL-NOS.[132-134] Mogamulizumab is a humanized monoclonal antibody targeting CCR4, featuring a defucosylated Fc region that amplifies antibody-dependent cellular cytotoxicity.[135] It was approved by the FDA in 2018 for adult patients with relapsed and refractory (r/r) mycosis fungoides or Sézary syndrome,[20] and by

Table 1. Intrinsic pathogenic mechanisms relevant to the most frequent PTCL entities

Lymphoma type	Associated genomic events (Mutations, CNVs, and fusion genes)	Dysregulated translational pathways	Related TFs	Epigenetic features	Metabolism signatures
TFH lymphoma	Mutations: *TET2, DNMT3A, IDH2, RHOA, CD28, VAV1, PLCG1, CTNNB1, GTF2I*, PI3K pathway components CNVs: Generally not well-defined, but likely involve specific genes like *VAV1* Fusions: Not a prominent feature, but some cases may have unique fusion events, such as *VAV1* fusions, *ITK::SYK*, and *FYN::TRAF3IP2*, *ICOS::CD28*, *CTLA4::CD28*, etc.	TCR, JAK-STAT, PI3K-AKT-mTOR, NF-κB	GATA3, BCL6, BATF, IRF4, MAF	Multiple epigenetic-related mutations; DNA methylation and hydroxymethylation alterations; overexpression of a specific subset of miRNAs interacting with BCL6 to induce T_{FH} phenotype	GAPDH overexpression; 2-HG accumulation due to *IDH2 R172* mutations inhibiting α-KG-dependent dioxygenases; potential perturbation of tricarboxylic acid cycle and glutamine metabolism
PTCL-NOS	Mutations/CNVs: *TET2, DNMT3A, KMT2C, KMT2D, SETD1B, SETD2, CREBBP, EP300, ARID1A, KDM6A, CDKN2A/2B, TP53, PTEN, MYC, STAT3, REL, NOTCH1, CCR4, CCR7*, etc. Fusions: Not a prominent feature, but some cases may have unique fusion events, such as *VAV1* fusions, *ITK::SYK*, and *FYN::TRAF3IP2*, etc.	TCR, NF-κB, JAK-STAT, PI3K-AKT-mTOR, Notch, Translation initiation factors alteration	GATA3 or TBX21/EOMES depending on molecular subgroup	Multiple epigenetic-related mutations; histone acetylation or deacetylation; DNA hypermethylation or hypomethylation; complicated miRNA dysregulation	Overexpression of proteins linked to lipid metabolism; reprogramming of metabolic pathways towards glucose and glutamine upon demethylating agent treatment; dysregulated choline metabolism sustaining RAS, AKT, ERK, and MYC activity
ALK^+ ALCL	Mutations/CNVs: Generally not a major factor in ALK^+ ALCL Fusions: *NPM1::ALK* and other ALK fusions	TCR (bypassed by ALK), JAK-STAT, PI3K-AKT-mTOR, Notch, AP-1	STAT3, STAT5B, NFAT, JUN, JUNB, AP-1, BATF	*TET2* mutations; low genomic complexity; global hypomethylation; promoter hypermethylation of tumor-suppressive miRNAs; overexpression of miRNAs targeting apoptosis, differentiation, and signal transduction	High glucose uptake and glycolytic activity; increased nucleotide biosynthesis; cholesterol auxotroph due to squalene monooxygenase loss
ALK^- ALCL	Mutations: *TP53, TP63, TET2, JAK1, STAT3*, etc. CNVs: *TP53* and *PRDM1* deletions; loss of phosphatases Fusions: *DUSP22::IRF4* and other *DUSP22* fusions; *TP63::TBL1XR1* fusion; *NCOR2::ROS1* and other *ROS1* fusions; *PABCA2::TYK2* and other *TYK2* fusions	TCR, JAK-STAT, PI3K-AKT-mTOR, Notch	IRF4, TP63, STAT3, STAT5B	*TET2* mutations; low genomic complexity; global hypomethylation; lower expression of miRNAs regulating angiogenesis, survival, and metabolism	Altered cellular metabolism affecting energy production and macromolecule biosynthesis; specific metabolic changes may vary based on underlying genetic alterations

Note: GAPDH, glyceraldehyde-3-phosphate dehydrogenase; 2-HG, 2-hydroxyglutarate; α-KG, alpha-ketoglutarate.

Japan in 2012 for ATLL (Table 2).[136] CD25, a T-cell activation marker, is highly expressed in tumor cells of PTCLs and Hodgkin's lymphoma. Camidanlumab tesirine is an anti-CD25 antibody-drug conjugate with a pyrrolobenzodiazepine dimer cytotoxin SG3199.[128] It has shown antitumor activity in PTCLs as a single drug and needs more mechanistic and pre-clinical studies.[128,137]

CAR-T cell therapies. CAR-T cells are generated by transducing a CAR fusion protein designed to target specific surface markers on tumor cells.[14] The success of CAR-T cell therapies in treating B-cell lymphomas has spurred its exploration for potential use in PTCLs. Pre-clinical studies have demonstrated the promise of CAR-T cell therapies targeting multiple T-cell markers.[138,139] A spectrum of clinical trials with diverse targets for r/r PTCLs are currently underway, as reviewed elsewhere.[140] Notably, there are at least 28 completed phase I trials, 15 completed phase II trials, and over 250 ongoing phase I/II trials for T-cell lymphomas utilizing CAR-T cells (source: https://clinicaltrials.gov). However, CAR-T cell therapy for PTCLs faces challenges due to the similarity between malignant T-cells and CAR-T cells, which can cause CAR-T cell fratricide, product contamination, and T-cell aplasia.[141] Therefore, choosing suitable antigens is crucial to avoid off-target effects. Currently tested antigens mainly encompass CD4, CD5, CD7, CD30, CD37, and TRBC.[140] Among these markers, TRBC represents a more personalized target for CAR-T cell production than the common cell markers in T-cells. The T-cell receptor (TCR) is composed of six polypeptides, including the αβ subunits, with the β-constant region encoded by two distinct genes, *TRBC1* and *TRBC2*.[142] Each T-cell, as well as malignant T-cells, exclusively expresses one of these genes. In a healthy individual, approximately 35% of T-cells are $TRBC1^+$, and 65% are $TRBC2^+$.[129] Importantly, targeting either of these T-cell subgroups does not compromise the function of the other. While in PTCLs, the malignant clone typically dominates gene expression due to the monoclonal or oligoclonal expansion of mature T-cells.[143,144] This principle underpins the development of anti-TRBC CAR-T cell therapies. Ideally, anti-TRBC1 or anti-TRBC2 CAR-T cells can selectively target malignant and normal T-cells sharing the same TRBC molecule, while preserving T-cells with the alternative TRBC variant. This approach minimizes the risk of fratricide and non-specific killing of T-cells. Both in vitro and in vivo studies have demonstrated that anti-TRBC1 CAR-T cells specifically eliminate $TRBC1^+$ cells, sparing $TRBC2^+$ cells, thereby reducing tumor burden and significantly prolonging survival in murine models.[143]

The key strategy for improving PTCL treatment and reducing side effects is to choose a highly specific target for CAR-T cell production.[129] The optimal target should exhibit exclusive expression on malignant cells without being present on normal T-cells, so that CAR-T cells can precisely discern and target tumor cells. As highly specific markers, neoantigens refer to de novo

Table 2. Major clinical results of new treatment for PTCLs

Agent	Target	Mechanism	Lymphoma type	Setting	Response rate	PFS (months)	OS (months)	Adverse effects
Brentuximab vedotin	CD30	Antibody-drug conjugate that targets $CD30^+$ cells and delivers a cytotoxic agent	$CD30^+$ PTCLs, including ALCL and PTCL-NOS	r/r, frontline (with CHP)	83% ORR, 68% CR in newly diagnosed; 86% ORR, 57% CR in r/r	20 (r/r); 48.2 (frontline)	Not reached (r/r); not reached (frontline)	Peripheral neuropathy, neutropenia, anemia, thrombocytopenia, nausea, fatigue
HDAC inhibitors (belinostat, romidepsin, chidamide)	Histone acetylation	Histone deacetylase inhibitors that modulate gene expression and induce apoptosis, cell cycle arrest, and differentiation of tumor cells	Various PTCL subtypes, including PTCL-NOS, TFH lymphoma, ALCL	r/r	25.8% ORR, 10.8% CR for belinostat; 25% ORR, 15% CR for romidepsin; 28% ORR, 14% CR for chidamide	1.6 for belinostat; 4 for romidepsin; 2.1 for chidamide	7.9 for belinostat; 11.3 for romidepsin; 21.4 for chidamide	Thrombocytopenia, neutropenia, anemia, nausea, vomiting, diarrhea, fatigue
Hypomethylating agents (azacytidine, decitabine)	DNA methylation and TET2/DNMT3A/IDH 2 mutations	Hypomethylating agents that inhibit DNA methyltransferases and restore the expression of tumor suppressor genes	TFH lymphoma	r/r	75% ORR, 50% CR for azacytidine; 40% ORR for decitabine	15 for azacytidine; not reported for decitabine	21 for azacytidine; not reported for decitabine	Neutropenia, thrombocytopenia, anemia, infection, nausea, vomiting
Immune checkpoint inhibitors (pembrolizumab, nivolumab)	PD-1/PD-L1 pathway and EBV infection or PD-L1 amplification in tumor cells or microenvironment	Immunomodulation and antitumor immunity enhancement	Various PTCL subtypes, including PTCL-NOS, TFH lymphoma, ALK^- ALCL, ATLL	r/r	33% ORR, 27% CR for pembrolizumab; 33% ORR, 17% CR for nivolumab	2.9 for pembrolizumab; 3.6 for nivolumab	3.2 for pembrolizumab; 1.9 for nivolumab	Rash, pruritus, colitis, pneumonitis, hepatitis, endocrinopathies
Tyrosine kinase inhibitors (crizotinib, alisertib)	ALK in ALK^+ ALCL (crizotinib); other kinases in various PTCL subtypes (alisertib)	Signal transduction inhibition and tumor cell apoptosis induction	ALK^+ ALCL (crizotinib); various PTCL subtypes kinase activation or mutation (alisertib)	r/r	100% ORR, 100% CR for crizotinib; 33% ORR, 16% CR for alisertib	63.7% at 2 years for crizotinib; 2.7 for alisertib	72.7% at 2 years for crizotinib; 9.9 for alisertib	Nausea, vomiting, diarrhea, edema, fatigue, elevated liver enzymes
JAK-STAT inhibitors (ruxolitinib)	JAK/STAT pathway and cytokine signaling in various PTCL subtypes	Signal transduction inhibition and tumor cell apoptosis induction	Various PTCL subtypes with JAK/STAT pathway activation or mutation	r/r	42% ORR, 11% CR for ruxolitinib	3 for ruxolitinib	10 for ruxolitinib	Anemia, thrombocytopenia, neutropenia, infection, weight gain
PI3K inhibitors (duvelisib)	PI3K-δ/γ pathway in various PTCL subtypes	Signal transduction inhibition and tumor cell apoptosis induction	Various PTCL subtypes, especially TFH lymphoma, angioimmunoblastic subtype with PI3K mutations	r/r	50% ORR, 19% CR for duvelisib	4.4 for duvelisib	Not reported for duvelisib	Diarrhea, colitis, neutropenia, pyrexia, rash, nausea, fatigue, cough
mTOR inhibitors (everolimus)	mTOR pathway and cell cycle progression in various PTCL subtypes	Signal transduction inhibition and tumor cell apoptosis induction	Various PTCL subtypes with mTOR pathway activation or mutation	r/r	44% ORR for everolimus	4.1 for everolimus	10.2 for everolimus	Myelosuppression
Immunomodulatory agents (lenalidomide)	Tumor microenvironment and immune system modulation in various PTCL subtypes	Immunomodulation and antitumor immunity enhancement	Various PTCL subtypes with immune dysregulation or evasion	r/r	22% ORR, 11% CR for lenalidomide	2.5 for lenalidomide	Not reported for lenalidomide	Myelosuppression, infections, rash
Anti-CCR4 mAb (mogamulizumab)	CCR4	Antibody mediated cytotoxity	Various PTCL subtypes, including ATLL, PTCL-NOS, TFH lymphoma	r/r	34% ORR, 13.5% CR for mogamulizumab	2 for mogamulizumab	14.2 for mogamulizumab	Lymphopenia, neutropenia, leukopenia, skin rash
Antifolate (pralatrexate)	Dihydrofolate reductase	Folate analogue metabolic inhibitor	Various PTCL subtypes, including PTCL-NOS, TFH lymphoma, ALCL	r/r	29% ORR, 11% CR for pralatrexate	3.5 for pralatrexate	14.5 for pralatrexate	Mucositis, thrombocytopenia, neutropenia, anemia

Note: r/r, relapsed and refractory; ORR, objective response rate; CR, complete response; PFS, progression free survival; OS, overall survival; mAb, monoclonal antibody.

epitopes derived from mutational events, which can escape T-cell tolerance of self-epitopes and trigger immune responses to tumors.[145] Computational methods for neoantigen discovery and prioritization have demonstrated their efficacy in various studies such as therapeutic cancer vaccines,[146-148] but their application in CAR design remains uncharted territory.[149] These methods may help identify and select optimal targets for CAR-T cell therapies.

In addition to cell surface markers, cytokines are also cell identity-dependent factors that influence the differentiation and expansion of tumor T-cells.[150] Cytokines promote the growth of certain subpopulations while suppressing others, which can be exploited to block the abnormal differentiation of tumor cells with specific phenotypes.[151] Cytokine therapy used to be limited by short half-lives, low specificity, and bad biodistribution.[152] However, recent advancements in bioengineering have yielded new technologies for cytokine engineering, which have found application in the treatment of various autoimmune diseases.[153,154] This may offer new opportunities for targeting PTCL cell identity in the future.

Genomic aberrations and targeted therapies

Large-scale genomic sequencing studies have revealed the complex and diverse genomic landscape of PTCLs, with a spectrum of characteristic mutations, copy number variations (CNVs), and gene fusions that vary significantly among different entities (Table 1).[68,116,155] Despite the efforts invested in PTCL genomics over the past decade, our understanding of its driving defects remains limited.

In contrast to the highly prevalent mutations typically observed in other malignancies, gene defects in PTCLs often exhibit enrichment within specific pathways, which implies their potential pathogenic significance.[14,116] For example, TFH lymphoma often carries mutations related to Ras family signaling (*RHOA G17V*), epigenetic regulators (*TET2*, *DNMT3A*, and *IDH2 R172*), and TCR pathway (*CD28*, *VAV1*, and *PLCG1*).[156-158] PTCL-NOS features mutations or CNVs within epigenetic regulators (*TET2*, *DNMT3A*, *IDH2 R172*, *KMT2C/2D*, *KMT6A*, *SETD1B*, *SETD2*, *CREBBP*, and *EP300*), TCR pathway (*CD28*, *VAV1*, *PLCG1*, *CARD11*, and *FYN*), tumor suppressors (*TP53*, *CDKN2A/2B*, *PRDM1*, and *PTEN*), and chromatin remodelers (*ARID2/4* and *SMARCA2B*).[49,51,159] Within the PTCL-NOS entity, the PTCL-GATA3 shows greater genomic instability, with frequent deletion of tumor suppressor genes (*PRDM1*, *CDKN2A/2B*, *TP53*, and *PTEN*).[160] The PTCL-TBX21 subgroup has fewer CNVs and more frequent mutations involving DNA methylation.[161] ALK$^-$ ALCL acquires mutations or deletions within epigenetic regulators and tumor suppressors (*TP53*, *TP63*, and *PRDM1*).[162] Recurrent gains and increased expression of TFs (*STAT3/5A/5B*, *JAK2/3*, and *NOTCH1/3*) and cell cycling (*CDK6*) were frequently detected in PTCL-NOS and ALCL.[163]

Fusion genes were also discovered in many entities, often at low frequencies, and recurrent ones are mainly seen in ALCL. The expression of ALK fusion proteins is a characteristic feature of ALK$^+$ ALCL, which results from the translocation of *ALK* with various partners.[37] The most common partner is *NPM1* (85%), while others include *TPM3*, *TPM4*, *TFG*, *ATIC*, *MYH9*, *TRAF1*, *CLTC*, *MSN*, *RNF213*, and *TRAF1*.[164] The novel fusion proteins aberrantly activate intracellular signaling pathways, such as STAT3, leading to uncontrolled cell proliferation, evasion of immune response, and the development of ALCL.[165-167] Preliminary clinical trials suggest that targeting *NMP1::ALK* induces enduring complete remissions in a large proportion of pre-treated adult patients and most children diagnosed with advanced-stage ALK$^+$ ALCL (Figure 4).[168-170] Recurrent rearrangements of *IRF4*, *DUSP22*, *TP63*, *ROS1*, and *TYK2* have been observed in ALK$^-$ ALCL, each carrying distinct prognostic implications.[171-173] *VAV1*,[174] *ITK::SYK*,[175] *FYN::TRAF3IP2*,[176,177] and *ICOS/CTLA4::CD28*[178] fusions have been reported in the angioimmunoblastic form of TFH lymphoma and PTCL-NOS cases, all with relatively low frequencies.

With the extensive accessibility of NGS technology, mutational screening becomes a common diagnostic procedure using a targeted panel approach that covers the most frequently mutated genes in PTCLs.[179] The panel should include "targetable" mutations (e.g., *TET2*, *DNMT3A*, and *IDH2 R172*), as well as other prognostic biomarkers (e.g., *TP53*, *PRDM1*, and *CDKN2A/2B*).[10] The detection of characteristic mutations, such as the *RHOA G17V* mutation in the angioimmunoblastic form of TFH lymphoma, can also aid the diagnosis of patients with atypical pathological features.[180]

Despite this understanding, the clinical impact of genomic profiling in PTCLs has yet to be limited by the scarcity of highly prevalent, actionable driver mutations. The main exceptions are recurrent mutations involving DNA methylation, especially in TFH lymphoma patients.[15] Targeted therapies available for these genomic alterations are limited to hypomethylating agents (HMAs), such as 5-azacitidine and decitabine (Figure 4, Table 2).[181,182]

RHOA, the representative mutated gene in TFH lymphoma, is a member of the RHO family of small GTPases.[183] Rhoa operates as a molecular switch, transitioning between an active state bound to guanosine triphosphate (GTP) and an inactive state bound to guanosine diphosphate (GDP).[184] The activation of Rhoa is orchestrated by RHO guanine nucleotide exchange factors (GEFs), which facilitate the exchange of GDP with GTP.[185] In biochemical and cellular assays, *RHOA G17V* exhibits impaired GTP loading and fails to activate downstream *RHOA* effector proteins.[186,187] Furthermore, it disrupts the function of wild-type Rhoa, possibly by sequestering or modifying the activity of RHO GEFs. In vivo and in vitro investigations have confirmed that *RHOA G17V* induces T_{FH} specification and promotes lymphomagenesis, rendering it a potential therapeutic target.[188,189] However, small GTPases have long been deemed "undruggable", primarily due to the lack of pharmacologically accessible binding pockets within both wild-type and mutant isoforms.[190] In the past decade, the covalent inhibitors targeting KRAS G12C have proven an enormous success, which induced conformational changes of switch II to form an allosteric pocket for drug targeting.[191,192] The 59DXXGQ63 motif in switch II is conserved among Ras superfamily members, including *RHOA*.[193] Recent crystal structure analysis and molecular dynamics simulation studies have elucidated similar dynamics of switch II in wild type Rhoa and identified a homologous allosteric pocket for small molecule binding.[194] However, unlike Kras G12C, which binds GDP with lower affinity,[195] Rhoa G17V does not bind either nucleotide, suggesting a different pathogenic mechanism. With *RHOA* no longer an undruggable target, future structural studies on its G17V mutant will help us understand the pathogenic mechanism and facilitate the design of mutant-specific drugs.

