Underlying biology, challenges and emergent concepts in the treatment of relapsed and refractory pediatric T-cell acute lymphoblastic leukemia

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Abstract

Relapsed and refractory disease in children with T-cell acute lymphoblastic leukemia (R/R T-ALL) remains a major clinical challenge. Outcomes for children who relapse or exhibit resistance to initial treatments are dismal, with survival rates frequently below 25% despite aggressive therapy. To minimize toxicities and improve outcomes, individualized precision medicine approaches targeting the underlying biology of R/R T-ALL are especially important, considering that T-ALL is characterized by genetic, epigenetic and posttranscriptional heterogeneity, and organ and niche specificities (e.g. the central nervous system), all of which underlie disease progression and therapy resistance. Here, we summarize the current understanding of the complexity of pediatric T-ALL biology and how such knowledge may be clinically leveraged, emphasizing the need for innovative therapeutic routes to improve outcomes for children with R/R T-ALL. Emerging approaches that hold promise or show palpable results include proteasome inhibitors, BCL-2 antagonists, and JAK (for JAK- and IL-7R-driven cases), ABL and SRC family tyrosine kinase (for LCK-activated cases), MEK or PI3K-mTOR inhibitors. MYC-targeting agents, DNA demethylating agents, histone deacetylase inhibitors, splicing modulators, or drugs exploring T-ALL metabolic vulnerabilities, are other examples for potential pharmacological intervention. Immunotherapies, particularly CAR T-cell products targeting CD7 and other markers, but also biologics (e.g. targeting CD38), are under development and increasing interest. These agents should be rationally integrated into precision medicine combination therapies informed by genetic, epigenetic, and posttranscriptional insights that will be essential to refine risk stratification and minimize the risk of resistance. Novel strategies leveraging artificial intelligence and machine learning could accelerate discovery and optimize treatment frameworks.

Relapsed and refractory disease: a major clinical challenge in pediatric T-ALL

Relapsed and refractory (R/R) T-cell acute lymphoblastic leukemia (T-ALL) remains a significant challenge in pediatric oncology. Despite advances in front-line therapies that have improved survival rates, children who relapse or show resistance to initial treatments have a dismal outcome, with survival rates often below 25%.

Refractory disease can occur during frontline therapy (i.e. primary refractory disease or induction failure) or at the time of relapse. On frontline protocols, children with T-ALL are three times more likely to experience primary refractory disease than those with B-ALL, accounting for 10% of all T-ALL cases (1). This early treatment failure portends a poor outcome despite therapy intensification including hematopoietic stem cell transplantation (HSCT) (2, 3).

Relapse rates of children with ALL on current treatment protocols range from 8-20% (4), with T-ALL consistently showing higher relapse rates than B-ALL. In addition, relapses occur earlier and frequently involve the CNS (4). Significant advances in therapy for relapsed B-ALL, with the integration of immunotherapeutic agents, such as blinatumomab, have led to an improved overall survival (OS) of up to 80% even in aggressive, early relapsing, disease (5). In contrast, children with relapsed T-ALL enrolled on Children's Oncology Group frontline ALL trials between 1996-2014 showed a post-relapse 5-year OS of only 35.5 ± 3.3% (4), with many patients failing to achieve remission. Relapsed T-ALL has long been recognized as an adverse prognostic factor and regarded as an indication for intensive therapy including HSCT, irrespective of relapse timing or the site of relapse (6).

Unfortunately, there has been limited progress in the treatment of R/R T-ALL despite testing of several novel agents. Nelarabine, a pro-drug of the deoxyguanosine-analogue

ara-G showed promising T-ALL specific activity *in vitro.* However, efficacy was relatively limited as single agent in a phase 2 study in R/R T-ALL (NCT00981799, Table 1), and was not improved when combined with other chemotherapy (7). Recently, Horton et al. investigated the addition of the proteasome inhibitor bortezomib in relapsed ALL, reporting an encouraging 68% CR2 rate in relapsed T-ALL patients (8). However, in the randomized frontline COG AALL1231 trial (NCT02112916), bortezomib did not impact event-free survival (EFS) or OS for newly diagnosed T-ALL, contrary to T-lymphoblastic lymphoma (9). In the current IntReALL-2010 trial for high-risk relapses, the addition of bortezomib is under investigation in a randomized study (NCT03590171), with preliminary results expected shortly.

With current poor prognosis of relapsed T-ALL despite aggressive therapy, individualized precision medicine approaches for patients in first relapse are particularly relevant. For instance, patients with activated IL-7R or JAK-STAT signaling may respond favorably to JAK inhibitors, whereas dasatinib and other tyrosine kinase inhibitors may benefit those with activated LCK (10) or with *ABL*-class fusions. Venetoclax and navitoclax, BCL-2/BCL-X protein family inhibitors, have shown promising activity in preclinical models, leading to a phase 1 trial using a venetoclax/navitoclax combination in patients with R/R ALL (11). The trial demonstrated an impressive 60% CR rate, with particularly favorable responses in T-ALL, but, unfortunately, navitoclax was recently withdrawn by the manufacturer. Navitoclax unavailability may be compensated by newer BCL-X_L and BCL-2/BCL-X_L dual inhibitors. For example, LP-118 showed preclinical efficacy in CLL (12) and is currently being evaluated in Phase 1 or 1/2 (NCT04771572, NCT06207123) trials that include ALL patients. Other agents, such as DT2216, Lisaftoclax (APG-2575), Pelcitoclax (APG-1252), S65487, and Sonrotoclax (BGB-11417), are undergoing clinical trials in AML,

CLL, and other malignancies, but further investigation is needed to assess their potential in R/R T-ALL. Immunotherapies are also now showing promise in T-ALL, as discussed below.

To design the most efficient precision medicine approaches for the treatment of R/R T-ALL, a better understanding of the underlying biology of the disease is mandatory. In the following sections, we summarize our current understanding of pediatric T-ALL and how this knowledge may be leveraged for the treatment of relapsed and refractory disease.

Genetics

T-ALL is characterized by dysregulation of master transcription factor (TF) oncogenes that lead to differentiation arrest, thereby governing the overall gene expression and immunophenotypic signature of the leukemia. Such class-defining lesions can drive ectopic expression of TFs that are not present in thymocytes (e.g. *TLX1* and *TLX3*) or lead to continued overexpression of developmentally important TFs (e.g. *TAL1*). While the molecular dissection of T-ALL is complex due to its genetic heterogeneity, one may conceptualize T-ALL subtypes according to their level of differentiation arrest: i) pre-cortical, referred to as early T-cell progenitor ALL (ETP-ALL); ii) cortical T-ALL, characterized by CD1a positivity; and iii) post-cortical T-ALL, often characterized by *TAL1/LMO* lesions.