Transcriptional abnormalities and targeted therapies

Advances in sequencing technologies have enabled deep dissection of the PTCL transcriptome. Revealed by large-scale GEP and RNA sequencing (RNAseq), PTCLs exhibit different transcriptional profiles depending on their subtype and cell of origin (Table 1). For example, TFH lymphoma possesses a T_{FH}-like transcriptomic signature that reflects its heritage from normal T_{FH}.[26] ALK$^+$ ALCL has a unique transcriptional signature driven by the *NPM1::ALK* fusion.[37] The expression level of *ERBB4*[196] and *GATA3/TBX21*[48] within ALK$^-$ ALCL and PTCL-NOS, respectively, has led to recognition of new subclasses, with distinct transcriptional signatures and clinical manifestations. The transcripts involving cell cycle progression, survival, metabolism, and immune evasion (e.g., *MYC*, *BCL2*, *MCL1*, *HIF1A*, and *PD-L1*) are upregulated by oncogenic TFs, such as STAT3, NF-κB, AP-1, and IRF4.[3] PTCLs also show altered expression of genes that determine T-cell differentiation and function, such as *TBX21*, *GATA3*, *RORC*, *BCL6*, and *FOXP3*. These genes are controlled by master TFs that define the phenotype and plasticity of T-cells.

Dysregulated signaling pathways. Dysregulated signaling pathways are pivotal in the pathogenesis of PTCLs, with TCR, JAK-STAT, PI3K-AKT, and NF-κB pathways prominently involved. These pathways undergo profound alterations, driving disease progression and offering therapeutic opportunities.

In PTCLs, the TCR signaling pathway experiences aberrant activation due to genetic or epigenetic alterations affecting key components and regulators like *CD28*, *PLCG1*, *CARD11*, *VAV1*, *RHOA*, and *DUSP22*.[197-200] These changes result in antigen-independent TCR signaling, amplified co-stimulatory signals, disrupted negative feedback loops, and rewired downstream pathways.[197] Intriguingly, some genetic defects uncouple TCR signaling from TCR engagement, exemplified by *ALK* fusions in ALK$^+$ ALCL[201-203] or *ITK::SYK* fusion in the angioimmunoblastic form of TFH lymphoma and PTCL-NOS.[204,205] The JAK-STAT pathway is also constitutively activated in PTCLs as supported by immunohistochemistry and GEP,[108,206] partly due to alterations in *JAK1*, *JAK3*, *STAT3*, *STAT5*, *SH2B3*, and *DUSP22*.[207] This activation leads to the upregulation of genes essential for cell growth, survival, angiogenesis, and immune evasion.[208] Additionally, cytokines released by tumor cells or microenvironment can stimulate the JAK-STAT pathway.[209,210] The PI3K-AKT signaling pathway, a significant regulator of cell metabolism, growth, and survival, also

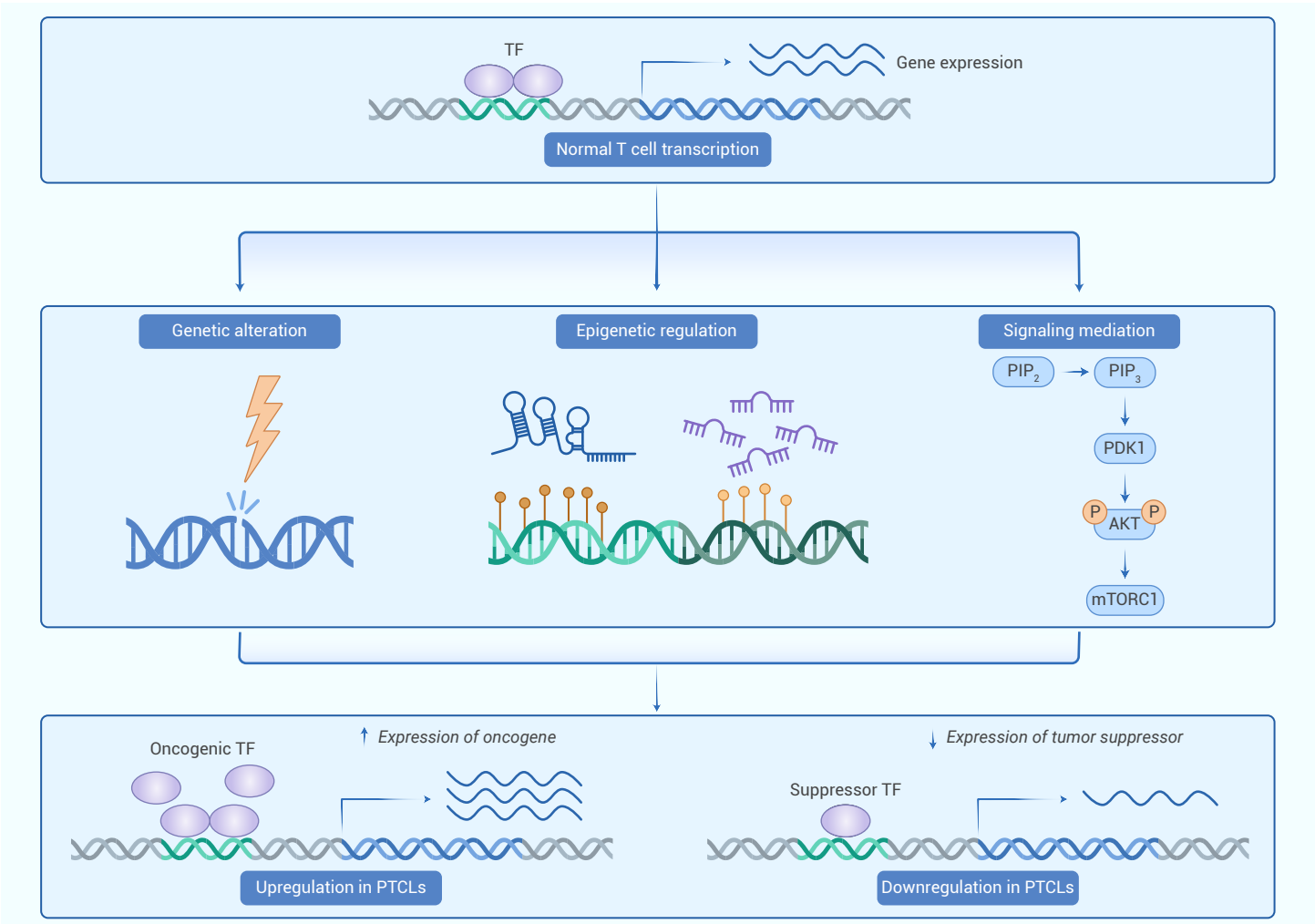


Figure 5. Common mechanisms of transcriptional factor dysregulation in PTCLs Various mechanisms by which the normal function of an example TF can be dysregulated in PTCLs (top), including genetic alteration (medium left), epigenetic regulation (medium), and upstream signaling mediation (medium right). TFs that drive a disease state can be overactive and/or overabundant, often resulting from TF gain-of-function mutations, TF gene amplification, epigenetic overexpression, or activation of signaling pathways (bottom left). In contrast, TFs that play a protective role against disease can be aberrantly downregulated by TF loss-of-function mutations, TF gene deletions, epigenetic silencing, or activation of repressor proteins targeting the TF (bottom right).

plays a central role in pathogenesis. Related genetic alterations include *PI3K*, *AKT*, *PTEN*, *RHOA*, *CD28*, and *ICOS*.[188,211,212] The activation of the PI3K-AKT signaling pathway exhibits dual intrinsic and extrinsic functions. It conveys mitogenic and survival signals, facilitates the release of cytokines and chemokines, and induces tumor-suppressive effects through M2 macrophages.[3] In TFH lymphoma, mutations or translocations involving *RHOA G17V*[89], *CD28*[200], *FYN::TRAF3IP2*,[176] and *VAV1*,[174] result in constitutive activation of NF-κB. Recently, a TFH lymphoma, angioimmunoblastic type mouse model generated by overexpressing glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in T-cells revealed a strong activation of the non-canonical NF-κB pathway, which results in oncogenesis.[213] In vivo experiments demonstrated the potential therapeutic efficacy of targeting NIK, a critical kinase within the non-canonical NF-κB pathway, for treating the angioimmunoblastic form of TFH lymphoma.[213]

Targeting these signaling pathways is a promising therapeutic strategy for PTCLs. Several inhibitors of TCR-related kinases (such as LCK and ZAP70), JAKs (such as ruxolitinib and fedratinib), STATs (such as napabucasin and stattic), PI3K (such as idelalisib and duvelisib), AKT (such as crizotinib and perifosine) or mTOR (such as temsirolimus and everolimus) have been developed and tested in pre-clinical and clinical studies. Some of these inhibitors (e.g., ruxolitinib,[214] duvelisib,[22] and everolimus[215]) have shown anti-tumor activity with manageable toxicity in PTCL patients (Figure 4, Table 2), especially in combination with other agents. However, the efficacy of these inhibitors is limited by the heterogeneity of PTCLs, the presence of alternative or compensatory signaling pathways, and the development of resistance mechanisms. Therefore, further research is needed to identify biomarkers capable of predicting the response to these inhibitors, optimize the dosing and scheduling of these agents, and explore novel combinations with other targeted therapies or immunotherapies.

Dysfunctional TFs. Dysfunctional TFs in PTCLs can be classified into three categories: (1) TFs that are mutated or translocated, resulting in their gain or loss of function; (2) TFs that are overexpressed or silenced by epigenetic mechanisms, leading to their altered activity or interaction; and (3) TFs that are modulated by upstream signaling pathways (Figure 5). Targeted strategies can be designed based on different mechanisms underlying these categories.

Mutations or CNVs involving *STAT3*, *STAT5A*, *STAT5B*, *JAK1*, *JAK2*, *JAK3*, *NOTCH1*, and *NOTCH3* have been documented in PTCL-NOS, TFH lymphoma, and ALCL, which are related to poor prognosis.[14] *IRF4* is also frequently overexpressed in ALK$^-$ ALCL due to translocations of *DUSP22* or *TP63*,[173] which promotes STAT3-mediated oncogenesis and CD30 expression.[216] Genetic aberrations in TFs often lead directly to cell proliferation. Inhibitors of mutated proteins or their downstream effectors, such as JAK, STAT, and NOTCH inhibitors, can be used as targeted therapies.

TFs associated with T-cell differentiation and cell identity are often dysregulated by epigenetic modifications, such as *TET2*, *DNMT3A*, and *IDH2* mutations. BCL6 is a TF characteristically overexpressed in TFH lymphoma and a subset of ALCL.[217] It controls contact-dependent help delivery during T-B cell interactions, leading to the expression of T_{FH} markers and TFH lymphoma progression.[218,219] Expression of GATA3 or TBX21 divide PTCL-NOS into two

distinct subtypes with different cell identity, GEP, and prognosis.[48] RORγ is a crucial factor for the differentiation of T_H17 cells and is ectopically expressed in some CTCLs and CD30-positive lymphomas.[220,221] These key TFs fine-tuning T-cell fate are essential for tumor cell identities and the development of certain entities. Drugs that target the epigenetic machinery are anticipated to have some clinical efficacy for this category.

AP-1 TFs comprise a family of proteins that bind to specific DNA sequences known as AP-1 sites and hand in a wide range of cellular processes, encompassing cell growth, differentiation, and apoptosis.[222] In PTCLs, AP-1 TFs are often dysregulated in response to various abnormal stimuli, such as cytokines, growth factors and TCR signaling.[220,223,224] The expression of AP-1 TFs and their target genes regulates tumor growth, which can be used as biomarkers to identify different subtypes of PTCLs and to predict their clinical outcomes. For instance, the amplification or overexpression of *JUNB* is associated with CTCL and CD30-positive PTCLs,[223] whereas low expression of *JUNB* and high expression of *BATF3* is characteristic of the angioimmunoblastic form of TFH lymphoma.[220] The upstream signaling pathways of these TFs can be exploited as therapeutic targets. For instance, inhibitors of JAK-STAT signaling, ERK signaling, or NF-κB signaling can potentially block the activation of AP-1 TFs and their downstream effects on pathogenesis.

The dysfunction of key TFs leads to aberrant gene expressions that underlie the hallmarks of PTCLs, highlighting the need to discover selective and efficient therapies that target their activity. In recent years, multiple approaches have been demonstrated, pre-clinically and, in some cases, clinically. Traditional approaches encompass inhibiting protein-protein interactions between TFs and their cofactors, impeding the binding of TFs to DNA, and altering ubiquitylation levels and subsequent proteasome-mediated degradation. Innovative techniques have also emerged, such as modulating auto-inhibition, employing proteolysis targeting chimeras, utilizing cysteine-reactive inhibitors, and targeting intrinsically disordered regions within TFs.[225] For instance, BCL6 is a pivotal TF implicated in the pathogenesis and progression of T_{FH}-derived PTCLs, diffuse large B-cell lymphoma, Burkitt lymphoma, and follicular lymphoma, which is a potential druggable target for these diseases.[226] Nevertheless, many BCL6 inhibitors have low activity in vivo and are unsuitable for clinical use. A recent study has identified a small molecule, BI-3802, that can induce polymerization and specific protein degradation, resulting in enhanced activity compared with other BCL6 inhibitors.[227] These advances in drug design offer opportunities for the future development of TF-targeting therapeutics for PTCLs.

Epigenetic features and targeted therapies

Although TFs ultimately govern gene expression programs, the impact of epigenetic modifications on DNA and histones cannot be overlooked, as they shape transcriptional outcomes by altering chromatin structure and the recruitment of effector proteins (Figure 5).[228] PTCLs, especially T_{FH}-derived entities, feature recurrent mutations in genes encoding epigenetic regulators, including *TET2*, *DNMT3A*, and *IDH2*.[15] Moreover, deficits in histone acetylation reflected by related mutations, such as *EP300* and *CREBBP*, have been detected in several entities of PTCLs, mainly PTCL-NOS and ALCL.[79]

As discussed earlier, mutations related to CHIP are common in ageing patients and significantly contribute to the etiology of PTCLs. *TET2*, which encodes a DNA demethylase, is mutated in 34%-76% of TFH lymphoma, angioimmunoblastic type and 38% of TFH lymphoma, follicular type cases.[229,230] *DNMT3A*, which encodes a DNA methyltransferase, is mutated in 10%-30% of TFH lymphoma, angioimmunoblastic type cases and often co-exists with *TET2* mutations (Figure 4).[78,85] Recent research reported that *DNMT3A* mutations perturb early progenitor states through selective hypomethylation in binding motifs of key hematopoietic TFs, suggesting a potential mechanistic link between *DNMT3A* mutations and aberrant transcriptional phenotypes.[90] Current hypotheses suggest that they represent a pre-malignant condition that can lead to the transformation of lymphoid or myeloid tumors when additional mutations are acquired, such as *RHOA*, *IDH2*, *CD28*, *PLCG1*, and *NOTCH2*.[231]

IDH2 mutations are found in 20-45% of TFH lymphoma patients and may affect T-cell activation, differentiation, and signaling.[232] *IDH2* encodes for a mitochondria enzyme that converts isocitrate to alpha-ketoglutarate (α-KG).[233] The gain-of-function *IDH2 R172* substitutions further convert α-KG into 2-hydroxyglutarate (2-HG) and lead to the accumulation of this oncometabolite in T-cells.[234] 2-HG inhibits a panel of α-KG-dependent dioxygenases, including the *TET* family, and decreases the levels of 5-hydroxymethylcytosine (5hmC) in the nuclear, resulting in defective lymphoid development (Figure 4).[235,236] Of note, *IDH1 R132* and *IDH2 R172* mutations are also frequently detected in acute myeloid leukemia (AML) and confer adverse prognosis.[237,238] Enasidenib, an allosteric IDH2 inhibitor, functions by binding to the IDH2 dimer interface, thereby obstructing the production of 2-HG.[239] It has been approved for treating r/r AML patients with *IDH2* mutations since 2017.[240] An ongoing clinical trial of Enasidenib for r/r TFH lymphoma, angioimmunoblastic type (NCT02273739) may provide novel approaches for targeting genomic aberrations in PTCLs.[241] Other mutations involving epigenetic regulation include *KMT2D*, *KMT2A*, *SETD2*, *EZH2*, *MLL2*, *KDM6A*, *CREBBP*, *EP300*, *MEF2B*, *ARID1B* and *ARID2*. These genes encode for histone methyltransferases, histone demethylases, histone acetyltransferases, or chromatin remodelers that regulate gene transcription by altering chromatin accessibility.

Histone deacetylase inhibitors (HDACi) and HMAs are the main classes of epigenetic modulators that have been validated in PTCL treatment.[242] HDACi block the removal of acetyl groups from histones, resulting in increased histone acetylation and gene expression of related tumor suppressor genes that affect cell survival, apoptosis and signaling (Figure 4). HDACi have proven clinical efficacy in r/r PTCLs, and romidepsin and belinostat are FDA-approved for this indication.[243-244] HMAs inhibit DNA methyltransferases, which add methyl groups to DNA and downregulate gene expression (Figure 4). HMAs can reverse the epigenetic silencing of tumor suppressor genes or negative regulators of T-cell signaling. Two HMAs, azacitidine and decitabine, have demonstrated activity in PTCLs (Table 2).[245-247] Other epigenetic modulators under investigation include IDH inhibitors, EZH2 inhibitors, and more selective HDACi.

As CHIP garners increasing attention within PTCLs, hematologists are increasingly intrigued by the prospect of early intervention to identify and address ACH before it manifests into associated clinical consequences. Initiatives to achieve early detection include increasing lymphoma studies that perform NGS assays on cell-free DNA (cfDNA) from blood plasma.[248-251] These efforts can identify ACH variants, thus improving risk stratification or monitoring treatment responses.[252] However, the available mutant-specific targeted therapies (e.g., HMAs and IDH2 inhibitors) face several concerns when used for early intervention. The risk of transformation is relatively low, so the potential toxicity of these drugs must be weighed against the potential benefit. Moreover, there is a long time gap between the detection of ACH and the occurrence of clinical events, which requires surrogate endpoints or biomarkers to evaluate the efficacy of these drugs.[253] Future studies on the molecular mechanisms that control the expansion and progression of ACH pre-malignant clones will help to identify high-risk individuals and optimize therapeutic interventions.