Off-target RAG activity has often been implicated in the mutagenic process leading to these driver lesions. RAG-induced chromosomal breaks can juxtapose powerful developmentally active enhancers, such as those regulating *TCRA/B/D* and *BCL11B*, to the oncogenic TFs mentioned above. Activation of these TFs also results from noncoding driver mutations. For instance, noncoding somatic mutations introduce binding sites for

MYB, subsequently creating a super-enhancer driving aberrant *TAL1* expression (13). Noncoding lesions can also activate *LMO2* through creation of a neomorphic promoter (14). Notably, these are likely early disease-initiating events, sometimes detectable at birth (15).

A recent landmark study has stratified T-ALL into 15 genetically distinct subtypes through comprehensive genome and transcriptome sequencing of >1,300 childhood diagnosis and remission samples (16). This work highlighted the value in whole genome sequencing (with ~60% of patients harboring noncoding driver lesions), added granularity to previously recognized subgroups and identified prognostically important additional groups. Namely, the TAL/LMO subtype can be subdivided into TAL1 DP-like (CD4+CD8+) and TAL1 αβ-like (TRAC overexpression) due to their high RAG1/2 expression and TCRαβ rearrangements, respectively. T-ALLs with the KMT2A, TLX3 and MLLT10 subtype had similar signatures to pro/pre-T-cells, whereas HOXA9-TCR, TLX1, NKX2-1 and TAL1 DP-like closely resembled cycling double-positive T-cell signatures. The LMO2 subtype was associated with positive minimal residual disease (MRD) at end of induction, and could be subdivided into LMO2 γδ-like, due to the similarity to γδ/effector T-cells, and STAG2/LMO2 with a myeloid signature.

The study also proposes important changes to the classification of ETP-ALL (16). Enriched for alterations impairing the function of factors involved in hematopoiesis (e.g. *RUNX1*, *ETV6*) and epigenetic regulation (e.g. *EZH2*, *SUZ12*), and mutations that activate signaling pathways (e.g., IL-7R-JAK-STAT, RAS-RAF-MEK-ERK) (17), the ETP-ALL genotype is broadly similar in adult and pediatric cases (18, 19) – except for *DNMT3A* mutations, which are rarely found in children (18, 19). These genetic alterations may directly influence treatment response, as described for *STAT5* mutations (20), PRC2 loss-of-function (21), BCL2 dependence (22), and *HOXA* overexpression (23, 24). ETP-ALL,

traditionally identified by immunophenotype (25), is now more accurately defined as a transcriptional entity encompassing 'ETP-like' cases that do not meet the original phenotypic definition. In line with early differentiation arrest, there is enrichment for immature hematopoietic transcriptional signatures including hematopoietic stem and progenitor cells, common lymphoid progenitors, lymphoid-primed multipotent progenitors and normal ETPs. Intriguingly, single cell profiling revealed plasticity within ETP-ALL populations, including heterogeneous stem cell states that could be linked both to relapse risk and impaired microenvironmental immune response (16, 26). Positivity for MRD was common in the ETP-like cases, with ETP-like KMT2A patients having a significantly inferior EFS.

Underpinning the mechanisms of relapse requires an in-depth understanding of the genomic drivers and their associated disease outcomes. However, the significance of distinct prognostic markers often remains controversial given the difficulty in adequately powering studies in such a rare disease. Furthermore, treatment protocols, particularly with the introduction of risk-adapted studies, have significantly impacted the prognostic relevance of different biomarkers such as the already mentioned ETP-ALL immunophenotype (27). Nonetheless, studies have reported a relatively favorable prognosis for patients with TAL1 DP-like (with *RPL10* mutations) and TLX1+ T-ALL, and those harboring *NOTCH1* (with the exception of *NOTCH1* intronic SNV and intragenic losses), *FBXW7*, or *PHF6* mutations (16, 28). In contrast, TAL1 αβ-like and the STAG2/LMO2 group, or those harboring mutations in *PTEN*, *RAS*, *EZH2* and *TP53* (28) have all been associated with inferior outcome (16, 29, 30). Patients with *TAL1* noncoding drivers, MYC activating lesions and/or RAS pathway mutations (so-called TMR genotype) who experience induction failure have a particularly dismal outcome, with less than 25% 5-year OS (2). Targeting MYC may be particularly relevant in this

context. In solid tumors, MYC degraders, such as the cereblon E3 ligase targeting agent A80.2HCl, demonstrated pre-clinical activity (31) and the cell-penetrable peptide Omomyc showed promising efficacy and safety in a phase 1 study (32). Furthermore, new compounds targeting gene products that show synthetic lethality with MYC, such as the BET family protein BRD4 or members of the Aurora kinase family, are being explored in early clinical trials (33).

Notably, certain mutations are solely detected at relapse. For instance, *NT5C2* mutations (which occur in approximately 20% of T-ALL relapse cases) lead to resistance to mercaptopurine, a drug used during maintenance therapy (34). Interestingly, mutations in *NT5C2*, and in genes such as *PRPS1*, *NR3C1*, and *TP53*, are induced by mercaptopurine and other thiopurines (35). Recognizing such lesions during treatment would enable clinicians to alter their approach to maintenance therapy in real time.

Epigenetics

Given the central role of epigenetics in normal embryogenesis and cell differentiation, not only genetic but also epigenetic aberrations in thymocytes may drive the pathogenesis of T-ALL. While genomic alterations affecting genes such as *PHF6*, *IDH1/2*, *DNMT3A*, *TET1/2/3*, *KMT2A*, *KDM6A*, *CREBBP*, *EP300*, *EZH2*, *EED*, *SUZ12*, *CTCF* and others (many of which are associated with relapse) demonstrate the functional importance of different epigenetic regulators in T-ALL (36), this section focuses on the potential relevance of epigenetic alterations themselves for biological subgrouping and treatment stratification.

Over the past decade, DNA methylation (DNAm) of cytosine bases (Cytosine-phosphate-Guanine, CpG sites) has been extensively studied. Distinct hyper- and hypo-methylated subgroups were identified in both pediatric and adult T-ALL (37, 38). Whole-

genome methylation sequencing revealed gradual global hypermethylation, ranging from a hypomethylated profile close to healthy precursor T-cells, to extensively hypermethylated profiles in CpG-dense genomic regions (39). These divergent genome-wide methylation phenotypes are reflected in the CpG island methylator phenotype (CIMP) T-ALL subgroups, identified through array technologies, including a hypermethylated CIMP-high subgroup, and a hypomethylated CIMP-low subgroup (38). The CIMP subgroups overlap strongly with the CpG island and Open Sea Methylation (COSMe) subgroups (40). Hypomethylated subgroups including the CIMP-low/COSMe-I subgroups have been repeatedly associated with poorer prognosis in T-ALL (38, 40).

Interestingly, the DNAm subgroups have been associated with replicative history (40, 41), suggesting different routes to leukemia development. The CIMP-low/COSMe-I subgroup was associated with shorter proliferative history, *STIL::TAL1* fusions, *TAL1* overexpression, *PTEN* aberrations, and 6q deletions, whereas the CIMP-high/COSME-II subgroup has a predicted longer proliferative history and was associated with *WT1* mutations, and overexpression of *TLX1/3*, *NKX2-1* and *HOXA* genes (**Fig. 1**) (40, 41).