Metabolic processes and targeted therapies

The uptake and metabolism of nutrients enable cells to perform essential functions such as energy generation, biosynthesis, and cell fate determination.[228] Like other tumors, lymphomas exhibit diverse metabolic changes that influence both malignant cells and host cells.[254] The unique metabolic profiles of PTCL cells are different from those of resting or activated T-cells and are closely related to pathogenesis (Table 1).[255-257] Overexpression of GAPDH, a product of aerobic glycolysis, in T-cell lineage was found to promote TFH lymphoma pathogenesis in vivo through NF-κB signaling.[213] Proteins involved in lipid metabolism are overexpressed in PTCL-NOS,[258] and HMA application induces a metabolic shift in this subtype, reducing lipid synthesis, increasing glucose and glutamine utilization, and upregulating cell cycle arrest gene expression.[259] In ALK^+ ALCL, NPM-ALK protein phosphorylates PKM2, leading to a metabolic shift to aerobic glycolysis, lactate production, and biomass production.[260] Cholesterol dependency in ALK^+ ALCL cells results from the deficiency of squalene monooxygenase, which catalyzes the conversion of squalene to lanosterol.[260] Squalene accumulation protects these cells from ferroptosis, a form of regulated cell death induced by oxidative stress, and confers a growth advantage.[261] PI3K pathway dysregulation also affects the metabolism and phenotype of malignant T-cells,[262,263] as the PI3K-AKT-mTOR axis controls the uptake and utilization of glucose, glutamine,

Table 3. Extrinsic pathogenic mechanisms relevant to the most frequent PTCL entities

Lymphoma type	Cellular components of LME	Non-cellular components of LME	Immune checkpoints	Co-stimulatory signals	Viral factors
TFH lymphoma	Follicular dendritic cells, B-cells, T_{reg} cells, TAMs, eosinophils, and endothelial cells	CXCL13, IL-21, IL-4, IL-10	PD-1 (61.6%-93%), PD-L1 (78.9%-80%), TIGIT, and CD27	ICOS and CD28	EBV infecting microenvironment B or malignant T-cells; HHV6B
PTCL-NOS	T_{reg} cells, myeloid-derived suppressor cells, TAMs, B-cells, follicular dendritic cells,	IL-2, IL-4, IL-5, IL-10, IL-13, IFN-γ, and TNF-α depending on their differentiation stage and activation status	PD-1 (39.3%-62%), PD-L1 (26%-35.7%), TIM-3 (8%)	CD28	EBV (rare)
ALK^+ ALCL	Fibroblasts, T_{reg} cells, TAMs, eosinophils, mast cells	Extracellular matrix components, IL-6, IL-8, IL-13, and VEGF	PD-L1 (71.4%-80%), PD-1 barely detectable	CD28	None
ALK^- ALCL	Fibroblasts, T_{reg} cells, TAMs, eosinophils, mast cells	Extracellular matrix components, IL-6, IL-8, IL-13, and VEGF	PD-1 (13.3%), PD-L1 (38.5%-80%)	CD28	None

Note: TAM, tumor-associated macrophage; Treg, regulatory T-cell; VEGF, vascular endothelial growth factor; EBV, Epstein-Barr virus; HHV6B, Human herpesvirus 6B.

nucleotides, and lipids for tumor cell survival and proliferation.[264] Furthermore, altered choline metabolism in PTCLs activates RAS signaling, AKT, ERK phosphorylation, and MYC oncoprotein expression.[265]

Metabolites also intersect with the chromatin remodeling. 2-HG-accumulating tumors resulting from *IDH2 R172* mutation share the characteristic of chromatin hypermethylation and impaired differentiation, while the chromatin modifications and genetic loci involved differ according to lineage.[228] *TET2* loss-of-function mutations are involved in PTCLs, where they often coexist with *IDH2* mutations, especially in the angioimmunoblastic type of TFH lymphoma, suggesting crosstalk between metabolism and epigenetic regulation in the pathogenic mechanism.[266] The *IDH2* mutation alters the metabolism of α-KG, a key intermediate of the TCA cycle and the malate-aspartate shuttle, which are essential for oxidative phosphorylation and glutamine utilization.[236]

Metabolic networks are attractive targets for pathogenesis, but their effective inhibition faces challenges. A significant obstacle is toxicity, as tumor and normal cells share these networks, complicating selective targeting. Metabolic viability is another challenge, as cells employ redundant mechanisms to maintain essential metabolic processes, enabling them to bypass pathway inhibition over time. To date, the most significant success in hematology metabolism is the inhibition of mutated *IDH*.[267] Small molecules designed to inhibit IDH2 mutants reduce the production of 2-HG specifically and have demonstrated efficacy in AML, although relapse can occur.[268] Some tumor cells in other hematology malignancies harbor inherent liabilities. In NK/T-cell lymphoma, metabolomic profiling revealed that lymphoma cells often possess impaired asparagine synthetase activity, leading to elevated levels of alanine, aspartic acid, glutamine, and succinic acid in the serum.[269,270] A parallel observation exists in acute lymphoblastic leukemia cells, which exhibit a substantial demand for asparagine but possess limited capacity for de novo asparagine synthesis.[271] Consequently, treatment with asparaginase has proven to be efficacious in combating these tumors.[272] These achievements may guide PTCL treatment, and the more specific metabolic characteristics may facilitate the discovery of new therapeutic targets, besides *IDH2* mutations.

As a measure of heightened glucose metabolism, [18F]2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) / computed tomography (CT) is now recommended for PTCL staging, as most PTCL cases exhibit high FDG uptake.[273] Recent investigations have explored the potential of quantitative parameters derived from baseline FDG-PET/CT, such as metabolic tumor volume, for predicting prognosis during interim and post-treatment phases in PTCLs.[274,275] AI methods, especially deep learning techniques, can also enhance the analysis of PET-CT data by extracting rich and robust features and combining them with other modalities, such as histology and genomics, to provide more accurate and personalized predictions with less cost and invasiveness.

EXTRINSIC PATHOGENIC MECHANISMS AND TARGETED THERAPIES

Microenvironmental signatures of different entities and specific therapeutics

The lymphoma microenvironment (LME) of PTCLs is a complex network of cellular and molecular interactions that influences tumor growth, survival, and treatment response. The LME comprises various components, such as stromal cells, immune cells, cytokines, chemokines, extracellular matrix (ECM), and blood vessels (Table 3). It modulates the phenotype and function of PTCL cells through direct cell-cell contact or paracrine stimuli. Moreover, the LME also affects the immunogenicity and immunosuppression of tumor cells, creating a favorable niche for tumor evasion and progression. Despite its critical role in pathogenesis, the LME of PTCLs has not been researched so rigorously compared with other lymphomas.[276]

The characteristic T-cell identities of PTCL entities enable them to selectively release cytokines and chemicals, thereby recruiting functionally diverse LME cells. TFH lymphoma, which has a distinct cell origin and associated LME features, is the most extensively studied entity.[277] The malignant T_{FH} cells in TFH lymphoma exhibit co-stimulatory markers like ICOS, as well as expression of multiple immune checkpoint molecules, such as PD-1, TIGIT, and CD27.[278] Accordingly, the survival and proliferation of these malignant T_{FH} cells are highly dependent on their collaboration with GCB cells.[279] Intriguingly, *TET2*-mutated GCB cells were discovered in the LME, which undergo independent clonal evolution and support the growth of T_{FH}-like tumor cells via the CD40-CD40LG axis in ACH-related TFH lymphoma, angioimmunoblastic type.[96] These genetically aberrant B-cells exhibit a global shift in phenotypes, marked by a decreased expression of CD73 and CXCR5, which are critical molecules for B-cell homing and germinal center formation.[278] It was speculated that the altered B-cell phenotypes in the angioimmunoblastic type of TFH lymphoma may contribute to the disruption of follicular dendritic cell networks and the production of autoantibodies. *IDH2* mutation in these neoplastic T_{FH} cells results in modified intercommunication with GCB cells.[266] This alteration promotes clonal expansion of B-cells while diminishing the Fas-FasL interaction and reducing B-cell apoptosis.[266] The plasma cell count and angiogenesis are also elevated in the *IDH2*-mutated TFH lymphoma. Additionally, the angioimmunoblastic type of TFH lymphoma features the expansion of a unique $CD8^+$ T-cell subset with an exhausted phenotype ($PD\text{-}1^+$, $TIGIT^+$).[280] Their GEP suggests impaired cytotoxicity and increased expression of specific chemokines, such as XCL2 and XCL1. Depending on their differentiation state and interaction with other cell types, these expanded CD8+ T-cells may serve a dual role, potentially promoting tumor growth and suppressing anti-tumor immunity.[278]

A GEP study of PTCL-NOS revealed three LME cell signatures representing B-cells, DC cells, and macrophages, respectively.[281] B-cell and DC cell signatures were related to favorable prognosis, whereas macrophage signature exhibited a poor outlook. A clinical study (jRCT2071210101) is ongoing to determine if these LME cell traits can predict responders to immune checkpoint inhibitors (ICIs). Macrophages can have different phenotypes and functions depending on the signals they receive from the LME. M1 macrophages have pro-inflammatory and tumoricidal properties, while M2 macrophages have anti-inflammatory and tumor-promoting properties.[282] Some PTCL entities, such as the angioimmunoblastic type of TFH lymphoma and PTCL-GATA3, secrete T_H2 cytokines (e.g., IL-4 and IL-13) and IL-10 that induce M2 macrophage differentiation.[112] *Vav1::Myo1f* fusion promotes a PTCL-GATA3 phenotype, thereby inducing a therapeutically targetable M2 macrophage-enriched microenvironment.[283] M2 macrophages support PTCL growth by producing growth factors, angiogenic factors, or immunosuppressive factors,

leading to poor clinical outcomes.[284-286] Suppressive T_{reg} cells are recruited by PTCL-NOS and ALCL, which protect PTCL cells from immune surveillance and enhance their survival.[287] While tumor-killing T_{reg} cells are found in NK/T-cell lymphoma, incompetent T_{reg} cells contributing to the development of autoimmune clones are associated with the angioimmunoblastic type of TFH lymphoma. Meanwhile, tumor and endothelial cells produce vascular endothelial growth factors, also linked to lymphoma progression.[288]

The expression of immune checkpoints, such as PD-1 and PD-L1, inhibit the anti-tumor immune response by binding to their ligands on effector T-cells or macrophages (Figure 4).[289] In recent years, there has been active research into immune checkpoints in PTCLs and related agents.[290] PD-1 and PD-L1 expression is detectable in both tumor and immune cells within the LME, with varying expression profiles in different entities (Table 3).[291-295] Blocking the PD-1/PDL-1 axis with monoclonal antibodies has shown promising results in some PTCL subtypes (Table 2).[296-298] PD-1/PD-L1 inhibitors in combination with chemotherapy or targeted therapy, have demonstrated significant clinical efficacy. Research on other immune checkpoints, including CTLA-4, TIM-3, LAG-3, and TIGIT, holds promise for identifying novel targets in immunotherapy.

The LME of PTCLs is a dynamic and heterogeneous system that shapes the biology and behavior of neoplastic cells. Current therapies targeting the LME focused on different ICIs (Figure 4). Although B-cells play a crucial role in the pathogenesis of T_{FH}-derived PTCLs, anti-CD20 monoclonal antibody rituximab was found ineffective in treating the angioimmunoblastic type of TFH lymphoma.[299] A deeper understanding of molecular mechanisms may yield new insights into therapeutic possibilities within the LME. Challenges in this field stem from the lack of pre-clinical or translational models for PTCL, including patient-derived xenografts (PDXs) and organoids. Compared to transgenic animals, these models better replicate the LME conditions within the patient's body, thereby facilitating disease research. In addition, single-cell transcriptomics and proteomics studies are more promising for dissecting the PTCL microenvironment than bulk sequencing methods, due to the significant overlap in phenotype between tumor and normal T-cells. Therefore, exploring these avenues should be a focal point for future research.

Pathogen-related oncogenesis and specific therapies

EBV can infect up to 90% of the human population and persist in the host for life without any clinical manifestation.[300] The extended latency and sporadic reactivation of EBV leads to malignant transformation, giving rise to various lymphoproliferative diseases, encompassing the angioimmunoblastic type of TFH lymphoma and primary EBV-positive peripheral T-cell lymphoma (PTCL-EBV) (Table 3).[301,302] PTCL-EBV represents a variant of PTCL-NOS with poor prognosis, which shows a $CD8^+/CD56^-$ cytotoxic T-cell phenotype.[303,304] Most TFH lymphoma, angioimmunoblastic type and PTCL-EBV display a latency II pattern, expressing *EBNA1*, *LMP1* and *LMP2*.[305] However, the precise pathogenic mechanisms responsible for these diseases and how EBV-positive cells evade immune surveillance remain incompletely understood. Notably, both tumoral T-cells and LME cells can be infected, implying distinct pathogenic mechanisms. Recurrent mutations are detected in chronic active EBV infection, and the sequential accumulation of genetic and/or viral abnormalities may underlie the neoplastic proliferation of EBV-infected cells. Additionally, oligoclonal or polyclonal EBV-infected B-cells are observed in some PTCL entities,[306,307] especially the angioimmunoblastic type of TFH lymphoma (80-90%).[308] It is speculated that EBV within neighboring cells contributes to PTCL pathogenesis through chronic antigen stimulation and/or cytokine production.

PTCL-EBV features lower genomic instability compared to NK/T-cell lymphoma and other EBV-negative PTCL-NOS, with frequent mutations focusing on *TET2*, *PIK3CD*, and *STAT3*.[309] Both angioimmunoblastic form of TFH lymphoma and PTCL-EBV exhibit upregulation of immune-related pathways in tumor and non-tumor cells, particularly NF-κB and its downstream genes, such as *BIRC3*, *NFKB1*, and *CD27*.[213,309] Transcriptomic studies also revealed an elevated expression of Bam-HI A rightward transcripts (BARTs) in the angioimmunoblastic type of TFH lymphoma, which are complex non-coding RNAs that may regulate viral and cellular gene expression and contribute to tumor development.[310] BARTs are implicated in the immune escape of EBV-associated tumors, such as nasopharyngeal carcinoma and gastric carcinoma,[311-313] by suppressing FOXP1 and PBRM1 and enhancing PD-L1 transcription in antigen-presenting cells.[314] PD-L1 overexpression is also observed in the angioimmunoblastic type of TFH lymphoma and PTCL-EBV, which may result from BARTs and immune-related pathways (e.g., IFNγ, IL6-JAK-STAT3, and NF-κB)[304,315].

Human T-lymphotropic virus type 1 (HTLV-1) is a retrovirus that infects mainly $CD4^+$ T-cells and persists as a provirus in the host genome.[316] HTLV-1 can cause the fatal malignancy ATLL in about 5% of infected individuals, which is characterized by the clonal expansion of leukemic T-cells.[317] HTLV-1 oncogenesis is mediated by the expression of two viral genes, Tax and HBZ, which have opposite effects on viral replication and host immune response.[318] Tax activates viral transcription and several cellular pathways that promote T-cell proliferation and survival, but also triggers immune clearance by cytotoxic T-cells. HBZ represses viral transcription, antagonizes Tax-mediated activation of NF-κB and other pathways, and enhances the survival and infectivity of HTLV-1 infected cells. HBZ expression is more persistent and less immunogenic than Tax, and its mRNA has a dual function as a protein-coding and a long non-coding RNA.[319] HTLV-1 integration into transcriptionally active regions of the host genome may also contribute to oncogenesis by disrupting the expression of cancer driver genes or affecting the chromatin structure.[320-322]

Based on the knowledge gained from other EBV-associated tumors, targeting viral factors may offer therapeutic opportunities for PTCLs. Specific antivirals or vaccines against EBV or HTLV-1 could be incorporated into PTCL treatment. Cell-based immunotherapies, such as EBV-specific CTL, have shown efficacy in treating post-transplantation lymphoproliferative disorder and other EBV-associated lymphomas,[300] which could potentially be extended to EBV-positive PTCLs. Moreover, novel antiviral agents, such as tenofovir alafenamide, may inhibit EBV DNA polymerase and reduce viral loads.[323]

Biomarkers-driven precise diagnosis and treatment

Biomarkers are measurable indicators of biological processes or states that can inform clinical decision-making and enable personalized cancer care in PTCLs (Table 4). For instance, CD30 expression can predict the response to BV, and epigenetic modifiers can target epigenetic defects. However, biomarkers are only sometimes reliable, as the detection is based on single data modalities, such as genomics, histology, or radiology, which may not capture the full complexity and heterogeneity of tumors. Moreover, most current PTCL biomarkers require invasive procedures, such as lymph nodes or bone marrow biopsies, which may not be feasible or accessible for all patients. Hence, novel and highly specific biomarkers integrating multiple data modalities are needed.

AI can leverage diverse and complementary information from clinical, radiological, histological, and laboratory data to provide more accurate and reliable predictions of clinical outcomes (Figure 6).[324,325] It can also identify novel patterns and associations within and across modalities that can reveal new biological insights and potential biomarkers. For example, AI models can discover correlations between genomic mutations and tissue morphology; or between radiomic features and histological subtypes.[326] These associations can serve as non-invasive or surrogate biomarkers that facilitate early diagnosis, risk stratification, treatment selection, and monitoring. When provided with clinical data, AI can identify biomarkers that indicate treatment resistance or toxicity, enabling timely adjustments or preventive measures. Hence, AI serves as a vital aid in future biomarker detection of PTCLs.

UNANSWERED QUESTIONS AND FUTURE DIRECTIONS

1. Pre-clinical models for pathogenic mechanism study. Pre-clinical models of PTCLs are essential for understanding the molecular mechanisms and testing novel therapeutic strategies. However, PTCLs are a heterogeneous group of non-Hodgkin's lymphomas with complex molecular features and strong dependence on LME interactions, which hinder the development of representative models for effective therapy evaluation. Currently, only a few PTCL cell lines are available, mainly representing ALCL and ATLL subtypes. However, these cell lines do not fully capture the molecular intricacies and LME interactions observed in primary PTCLs. Several genetically engineered murine models that mimic specific genetic alterations and immune dysregulation of human PTCLs have also been developed, mainly

Table 4. Biomarkers with potential relevance to the most frequent PTCL entities

Lymphoma type	Biomarker	Test	Purpose	Comment
PTCLs	TCR gene rearrangements	PCR	Diagnosis	Characteristic event in T-cell lymphomas
	EBER	IHC	Diagnosis and treatment	Diagnosis for TFH lymphoma and potentially targetable
	CD30 expression	IHC	Diagnosis and treatment	Diagnosis for ALCL; Predict response to anti-CD30 therapy
	CCR4 expression	IHC	Treatment	Predict response to anti-CCR4 therapy
TFH lymphoma	*RHOA*^{G17V} mutations	NGS	Diagnosis	Characteristic event in TFH lymphoma
	TET2 mutations	NGS	Diagnosis and treatment	Characteristic event in TFH lymphoma; Predict response to HMA and HDACi
	DNMT3A mutations	NGS	Diagnosis and treatment	Characteristic event in TFH lymphoma; Predict response to HMA and HDACi
	IDH2^{R172} mutations	NGS and IHC	Diagnosis and treatment	Characteristic event in TFH lymphoma; Predict response to HMA and HDACi
PTCL-TBX21	TBX21/CXCR3 expression	IHC	Diagnosis and prognosis	Biological and prognostic subgroup of PTCL-NOS with a more favorable outcome
PTCL-GATA3	GATA3/CCR4 expression	IHC	Diagnosis and prognosis	Biological and prognostic subgroup of PTCL-NOS with a more adverse outcome
PTCL-NOS	*DNMT3A* mutations	NGS	Diagnosis and prognosis	Biological and prognostic subgroup of PTCL-NOS associated with cytotoxic T-cells
	CDKN2A deletion	FISH	Prognosis	Deletion of *CDKN2A* and *PTEN* highly specific for PTCL-NOS
	PTEN deletion	FISH	Prognosis	Deletion of *CDKN2A* and *PTEN* highly specific for PTCL-NOS
	TP53 deletions and mutations	FISH and NGS	Prognosis	Enriched in PTCL-GATA3 cases; Adverse prognosis.
ALK$^+$ ALCL	ALK expression	IHC	Diagnosis	Differential diagnosis of ALK$^+$ ALCL from ALK$^-$ ALCL
	ALK rearrangement	IHC	Diagnosis	Differential diagnosis of ALK$^+$ ALCL from ALK$^-$ ALCL
	NOTCH1 mutation	NGS	Treatment	Predict response to Notch-targeted therapy
ALK$^-$ ALCL	*DUSP22* rearrangement	FISH	Prognosis	Favorable prognosis in sALCL
	TP63 rearrangement	FISH	Prognosis	Aggressive behavior in sALCL
	JAK1 and *STAT3* mutations	NGS	Diagnosis and treatment	Characteristic event in ALK$^-$ ALCL and potentially targetable

Note: PCR, polymerase chain reaction; IHC, immunohistochemistry; NGS, next-generation sequencing; FISH, fluorescence in situ hybridization; HMA, hypomethylating agent; HDACi, histone deacetylase inhibitor; sALCL, systemic anaplastic large cell lymphoma.

focusing on *TET2* loss[327,328], *RHOA G17V*[188,189], *DNMT3A*[329], and *IDH2 R172* mutations[266], as well as MYC[330] and GAPDH[213] overexpression. Although these models mimic some phenotypes of human PTCLs, they do not reflect the variable human disease landscape and only provide materials for studying mechanisms related to these molecular events. Moreover, these transgenic models have limitations regarding availability, cost, and time consumption. PDXs can preserve the genetic and phenotypic diversity of human PTCLs and can be used to evaluate various treatments in a personalized manner.[331,332] Possible obstacles include low engraftment rate, loss of tumor heterogeneity, immune deficiency, and ethical concerns.

Future endeavors should focus on optimizing methods to establish PDXs and enhance the engraftment rate. For example, humanized mice may be advantageous for simulating LME, and introducing different humanized cytokines may promote the growth of certain PTCL entities.[333] Other potential pre-clinical models include organoids. While conventional organoids are predominantly employed for studying tumors derived from endothelial and epithelial sources, *Khan* et al. recently established bone marrow organoids generated from induced pluripotent stem cells committed to mesenchymal, endothelial, and hematopoietic lineages.[334] These bone marrow organoids provide a conducive environment for the engraftment, viability, and expansion of primary cells from various hematologic malignancies. Thus, it may provide an alternative for culturing PTCL primary cells in three-dimensional structures.

2. Understanding clonal evolution and targeting implications. Clonal evolution remains one of the major cancer hallmarks that is not yet therapeutically actionable. This process witnesses a population of cells acquiring genetic changes over time, leading to the emergence of new subclones with different phenotypes and behaviors.[335] Clonal outgrowth in response to therapeutic pressure stands as the primary driver of relapse or therapy resistance, thus presenting a significant therapeutic hurdle. In the realm of precise medicine, this concept holds importance because the actionable targets identified by molecular diagnosis (e.g., immunohistochemistry, FISH, and bulk NGS) often pertain to sub-clonal events found within a limited fraction of tumor cells. To study clonal evolution, paired single-cell sequencing offers a finer-grained insight into clonality dynamics before and after treatments, surpassing the capabilities of bulk NGS.[336] Additionally, it can unveil the evolutionary trajectory reshaped by selective pressures, which is a critical factor in predicting an individual's response to targeted therapies. Liquid biopsies, by enabling genetic sequencing of DNA shed from multiple lymphoma sites, also prove valuable in reflecting clonal evolution.[337]

Underlying this concept is the notion that the effectiveness of precise treatment hinges largely on the ability to simultaneously target as many subclones as possible while avoiding treatment-related side effects. Given that different subclones might bear both overlapping and distinct molecular alterations, the convergent pathways should be highlighted. Lineage tracing may help elucidate when alterations occur throughout the lineage. Targeting early events with key pathogenic functions can maximize the disruption of malignant subclones.

3. Pinpointing the moment of transformation. A plethora of PTCL genomes and transcriptomes are under extensive investigation, and the advent of NGS in molecular diagnosis has yielded accumulating data about pathogenic mutations. Interestingly, whereas *TET2* mutations are hallmarks of hematological malignancies, they were also frequently found in the bone marrow of healthy individuals with negligible risk of tumor transformation.[338,339] *TET2* loss in CD34$^+$ or CD4$^+$ cells is insufficient to induce PTCL tumorigenesis in murine models,[327,328] but co-occurring mutations in *RHOA* or *IDH2* can accelerate this process.[188,189,266] The preceding observations imply a multi-step pathogenesis within PTCLs. However, high-throughput sequencing often reveals multiple pathogenic-related mutations in the same patient.[340] These co-occurring hits involve various signaling pathways,

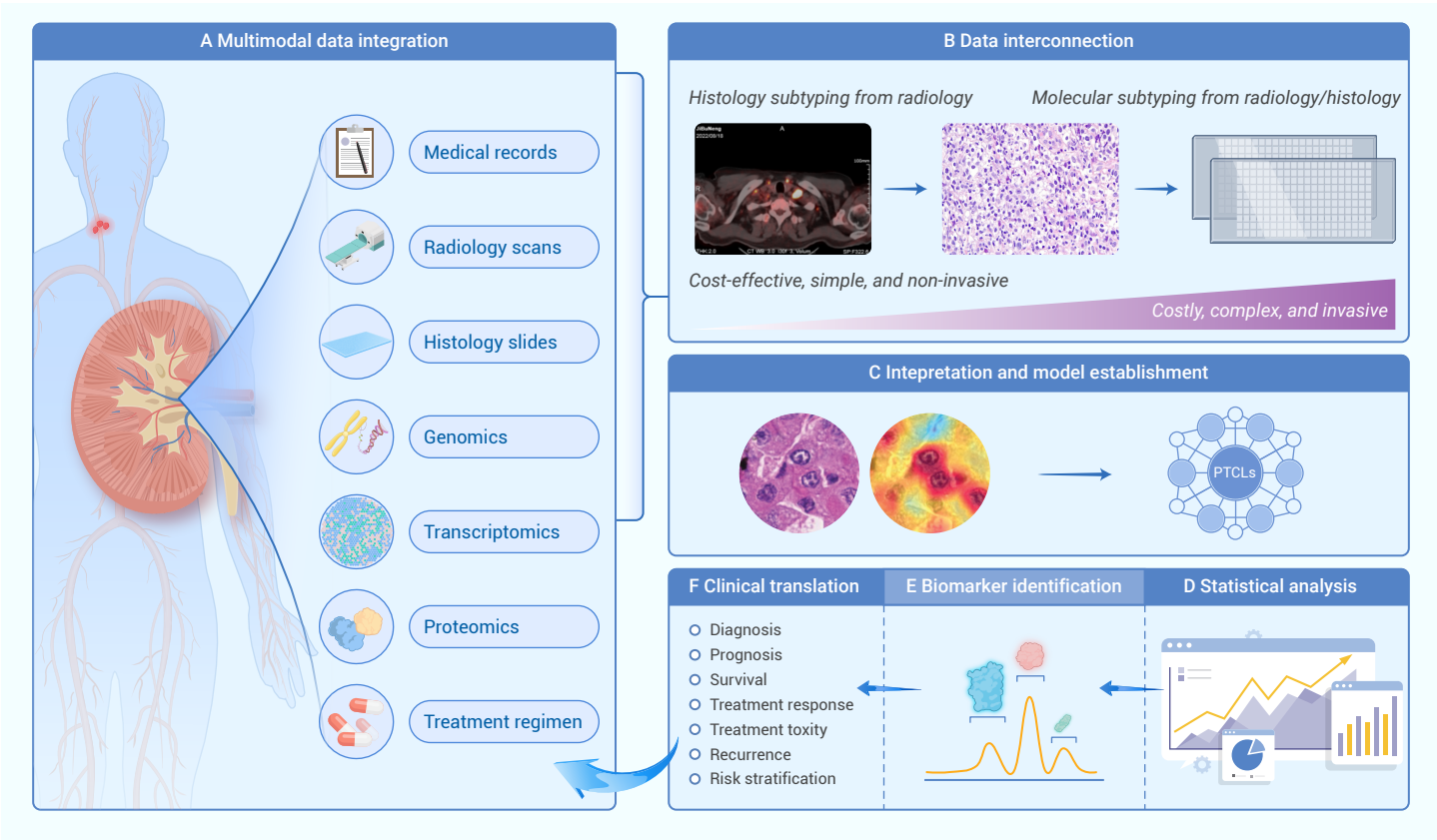


Figure 6. AI-aided biomarker identification from multimodal data (A) Integration of multimodal data and clinical context collected from PTCL patients. (B) Detection of associations across multiple modalities. Such associations identify non-invasive or cost-effective alternative biomarkers to support large-scale patient screening.[325] (C) Elucidation of AI models using interpretability methods. (D-F) Statistical analysis accelerates the discovery of novel biomarkers and translation into clinical practice.

each displaying the potential to induce full transformation. This raises a question as to which molecular events are necessary for malignant transformation, if not solely deleterious mutation. Importantly, answering this question can help better determine the selection of genomic aberrations when assessing targets for therapy.

4. Neoplastic T-cell interactions with LME cells. Compared to other lymphomas, PTCLs feature highly heterogeneous LME constitutions, varying extensively in both cellular and non-cellular components. The microenvironment in solid tumors mainly functions by maintaining immunosuppression and creating physical barriers to hinder drug delivery. Previous studies have unraveled similar mechanisms in PTCL LME, involving T_{reg} cells, CTLs, and TAMs. However, due to the unique nature of neoplastic T-cells, the LME immune cells may directly participate in PTCL pathogenesis. For instance, EBV-positive B-cells can promote T-cell transformation via chronic antigen stimulation. Further, *TET2*-deficient B-cells play a supportive role in *TET2*-mutated TFH lymphoma, angioimmunoblastic type, indicating that PTCL development could initiate from clonal hematopoiesis in HSCs.[96] During this process, abnormal stem cells may differentiate into other cell types. These pre-malignant immune cells reside in the LME and assist T-cell survival and transformation. Hence, regulating the interactions between T-cells and LME cells in PTCL may not only modulate immune functions but also directly inhibit PTCL pathogenesis. Of note, single-cell sequencing methods could distinguish tumor and normal T-cells, thus more suitable for studying lymphoma.

5. Pathogenic role of EBV and insights from other EBV-associated oncogenesis. EBV, the most potent and widely prevalent human pathogen, can easily transform human B-cells into continuously growing lymphoblastoid cell lines in laboratory cultures. However, despite its strong tumorigenic capabilities, over 95% of the adult population with persistent EBV infections never develop EBV-related tumors.[314] The current model suggests that the immune system can control the virus and prevent excessive proliferation and transformation of infected cells. Only under certain conditions, such as immune suppression, genetic mutations, or co-infection with other pathogens, can EBV escape from immune control and cause tumors.[314] In agreement with this model, abnormalities of *IFIH1* and/or *DDX3X* genes in EBV-associated NK/T-cell lymphoma led to elevated levels of EBV in plasma and NK cells, resulting in an unfavorable prognosis.[341] Moreover, EBV-positive diffuse large B-cell lymphoma are less prone to *MYD88* and *CD79B* gene mutations than EBV-negative diffuse large B-cell lymphoma.[342] Gastric cancer features extensive tumor genome methylation, and EBV-positive gastric cancer is particularly notable for its markedly elevated methylation known as the CpG island methylator phenotype.[343] These clues from other tumors suggest that the pathogenic role of EBV in PTCLs may also associate with specific genetic alterations or epigenetic traits, such as the recurrent *TET2*/*DNMT3A* mutations and DNA modifications in TFH lymphoma and PTCL-NOS. Future research should focus on the association between EBV infection and host intrinsic characteristics.

6. Discrepancy between pathogenic mechanisms and clinical results. Despite the promising biological rationale for targeting PTCLs with novel agents discussed above, the clinical results have been disappointing so far. The response rates and survival outcomes of these treatments are generally low and variable across different PTCL subtypes and settings (Table 2). Several factors may contribute to the poor efficacy of these treatments, such as tumor heterogeneity, immune evasion, and resistance mechanisms. For example, PTCLs express different levels of surface antigens that affect the binding of antibody drugs or CAR-T cells.[119] PTCLs also modulate their epigenetic landscape or signaling pathways to escape from the effects of HDACi or HMAs.[12] Moreover, PTCL tumor cells interact with their microenvironment to create an immunosuppressive niche that protects them from immune-mediated killing.[96,278] Therefore, there is a need to identify biomarkers that can predict the response and resistance to these treatments and develop rational combination strategies to overcome these challenges.

CONCLUDING REMARKS

The field of PTCLs has witnessed a plethora of multi-omics analyses over the past decade, which have provided researchers and clinicians with a more

profound comprehension of the molecular characteristics inherent to this ailment. Nevertheless, translating these molecular features into precision medicine has encountered impediments, primarily stemming from the insufficient elucidation of the pathogenic mechanisms. In addition to genomic studies, further investigations into transcriptional traits, epigenetic modulation, metabolic processes, lymphoma microenvironment, and virus-mediated tumorigenesis may yield innovative strategies for targeting both intrinsic and extrinsic pathogenic factors. Concurrently, emerging bioengineering approaches hold promise in bridging the gap between basic research and clinical application. Given the relative rarity of PTCLs, the imperative lies in the establishment of multi-center, large-scale clinical trials, which will provide significant support for future mechanism-driven therapeutics. These efforts require new partnerships and a collaborative approach from both academia and industry.

REFERENCES

1. Ma, H., Marchi, E., and O'Connor, O.A. (2020). The peripheral T-cell lymphomas: an unusual path to cure. Lancet Haematol **7**: e765–e771. DOI: 10.1016/S2352-3026(20)30207-6.
2. Marchi, E., and O'Connor, O.A. (2020). The rapidly changing landscape in mature T-cell lymphoma (MTCL) biology and management. CA Cancer J Clin **70**: 47–70. DOI: 10.3322/caac.21589.
3. Fiore, D., Cappelli, L.V., Broccoli, A., et al. (2020). Peripheral T cell lymphomas: from the bench to the clinic. Nat. Rev. Cancer **20**: 323–342. DOI: 10.1038/s41568-020-0247-0.
4. Zhang, Y., Xu, W., Liu, H., and Li, J. (2016). Therapeutic options in peripheral T cell lymphoma. J Hematol Oncol **9**: 37. DOI: 10.1186/s13045-016-0267-0.
5. Moffitt, A.B., and Dave, S.S. (2017). Clinical Applications of the Genomic Landscape of Aggressive Non-Hodgkin Lymphoma. J Clin Oncol **35**: 955–962. DOI: 10.1200/JCO.2016.71.7603.
6. Miao, Y., Medeiros, L.J., Li, Y., et al. (2019). Genetic alterations and their clinical implications in DLBCL. Nat Rev Clin Oncol **16**: 634–652. DOI: 10.1038/s41571-019-0225-1.
7. Alaggio, R., Amador, C., Anagnostopoulos, I., et al. (2022). The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia **36**: 1720–1748. DOI: 10.1038/s41375-022-01620-2.
8. Lopez-Guillermo, A., Cid, J., Salar, A., et al. (1998). Peripheral T-cell lymphomas: initial features, natural history, and prognostic factors in a series of 174 patients diagnosed according to the R. E.A.L. Classification. Ann. Oncol. **9**: 849–855. DOI: 10.1023/a:1008418727472.
9. Armitage, J.O. (2017). The aggressive peripheral T-cell lymphomas: 2017. Am J Hematol **92**: 706–715. DOI: 10.1002/ajh.24791.
10. Mulvey, E., and Ruan, J. (2020). Biomarker-driven management strategies for peripheral T cell lymphoma. J Hematol Oncol **13**: 59. DOI: 10.1186/s13045-020-00889-z.
11. Yap, D.R.Y., Lim, J.Q., Huang, D., et al. (2023). Emerging predictive biomarkers for novel therapeutics in peripheral T-cell and natural killer/T-cell lymphoma\. Front Immunol **14**: 1068662. DOI: 10.3389/fimmu.2023.1068662.
12. Izykowska, K., Rassek, K., Korsak, D., and Przybylski, G.K. (2020). Novel targeted therapies of T cell lymphomas. J Hematol Oncol **13**: 176. DOI: 10.1186/s13045-020-01006-w.
13. Pizzi, M., Margolskee, E., and Inghirami, G. (2018). Pathogenesis of Peripheral T Cell Lymphoma. Annu Rev Pathol **13**: 293–320. DOI: 10.1146/annurev-pathol-020117-043821.
14. Xie, C., Li, X., Zeng, H., and Qian, W. (2020). Molecular insights into pathogenesis and targeted therapy of peripheral T cell lymphoma. Exp Hematol Oncol **9**: 30. DOI: 10.1186/s40164-020-00188-w.
15. Palomero, T., Couronné, L., Khiabanian, H., et al. (2014). Recurrent mutations in epigenetic regulators, RHOA and FYN kinase in peripheral T cell lymphomas. Nat. Genet. **46**: 166–170. DOI: 10.1038/ng.2873.
16. Dupuis, J., Emile, J.F., Mounier, N., et al. (2006). Prognostic significance of Epstein-Barr virus in nodal peripheral T-cell lymphoma, unspecified: A Groupe d'Etude des Lymphomes de l'Adulte (GELA) study. Blood **108**: 4163–4169. DOI: 10.1182/blood-2006-04-017632.
17. Foss, F. (2011). Hematology: relapsed and refractory PTCL--into the therapeutic abyss. Nat Rev Clin Oncol **8**:321-322. DOI: 10.1038/nrclinonc.2011.51.
18. Horwitz, S., Coiffier, B., Foss, F., et al. (2015). Utility of (1)(8)fluoro-deoxyglucose positron emission tomography for prognosis and response assessments in a phase 2 study of romidepsin in patients with relapsed or refractory peripheral T-cell lymphoma. Ann. Oncol. **26**: 774–779. DOI: 10.1093/annonc/mdv010.
19. Prince, H.M., Kim, Y.H., Horwitz, S.M., et al. (2017). Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. Lancet **390**: 555–566. DOI: 10.1016/S0140-6736(17)31266-7.
20. Kim, Y.H., Bagot, M., Pinter-Brown, L., et al. (2018). Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. Lancet Oncol **19**: 1192–1204. DOI: 10.1016/S1470-2045(18)30379-6.
21. Shi, Y., Jia, B., Xu, W., et al. (2017). Chidamide in relapsed or refractory peripheral T cell lymphoma: a multicenter real-world study in China. J Hematol Oncol **10**: 69. DOI: 10.1186/s13045-017-0439-6.
22. Horwitz, S.M., Koch, R., Porcu, P., et al. (2018). Activity of the PI3K-delta,gamma inhibitor duvelisib in a phase 1 trial and preclinical models of T-cell lymphoma. Blood **131**: 888–898. DOI: 10.1182/blood-2017-08-802470.
23. Vanden Bempt, M., Debackere, K., Demeyer, S., et al. (2022). Aberrant MYCN expression drives oncogenic hijacking of EZH2 as a transcriptional activator in peripheral T-cell lymphoma. Blood **140**: 2463–2476. DOI: 10.1182/blood.2022016428.
24. Ruan, J., Zain, J., Palmer, B., et al. (2023). Multicenter phase 2 study of romidepsin plus lenalidomide for previously untreated peripheral T-cell lymphoma. Blood Adv. DOI: 10.1182/bloodadvances.2023009767.
25. Mondal, D., Shinde, S., Paul, S., et al. (2023). Diagnostic significance of dysregulated miRNAs in T-cell malignancies and their metabolic roles. Front Oncol **13**: 1230273. DOI: 10.3389/fonc.2023.1230273.
26. Ahearne, M.J., Allchin, R.L., Fox, C.P., and Wagner, S.D. (2014). Follicular helper T-cells: expanding roles in T-cell lymphoma and targets for treatment. Br. J. Haematol. **166**: 326–335. DOI: 10.1111/bjh.12941.
27. Saito, T., Matsuno, Y., Tanosaki, R., et al. (2002). Gamma delta T-cell neoplasms: a clinicopathological study of 11 cases. Ann. Oncol. **13**: 1792–1798. DOI: 10.1093/annonc/mdf293.
28. Lunning, M.A., and Vose, J.M. (2017). Angioimmunoblastic T-cell lymphoma: the many-faced lymphoma. Blood **129**: 1095–1102. DOI: 10.1182/blood-2016-09-692541.
29. Frizzera, G., Moran, E.M., and Rappaport, H. (1975). Angio-immunoblastic lymphadenopathy. Diagnosis and clinical course. Am. J. Med. **59**: 803–818. DOI: 10.1016/0002-9343(75)90466-0.
30. Federico, M., Rudiger, T., Bellei, M., et al. (2013). Clinicopathologic characteristics of angioimmunoblastic T-cell lymphoma: analysis of the international peripheral T-cell lymphoma project. J Clin Oncol **31**: 240–246. DOI: 10.1200/JCO.2011.37.3647.
31. Vose, J., Armitage, J., Weisenburger, D., and International, T.C.L.P. (2008). International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol **26**: 4124–4130. DOI: 10.1200/JCO.2008.16.4558.
32. Vinuesa, C.G., Tangye, S.G., Moser, B., and Mackay, C.R. (2005). Follicular B helper T cells in antibody responses and autoimmunity. Nat. Rev. Immunol. **5**: 853–865. DOI: 10.1038/nri1714.
33. de Leval, L., Rickman, D.S., Thielen, C., et al. (2007). The gene expression profile of nodal peripheral T-cell lymphoma demonstrates a molecular link between angioimmunoblastic T-cell lymphoma (AITL) and follicular helper T (TFH) cells. Blood **109**: 4952–4963. DOI: 10.1182/blood-2006-10-055145.
34. Willenbrock, K., Brauninger, A., and Hansmann, M.L. (2007). Frequent occurrence of B-cell lymphomas in angioimmunoblastic T-cell lymphoma and proliferation of Epstein-Barr virus-infected cells in early cases. Br. J. Haematol. **138**: 733–739. DOI: 10.1111/j.1365-2141.2007.06725.x.
35. Dobay, M.P., Lemonnier, F., Missiaglia, E., et al. (2017). Integrative clinicopathological and molecular analyses of angioimmunoblastic T-cell lymphoma and other nodal lymphomas of follicular helper T-cell origin. Haematologica **102**: e148–e151. DOI: 10.3324/haematol.2016.158428.
36. Satou, A., Takahara, T., and Tsuzuki, T. (2022). Pathological and Molecular Features of Nodal Peripheral T-Cell Lymphomas. Diagnostics (Basel) **12**. DOI: 10.3390/diagnostics12082001.
37. Kutok, J.L., and Aster, J.C. (2002). Molecular biology of anaplastic lymphoma kinase-positive anaplastic large-cell lymphoma. J Clin Oncol **20**: 3691–3702. DOI: 10.1200/JCO.2002.12.033.
38. Stein, H., Foss, H.D., Durkop, H., et al. (2000). CD30(+) anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features. Blood **96**: 3681–3695. DOI: 10.1182/blood.V96.12.3681.
39. Mora, J., Filippa, D.A., Thaler, H.T., et al. (2000). Large cell non-Hodgkin lymphoma of childhood. Cancer **88**: 186–197. DOI: 10.1002/(sici)1097-0142(20000101)88:1<186::Aid-cncr26>3.0.Co;2-5.
40. Savage, K.J., Harris, N.L., Vose, J.M., et al. (2008). ALK- anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. Blood **111**: 5496–5504. DOI: 10.1182/blood-2008-01-134270.
41. Falini, B., Pileri, S., Zinzani, P.L., et al. (1999). ALK+ lymphoma: clinico-pathological findings and outcome. Blood **93**: 2697–2706. DOI.
42. Chiarle, R., Voena, C., Ambrogio, C., et al. (2008). The anaplastic lymphoma kinase in the pathogenesis of cancer. Nat. Rev. Cancer **8**: 11–23. DOI: 10.1038/nrc2291.
43. Vasmatzis, G., Johnson, S.H., Knudson, R.A., et al. (2012). Genome-wide analysis reveals recurrent structural abnormalities of TP63 and other p53-related genes in peripheral T-cell lymphomas. Blood **120**: 2280–2289. DOI: 10.1182/blood-2012-03-419937.
44. Feldman, A.L., Dogan, A., Smith, D.I., et al. (2011). Discovery of recurrent t(6;7)(p25.3;q32.3) translocations in ALK-negative anaplastic large cell lymphomas by massively parallel genomic sequencing. Blood **117**:915-919. DOI: 10.1182/blood-2010-08-303305.