An evaluation of the CIMP classifier, in combination with MRD status after induction therapy, was conducted in 348 T-ALL samples treated according to modern protocols in the Nordic countries and the Netherlands. The study confirmed that CIMP classification has the potential to enhance current MRD-based risk stratification (42). DNA methylation classification may be rapidly integrated into clinical diagnostics, as it is already established for WHO classification of central nervous system (CNS) tumors.

The next step is to evaluate whether DNAm subgroups, based on their different underlying biology, would benefit from distinct treatment strategies. Considering the overall pattern of hypermethylation, demethylating agents could potentially be used. DNMT-inhibiting drugs, such as decitabine and 5-azacytidine, are already approved for

treating other hematological malignancies (e.g. AML). However, clinical trials in T-ALL are limited (NCT05376111, NCT01483690, Table 1) and have yet to yield conclusive results. A few pediatric *in vivo* patient-derived xenograft T-ALL models were treated with decitabine, showing genome-wide hypomethylation and altered transcriptome profiles, along with improved leukemia-free survival (40). The potential of combining decitabine and venetoclax in R/R T-ALL was highlighted in several case reports (43, 44)**,** but conclusive clinical trials (e.g. NCT06686108, NCT05740449) are needed. Furthermore, clinical evaluation of the recent DNMT1-selective inhibitor GSK3685032 (45) is anticipated, given its reversible effects and potential for fewer side-effects compared to decitabine.

Histones represent an essential component of the epigenetic landscape. They undergo a variety of dynamic post-translational modifications (PTMs), collectively known as the "histone code". Evidence of altered histone codes in T-ALL emerged from identification of genetic alterations in genes associated with histone methylation and acetylation (36). Recently, a histone PTM atlas of 18 T-ALL cell lines was published (46), documenting the levels of a plethora of histone PTMs (e.g. methylation, acetylation, phosphorylation, ubiquitylation). Supporting previous studies, levels of H3K27me3 showed considerable variation among the cell lines, attributed to mutations and deletions within the PRC2 complex (47). The enrichment for specific mutations in histone PTM modulators at relapse (21, 48) and the impact these have on chemosensitivity of T-ALL cell lines (21), demonstrate the relevance of the altered histone code in therapy response. However, to fully elucidate the relationship between histone PTMs and disease biology, molecular subtypes and clinical outcome, a large patient cohort should be investigated. Moreover, integrating single-cell histone PTM dynamics with single-cell transcriptomics should

provide single-cell insights into the interplay between histone PTMs and the transcriptome, allowing for characterization of drug-tolerant persistent T-ALL cells.

The reversible nature of histone PTMs opens therapeutic opportunities and challenges. Preclinical studies showed that inhibitors of HDACs (e.g., vorinostat, panobinostat), histone methyltransferases (DOT1L inhibitors) and histone demethylases (KDM1A inhibitors) can target primary and relapsed/refractory T-ALL (49, 50), although recurrence after prolonged treatment with histone PTM-targeted drugs may be an issue, as reported in other settings (51). Clinical implementation of epigenetic drugs will require further investigation into efficiency and potential toxicities (NCT02518750, NCT01483690), particularly in combination therapies.

In short, different lines of evidence indicate the importance of epigenetics in T-ALL biology and the relevance of epigenetic subgrouping in T-ALL. To advance precision medicine in T-ALL, it will be important to further assess the role of epigenetics in risk stratification and development of new therapeutic strategies.

Posttranscriptional dysregulation

Dysregulation of RNA homeostasis, including polyadenylation, splicing, and translation, contributes to disease progression and drug resistance. In 2004, De Keersmaecker et al. identified mutations in ribosomal subunits (RPL5, RPL10) and the polyadenylation factor CNOT3 in T-ALL (52). The RPL10 R98S mutation disrupts ribosome biogenesis, causing oxidative stress and metabolic changes that promote leukemia cell survival via BCL-2 and JAK-STAT signaling. *CNOT3* mutations are either truncating or missense located at the splice donor site of exon 5, leading to splicing defects, and reduced mRNA expression, suggesting a tumor suppressor role in T-ALL.

Dysregulated splicing is the most studied posttranscriptional regulation in leukemic settings (**Fig. 2**) impacting critical signaling pathways, cell-cycle, DNA damage response and apoptosis (53, 54). In T-ALL, analysis of glucocorticoid-sensitive and -resistant samples revealed distinct splicing patterns, indicating global dysfunction. Key splicing factors (SFs), including U2AF1 and HNRNPA1, were significantly altered. Energy metabolism genes, including those encoding glycolytic enzymes (*PFKL*, *PFKM*), ubiquinol-cytochrome c reductase members (*UQCRC1*, *UQCRC2*), and NADH dehydrogenase subunits, exhibit differential splicing in glucocorticoid-resistant T-ALL. These splicing changes involve intron retention and alternative splice site selection. Moreover, transcripts with oncogenic impact, such as those of proteasomal chaperon PSMG1 and the DNA damage response signaling kinase CHEK2 are plagued by splicing changes in T-ALL (54). Inhibition of the U2 spliceosome complex component SF3B1 disrupted splicing of *CHECK2* and *PSMG1*, synergizing with CHEK2 and proteasomal inhibitors to block T-ALL growth (54, 55). E7820 and indisulam, which degrade the splicing regulator RBM39 via DCAF15, demonstrated clinical responses as single agents and in combination with chemotherapy in R/R AML, although toxicity remained a challenge (56, 57). Indisulam causes widespread splicing defects in T-ALL cells, driving cell death and delaying T-ALL growth *in vivo* (58). Inhibitors of kinases that impact splicing, such as CLKs and SRPK1, are being tested in solid tumors and myeloid malignancies (JapicCTI-184188 and NCT05732103). Further research is warranted to fully explore the potential of splicing inhibitors and their combination with disease-relevant pathway (e.g. proteasome, apoptosis) inhibitors in R/R T-ALL.

Other aspects of posttranscriptional dysregulation remain relatively unexplored in T-ALL. To date, more than 170 RNA modifications were identified. RNA methylation, such as N6-methyladenosine (m6A), or RNA deamination (A-to-I conversion) might play a

role in T-ALL pathophysiology. *NOTCH1* and *IRF8* are modified by m6A, affecting their expression (59). The m6A reader IGF2BP2 binds to methylated *NOTCH1* mRNA, enhancing its stability and translation, thus promoting T-ALL progression and resistance (60). Inhibition of IGF2BP2 using JX5 reduces tumor burden, suggesting that targeting m6A components might hold therapeutic promise for T-ALL. ADAR1, an RNA-binding protein and deaminase that catalyzes A-to-I RNA editing, is overexpressed in T-ALL cells and supports leukemia stem cell self-renewal and chemotherapy resistance(61). By enhancing RNA editing, ADAR1 suppresses apoptosis through inhibition of interferon production and ISGs by reducing cytoplasmic dsRNA. Targeting RNA methylation homeostasis, particularly the activity of erasers such as FTO demethylase and ALKBH5, in T-ALL also merits attention based on the broad tumor-promoting functions of these players.