45. Parrilla Castellar, E.R., Jaffe, E.S., Said, J.W., et al. (2014). ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes. Blood **124**: 1473–1480. DOI: 10.1182/blood-2014-04-571091.
46. Weisenburger, D.D., Savage, K.J., Harris, N.L., et al. (2011). Peripheral T-cell lymphoma, not otherwise specified: a report of 340 cases from the International Peripheral T-cell Lymphoma Project. Blood **117**: 3402–3408. DOI: 10.1182/blood-2010-09-310342.
47. Iqbal, J., Weisenburger, D.D., Greiner, T.C., et al. (2010). Molecular signatures to improve diagnosis in peripheral T-cell lymphoma and prognostication in angioimmunoblastic T-cell lymphoma. Blood **115**: 1026–1036. DOI: 10.1182/blood-2009-06-227579.
48. Iqbal, J., Wright, G., Wang, C., et al. (2014). Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma. Blood **123**: 2915–2923. DOI: 10.1182/blood-2013-11-536359.
49. Amador, C., Greiner, T.C., Heavican, T.B., et al. (2019). Reproducing the molecular subclassification of peripheral T-cell lymphoma-NOS by immunohistochemistry. Blood **134**: 2159–2170. DOI: 10.1182/blood.2019000779.
50. Jassim, A., Rahrmann, E.P., Simons, B.D., and Gilbertson, R.J. (2023). Cancers make their own luck: theories of cancer origins. Nature Reviews Cancer. DOI: 10.1038/s41568-023-00602-5.
51. Watatani, Y., Sato, Y., Miyoshi, H., et al. (2019). Molecular heterogeneity in peripheral T-cell lymphoma, not otherwise specified revealed by comprehensive genetic profiling. Leukemia **33**: 2867–2883. DOI: 10.1038/s41375-019-0473-1.
52. da Silva Almeida, A.C., Abate, F., Khiabanian, H., et al. (2015). The mutational landscape of cutaneous T cell lymphoma and Sézary syndrome. Nat. Genet. **47**: 1465–1470. DOI: 10.1038/ng.3442.
53. Soverini, S., Martelli, M., and Bavaro, L. (2019). BCR-ABL1 mutation screening in chronic myeloid leukaemia: is next now. Lancet Haematol **6**: e236–e237. DOI: 10.1016/S2352-3026(19)30046-8.
54. Kaufman, C.K., Mosimann, C., Fan, Z.P., et al. (2016). A zebrafish melanoma model reveals emergence of neural crest identity during melanoma initiation. Science **351**: aad2197. DOI: 10.1126/science.aad2197.
55. Wahida, A., Buschhorn, L., Frohling, S., et al. (2023). The coming decade in precision oncology: six riddles. Nat. Rev. Cancer **23**: 43–54. DOI: 10.1038/s41568-022-00529-3.
56. Tomasetti, C., and Vogelstein, B. (2015). Cancer etiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. Science **347**: 78–81. DOI: 10.1126/science.1260825.
57. Abascal, F., Harvey, L.M.R., Mitchell, E., et al. (2021). Somatic mutation landscapes at single-molecule resolution. Nature **593**: 405–410. DOI: 10.1038/s41586-021-03477-4.
58. Zhu, L., Finkelstein, D., Gao, C., et al. (2016). Multi-organ Mapping of Cancer Risk. Cell **166**: 1132–1146.e1137. DOI: 10.1016/j.cell.2016.07.045.
59. Lehar, S.M., and Bevan, M.J. (2002). T cell development in culture. Immunity **17**: 689–692. DOI: 10.1016/s1074-7613(02)00477-6.
60. Na, I.K., Markley, J.C., Tsai, J.J., et al. (2010). Concurrent visualization of trafficking, expansion, and activation of T lymphocytes and T-cell precursors in vivo. Blood **116**: e18–25. DOI: 10.1182/blood-2009-12-259432.
61. Belver, L., and Ferrando, A. (2016). The genetics and mechanisms of T cell acute lymphoblastic leukaemia. Nat. Rev. Cancer **16**: 494–507. DOI: 10.1038/nrc.2016.63.
62. Coustan-Smith, E., Mullighan, C.G., Onciu, M., et al. (2009). Early T-cell precursor leukaemia: a subtype of very high-risk acute lymphoblastic leukaemia. Lancet Oncol **10**: 147–156. DOI: 10.1016/S1470-2045(08)70314-0.
63. Van Vlierberghe, P., Ambesi-Impiombato, A., Perez-Garcia, A., et al. (2011). ETV6 mutations in early immature human T cell leukemias. J. Exp. Med. **208**: 2571–2579. DOI: 10.1084/jem.20112239.
64. Hunger, S.P., and Mullighan, C.G. (2015). Acute Lymphoblastic Leukemia in Children. N Engl J Med **373**: 1541–1552. DOI: 10.1056/NEJMra1400972.
65. Litzow, M.R., and Ferrando, A.A. (2015). How I treat T-cell acute lymphoblastic leukemia in adults. Blood **126**: 833–841. DOI: 10.1182/blood-2014-10-551895.
66. Weng, A.P., Ferrando, A.A., Lee, W., et al. (2004). Activating mutations of NOTCH1 in human T cell acute lymphoblastic leukemia. Science **306**: 269–271. DOI: 10.1126/science.1102160.
67. Grabher, C., von Boehmer, H., and Look, A.T. (2006). Notch 1 activation in the molecular pathogenesis of T-cell acute lymphoblastic leukaemia. Nat. Rev. Cancer **6**: 347–359. DOI: 10.1038/nrc1880.
68. Li, Z., Song, Y., Zhang, M., et al. (2022). Genomic landscape of T-cell lymphoblastic lymphoma. Chin J Cancer Res **34**: 83–94. DOI: 10.21147/j.issn.1000-9604.2022.02.03.
69. O'Neil, J., Grim, J., Strack, P., et al. (2007). FBW7 mutations in leukemic cells mediate NOTCH pathway activation and resistance to gamma-secretase inhibitors. J. Exp. Med. **204**: 1813–1824. DOI: 10.1084/jem.20070876.
70. Thompson, B.J., Buonamici, S., Sulis, M.L., et al. (2007). The SCFFBW7 ubiquitin ligase complex as a tumor suppressor in T cell leukemia. J. Exp. Med. **204**: 1825–1835. DOI: 10.1084/jem.20070872.
71. Pear, W.S., Aster, J.C., Scott, M.L., et al. (1996). Exclusive development of T cell neoplasms in mice transplanted with bone marrow expressing activated Notch alleles. J. Exp. Med. **183**: 2283–2291. DOI: 10.1084/jem.183.5.2283.
72. Chiang, M.Y., Shestova, O., Xu, L., et al. (2013). Divergent effects of supraphysiologic Notch signals on leukemia stem cells and hematopoietic stem cells. Blood **121**: 905–917. DOI: 10.1182/blood-2012-03-416503.
73. Girardi, T., Vicente, C., Cools, J., and De Keersmaecker, K. (2017). The genetics and molecular biology of T-ALL. Blood **129**: 1113–1123. DOI: 10.1182/blood-2016-10-706465.
74. Koch, U., and Radtke, F. (2011). Notch in T-ALL: new players in a complex disease. Trends Immunol. **32**: 434–442. DOI: 10.1016/j.it.2011.06.005.
75. Ferrando, A.A. (2009). The role of NOTCH1 signaling in T-ALL. Hematology Am Soc Hematol Educ Program:353-361. DOI: 10.1182/asheducation-2009.1.353.
76. Lemonnier, F., Couronné, L., Parrens, M., et al. (2012). Recurrent TET2 mutations in peripheral T-cell lymphomas correlate with TFH-like features and adverse clinical parameters. Blood **120**: 1466–1469. DOI: 10.1182/blood-2012-02-408542.
77. Cairns, R.A., Iqbal, J., Lemonnier, F., et al. (2012). IDH2 mutations are frequent in angioimmunoblastic T-cell lymphoma. Blood **119**: 1901–1903. DOI: 10.1182/blood-2011-11-391748.
78. Couronné, L., Bastard, C., and Bernard, O.A. (2012). TET2 and DNMT3A mutations in human T-cell lymphoma. N Engl J Med **366**: 95–96. DOI: 10.1056/NEJMc1111708.
79. Ji, M.M., Huang, Y.H., Huang, J.Y., et al. (2018). Histone modifier gene mutations in peripheral T-cell lymphoma not otherwise specified. Haematologica **103**: 679–687. DOI: 10.3324/haematol.2017.182444.
80. Jaiswal, S., Fontanillas, P., Flannick, J., et al. (2014). Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med **371**: 2488–2498. DOI: 10.1056/NEJMoa1408617.
81. Genovese, G., Kahler, A.K., Handsaker, R.E., et al. (2014). Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. N Engl J Med **371**: 2477–2487. DOI: 10.1056/NEJMoa1409405.
82. Loh, P.R., Genovese, G., Handsaker, R.E., et al. (2018). Insights into clonal haematopoiesis from 8,342 mosaic chromosomal alterations. Nature **559**: 350–355. DOI: 10.1038/s41586-018-0321-x.
83. Loh, P.R., Genovese, G., and McCarroll, S.A. (2020). Monogenic and polygenic inheritance become instruments for clonal selection. Nature **584**: 136–141. DOI: 10.1038/s41586-020-2430-6.
84. Venugopal, K., Feng, Y., Shabashvili, D., and Guryanova, O.A. (2021). Alterations to DNMT3A in Hematologic Malignancies. Cancer Res. **81**: 254–263. DOI: 10.1158/0008-5472.Can-20-3033.
85. Lopez-Moyado, I.F., and Rao, A. (2020). DNMT3A and TET2 mutations reshape hematopoiesis in opposing ways. Nat. Genet. **52**: 554–556. DOI: 10.1038/s41588-020-0641-2.
86. Xie, M., Lu, C., Wang, J., et al. (2014). Age-related mutations associated with clonal hematopoietic expansion and malignancies. Nat. Med. **20**: 1472–1478. DOI: 10.1038/nm.3733.
87. Yao, W.Q., Wu, F., Zhang, W., et al. (2020). Angioimmunoblastic T-cell lymphoma contains multiple clonal T-cell populations derived from a common TET2 mutant progenitor cell. J. Pathol. **250**: 346–357. DOI: 10.1002/path.5376.
88. von Beck, K., von Beck, T., Ferrell, P.B., Jr., et al. (2023). Lymphoid clonal hematopoiesis: implications for malignancy, immunity, and treatment. Blood Cancer J **13**: 5. DOI: 10.1038/s41408-022-00773-8.
89. Kikushige, Y., Ishikawa, F., Miyamoto, T., et al. (2011). Self-renewing hematopoietic stem cell is the primary target in pathogenesis of human chronic lymphocytic leukemia. Cancer Cell **20**: 246–259. DOI: 10.1016/j.ccr.2011.06.029.
90. Nam, A.S., Dusaj, N., Izzo, F., et al. (2022). Single-cell multi-omics of human clonal hematopoiesis reveals that DNMT3A R882 mutations perturb early progenitor states through selective hypomethylation. Nat. Genet. **54**: 1514–1526. DOI: 10.1038/s41588-022-01179-9.
91. Izzo, F., Lee, S.C., Poran, A., et al. (2020). DNA methylation disruption reshapes the hematopoietic differentiation landscape. Nat. Genet. **52**: 378–387. DOI: 10.1038/s41588-020-0595-4.
92. Jaiswal, S., and Ebert, B.L. (2019). Clonal hematopoiesis in human aging and disease. Science **366**. DOI: 10.1126/science.aan4673.
93. Mitchell, S.R., Gopakumar, J., and Jaiswal, S. (2021). Insights into clonal hematopoiesis and its relation to cancer risk. Curr. Opin. Genet. Dev. **66**: 63–69. DOI: 10.1016/j.gde.2020.12.004.
94. Yang, L., Rau, R., and Goodell, M.A. (2015). DNMT3A in haematological malignancies. Nat. Rev. Cancer **15**: 152–165. DOI: 10.1038/nrc3895.
95. Lopez-Bigas, N., and Gonzalez-Perez, A. (2020). Are carcinogens direct mutagens. Nat. Genet. **52**: 1137–1138. DOI: 10.1038/s41588-020-00730-w.
96. Fujisawa, M., Nguyen, T.B., Abe, Y., et al. (2022). Clonal germinal center B cells function as a niche for T-cell lymphoma. Blood **140**: 1937–1950. DOI: 10.1182/blood.2022015451.
97. Liu, Y.F., Wang, B.Y., Zhang, W.N., et al. (2016). Genomic Profiling of Adult and Pediatric B-cell Acute Lymphoblastic Leukemia. EBioMedicine **8**: 173–183. DOI: 10.1016/j.ebiom.2016.04.038.
98. Zhang, M.C., Tian, S., Fu, D., et al. (2023). Genetic subtype-guided immunochemotherapy in diffuse large B cell lymphoma: The randomized GUIDANCE-01 trial. Cancer Cell **41**: 1705–1716.e1705. DOI: 10.1016/j.ccell.2023.09.004.
99. Schmitz, R., Wright, G.W., Huang, D.W., et al. (2018). Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma. N Engl J Med **378**: 1396–1407. DOI: 10.1056/NEJMoa1801445.
100. Eide, C.A., Zabriskie, M.S., Savage Stevens, S.L., et al. (2019). Combining the Allosteric Inhibitor Asciminib with Ponatinib Suppresses Emergence of and Restores

Efficacy against Highly Resistant BCR-ABL1 Mutants. Cancer Cell **36**:431-443 e435. DOI: 10.1016/j.ccell.2019.08.004.
101. Voldborg, B.R., Damstrup, L., Spang-Thomsen, M., and Poulsen, H.S. (1997). Epidermal growth factor receptor (EGFR) and EGFR mutations, function and possible role in clinical trials. Ann. Oncol. **8**: 1197–1206. DOI: 10.1023/a:1008209720526.
102. Masopust, D., and Schenkel, J.M. (2013). The integration of T cell migration, differentiation and function. Nat. Rev. Immunol. **13**: 309–320. DOI: 10.1038/nri3442.
103. O'Shea, J.J., and Paul, W.E. (2010). Mechanisms underlying lineage commitment and plasticity of helper CD4+ T cells. Science **327**: 1098–1102. DOI: 10.1126/science.1178334.
104. DuPage, M., and Bluestone, J.A. (2016). Harnessing the plasticity of CD4(+) T cells to treat immune-mediated disease. Nat. Rev. Immunol. **16**: 149–163. DOI: 10.1038/nri.2015.18.
105. Cuadros, M., Dave, S.S., Jaffe, E.S., et al. (2007). Identification of a proliferation signature related to survival in nodal peripheral T-cell lymphomas. J Clin Oncol **25**: 3321–3329. DOI: 10.1200/JCO.2006.09.4474.
106. Piccaluga, P.P., Agostinelli, C., Califano, A., et al. (2007). Gene expression analysis of angioimmunoblastic lymphoma indicates derivation from T follicular helper cells and vascular endothelial growth factor deregulation. Cancer Res. **67**: 10703–10710. DOI: 10.1158/0008-5472.CAN-07-1708.
107. Piccaluga, P.P., Fuligni, F., De Leo, A., et al. (2013). Molecular profiling improves classification and prognostication of nodal peripheral T-cell lymphomas: results of a phase III diagnostic accuracy study. J Clin Oncol **31**: 3019–3025. DOI: 10.1200/JCO.2012.42.5611.
108. Piva, R., Agnelli, L., Pellegrino, E., et al. (2010). Gene expression profiling uncovers molecular classifiers for the recognition of anaplastic large-cell lymphoma within peripheral T-cell neoplasms. J Clin Oncol **28**: 1583–1590. DOI: 10.1200/JCO.2008.20.9759.
109. Went, P., Agostinelli, C., Gallamini, A., et al. (2006). Marker expression in peripheral T-cell lymphoma: a proposed clinical-pathologic prognostic score. J Clin Oncol **24**: 2472–2479. DOI: 10.1200/JCO.2005.03.6327.
110. Piccaluga, P.P., Agostinelli, C., Califano, A., et al. (2007). Gene expression analysis of peripheral T cell lymphoma, unspecified, reveals distinct profiles and new potential therapeutic targets. J. Clin. Invest. **117**: 823–834. DOI: 10.1172/JCI26833.
111. Inghirami, G., Chan, W.C., Pileri, S., and malignancies, A.x.c.G.-d.t.m.o.l. (2015). Peripheral T-cell and NK cell lymphoproliferative disorders: cell of origin, clinical and pathological implications. Immunol. Rev. **263**: 124–159. DOI: 10.1111/imr.12248.
112. Wang, T., Feldman, A.L., Wada, D.A., et al. (2014). GATA-3 expression identifies a high-risk subset of PTCL, NOS with distinct molecular and clinical features. Blood **123**: 3007–3015. DOI: 10.1182/blood-2013-12-544809.
113. Herek, T.A., Bouska, A., Lone, W., et al. (2022). DNMT3A mutations define a unique biological and prognostic subgroup associated with cytotoxic T cells in PTCL-NOS. Blood **140**: 1278–1290. DOI: 10.1182/blood.2021015019.
114. Ho, I.C., and Glimcher, L.H. (2002). Transcription: tantalizing times for T cells. Cell **109 Suppl**:S109-120. DOI: 10.1016/s0092-8674(02)00705-5.
115. Oestreich, K.J., and Weinmann, A.S. (2012). Master regulators or lineage-specifying? Changing views on CD4+ T cell transcription factors. Nat. Rev. Immunol. **12**(11):799-804. DOI: 10.1038/nri3321.
116. Heavican, T.B., Bouska, A., Yu, J., et al. (2019). Genetic drivers of oncogenic pathways in molecular subgroups of peripheral T-cell lymphoma. Blood **133**: 1664–1676. DOI: 10.1182/blood-2018-09-872549.
117. Amador, C., Bouska, A., Wright, G., et al. (2022). Gene Expression Signatures for the Accurate Diagnosis of Peripheral T-Cell Lymphoma Entities in the Routine Clinical Practice. J Clin Oncol **40**: 4261–4275. DOI: 10.1200/JCO.21.02707.
118. Bera, K., Schalper, K.A., Rimm, D.L., et al. (2019). Artificial intelligence in digital pathology - new tools for diagnosis and precision oncology. Nat Rev Clin Oncol **16**: 703–715. DOI: 10.1038/s41571-019-0252-y.
119. Gleeson, M. (2019). Moving to a higher echelon in CD30-positive T-cell lymphoma. Lancet **393**: 201–202. DOI: 10.1016/S0140-6736(18)33127-1.
120. Stein, H., Mason, D.Y., Gerdes, J., et al. (1985). The expression of the Hodgkin's disease associated antigen Ki-1 in reactive and neoplastic lymphoid tissue: evidence that Reed-Sternberg cells and histiocytic malignancies are derived from activated lymphoid cells. Blood **66**: 848–858. DOI. DOI: 10.1182/blood.V66.4.848.848.
121. Cheson, B.D., Horwitz, S.M., and Weisenburger, D.D. (2011). Peripheral T-cell lymphomas: diagnosis and treatment options. Proceedings from a live roundtable, August 17, 2011, Kauai, Hawaii. Clin Adv Hematol Oncol **9**:1-14; quiz 15-16. DOI.
122. Duvic, M. (2011). CD30+ neoplasms of the skin. Curr Hematol Malig Rep **6**: 245–250. DOI: 10.1007/s11899-011-0096-8.
123. Beck, A., Goetsch, L., Dumontet, C., and Corvaia, N. (2017). Strategies and challenges for the next generation of antibody-drug conjugates. Nat. Rev. Drug Discov. **16**: 315–337. DOI: 10.1038/nrd.2016.268.
124. Batlevi, C.L., Matsuki, E., Brentjens, R.J., and Younes, A. (2016). Novel immunotherapies in lymphoid malignancies. Nat Rev Clin Oncol **13**: 25–40. DOI: 10.1038/nrclinonc.2015.187.
125. Horwitz, S., O'Connor, O.A., Pro, B., et al. (2022). The ECHELON-2 Trial: 5-year results of a randomized, phase III study of brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma. Ann. Oncol. **33**: 288–298. DOI: 10.1016/j.annonc.2021.12.002.
126. National Comprehensive Cancer Network (2023). T-Cell Lymphomas (Version 1.2023). https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf.
127. Suzuki, R. (2010). Dosing of a phase I study of KW-0761, an anti-CCR4 antibody, for adult T-cell leukemia-lymphoma and peripheral T-cell lymphoma. J Clin Oncol **28**:e404-405; author reply e406. DOI: 10.1200/JCO.2010.29.7242.
128. Hamadani, M., Collins, G.P., Caimi, P.F., et al. (2021). Camidanlumab tesirine in patients with relapsed or refractory lymphoma: a phase 1, open-label, multicentre, dose-escalation, dose-expansion study. Lancet Haematol **8**: e433–e445. DOI: 10.1016/S2352-3026(21)00103-4.
129. Luo, L., Zhou, X., Zhou, L., et al. (2022). Current state of CAR-T therapy for T-cell malignancies. Ther Adv Hematol **13**:20406207221143025. DOI: 10.1177/20406207221143025.
130. Nicolay, J.P., Albrecht, J.D., Alberti-Violetti, S., and Berti, E. (2021). CCR4 in cutaneous T-cell lymphoma: Therapeutic targeting of a pathogenic driver. Eur. J. Immunol. **51**: 1660–1671. DOI: 10.1002/eji.202049043.
131. Jones, D., O'Hara, C., Kraus, M.D., et al. (2000). Expression pattern of T-cell-associated chemokine receptors and their chemokines correlates with specific subtypes of T-cell non-Hodgkin lymphoma. Blood **96**: 685–690. DOI. DOI: 10.1182/blood.V96.2.685.014k26_685_690.
132. Yoshie, O., Fujisawa, R., Nakayama, T., et al. (2002). Frequent expression of CCR4 in adult T-cell leukemia and human T-cell leukemia virus type 1-transformed T cells. Blood **99**: 1505–1511. DOI: 10.1182/blood.v99.5.1505.
133. Wang, L., Ni, X., Covington, K.R., et al. (2015). Genomic profiling of Sezary syndrome identifies alterations of key T cell signaling and differentiation genes. Nat. Genet. **47**: 1426–1434. DOI: 10.1038/ng.3444.
134. Ishida, T., Utsunomiya, A., Iida, S., et al. (2003). Clinical significance of CCR4 expression in adult T-cell leukemia/lymphoma: its close association with skin involvement and unfavorable outcome. Clin. Cancer. Res. **9**:3625-3634.
135. Oka, S., Ono, K., and Nohgawa, M. (2019). Successful treatment with mogamulizumab of refractory/relapsed angioimmunoblastic T-cell lymphoma following autologous stem cell transplantation. Leuk. Lymphoma **60**: 1595–1597. DOI: 10.1080/10428194.2018.1537489.
136. Fuji, S., Inoue, Y., Utsunomiya, A., et al. (2016). Pretransplantation Anti-CCR4 Antibody Mogamulizumab Against Adult T-Cell Leukemia/Lymphoma Is Associated With Significantly Increased Risks of Severe and Corticosteroid-Refractory Graft-Versus-Host Disease, Nonrelapse Mortality, and Overall Mortality. J Clin Oncol **34**: 3426–3433. DOI: 10.1200/JCO.2016.67.8250.
137. Zammarchi, F., Havenith, K., Bertelli, F., et al. (2020). CD25-targeted antibody-drug conjugate depletes regulatory T cells and eliminates established syngeneic tumors via antitumor immunity. J Immunother Cancer **8**. DOI: 10.1136/jitc-2020-000860.
138. Safarzadeh Kozani, P., Safarzadeh Kozani, P., and Rahbarizadeh, F. (2021). CAR-T cell therapy in T-cell malignancies: Is success a low-hanging fruit. Stem Cell Res Ther **12**: 527. DOI: 10.1186/s13287-021-02595-0.
139. Fleischer, L.C., Spencer, H.T., and Raikar, S.S. (2019). Targeting T cell malignancies using CAR-based immunotherapy: challenges and potential solutions. J Hematol Oncol **12**: 141. DOI: 10.1186/s13045-019-0801-y.
140. Fang, K.K., Lee, J.B., and Zhang, L. (2022). Adoptive Cell Therapy for T-Cell Malignancies. Cancers (Basel) **15**. DOI: 10.3390/cancers15010094.
141. Alcantara, M., Tesio, M., June, C.H., and Houot, R. (2018). CAR T-cells for T-cell malignancies: challenges in distinguishing between therapeutic, normal, and neoplastic T-cells. Leukemia **32**: 2307–2315. DOI: 10.1038/s41375-018-0285-8.
142. Sims, J.E., Tunnacliffe, A., Smith, W.J., and Rabbitts, T.H. (1984). Complexity of human T-cell antigen receptor beta-chain constant- and variable-region genes. Nature **312**: 541–545. DOI: 10.1038/312541a0.
143. Maciocia, P.M., Wawrzyniecka, P.A., Philip, B., et al. (2017). Targeting the T cell receptor beta-chain constant region for immunotherapy of T cell malignancies. Nat. Med. **23**: 1416–1423. DOI: 10.1038/nm.4444.
144. Tunnacliffe, A., Kefford, R., Milstein, C., et al. (1985). Sequence and evolution of the human T-cell antigen receptor beta-chain genes. Proc Natl Acad Sci U S A **82**: 5068–5072. DOI: 10.1073/pnas.82.15.5068.
145. Lybaert, L., Lefever, S., Fant, B., et al. (2023). Challenges in neoantigen-directed therapeutics. Cancer Cell **41**: 15–40. DOI: 10.1016/j.ccell.2022.10.013.
146. Blass, E., and Ott, P.A. (2021). Advances in the development of personalized neoantigen-based therapeutic cancer vaccines. Nat Rev Clin Oncol **18**: 215–229. DOI: 10.1038/s41571-020-00460-2.
147. Yarchoan, M., Johnson, B.A., 3rd, Lutz, E.R., et al. (2017). Targeting neoantigens to augment antitumour immunity. Nat. Rev. Cancer **17**: 209–222. DOI: 10.1038/nrc.2016.154.
148. Lang, F., Schrors, B., Lower, M., et al. (2022). Identification of neoantigens for individualized therapeutic cancer vaccines. Nat. Rev. Drug Discov. **21**: 261–282. DOI: 10.1038/s41573-021-00387-y.
149. Yamamoto, T.N., Kishton, R.J., and Restifo, N.P. (2019). Developing neoantigen-targeted T cell-based treatments for solid tumors. Nat. Med. **25**: 1488–1499. DOI: 10.1038/s41591-019-0596-y.
150. Sun, L., Su, Y., Jiao, A., et al. (2023). T cells in health and disease. Signal Transduct Target Ther **8**: 235. DOI: 10.1038/s41392-023-01471-y.
151. Lin, J.X., Migone, T.S., Tsang, M., et al. (1995). The role of shared receptor motifs and common Stat proteins in the generation of cytokine pleiotropy and redundancy by IL-2, IL-4, IL-7, IL-13, and IL-15. Immunity **2**: 331–339. DOI: 10.1016/1074-7613(95)90141-8.

152. Pires, I.S., Hammond, P.T., and Irvine, D.J. (2021). Engineering Strategies for Immunomodulatory Cytokine Therapies - Challenges and Clinical Progress. Adv Ther (Weinh) **4**. DOI: 10.1002/adtp.202100035.
153. Saxton, R.A., Glassman, C.R., and Garcia, K.C. (2023). Emerging principles of cytokine pharmacology and therapeutics. Nat. Rev. Drug Discov. **22**: 21–37. DOI: 10.1038/s41573-022-00557-6.
154. Deckers, J., Anbergen, T., Hokke, A.M., et al. (2023). Engineering cytokine therapeutics. Nat Rev Bioeng **1**: 286–303. DOI: 10.1038/s44222-023-00030-y.
155. McKinney, M., Moffitt, A.B., Gaulard, P., et al. (2017). The Genetic Basis of Hepatosplenic T-cell Lymphoma. Cancer Discov **7**: 369–379. DOI: 10.1158/2159-8290.Cd-16-0330.
156. Odejide, O., Weigert, O., Lane, A.A., et al. (2014). A targeted mutational landscape of angioimmunoblastic T-cell lymphoma. Blood **123**: 1293–1296. DOI: 10.1182/blood-2013-10-531509.
157. Timmins, M.A., Wagner, S.D., and Ahearne, M.J. (2020). The new biology of PTCL-NOS and AITL: current status and future clinical impact. Br. J. Haematol. **189**: 54–66. DOI: 10.1111/bjh.16428.
158. Chiba, S., and Sakata-Yanagimoto, M. (2020). Advances in understanding of angioimmunoblastic T-cell lymphoma. Leukemia **34**: 2592–2606. DOI: 10.1038/s41375-020-0990-y.
159. Rodriguez Cortes, J., Cooke, A.R., Quinn, A., et al. (2019). Role of Vav1 Genomic Alterations in T-Cell Differentiation and Transformation in Peripheral T-Cell Lymphoma. Blood **134**: 1482–1482. DOI: 10.1182/blood-2019-129438.
160. Janikova, A. (2022). Editorial: PTCL from genes to therapy. Front Oncol **12**: 1014483. DOI: 10.3389/fonc.2022.1014483.
161. de Leval, L. (2020). Approach to nodal-based T-cell lymphomas. Pathology **52**: 78–99. DOI: 10.1016/j.pathol.2019.09.012.
162. Boi, M., Zucca, E., Inghirami, G., and Bertoni, F. (2015). Advances in understanding the pathogenesis of systemic anaplastic large cell lymphomas. Br. J. Haematol. **168**: 771–783. DOI: 10.1111/bjh.13265.
163. Zettl, A., Rudiger, T., Konrad, M.A., et al. (2004). Genomic profiling of peripheral T-cell lymphoma, unspecified, and anaplastic large T-cell lymphoma delineates novel recurrent chromosomal alterations. Am J Pathol **164**: 1837–1848. DOI: 10.1016/S0002-9440(10)63742-X.
164. Werner, M.T., Zhao, C., Zhang, Q., and Wasik, M.A. (2017). Nucleophosmin-anaplastic lymphoma kinase: the ultimate oncogene and therapeutic target. Blood **129**: 823–831. DOI: 10.1182/blood-2016-05-717793.
165. Chiarle, R., Simmons, W.J., Cai, H., et al. (2005). Stat3 is required for ALK-mediated lymphomagenesis and provides a possible therapeutic target. Nat. Med. **11**: 623–629. DOI: 10.1038/nm1249.
166. Zhang, Q., Wang, H., Kantekure, K., et al. (2011). Oncogenic tyrosine kinase NPM-ALK induces expression of the growth-promoting receptor ICOS. Blood **118**: 3062–3071. DOI: 10.1182/blood-2011-01-332916.
167. Zhang, Q., Wei, F., Wang, H.Y., et al. (2013). The potent oncogene NPM-ALK mediates malignant transformation of normal human CD4(+) T lymphocytes. Am J Pathol **183**: 1971–1980. DOI: 10.1016/j.ajpath.2013.08.030.
168. Gambacorti-Passerini, C., Messa, C., and Pogliani, E.M. (2011). Crizotinib in anaplastic large-cell lymphoma. N Engl J Med **364**: 775–776. DOI: 10.1056/NEJMc1013224.
169. Gambacorti Passerini, C., Farina, F., Stasia, A., et al. (2014). Crizotinib in advanced, chemoresistant anaplastic lymphoma kinase-positive lymphoma patients. J. Natl. Cancer Inst. **106**: djt378. DOI: 10.1093/jnci/djt378.
170. Mosse, Y.P., Lim, M.S., Voss, S.D., et al. (2013). Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: a Children's Oncology Group phase 1 consortium study. Lancet Oncol **14**: 472–480. DOI: 10.1016/S1470-2045(13)70095-0.
171. Irshaid, L., and Xu, M.L. (2020). ALCL by any other name: the many facets of anaplastic large cell lymphoma. Pathology **52**: 100–110. DOI: 10.1016/j.pathol.2019.09.007.
172. Pina-Oviedo, S., Ortiz-Hidalgo, C., Carballo-Zarate, A.A., and Zarate-Osorno, A. (2021). ALK-Negative Anaplastic Large Cell Lymphoma: Current Concepts and Molecular Pathogenesis of a Heterogeneous Group of Large T-Cell Lymphomas. Cancers (Basel) **13**. DOI: 10.3390/cancers13184667.
173. Feldman, A.L., Law, M., Remstein, E.D., et al. (2009). Recurrent translocations involving the IRF4 oncogene locus in peripheral T-cell lymphomas. Leukemia **23**: 574–580. DOI: 10.1038/leu.2008.320.
174. Abate, F., da Silva-Almeida, A.C., Zairis, S., et al. (2017). Activating mutations and translocations in the guanine exchange factor VAV1 in peripheral T-cell lymphomas. Proc Natl Acad Sci U S A **114**: 764–769. DOI: 10.1073/pnas.1608839114.
175. Streubel, B., Vinatzer, U., Willheim, M., et al. (2006). Novel t(5;9)(q33;q22) fuses ITK to SYK in unspecified peripheral T-cell lymphoma. Leukemia **20**: 313–318. DOI: 10.1038/sj.leu.2404045.
176. Moon, C.S., Reglero, C., Cortes, J.R., et al. (2021). FYN-TRAF3IP2 induces NF-kappaB signaling-driven peripheral T cell lymphoma. Nat Cancer **2**: 98–113. DOI: 10.1038/s43018-020-00161-w.
177. Debackere, K., Marcelis, L., Demeyer, S., et al. (2021). Fusion transcripts FYN-TRAF3IP2 and KHDRBS1-LCK hijack T cell receptor signaling in peripheral T-cell lymphoma, not otherwise specified. Nat Commun **12**: 3705. DOI: 10.1038/s41467-021-24037-4.
178. Vallois, D., Dupuy, A., Lemonnier, F., et al. (2018). RNA fusions involving CD28 are rare in peripheral T-cell lymphomas and concentrate mainly in those derived from follicular helper T cells. Haematologica **103**: e360–e363. DOI: 10.3324/haematol.2017.186767.
179. Pileri, S.A., Tabanelli, V., Fiori, S., et al. (2021). Peripheral T-Cell Lymphoma, Not Otherwise Specified: Clinical Manifestations, Diagnosis, and Future Treatment. Cancers (Basel) **13**. DOI: 10.3390/cancers13184535.
180. Dobson, R., Du, P.Y., Rásó-Barnett, L., et al. (2022). Early detection of T-cell lymphoma with T follicular helper phenotype by RHOA mutation analysis. Haematologica **107**: 489–499. DOI: 10.3324/haematol.2020.265991.
181. Goffin, J., and Eisenhauer, E. (2002). DNA methyltransferase inhibitors-state of the art. Ann. Oncol. **13**: 1699–1716. DOI: 10.1093/annonc/mdf314.
182. Cang, S., Ma, Y., and Liu, D. (2009). New clinical developments in histone deacetylase inhibitors for epigenetic therapy of cancer. J Hematol Oncol **2**: 22. DOI: 10.1186/1756-8722-2-22.
183. Cools, J. (2014). RHOA mutations in peripheral T cell lymphoma. Nat. Genet. **46**: 320–321. DOI: 10.1038/ng.2937.
184. Lu, S., Jang, H., Muratcioglu, S., et al. (2016). Ras Conformational Ensembles, Allostery, and Signaling. Chem Rev **116**: 6607–6665. DOI: 10.1021/acs.chemrev.5b00542.
185. Lu, S., Jang, H., Gu, S., et al. (2016). Drugging Ras GTPase: a comprehensive mechanistic and signaling structural view. Chem Soc Rev **45**: 4929–4952. DOI: 10.1039/c5cs00911a.
186. Sakata-Yanagimoto, M., Enami, T., Yoshida, K., et al. (2014). Somatic RHOA mutation in angioimmunoblastic T cell lymphoma. Nat. Genet. **46**: 171–175. DOI: 10.1038/ng.2872.
187. Yoo, H.Y., Sung, M.K., Lee, S.H., et al. (2014). A recurrent inactivating mutation in RHOA GTPase in angioimmunoblastic T cell lymphoma. Nat. Genet. **46**: 371–375. DOI: 10.1038/ng.2916.
188. Cortes, J.R., Ambesi-Impiombato, A., Couronné, L., et al. (2018). RHOA G17V Induces T Follicular Helper Cell Specification and Promotes Lymphomagenesis. Cancer Cell **33**: 259–273.e257. DOI: 10.1016/j.ccell.2018.01.001.
189. Ng, S.Y., Brown, L., Stevenson, K., et al. (2018). RhoA G17V is sufficient to induce autoimmunity and promotes T-cell lymphomagenesis in mice. Blood **132**: 935–947. DOI: 10.1182/blood-2017-11-818617.
190. Yin, G., Huang, J., Petela, J., et al. (2023). Targeting small GTPases: emerging grasps on previously untamable targets, pioneered by KRAS. Signal Transduct Target Ther **8**: 212. DOI: 10.1038/s41392-023-01441-4.
191. Moore, A.R., Rosenberg, S.C., McCormick, F., and Malek, S. (2020). RAS-targeted therapies: is the undruggable drugged. Nat. Rev. Drug Discov. **19**: 533–552. DOI: 10.1038/s41573-020-0068-6.
192. Kim, D., Xue, J.Y., and Lito, P. (2020). Targeting KRAS(G12C): From Inhibitory Mechanism to Modulation of Antitumor Effects in Patients. Cell **183**: 850–859. DOI: 10.1016/j.cell.2020.09.044.
193. Lin, Y., Lu, S., Zhang, J., and Zheng, Y. (2021). Structure of an inactive conformation of GTP-bound RhoA GTPase. Structure **29**: 553–563.e555. DOI: 10.1016/j.str.2020.12.015.
194. Jiang, H., Zu, S., Lu, Y., et al. (2023). A RhoA structure with switch II flipped outward revealed the conformational dynamics of switch II region. Journal of Structural Biology **215**(2). DOI: 10.1016/j.jsb.2023.107942.
195. Boike, L., Henning, N.J., and Nomura, D.K. (2022). Advances in covalent drug discovery. Nat. Rev. Drug Discov. **21**: 881–898. DOI: 10.1038/s41573-022-00542-z.
196. Scarfò, I., Pellegrino, E., Mereu, E., et al. (2016). Identification of a new subclass of ALK-negative ALCL expressing aberrant levels of ERBB4 transcripts. Blood **127**: 221–232. DOI: 10.1182/blood-2014-12-614503.
197. Vallois, D., Dobay, M.P., Morin, R.D., et al. (2016). Activating mutations in genes related to TCR signaling in angioimmunoblastic and other follicular helper T-cell-derived lymphomas. Blood **128**: 1490–1502. DOI: 10.1182/blood-2016-02-698977.
198. Gmyrek, G.B., Pingel, J., Choi, J., and Green, J.M. (2017). Functional analysis of acquired CD28 mutations identified in cutaneous T cell lymphoma. Cell. Immunol. **319**: 28–34. DOI: 10.1016/j.cellimm.2017.07.002.
199. Vaque, J.P., Gomez-Lopez, G., Monsalvez, V., et al. (2014). PLCG1 mutations in cutaneous T-cell lymphomas. Blood **123**: 2034–2043. DOI: 10.1182/blood-2013-05-504308.
200. Rohr, J., Guo, S., Huo, J., et al. (2016). Recurrent activating mutations of CD28 in peripheral T-cell lymphomas. Leukemia **30**: 1062–1070. DOI: 10.1038/leu.2015.357.
201. Ambrogio, C., Voena, C., Manazza, A.D., et al. (2008). The anaplastic lymphoma kinase controls cell shape and growth of anaplastic large cell lymphoma through Cdc42 activation. Cancer Res. **68**: 8899–8907. DOI: 10.1158/0008-5472.Can-08-2568.
202. Menotti, M., Ambrogio, C., Cheong, T.C., et al. (2019). Wiskott-Aldrich syndrome protein (WASP) is a tumor suppressor in T cell lymphoma. Nat. Med. **25**: 130–140. DOI: 10.1038/s41591-018-0262-9.
203. Turner, S.D., Yeung, D., Hadfield, K., et al. (2007). The NPM-ALK tyrosine kinase mimics TCR signalling pathways, inducing NFAT and AP-1 by RAS-dependent mechanisms. Cell. Signal. **19**: 740–747. DOI: 10.1016/j.cellsig.2006.09.007.
204. Pechloff, K., Holch, J., Ferch, U., et al. (2010). The fusion kinase ITK-SYK mimics a T cell receptor signal and drives oncogenesis in conditional mouse models of peripheral T cell lymphoma. J. Exp. Med. **207**: 1031–1044. DOI: 10.1084/jem.20092042.
205. Bonzheim, I., Geissinger, E., Roth, S., et al. (2004). Anaplastic large cell lymphomas