In short, targeting posttranscriptional regulation to improve the outcome of R/R T-ALL is a promising therapeutic avenue that warrants further investigation.

Signaling

T-cell development in the thymus is orchestrated by signaling pathways such as those triggered by NOTCH, IL-7R, and the pre-T-cell receptor (preTCR) and TCR, which are often subverted and contribute to T-ALL development and progression (**Fig. 3**).

NOTCH pathway mutations occur in a majority of T-ALL cases. While *NOTCH1* intragenic deletions (exon 3–27 or 16–27) and intronic SNV are associated with inferior OS and EFS (16), NOTCH pathway mutations are generally associated with low risk in the absence of *RAS*, PI3K pathway (*PTEN*, *PIK3CA*, and *PIK3R1*), *TP53*, *DNMT3A*, *IDH1/2*, and *IKZF1* alterations (28). This, together with on-target gastric toxicities and/or limitations in efficacy using NOTCH inhibitors challenges their utility in the context of

R/R T-ALL. Nonetheless, results from studies using gamma secretase inhibitors to determine the optimal dosage in T-ALL patients (NCT01363817) and assess their efficacy in R/R T-ALL (NCT00100152) have yet to be reported. Interestingly, recent pre-clinical evidence indicates that concomitant pharmacologic inhibition of the neddylation pathway prevents gut toxicities and prolongs the survival of gamma secretase-treated leukemic mice (62).

Blasts derived from cortical thymocytes express the preTCR, which provides survival and proliferative signals to developing CD4-CD8 double-negative thymocytes, permitting *TCRA* gene rearrangements and formation of TCRαβ CD4-CD8 double-positive T-cells. PreTCR signaling remains functional in leukemia blasts. Phosphorylation of LCK, a critical kinase in the preTCR pathway, is enriched in patients with T-ALL and poor response to glucocorticoid induction therapy (63). The tyrosine kinase inhibitor (TKI) dasatinib was shown to dephosphorylate LCK and induce cell cycle arrest (63, 64). Dasatinib and dexamethasone synergize, reverse glucocorticoid resistance and impair T-ALL expansion *in vivo* (64). *In vitro*, two independent studies showed that ~30–40% of T-ALL pediatric patients are sensitive to dasatinib at nanomolar concentrations (10, 65). These preclinical results (22) led to the prospective evaluation of the combination of dexamethasone, dasatinib and the BH3 mimetic venetoclax in the early phase clinical trial HEM-iSmart-B (NCT05751044) and NCT06686108. Using dexamethasone and dasatinib as backbone, recent preclinical studies suggested synergy in combination with the MTORC1 inhibitor temsirolimus (66). In frontline setting, standard induction therapy will be tested with (versus without) venetoclax for ETP-ALL or near ETP-ALL, and dasatinib (versus no TKI) for all other patients (NCT06390319). Future clinical approaches targeting LCK could employ proteolysis-targeting chimeras (PROTAC), which demonstrated prolonged LCK suppression *in vivo* (67).

TKIs are likely also of clinical benefit for T-ALL patients with kinase activating lesions such as those involving gene rearrangements of *ABL1/2*, *PDGFRA/B*, or *TYK2* (29, 68). Emerging clinical data suggest that addition of kinase inhibitors to conventional chemotherapy might enhance treatment response in at least a proportion of these patients (69). To evaluate this prospectively in T-ALL, newly diagnosed T-ALL patients on the ALLTogether 1 trial will receive imatinib on recognition of such a lesion. The phase 3 clinical trial NCT03007147 will also evaluate the combination of imatinib in combination with conventional therapy in newly diagnosed Philadelphia positive acute lymphoblastic leukemia.

RAS pathway lesions (*NRAS* and *KRAS* gain-of-function mutations or *NF1* and *cCBL* inactivating mutations or deletion) represent common drivers in newly diagnosed and relapsed ALL, varying between 12-30% (16, 29). In certain treatment protocols, RAS pathway mutations can help identify T-ALL patients at increased risk of treatment failure (28). Several RAS pathway inhibitors entered the clinical arena, the benefits of which need to be established due to the frequent subclonal nature of mutations (70). The MEK inhibitor selumetinib and dexamethasone synergize in preclinical models of ALL (71). Another MEK inhibitor, trametinib, will be evaluated in the Hem-iSmart trial together with dexamethasone (NCT05658640).

IL7R gain-of-function mutations (72) and lesions in signaling effectors (most notably JAK-STAT, but also PI3K-AKT-mTOR and MEK-ERK pathway members, all of which can be activated downstream of IL-7R) can affect >40% of T-ALL cases (73). High levels of wild-type IL-7R can also drive T-ALL (74) and IL-7 promotes leukemia maintenance in T-ALL cases with IL-7R expression (75, 76). Of importance to R/R T-ALL, IL-7R signaling promotes glucocorticoid resistance, which can be bypassed using inhibitors of

downstream signaling, and *IL7R* mutations were associated with very high risk in relapsed cases (73, 77).

Ruxolitinib, a JAK1/2 inhibitor, reduces T-ALL cell proliferation and cell survival, showing significant efficacy even in cases without IL-7R or JAK-STAT pathway mutations but with IL-7R expression (75). Ruxolitinib in combination with venetoclax and dexamethasone, cyclophosphamide and cytarabine will be evaluated in the HEM-iSMART-C trial (NCT05745714). Another phase 1/2 trial, currently recruiting, will evaluate the combination of ruxolitinib with chidamide in T-ALL (NCT05075681). Other JAK/STAT inhibitors, such as tofacitinib, demonstrated effectiveness in preclinical models, particularly in cases involving *IL7R*, *JAK1*, and *JAK3* mutations.

Constitutive activation of PI3K-Akt-mTOR pathway is common in T-ALL and drives chemotherapy resistance, especially to glucocorticoids, and relapse (73). While PI3K and/or mTOR inhibitors such as dactolisib, idelalisib, and duvelisib are approved for other cancers (78), their use in T-ALL remains experimental (**Fig. 3**). Notably, no clinical trials have yet evaluated the impact of PI3K inhibitors in T-ALL, highlighting the need for further research to assess their safety and effectiveness. In contrast, several phase 1 or phase 1/2 trials have been completed recently involving the use of the mTOR inhibitors everolimus, and temsirolimus for R/R leukemia/lymphoma, including T-ALL (NCT03328104, NCT00081874, NCT01614197 and NCT01403415). Only the temsirolimus dose-escalation NCT01614197 trial has posted results. None of the patients experienced dose-limiting toxicities. However, MRD disease levels remained high across different doses. The results from the remaining studies will offer a more comprehensive view on the therapeutic potential of mTOR inhibitors.

In addition to *CDKN2A/B* genetic inactivation in >70% of T-ALL cases, most of the signaling pathways mentioned above upregulate CDK4/6 leading to G1-to-S phase cell

cycle progression. Pre-clinical work demonstrating the efficacy of palbociclib and ribociclib, particularly in cooperation with glucorticoids, has driven phase 1 pediatric clinical trials combining ribociclib or palbociclib with chemotherapy (**Table 1**) (79, 80).

Metabolism

A dysregulated metabolic profile underpins T-ALL pathogenesis and subsequently, treatment resistance. T-ALL blasts upregulate both tricarboxylic acid (TCA) cycling and oxidative phosphorylation (OxPhos) concurrently to increased glycolysis levels. These pathways serve to fuel biosynthetic and energetic processes required for disease progression.

Oncogenic drivers of T-ALL (e.g., *NOTCH1*, *RUNX2*, *AKT*) or loss of tumor suppressor genes (e.g., *PTEN*) have been implicated in rewiring metabolism during T-ALL pathogenesis or therapy resistance (81, 82). For example, NOTCH1 signaling is associated with enhanced levels of glutamine metabolism to promote leukemogenesis, whereby anti-NOTCH1 therapy causes metabolic arrest (83). Furthermore, loss of *Pten* enhances glycolysis levels to compensate for this metabolic crisis, thus circumventing anti-NOTCH1 therapy (82). This dynamic ability of T-ALL blasts to rewire central metabolic processes maintains their biosynthetic demands, thus conferring mechanistic changes pertaining to disease resistance and treatment evasion.

While roles of oncogenic drivers in T-ALL metabolism have recently been recognized, clinically, two stalwarts of T-ALL therapy in methotrexate and L-asparaginase have been used historically as metabolically targeting agents. Methotrexate (an anti-folate) inhibits one carbon metabolism thus impairing nucleotide biogenesis, whereas L-asparaginase breaks down the amino acid asparagine required for nucleotide synthesis. While effective, resistance mechanisms mediated by metabolic reprogramming

have emerged, leading to aggressive R/R T-ALL. Briefly, resistance to methotrexate is attributed to mutations in the folylpolyglutmate synthase gene (the enzyme responsible for the polyglutamation of methotrexate), amplification of methotrexate target dihydrofolate reductase, and impaired transport of methotrexate, amongst others (84). In contrast, mechanisms associated with resistance to L-asparaginase include increased asparagine synthase expression, loss of HAP1 and subsequent downregulation of calpain-1-Bid-caspase-3/12 pathway, perturbations in Wnt signaling promoting GSK3-dependent ubiquitination/degradation activities to circumvent asparagine depletion, and expression of the cystine/glutamate antiporter SLC7A11/xCT (85, 86).

Recently, the proposition of metabolism-targeting agents is being examined in a wealth of pre-clinical studies to overcome R/R T-ALL. For example, cells resistant to methotrexate *in vitro* showed enhanced sensitivity towards a novel serine hydroxymethyltransferase (SHMT) inhibitor, SHIN2 (87). Moreover, another SHMT1/2 inhibitor, RZ-2994, proved effective in methotrexate-resistant T-ALL (88). RZ-2994 induces cell cycle arrest at S/G2 stages, while inhibition of SHMT1/2 restricts leukemia progression *in vivo*.

Additionally, L-asparaginase sensitivity fluctuates depending on T-ALL metabolic profile. Cells deficient in PTEN express increased glycolytic response and this, alongside prolific AKT activity, confers L-asparaginase resistance (86). Interestingly, inhibiting autophagy increases the cytotoxicity of L-asparaginase via a ROS-p53 positive feedback loop (89).

Overall, adaptive metabolic rewiring enables development of R/R T-ALL by subverting pharmacological activity of current chemotherapeutic strategies. Despite waning effectiveness of these treatments, a host of recent pre-clinical studies have highlighted adjacent metabolic avenues vulnerable to intervention promoting renewed

sensitivity of resistant T-ALL to therapy. Whilst further refinement of these mechanisms is required, novel oncometabolic therapeutics show promise in treating R/R T-ALL.

The microenvironment

Cancer progression is not only driven by cell-intrinsic alterations but also by a dynamic interplay between tumor cells and their surrounding microenvironment. Within the microenvironment, cells can be influenced by a broad range of soluble factors, cell-cell interactions, extracellular matrix, hypoxia or metabolic stimuli. Most research focused on the bone marrow (BM) microenvironment, the origin of HSCs. Learning from advanced three-dimensional imaging studies, it is known that there are multiple microanatomical sites and cell types in dependence of the functional heterogeneity of HSCs. In contrast to HSCs, recent research uncovered a highly dynamic behavior of T-ALL cells, without a preferential sub-localization within the BM space (90). Furthermore, single-cell sequencing of BM cells from T-ALL cases revealed multipotent progenitor cells as potential cell of disease origin in some cases (91). From there, pre-leukemic clones migrate to the thymus where they accumulate further mutations leading to uncontrolled cell growth, proliferation, and leukemia onset (**Fig. 4**). Hawkins et al. demonstrated elevated blast motility within the BM upon administration of chemotherapy, raising the possibility that T-ALL cells do not even require protective effects from the BM microenvironment (90).

Thymus, BM, blood, lymph nodes, and CNS represent the main organs impacting not only T-ALL development and progression but also therapeutic resistance. For example, xenografted ETP-ALL cells showed tissue microenvironment-dependent sensitivity to venetoclax, with resistance to single-agent venetoclax in the spleen being associated with

upregulation of differentiation factors and BCL2 downregulation (92), in agreement with ETP-ALLs being more BCL2-dependent than more differentiated T-ALLs.

'Thymus autonomy' (i.e. thymocyte self-renewal in the absence of incoming BM progenitors) plays a crucial role in T-cell differentiation regulation and may contribute to the initiation and proliferation of T-ALL (93). The chemokine receptor CXCR4 is widely overexpressed in T-ALL and its ligand CXCL12 is necessary for the engraftment and progression of T-ALL *in vivo* (94). Leukemia progression in the thymus results in high CXCL12 consumption rates, leading to a concentration decrease and allowing T-ALL cells to leave the thymus to lodge in secondary CXCL12-producing niches, e.g. in the BM (95). Targeting the CXCL12-CXCR4 axis might be a powerful option for T-ALL therapy. T-ALL cells are also highly dependent on IL-7, a cytokine crucial for normal T-cell development (76, 96). IL-7-deficiency in mouse models reduced the extramedullary organ infiltration by T-ALL, leading to the assumption that targeting IL-7-signaling may provide a therapeutic effect in T-ALL. Targeting the IGF1/IGF1R-axis represents another interesting therapeutic option. Dendritic cells from the thymus can activate IGF1R signaling in T-ALL cells, promoting leukemia cell survival (97). Furthermore, IGFBP7 is linked to the perdurance of the IGF1R activation and it is known to induce resistance of T-ALL to vincristine (98). Therefore, the niche-mediated activation of IGF1R represents a potential target for T-ALL therapy, including R/R disease. Signaling of CCL19 via CCR7 and CXCL12 via CXCR4 were shown to play a crucial role in T-ALL CNS involvement (99).The importance of the CNS for R/R T-ALL is discussed in more detail below. In any case, agents that target these two axes may be of therapeutic relevance.