lack the expression of T-cell receptor molecules or molecules of proximal T-cell receptor signaling. Blood **104**: 3358–3360. DOI: 10.1182/blood-2004-03-1037.
206. Zamo, A., Chiarle, R., Piva, R., et al. (2002). Anaplastic lymphoma kinase (ALK) activates Stat3 and protects hematopoietic cells from cell death. Oncogene **21**: 1038–1047. DOI: 10.1038/sj.onc.1205152.
207. Manso, R., Sánchez-Beato, M., Monsalvo, S., et al. (2014). The RHOA G17V gene mutation occurs frequently in peripheral T-cell lymphoma and is associated with a characteristic molecular signature. Blood **123**: 2893–2894. DOI: 10.1182/blood-2014-02-555946.
208. Aaronson, D.S., and Horvath, C.M. (2002). A road map for those who don't know JAK-STAT. Science **296**: 1653–1655. DOI: 10.1126/science.1071545.
209. Chen, J., Zhang, Y., Petrus, M.N., et al. (2017). Cytokine receptor signaling is required for the survival of ALK- anaplastic large cell lymphoma, even in the presence of JAK1/STAT3 mutations. Proc Natl Acad Sci U S A **114**: 3975–3980. DOI: 10.1073/pnas.1700682114.
210. Abraham, R.M., Zhang, Q., Odum, N., and Wasik, M.A. (2011). The role of cytokine signaling in the pathogenesis of cutaneous T-cell lymphoma. Cancer Biol Ther **12**: 1019–1022. DOI: 10.4161/cbt.12.12.18144.
211. Rolf, J., Fairfax, K., and Turner, M. (2010). Signaling pathways in T follicular helper cells. J. Immunol. **184**: 6563–6568. DOI: 10.4049/jimmunol.1000202.
212. Slupianek, A., Nieborowska-Skorska, M., Hoser, G., et al. (2001). Role of phosphatidylinositol 3-kinase-Akt pathway in nucleophosmin/anaplastic lymphoma kinase-mediated lymphomagenesis. Cancer Res. **61**: 2194–2199.
213. Mondragon, L., Mhaidly, R., De Donatis, G.M., et al. (2019). GAPDH Overexpression in the T Cell Lineage Promotes Angioimmunoblastic T Cell Lymphoma through an NF-kappaB-Dependent Mechanism. Cancer Cell **36**:268-287 e210. DOI: 10.1016/j.ccell.2019.07.008.
214. Moskowitz, A.J., Ghione, P., Jacobsen, E., et al. (2021). A phase 2 biomarker-driven study of ruxolitinib demonstrates effectiveness of JAK/STAT targeting in T-cell lymphomas. Blood **138**: 2828–2837. DOI: 10.1182/blood.2021013379.
215. Kim, S.J., Shin, D.Y., Kim, J.S., et al. (2016). A phase II study of everolimus (RAD001), an mTOR inhibitor plus CHOP for newly diagnosed peripheral T-cell lymphomas. Ann. Oncol. **27**: 712–718. DOI: 10.1093/annonc/mdv624.
216. Boddicker, R.L., Kip, N.S., Xing, X., et al. (2015). The oncogenic transcription factor IRF4 is regulated by a novel CD30/NF-κB positive feedback loop in peripheral T-cell lymphoma. Blood **125**: 3118–3127. DOI: 10.1182/blood-2014-05-578575.
217. Nishizawa, S., Sakata-Yanagimoto, M., Hattori, K., et al. (2017). BCL6 locus is hypermethylated in angioimmunoblastic T-cell lymphoma. Int. J. Hematol. **105**: 465–469. DOI: 10.1007/s12185-016-2159-z.
218. Nurieva, R.I., Chung, Y., Martinez, G.J., et al. (2009). Bcl6 mediates the development of T follicular helper cells. Science **325**: 1001–1005. DOI: 10.1126/science.1176676.
219. Liu, D., Yan, J., Sun, J., et al. (2021). BCL6 controls contact-dependent help delivery during follicular T-B cell interactions. Immunity **54**: 2245–2255.e2244. DOI: 10.1016/j.immuni.2021.08.003.
220. Schleussner, N., Merkel, O., Costanza, M., et al. (2018). The AP-1-BATF and -BATF3 module is essential for growth, survival and TH17/ILC3 skewing of anaplastic large cell lymphoma. Leukemia **32**: 1994–2007. DOI: 10.1038/s41375-018-0045-9.
221. Bandini, C., Pupuleku, A., Spaccarotella, E., et al. (2018). IRF4 Mediates the Oncogenic Effects of STAT3 in Anaplastic Large Cell Lymphomas. Cancers (Basel) **10**(1). DOI: 10.3390/cancers10010021.
222. Shaulian, E., and Karin, M. (2002). AP-1 as a regulator of cell life and death. Nat. Cell Biol. **4**: E131–136. DOI: 10.1038/ncb0502-e131.
223. Watanabe, M., Sasaki, M., Itoh, K., et al. (2005). JunB induced by constitutive CD30-extracellular signal-regulated kinase 1/2 mitogen-activated protein kinase signaling activates the CD30 promoter in anaplastic large cell lymphoma and reed-sternberg cells of Hodgkin lymphoma. Cancer Res. **65**: 7628–7634. DOI: 10.1158/0008-5472.Can-05-0925.
224. Atsaves, V., Zhang, R., Ruder, D., et al. (2015). Constitutive control of AKT1 gene expression by JUNB/CJUN in ALK+ anaplastic large-cell lymphoma: a novel crosstalk mechanism. Leukemia **29**: 2162–2172. DOI: 10.1038/leu.2015.127.
225. Yin, H., Wang, J., Tan, Y., et al. (2023). Transcription factor abnormalities in B-ALL leukemogenesis and treatment. Trends Cancer. DOI: 10.1016/j.trecan.2023.06.004.
226. Pighi, C., Cheong, T.C., Compagno, M., et al. (2021). Frequent mutations of FBXO11 highlight BCL6 as a therapeutic target in Burkitt lymphoma. Blood Adv **5**: 5239–5257. DOI: 10.1182/bloodadvances.2021005682.
227. Słabicki, M., Yoon, H., Koeppel, J., et al. (2020). Small-molecule-induced polymerization triggers degradation of BCL6. Nature **588**: 164–168. DOI: 10.1038/s41586-020-2925-1.
228. Finley, L.W.S. (2023). What is cancer metabolism. Cell **186**: 1670–1688. DOI: 10.1016/j.cell.2023.01.038.
229. Yoon, S.E., Cho, J., Kim, Y.J., et al. (2021). Comprehensive analysis of clinical, pathological, and genomic characteristics of follicular helper T-cell derived lymphomas. Exp Hematol Oncol **10**: 33. DOI: 10.1186/s40164-021-00224-3.
230. Ye, Y., Ding, N., Mi, L., et al. (2021). Correlation of mutational landscape and survival outcome of peripheral T-cell lymphomas. Exp Hematol Oncol **10**: 9. DOI: 10.1186/s40164-021-00200-x.
231. Wilcox, R.A. (2016). A three-signal model of T-cell lymphoma pathogenesis. Am J Hematol **91**: 113–122. DOI: 10.1002/ajh.24203.
232. Vega, F., Amador, C., Chadburn, A., et al. (2022). Genetic profiling and biomarkers in peripheral T-cell lymphomas: current role in the diagnostic work-up. Mod Pathol **35**: 306–318. DOI: 10.1038/s41379-021-00937-0.
233. Dang, L., Yen, K., and Attar, E.C. (2016). IDH mutations in cancer and progress toward development of targeted therapeutics. Ann. Oncol. **27**: 599–608. DOI: 10.1093/annonc/mdw013.
234. Wang, C., McKeithan, T.W., Gong, Q., et al. (2015). IDH2R172 mutations define a unique subgroup of patients with angioimmunoblastic T-cell lymphoma. Blood **126**: 1741–1752. DOI: 10.1182/blood-2015-05-644591.
235. Churchill, H., Naina, H., Boriack, R., et al. (2015). Discordant intracellular and plasma D-2-hydroxyglutarate levels in a patient with IDH2 mutated angioimmunoblastic T-cell lymphoma. Int J Clin Exp Pathol **8**: 11753–11759.
236. Lemonnier, F., Cairns, R.A., Inoue, S., et al. (2016). The IDH2 R172K mutation associated with angioimmunoblastic T-cell lymphoma produces 2HG in T cells and impacts lymphoid development. Proc Natl Acad Sci U S A **113**: 15084–15089. DOI: 10.1073/pnas.1617929114.
237. Green, A., and Beer, P. (2010). Somatic mutations of IDH1 and IDH2 in the leukemic transformation of myeloproliferative neoplasms. N Engl J Med **362**: 369–370. DOI: 10.1056/NEJMc0910063.
238. Ward, P.S., Patel, J., Wise, D.R., et al. (2010). The common feature of leukemia-associated IDH1 and IDH2 mutations is a neomorphic enzyme activity converting alpha-ketoglutarate to 2-hydroxyglutarate. Cancer Cell **17**: 225–234. DOI: 10.1016/j.ccr.2010.01.020.
239. Stein, E.M., DiNardo, C.D., Pollyea, D.A., et al. (2017). Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. Blood **130**: 722–731. DOI: 10.1182/blood-2017-04-779405.
240. Thol, F., and Ganser, A. (2020). Treatment of Relapsed Acute Myeloid Leukemia. Curr Treat Options Oncol **21**: 66. DOI: 10.1007/s11864-020-00765-5.
241. Guo, J., Zhang, R., Yang, Z., et al. (2021). Biological Roles and Therapeutic Applications of IDH2 Mutations in Human Cancer. Front Oncol **11**: 644857. DOI: 10.3389/fonc.2021.644857.
242. Mercurio, C., Minucci, S., and Pelicci, P.G. (2010). Histone deacetylases and epigenetic therapies of hematological malignancies. Pharmacol. Res. **62**: 18–34. DOI: 10.1016/j.phrs.2010.02.010.
243. Bachy, E., Camus, V., Thieblemont, C., et al. (2022). Romidepsin Plus CHOP Versus CHOP in Patients With Previously Untreated Peripheral T-Cell Lymphoma: Results of the Ro-CHOP Phase III Study (Conducted by LYSA). J Clin Oncol **40**: 242–251. DOI: 10.1200/jco.21.01815.
244. O'Connor, O.A., Horwitz, S., Masszi, T., et al. (2015). Belinostat in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma: Results of the Pivotal Phase II BELIEF (CLN-19) Study. J Clin Oncol **33**: 2492–2499. DOI: 10.1200/jco.2014.59.2782.
245. Ruan, J., Moskowitz, A., Mehta-Shah, N., et al. (2023). Multicenter phase 2 study of oral azacitidine (CC-486) plus CHOP as initial treatment for PTCL. Blood **141**: 2194–2205. DOI: 10.1182/blood.2022018254.
246. Falchi, L., Ma, H., Klein, S., et al. (2021). Combined oral 5-azacytidine and romidepsin are highly effective in patients with PTCL: a multicenter phase 2 study. Blood **137**: 2161–2170. DOI: 10.1182/blood.2020009004.
247. Provez, L., Putteman, T., Landfors, M., et al. (2023). Pre-Clinical Evaluation of the Hypomethylating Agent Decitabine for the Treatment of T-Cell Lymphoblastic Lymphoma. Cancers (Basel) **15**. DOI: 10.3390/cancers15030647.
248. Veltmaat, N., Zhong, Y., de Jesus, F.M., et al. (2023). Genomic profiling of post-transplant lymphoproliferative disorders using cell-free DNA. J Hematol Oncol **16**: 104. DOI: 10.1186/s13045-023-01500-x.
249. Cirillo, M., Craig, A.F.M., Borchmann, S., and Kurtz, D.M. (2020). Liquid biopsy in lymphoma: Molecular methods and clinical applications. Cancer Treat Rev **91**: 102106. DOI: 10.1016/j.ctrv.2020.102106.
250. Camus, V., Viennot, M., Lequesne, J., et al. (2021). Targeted genotyping of circulating tumor DNA for classical Hodgkin lymphoma monitoring: a prospective study. Haematologica **106**: 154–162. DOI: 10.3324/haematol.2019.237719.
251. Miljkovic, M.D., Melani, C., Pittaluga, S., et al. (2021). Next-generation sequencing-based monitoring of circulating tumor DNA reveals clonotypic heterogeneity in untreated PTCL. Blood Adv **5**: 4198–4210. DOI: 10.1182/bloodadvances.2020003679.
252. Kohnke, T., and Majeti, R. (2021). Clonal Hematopoiesis: From Mechanisms to Clinical Intervention. Cancer Discov **11**: 2987–2997. DOI: 10.1158/2159-8290.CD-21-0901.
253. Desai, P., Mencia-Trinchant, N., Savenkov, O., et al. (2018). Somatic mutations precede acute myeloid leukemia years before diagnosis. Nat. Med. **24**: 1015–1023. DOI: 10.1038/s41591-018-0081-z.
254. Calvo-Vidal, M.N., and Cerchietti, L. (2013). The metabolism of lymphomas. Curr Opin Hematol **20**: 345–354. DOI: 10.1097/MOH.0b013e3283623d16.
255. Fox, C.J., Hammerman, P.S., and Thompson, C.B. (2005). Fuel feeds function: energy metabolism and the T-cell response. Nat. Rev. Immunol. **5**: 844–852. DOI: 10.1038/nri1710.
256. Kishton, R.J., Sukumar, M., and Restifo, N.P. (2017). Metabolic Regulation of T Cell Longevity and Function in Tumor Immunotherapy. Cell Metab **26**: 94–109. DOI: 10.1016/j.cmet.2017.06.016.
257. Chapman, N.M., Boothby, M.R., and Chi, H. (2020). Metabolic coordination of T cell quiescence and activation. Nat. Rev. Immunol. **20**: 55–70. DOI: 10.1038/s41577-019-0203-y.
258. Mahadevan, D., Spier, C., Della Croce, K., et al. (2005). Transcript profiling in