Over the past decades, we have improved our understanding of the T-ALL microenvironment in the BM, allowing for the identification of druggable targets. On the

other hand, the highly motile behavior of T-ALL blasts, which mirrors that of normal T-cells, emphasizes the need to define whether niche-blast interactions can be specifically inhibited using targeted therapies. Research is warranted on how the migration of T-ALL cells through different extramedullary microenvironments occurs, to provide potential new options for targeted therapy.

Central nervous system

T-ALL has higher CNS relapse rates than B-ALL, however the precise mechanisms underlying this difference remain unknown (100). Current CNS-directed therapy, although broadly effective, has significant acute and chronic neurotoxic sequelae, including seizures, stroke-like syndrome and long-term impacts on learning and memory with 20-40% of survivors living with adverse neurocognitive outcomes (101).

CNS involvement presents considerable diagnostic and therapeutic challenges precipitated by the unique CNS niche (**Fig. 5**). Current diagnostic methods, using cytomorphology of cerebrospinal fluid (CSF) samples, significantly underestimate rates of CNS involvement at primary diagnosis, and traditional CNS-1/2/3 staging fails to accurately stratify relapse risk in T-ALL (102). More recent use of CSF flow cytometry reveals much higher rates of sub-clinical CNS infiltration (103). These observations support the universal use of CNS-directed treatment, but risk-adaptation of such treatment will require improved predictive biomarkers for risk of CNS relapse (100).

Treatment approaches need to carefully balance effective eradication of leukemia cells from the CNS with the risks of neurotoxicity, particularly in children whose brains are still actively developing. One of the most controversial areas is cranial radiotherapy (CRT), whose widespread use has declined due to unacceptably high rate of secondary neoplasms, endocrinopathies and neurotoxicity. Recent analysis of COG T-ALL trials,

AALL0434 and AALL1231, did not find any benefit of CRT in patients with CNS-2 status (102). Further analysis of T-ALL patients in UKALL2003 and UKALL2011 argues for CRT removal also in CNS-3 patients (104). To replace CRT, systemic agents shown to reduce CNS relapse rates include dexamethasone, Capizzi-Methotrexate and nelarabine. Most recent interest has focused on nelarabine which, when used in combination therapy in AALL0434 (NCT00408005), appeared to significantly reduce the incidence of CNS relapse (105). However, other differences in systemic therapy in the two arms may have contributed to the improved outcome. CRT was used for all CNS-3 patients and, despite reduced CNS relapses, there was no impact on OS. Therefore, independent validation of these findings, optimal combination regimens without use of CRT, and biomarkers for nelarabine response are needed. Of note, nelarabine can cause significant neurotoxicity, although this is less common when used in frontline rather than relapse settings, and may be reduced by intermittent administration and strict dosage capping (106).

While the optimized application of current therapeutics is of great importance, novel therapeutics must be identified and implemented over conventional agents to make real progress against this disease. The CNS microenvironment is significantly different from the BM (**Fig. 4 and 5**), which may come with unique therapeutic vulnerabilities. Another important consideration is whether agents can penetrate the CNS and achieve sufficient concentration to be effective. Despite these challenges, several agents showed promise in targeting both invasion and survival mechanisms in preclinical models of CNS T-ALL, including dasatinib and MEK/PI3K inhibitors (64, 100). Bi-specific antibodies and cellular therapies for T-ALL remain at early stages and the efficacy of these treatments against CNS disease are still to be ascertained (107). Reassuringly, current evidence

suggests the severity of CAR T-cell-associated neurotoxicity is not significantly connected to CNS involvement in adult hematologic diseases (108).

The immune system and immunotherapy

While there is still much to learn about the immune landscape in the context of ALL and how immune cells modulate leukemia development and resistance to therapy, the treatment of B-ALL has been revolutionized by the emergence of highly effective immunotherapies in the form of monoclonal antibodies (mAbs) (109), bi-specific T-cell engagers (5) and chimeric antigen receptor (CAR) T-cell therapy (110). In contrast, there has been limited progress in T-ALL, due to the inherent challenges in targeting a disease that shares cell surface proteins with normal T-cells. For instance, whereas B-cell aplasia following CD19-directed therapy can be mitigated with immunoglobulin replacement, T-cell aplasia results in severe immunodeficiency with risk of life-threatening infection. In addition, manufacture of CAR T-cells is hampered by fratricide, the CAR-directed killing of the CAR T-cell population, and an increased risk of transduction of tumor cells (111). Despite these obstacles, immunotherapies are in active development against many antigens with the most promising discussed below (**Fig. 6**).

CD7 is a transmembrane protein that is almost universally present on T-cells and T-ALL (112) and therefore the target of most active development, with various strategies employed to circumvent fratricide. Several groups have used CD7 protein blocking strategies in patient- or donor-derived autologous CAR T-cells to inhibit surface expression (e.g. (113)). These products have been tested in relatively large patient cohorts with the majority achieving molecular remission. Importantly, most patients proceeded to HSCT to avoid long-term immunosuppression.

Multiple allogeneic CAR T-cell products have also been tested in patients with T-ALL to limit the potential transduction of leukemic blasts (e.g. (114)). They employ genome engineering with CRISPR or base-editing to knock-out CD7 and TCR to avoid fratricide and graft versus host disease (GvHD). These products showed good efficacy in small patient cohorts. Again, consolidative HSCT is required following remission.

Approximately 40% of T-ALLs express CD1a but most mature T-cells are negative making it a potentially attractive target. Notably, though, many relapsed and refractory T-ALL cases are CD1a-negative, which limits the use of anti-CD1a CAR T-cells in R/R disease (112). Nonetheless, preclinical work showed non-fratricide, good efficacy anti-CD1a CAR T-cell manufacturing (115) leading to ongoing clinical trials (NCT05679895, NCT05745181).

CCR9 is a chemokine receptor limited to thymocytes and intestinal T-cells but expressed in most T-ALL cases. Preclinical work has demonstrated good results with anti-CCR9 CAR T-cells in murine models, with a phase 1 trial planned to open shortly (116). Interestingly, preclinical evidence (117) suggests that dual anti-CCR9/CD1a CAR T-cells are more efficient than single-targeting CAR T-cells, especially in phenotypically-heterogeneous leukemic populations.

CD5 is a glycoprotein expressed on the majority of T-ALL cases (112). It is also expressed on most normal T-cells, albeit weakly, allowing CAR T-cell manufacturing without fratricide (111). CD5-directed CAR T-cells have demonstrated pre-clinical efficacy with promising results in a recent trial in 19 patients (118), and new trials actively recruiting (NCT06633354, NCT05596266, NCT06316856).

CD38 is induced on activated T-cells and highly expressed in T-ALL, including relapsed and refractory cases (112). Monoclonal antibodies, including daratumumab and isatuximab, directed against CD38 were approved for multiple myeloma and pre-clinical

testing demonstrated excellent efficacy against murine models of T-ALL (119). The phase 2 DELPHINUS study (NCT03384654) tested daratumumab in relapsed ALL, demonstrating an overall response rate of 83.3% in combination with chemotherapy in children with relapsed T-ALL, with plans to move daratumumab into phase 3 studies (120). Another phase 2 study using daratumumab is recruiting patients with chemotherapy-refractory T-ALL (NCT05289687). Clinical studies with isatuximab (NCT02999633, NCT03860844) were terminated by Sanofi due to unsatisfactory benefit/risk ratio and efficacy criteria not being met, respectively.

The importance of IL-7R signaling in T-ALL was described above. IL-7Rα-targeting mAbs demonstrated potential to induce antibody-dependent cell-mediated cytotoxicity and/or phagocytosis and improve outcomes in pre-clinical models, including of relapsed T-ALL (121-123). Lusvertikimab (OSE-127), a non-cytotoxic anti-IL-7R mAb with demonstrated good safety profile in healthy subjects, showed efficacy in B- and T-ALL pre-clinical xenografts, including of R/R T-ALL, particularly in combination with polychemotherapy (123).

Further immunotherapy developments may be potentiated by a better characterization of the immune cell compartment in T-ALL. Recent studies, using single-cell sequencing, revealed differences in the frequency of γδ T-cells and CD8 effector T-cells in patients at diagnosis that responded to chemotherapy versus those that eventually relapsed (124), suggesting that the immune system may play a key role in the response to chemotherapy in T-ALL that could be leveraged for therapeutic purposes.

The future?

In the previous sections, we provided an overview of the different levels of biological understanding of pediatric T-ALL, integrating them with the challenges in the treatment

of R/R disease, and the promises held by emerging therapeutic tools, including targeted therapies and immunotherapy. It is evident that improving the outcome and quality of life of pediatric patients with R/R T-ALL will require precision medicine strategies that will probably involve smart combination therapies, adapted to the specific features of the malignant cells (genetic, epigenetic, posttranscriptional, posttranslational, metabolic) in particular microenvironmental contexts that will vary from niche to niche (as dramatically exemplified by CNS involvement). Understanding why treatment-versus-organ-specific resistances emerge will require models that faithfully recapitulate the distinct human microenvironments to accurately evaluate disease evolution and treatment response, including to immunotherapy.

Although these multiple levels and the molecular landscape of T-ALL are increasingly well catalogued, translating such complexity of knowledge to meaningful clinical benefit is not straightforward. To tackle this, computational tools have been applied to genomic data to identify new oncogenic drivers (125), and to uncover novel therapeutic approaches through biological network analysis (10). We suggest that recent developments in machine learning/artificial intelligence (ML/AI) techniques can help us to fast-track T-ALL discovery and translational research. Specifically, ML/AI methods employing attention mechanisms, exemplified by transformer-based deep learning that has revolutionized natural language processing, provide opportunities for new mechanistic discoveries. These approaches can 'learn' context and meaning from large multidimensional data and have already been exploited for diverse biological aims (126-128). We predict that these tools will increasingly help us to unravel T-ALL molecular networks, streamline the identification and validation of new biomarkers (not only genetic but also epigenetic, protein expression-based, drug response-reliant, etc) that can be used in guiding rational avenues to improve therapy.

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Author contributions

All authors wrote at least one section of the manuscript and critically read and provided feedback on the remaining sections. DO'C and MH wrote section one; DG, MRM, JB and FvL wrote section two; SD, SG and TL wrote section three; LKX and PN wrote section four; FWvD, PA and JTB wrote section five; EL and NJ wrote section six; LB wrote section seven; RC and CH wrote section eight; DO'C, PA and JTB wrote section nine; JB and JTB wrote section ten. PA, SD, LB, RC, CH, and PN created the figures in the manuscript. JTB coordinated the review.

Competing interests

LKX is an employee of AstraZeneca Pharmaceuticals. The other authors have no competing interests to disclose.

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Figure legends

Figure 1. Most well-studied epigenetic modifications of histones and DNA in T-ALL. Histone posttranslational modifications (hPTM) have been associated with open (euchromatin) and closed (heterochromatin) genomic regions. The impact of most hPTMs in cancer, with exception of methylation and acetylation, remains understudied. Epigenetic alterations in T-ALL also include aberrant CpG methylation patterns. The CIMP (CpG island methylator phenotype) / COSMe (CpG island and Open Sea Methylation) subgroups of T-ALL exhibit different prognoses and are associated with aberrant DNA methylation patterns and distinct genomic and transcriptomic alternations. Created in BioRender: https://BioRender.com/8wt1a5o

Figure 2. Overview of RNA dysregulation and relevant mechanisms in T-ALL. Aberrant RNA modification (top left) and splicing (top right) mechanisms cooperatively disturb RNA homeostasis (middle panel) in T-ALL. This reflects on critical pathways including proteasomal function, apoptosis and cell cycle and DNA damage response (DDR) pathway ultimately affecting disease biology and therapy response. Created in BioRender: https://BioRender.com/x78r835

Figure 3. Signaling pathways and targeted therapies with potential for R/R T-ALL treatment. Different signaling pathways are implicated in the pathogenesis of T-ALL that may be exploited for therapeutic intervention in R/R T-ALL. Pathways with most potential and corresponding small molecule inhibitors are indicated. Created in BioRender: https://BioRender.com/o94c256

Figure 4. Mobility-driven T-ALL development involves the full organism to unfold the leukemic disease. Development of T-ALL is dependent on different organs, starting with a preleukemic T-cell clone in the bone marrow (BM). From here, the cells follow a multistep path throughout the body, first by migrating to the (1) thymus where they gain further mutations driving leukemic transformation and consequent uncontrolled proliferation (2). Next, cells migrate to the periphery, invading the central nervous system (CNS), spleen, blood and BM (3). In contrast to BCP-ALL, T-ALL cells persist only transiently within the BM niche, presenting a motile behavior, enabling them to cycle back to thymus and other hematopoietic organs (4). Created in BioRender: https://BioRender.com/23565rj