peripheral T-cell lymphoma, not otherwise specified, and diffuse large B-cell lymphoma identifies distinct tumor profile signatures. Mol. Cancer Ther. **4**: 1867–1879. DOI: 10.1158/1535-7163.Mct-05-0146.
259. Poirier, F., Joubert-Caron, R., Labas, V., and Caron, M. (2003). Proteomic analysis of a lymphoma-derived cell line (DG75) following treatment with a demethylating drug: modification of membrane-associated proteins. Proteomics **3**: 1028–1036. DOI: 10.1002/pmic.200300374.
260. McDonnell, S.R., Hwang, S.R., Rolland, D., et al. (2013). Integrated phosphoproteomic and metabolomic profiling reveals NPM-ALK-mediated phosphorylation of PKM2 and metabolic reprogramming in anaplastic large cell lymphoma. Blood **122**: 958–968. DOI: 10.1182/blood-2013-01-482026.
261. Garcia-Bermudez, J., Baudrier, L., Bayraktar, E.C., et al. (2019). Squalene accumulation in cholesterol auxotrophic lymphomas prevents oxidative cell death. Nature **567**: 118–122. DOI: 10.1038/s41586-019-0945-5.
262. McDonnell, S.R., Hwang, S.R., Basrur, V., et al. (2012). NPM-ALK signals through glycogen synthase kinase 3β to promote oncogenesis. Oncogene **31**: 3733–3740. DOI: 10.1038/onc.2011.542.
263. Kittipongdaja, W., Wu, X., Garner, J., et al. (2015). Rapamycin Suppresses Tumor Growth and Alters the Metabolic Phenotype in T-Cell Lymphoma. J Invest Dermatol **135**: 2301–2308. DOI: 10.1038/jid.2015.153.
264. Lien, E.C., Lyssiotis, C.A., and Cantley, L.C. (2016). Metabolic Reprogramming by the PI3K-Akt-mTOR Pathway in Cancer. Recent Results Cancer Res **207**: 39–72. DOI: 10.1007/978-3-319-42118-6_3.
265. Xiong, J., Bian, J., Wang, L., et al. (2015). Dysregulated choline metabolism in T-cell lymphoma: role of choline kinase-α and therapeutic targeting. Blood Cancer J **5**: 287. DOI: 10.1038/bcj.2015.10.
266. Leca, J., Lemonnier, F., Meydan, C., et al. (2023). IDH2 and TET2 mutations synergize to modulate T Follicular Helper cell functional interaction with the AITL microenvironment. Cancer Cell **41**:323-339 e310. DOI: 10.1016/j.ccell.2023.01.003.
267. Pirozzi, C.J., and Yan, H. (2021). The implications of IDH mutations for cancer development and therapy. Nature Reviews Clinical Oncology **18**: 645–661. DOI: 10.1038/s41571-021-00521-0.
268. Intlekofer, A.M., Shih, A.H., Wang, B., et al. (2018). Acquired resistance to IDH inhibition through trans or cis dimer-interface mutations. Nature **559**: 125–129. DOI: 10.1038/s41586-018-0251-7.
269. Wang, L., Li, L.R., Zhang, L., and Wang, J.W. (2020). The landscape of new drugs in extranodal NK/T-cell lymphoma. Cancer Treat Rev **89**: 102065. DOI: 10.1016/j.ctrv.2020.102065.
270. Xiong, J., Cui, B.W., Wang, N., et al. (2020). Genomic and Transcriptomic Characterization of Natural Killer T Cell Lymphoma. Cancer Cell **37**:403-419 e406. DOI: 10.1016/j.ccell.2020.02.005.
271. Rizzari, C., Zucchetti, M., Conter, V., et al. (2000). L-asparagine depletion and L-asparaginase activity in children with acute lymphoblastic leukemia receiving i. m. or i.v. Erwinia C. or E. coli L-asparaginase as first exposure. Ann. Oncol. **11**: 189–193. DOI: 10.1023/a:1008368916800.
272. Clavell, L.A., Gelber, R.D., Cohen, H.J., et al. (1986). Four-agent induction and intensive asparaginase therapy for treatment of childhood acute lymphoblastic leukemia. N Engl J Med **315**: 657–663. DOI: 10.1056/NEJM198609113151101.
273. Barrington, S.F., and Trotman, J. (2021). The role of PET in the first-line treatment of the most common subtypes of non-Hodgkin lymphoma. Lancet Haematol **8**: e80–e93. DOI: 10.1016/S2352-3026(20)30365-3.
274. Cottereau, A.S., Becker, S., Broussais, F., et al. (2016). Prognostic value of baseline total metabolic tumor volume (TMTV0) measured on FDG-PET/CT in patients with peripheral T-cell lymphoma (PTCL). Ann. Oncol. **27**: 719–724. DOI: 10.1093/annonc/mdw011.
275. Zeman, M.N., Akin, E.A., Merryman, R.W., and Jacene, H.A. (2023). Interim FDG-PET/CT for Response Assessment of Lymphoma. Semin. Nucl. Med. **53**: 371–388. DOI: 10.1053/j.semnuclmed.2022.10.004.
276. Miyawaki, K., and Sugio, T. (2022). Lymphoma Microenvironment in DLBCL and PTCL-NOS: the key to uncovering heterogeneity and the potential for stratification. J Clin Exp Hematop **62**: 127–135. DOI: 10.3960/jslrt.22027.
277. Gaulard, P., and de Leval, L. (2014). The microenvironment in T-cell lymphomas: emerging themes. Semin. Cancer Biol. **24**: 49–60. DOI: 10.1016/j.semcancer.2013.11.004.
278. Pritchett, J.C., Yang, Z.Z., Kim, H.J., et al. (2022). High-dimensional and single-cell transcriptome analysis of the tumor microenvironment in angioimmunoblastic T cell lymphoma (AITL). Leukemia **36**: 165–176. DOI: 10.1038/s41375-021-01321-2.
279. Witalis, M., Chang, J., Zhong, M.C., et al. (2020). Progression of AITL-like tumors in mice is driven by Tfh signature proteins and T-B cross talk. Blood Adv **4**: 868–879. DOI: 10.1182/bloodadvances.2019001114.
280. Chen, Z., Zhu, Q., Deng, X., et al. (2022). Angioimmunoblastic T-cell lymphoma with predominant CD8+ tumor-infiltrating T-cells is a distinct immune pattern with an immunosuppressive microenvironment. Front Immunol **13**: 987227. DOI: 10.3389/fimmu.2022.987227.
281. Sugio, T., Miyawaki, K., Kato, K., et al. (2018). Microenvironmental immune cell signatures dictate clinical outcomes for PTCL-NOS. Blood Adv **2**: 2242–2252. DOI: 10.1182/bloodadvances.2018018754.
282. Bronte, V., and Murray, P.J. (2015). Understanding local macrophage phenotypes in disease: modulating macrophage function to treat cancer. Nat. Med. **21**: 117–119. DOI: 10.1038/nm.3794.
283. Cortes, J.R., Filip, I., Albero, R., et al. (2022). Oncogenic Vav1-Myo1f induces therapeutically targetable macrophage-rich tumor microenvironment in peripheral T cell lymphoma. Cell Rep **39**: 110695. DOI: 10.1016/j.celrep.2022.110695.
284. Chen, J., Jiang, C.C., Jin, L., and Zhang, X.D. (2016). Regulation of PD-L1: a novel role of pro-survival signalling in cancer. Ann. Oncol. **27**: 409–416. DOI: 10.1093/annonc/mdv615.
285. Lin, Z.X., Bai, B., Cai, Q.C., et al. (2012). High numbers of tumor-associated macrophages correlate with poor prognosis in patients with mature T- and natural killer cell lymphomas. Med Oncol **29**: 3522–3528. DOI: 10.1007/s12032-012-0244-6.
286. Zhang, W., Wang, Z., Luo, Y., et al. (2016). GATA3 expression correlates with poor prognosis and tumor-associated macrophage infiltration in peripheral T cell lymphoma. Oncotarget **7**: 65284–65294. DOI: 10.18632/oncotarget.11673.
287. Wang, J., and Ke, X.Y. (2011). The four types of Tregs in malignant lymphomas. J Hematol Oncol **4**: 50. DOI: 10.1186/1756-8722-4-50.
288. Zhao, W.L., Mourah, S., Mounier, N., et al. (2004). Vascular endothelial growth factor-A is expressed both on lymphoma cells and endothelial cells in angioimmunoblastic T-cell lymphoma and related to lymphoma progression. Lab. Invest. **84**: 1512–1519. DOI: 10.1038/labinvest.3700145.
289. Villanueva, M.T. (2017). Cancer immunotherapy: Searching in the immune checkpoint black box. Nat. Rev. Drug Discov. **16**: 599. DOI: 10.1038/nrd.2017.163.
290. Chen, X., Wu, W., Wei, W., and Zou, L. (2022). Immune Checkpoint Inhibitors in Peripheral T-Cell Lymphoma. Front Pharmacol **13**: 869488. DOI: 10.3389/fphar.2022.869488.
291. Wilcox, R.A., Feldman, A.L., Wada, D.A., et al. (2009). B7-H1 (PD-L1, CD274) suppresses host immunity in T-cell lymphoproliferative disorders. Blood **114**: 2149–2158. DOI: 10.1182/blood-2009-04-216671.
292. Miyoshi, H., Kiyasu, J., Kato, T., et al. (2016). PD-L1 expression on neoplastic or stromal cells is respectively a poor or good prognostic factor for adult T-cell leukemia/lymphoma. Blood **128**: 1374–1381. DOI: 10.1182/blood-2016-02-698936.
293. Krishnan, C., Warnke, R.A., Arber, D.A., and Natkunam, Y. (2010). PD-1 expression in T-cell lymphomas and reactive lymphoid entities: potential overlap in staining patterns between lymphoma and viral lymphadenitis. Am J Surg Pathol **34**: 178–189. DOI: 10.1097/PAS.0b013e3181cc7e79.
294. Manso, R., Rodriguez-Perales, S., Torres-Ruiz, R., et al. (2021). PD-L1 expression in peripheral T-cell lymphomas is not related to either PD-L1 gene amplification or rearrangements. Leuk. Lymphoma **62**: 1648–1656. DOI: 10.1080/10428194.2021.1881511.
295. Kim, W.Y., Jung, H.Y., Nam, S.J., et al. (2016). Expression of programmed cell death ligand 1 (PD-L1) in advanced stage EBV-associated extranodal NK/T cell lymphoma is associated with better prognosis. Virchows Arch **469**: 581–590. DOI: 10.1007/s00428-016-2011-0.
296. Lesokhin, A.M., Ansell, S.M., Armand, P., et al. (2016). Nivolumab in Patients With Relapsed or Refractory Hematologic Malignancy: Preliminary Results of a Phase Ib Study. J Clin Oncol **34**: 2698–2704. DOI: 10.1200/JCO.2015.65.9789.
297. Shi, Y., Wu, J., Wang, Z., et al. (2021). Efficacy and safety of geptanolimab (GB226) for relapsed or refractory peripheral T cell lymphoma: an open-label phase 2 study (Gxplore-002). J Hematol Oncol **14**: 12. DOI: 10.1186/s13045-021-01033-1.
298. Merrill, M.H., Dahi, P.B., Redd, R.A., et al. (2023). A phase 2 study of pembrolizumab after autologous stem cell transplantation in patients with T-cell non-Hodgkin lymphoma. Blood **142**: 621–628. DOI: 10.1182/blood.2023020244.
299. Meeuwes, F.O., Brink, M., van der Poel, M.W.M., et al. (2022). Impact of rituximab on treatment outcomes of patients with angioimmunoblastic T-cell lymphoma; a population-based analysis. Eur. J. Cancer **176**: 100–109. DOI: 10.1016/j.ejca.2022.09.008.
300. Doubrovina, E., Oflaz-Sozmen, B., Prockop, S.E., et al. (2012). Adoptive immunotherapy with unselected or EBV-specific T cells for biopsy-proven EBV+ lymphomas after allogeneic hematopoietic cell transplantation. Blood **119**: 2644–2656. DOI: 10.1182/blood-2011-08-371971.
301. Kimura, H., Ito, Y., Kawabe, S., et al. (2012). EBV-associated T/NK-cell lymphoproliferative diseases in nonimmunocompromised hosts: prospective analysis of 108 cases. Blood **119**: 673–686. DOI: 10.1182/blood-2011-10-381921.
302. Hue, S.S., Oon, M.L., Wang, S., et al. (2020). Epstein-Barr virus-associated T- and NK-cell lymphoproliferative diseases: an update and diagnostic approach. Pathology **52**: 111–127. DOI: 10.1016/j.pathol.2019.09.011.
303. Kato, S., Takahashi, E., Asano, N., et al. (2012). Nodal cytotoxic molecule (CM)-positive Epstein-Barr virus (EBV)-associated peripheral T cell lymphoma (PTCL): a clinicopathological study of 26 cases. Histopathology **61**: 186–199. DOI: 10.1111/j.1365-2559.2012.04199.x.
304. Ng, S.B., Chung, T.H., Kato, S., et al. (2018). Epstein-Barr virus-associated primary nodal T/NK-cell lymphoma shows a distinct molecular signature and copy number changes. Haematologica **103**: 278–287. DOI: 10.3324/haematol.2017.180430.
305. Ho, J.W.Y., Li, L., Wong, K.Y., et al. (2023). Comprehensive Profiling of EBV Gene Expression and Promoter Methylation Reveals Latency II Viral Infection and Sporadic Abortive Lytic Activation in Peripheral T-Cell Lymphomas. Viruses **15**. DOI: 10.3390/v15020423.
306. Higgins, J.P., van de Rijn, M., Jones, C.D., et al. (2000). Peripheral T-cell lymphoma complicated by a proliferation of large B cells. Am J Clin Pathol **114**: 236–247. DOI: 10.1309/72cm-kaxf-66de-4xva.

307. Ho, J.W., Ho, F.C., Chan, A.C., et al. (1998). Frequent detection of Epstein-Barr virus-infected B cells in peripheral T-cell lymphomas. J. Pathol. **185**: 79–85. DOI: 10.1002/(sici)1096-9896(199805)185:1<79::Aid-path52>3.0.Co;2-3.
308. Weiss, L.M., Jaffe, E.S., Liu, X.F., et al. (1992). Detection and localization of Epstein-Barr viral genomes in angioimmunoblastic lymphadenopathy and angioimmunoblastic lymphadenopathy-like lymphoma. Blood **79**: 1789–1795. DOI. DOI: 10.1182/blood.V79.7.1789.1789.
309. Wai, C.M.M., Chen, S., Phyu, T., et al. (2022). Immune pathway upregulation and lower genomic instability distinguish EBV-positive nodal T/NK-cell lymphoma from ENKTL and PTCL-NOS. Haematologica **107**: 1864–1879. DOI: 10.3324/haematol.2021.280003.
310. Bayda, N., Tilloy, V., Chaunavel, A., et al. (2021). Comprehensive Epstein-Barr Virus Transcriptome by RNA-Sequencing in Angioimmunoblastic T Cell Lymphoma (AITL) and Other Lymphomas. Cancers (Basel) **13**. DOI: 10.3390/cancers13040610.
311. Qiu, J., Smith, P., Leahy, L., and Thorley-Lawson, D.A. (2015). The Epstein-Barr virus encoded BART miRNAs potentiate tumor growth in vivo. PLoS Pathog **11**: e1004561. DOI: 10.1371/journal.ppat.1004561.
312. Chen, H., Smith, P., Ambinder, R.F., and Hayward, S.D. (1999). Expression of Epstein-Barr virus BamHI-A rightward transcripts in latently infected B cells from peripheral blood. Blood **93**: 3026–3032. DOI. DOI: 10.1182/blood.V93.9.3026.409k28_3026_3032.
313. Bristol, J.A., Djavadian, R., Albright, E.R., et al. (2018). A cancer-associated Epstein-Barr virus BZLF1 promoter variant enhances lytic infection. PLoS Pathog **14**: e1007179. DOI: 10.1371/journal.ppat.1007179.
314. Münz, C. (2019). Latency and lytic replication in Epstein-Barr virus-associated oncogenesis. Nat. Rev. Microbiol. **17**: 691–700. DOI: 10.1038/s41579-019-0249-7.
315. de Mel, S., Soon, G.S., Mok, Y., et al. (2018). The Genomics and Molecular Biology of Natural Killer/T-Cell Lymphoma: Opportunities for Translation. Int J Mol Sci **19**. DOI: 10.3390/ijms19071931.
316. Matsuoka, M., and Jeang, K.T. (2007). Human T-cell leukaemia virus type 1 (HTLV-1) infectivity and cellular transformation. Nat. Rev. Cancer **7**: 270–280. DOI: 10.1038/nrc2111.
317. Ishitsuka, K., and Tamura, K. (2014). Human T-cell leukaemia virus type I and adult T-cell leukaemia-lymphoma. Lancet Oncol **15**: e517–526. DOI: 10.1016/s1470-2045(14)70202-5.
318. Ohsugi, T., Kumasaka, T., Okada, S., and Urano, T. (2007). The Tax protein of HTLV-1 promotes oncogenesis in not only immature T cells but also mature T cells. Nat. Med. **13**: 527–528. DOI: 10.1038/nm0507-527.
319. Rende, F., Cavallari, I., Corradin, A., et al. (2011). Kinetics and intracellular compartmentalization of HTLV-1 gene expression: nuclear retention of HBZ mRNAs. Blood **117**: 4855–4859. DOI: 10.1182/blood-2010-11-316463.
320. Melamed, A., Yaguchi, H., Miura, M., et al. (2018). The human leukemia virus HTLV-1 alters the structure and transcription of host chromatin in cis. Elife **7**. DOI: 10.7554/eLife.36245.
321. Barski, M.S., Vanzo, T., Zhao, X.Z., et al. (2021). Structural basis for the inhibition of HTLV-1 integration inferred from cryo-EM deltaretroviral intasome structures. Nat Commun **12**: 4996. DOI: 10.1038/s41467-021-25284-1.
322. Satou, Y., Miyazato, P., Ishihara, K., et al. (2016). The retrovirus HTLV-1 inserts an ectopic CTCF-binding site into the human genome. Proc Natl Acad Sci U S A **113**: 3054–3059. DOI: 10.1073/pnas.1423199113.
323. Drosu, N.C., Edelman, E.R., and Housman, D.E. (2020). Tenofovir prodrugs potently inhibit Epstein-Barr virus lytic DNA replication by targeting the viral DNA polymerase. Proc Natl Acad Sci U S A **117**: 12368–12374. DOI: 10.1073/pnas.2002392117.
324. Boehm, K.M., Khosravi, P., Vanguri, R., et al. (2022). Harnessing multimodal data integration to advance precision oncology. Nat. Rev. Cancer **22**: 114–126. DOI: 10.1038/s41568-021-00408-3.
325. Lipkova, J., Chen, R.J., Chen, B., et al. (2022). Artificial intelligence for multimodal data integration in oncology. Cancer Cell **40**: 1095–1110. DOI: 10.1016/j.ccell.2022.09.012.
326. Khosravi, P., Lysandrou, M., Eljalby, M., et al. (2021). A Deep Learning Approach to Diagnostic Classification of Prostate Cancer Using Pathology-Radiology Fusion. J. Magn. Reson. Imaging **54**: 462–471. DOI: 10.1002/jmri.27599.
327. Moran-Crusio, K., Reavie, L., Shih, A., et al. (2011). Tet2 loss leads to increased hematopoietic stem cell self-renewal and myeloid transformation. Cancer Cell **20**: 11–24. DOI: 10.1016/j.ccr.2011.06.001.
328. Muto, H., Sakata-Yanagimoto, M., Nagae, G., et al. (2014). Reduced TET2 function leads to T-cell lymphoma with follicular helper T-cell-like features in mice. Blood Cancer J **4**: e264. DOI: 10.1038/bcj.2014.83.
329. Zheng, J., Wang, Z., Pan, X., et al. (2023). DNMT3A(R882H) accelerates angioimmunoblastic T-cell lymphoma in mice. Oncogene **42**: 1940–1950. DOI: 10.1038/s41388-023-02699-2.
330. Li, W., Kou, J., Zhang, Z., et al. (2023). Cellular redox homeostasis maintained by malic enzyme 2 is essential for MYC-driven T cell lymphomagenesis. Proc Natl Acad Sci U S A **120**: e2217869120. DOI: 10.1073/pnas.2217869120.
331. Sato, F., Ishida, T., Ito, A., et al. (2013). Angioimmunoblastic T-cell lymphoma mice model. Leuk Res **37**: 21–27. DOI: 10.1016/j.leukres.2012.09.009.
332. Townsend, E.C., Murakami, M.A., Christodoulou, A., et al. (2016). The Public Repository of Xenografts Enables Discovery and Randomized Phase II-like Trials in Mice. Cancer Cell **30**: 183. DOI: 10.1016/j.ccell.2016.06.008.
333. Liu, Y., Wu, W., Cai, C., et al. (2023). Patient-derived xenograft models in cancer therapy: technologies and applications. Signal Transduct Target Ther **8**: 160. DOI: 10.1038/s41392-023-01419-2.
334. Khan, A.O., Rodriguez-Romera, A., Reyat, J.S., et al. (2023). Human Bone Marrow Organoids for Disease Modeling, Discovery, and Validation of Therapeutic Targets in Hematologic Malignancies. Cancer Discov **13**: 364–385. DOI: 10.1158/2159-8290.CD-22-0199.
335. Greaves, M., and Maley, C.C. (2012). Clonal evolution in cancer. Nature **481**: 306–313. DOI: 10.1038/nature10762.
336. Papalexi, E., and Satija, R. (2018). Single-cell RNA sequencing to explore immune cell heterogeneity. Nat. Rev. Immunol. **18**: 35–45. DOI: 10.1038/nri.2017.76.
337. Wan, J.C.M., Massie, C., Garcia-Corbacho, J., et al. (2017). Liquid biopsies come of age: towards implementation of circulating tumour DNA. Nat. Rev. Cancer **17**: 223–238. DOI: 10.1038/nrc.2017.7.
338. Niroula, A., Sekar, A., Murakami, M.A., et al. (2021). Distinction of lymphoid and myeloid clonal hematopoiesis. Nat. Med. **27**: 1921–1927. DOI: 10.1038/s41591-021-01521-4.
339. van Zeventer, I.A., de Graaf, A.O., Salzbrunn, J.B., et al. (2023). Evolutionary landscape of clonal hematopoiesis in 3,359 individuals from the general population. Cancer Cell **41**:1017-1031 e1014. DOI: 10.1016/j.ccell.2023.04.006.
340. Zhang, Y., Lee, D., Brimer, T., et al. (2020). Genomics of Peripheral T-Cell Lymphoma and Its Implications for Personalized Medicine. Front Oncol **10**: 898. DOI: 10.3389/fonc.2020.00898.
341. Luo, H., Liu, D., Liu, W., et al. (2023). Clinical and genetic characterization of Epstein-Barr virus-associated T/NK-cell lymphoproliferative diseases. J. Allergy Clin. Immunol. **151**: 1096–1109. DOI: 10.1016/j.jaci.2022.11.012.
342. Vermaat, J.S., Somers, S.F., de Wreede, L.C., et al. (2020). MYD88 mutations identify a molecular subgroup of diffuse large B-cell lymphoma with an unfavorable prognosis. Haematologica **105**: 424–434. DOI: 10.3324/haematol.2018.214122.
343. Ryan, J.L., Jones, R.J., Kenney, S.C., et al. (2010). Epstein-Barr virus-specific methylation of human genes in gastric cancer cells. Infect Agent Cancer **5**: 27. DOI: 10.1186/1750-9378-5-27.

FUNDING AND ACKNOWLEDGMENTS

We appreciate helpful discussions with Dr. Cong Wang. This work was supported by National Key R&D Program of China (2022YFC2502600), National Natural Science Foundation of China (81830007 and 82130004), Chang Jiang Scholars Program, Shanghai Municipal Education Commission Gaofeng Clinical Medicine Grant Support (20152206 and 20152208), Clinical Research Plan of Shanghai Hospital Development Center (SHDC2020CR1032B), Multicenter Clinical Research Project by Shanghai Jiao Tong University School of Medicine (DLY201601), Collaborative Innovation Center of Systems Biomedicine, and the Samuel Waxman Cancer Research Foundation. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

Y.Q. collected and interpreted studies and was a major contributor to the writing and editing of the manuscript. W.Z. provided direction and guidance throughout the preparation of this manuscript. All authors read and approved the final manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

Not applicable.

SUPPLEMENTAL INFORMATION

It can be found online at https://doi.org/10.59717/j.xinn-med.2024.100048