Figure 5. Challenges presented by the CNS niche in diagnosing and treating CNS-involved T-ALL. (A) Central Nervous System (CNS) infiltration at diagnosis is likely underdiagnosed; evidence indicates CNS-resident blasts form aggregate plaques along the leptomeninges. Therefore free-floating blasts acquired by lumbar puncture do not accurately reflect disease burden in the compartment. Developing strategies such as flow cytometry and biomarker discovery may improve the sensitivity of CNS diagnostics and allow tracking of response to treatment. **(B)** To impact CNS-resident blasts, drugs must be able to cross the blood brain barrier and/or blood-cerebrospinal fluid (CSF) barrier and enter the CSF. Current evidence suggests that bi-specific antibodies show limited CSF penetration whilst CAR-T cells can enter the CSF but efficacy in this niche is unclear. The CNS niche differs metabolically from the bone marrow niche providing potential new targets. Effective therapies must show selective killing of CNS-blasts whilst avoiding neuronal toxicity. Created in BioRender: https://BioRender.com/266mxn5

Figure 6. Major immunotherapy targets in T-ALL. CAR-T cell therapies are under investigation in clinical trials for markers such as CD1a, CD5, and CD7, with preclinical studies also demonstrating promising results in targeting CCR9. Monoclonal antibodies have also shown potential, including a phase 2 clinical trial evaluating Daratumumab, which targets CD38, in combination with conventional chemotherapy. Targeting IL-7R in T-ALL with Lusvertikimab has been explored in preclinical studies, with clinical trials in healthy individuals reporting a favorable safety profile. Created in BioRender: https://BioRender.com/p88q198

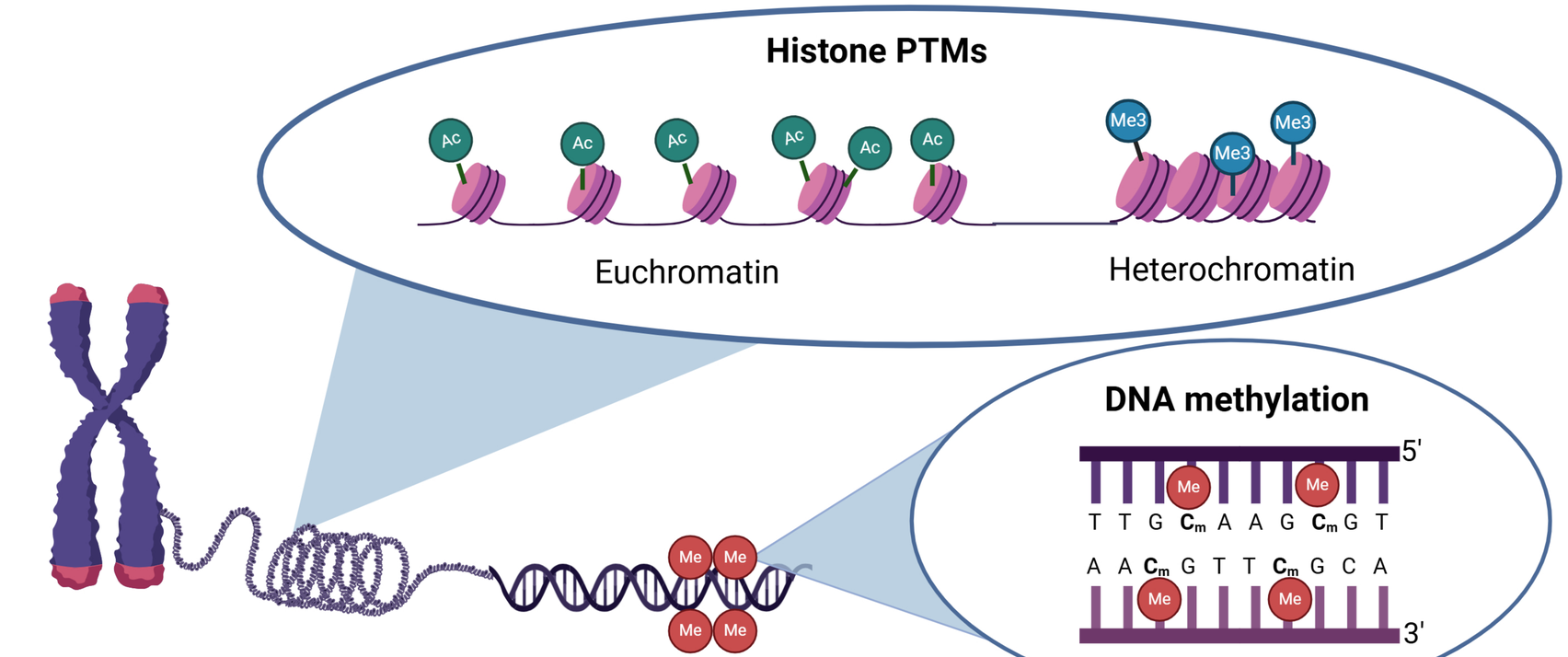
Table legends

Table 1. Therapeutic strategies under study for the treatment of R/R T-ALL. 1 – Recruiting, 2 – Terminated; 3 – Unknown status; 4 – active, not recruiting; 5 – Not yet recruiting; 6 – Completed; 7 – Withdrawn; a - Terminated due to departure of PI from St. Jude; b - Company stopped development and production of one of the IMP's; c - Terminated due to toxicity; d - Terminated due to slow accrual; e - Terminated for non-disclosed reasons; f - Terminated due to ethic committee decision; g - Terminated due to sponsor decision (unsatisfactory benefit/risk ratio); h - Terminated due to sponsor decision (stage 2 efficacy criteria not met); Bold – r/r (T-)ALL clinical trial. *ABL – Abelson tyrosine kinase; BCL-2 – B-cell lymphoma 2; BCL-XL – B-cell lymphoma-extra-large; CCR9 – C-C chemokine receptor type 9; CD – Cluster of differentiation; CDK4/6 – Cyclin-dependent kinase 4 and 6; DCAF15 – DDB1- and CUL4-associated factor 15; DNMT – DNA methyltransferase; HDAC – Histone deacetylase; IL7R – Interleukin-7 receptor; JAK – Janus kinase; MAPK – Mitogen-activated protein kinase; MEK1/2 – MAPK/ERK kinase 1 and 2; mTORC1 – Mechanistic target of rapamycin complex; PI3K – Phosphoinositide 3-kinase; pRB – Retinoblastoma protein; RBM39 – RNA-binding motif protein 39; SF3B1 – Splicing factor 3B subunit 1; SHMT1/2 – Serine hydroxymethyltransferase 1 and 2; SRC – SRC proto-oncogene, non-receptor tyrosine kinase.*

Table 1. Therapeutic strategies under study for the treatment of R/R T-ALL

Category	Therapy	Target/Mechanism of action	Development Stage	Section (Refs)
Proteasome Inhibitors	Bortezomib	Inhibits proteasome, disrupting protein degradation and inducing apoptosis	Phase II (**NCT03590171**[1]) and Phase III (NCT02112916[4]) Clinical Trials	1st (Teachey, 2022)
Cell Cycle Kinase Inhibitors	AZD1152	Inhibits Aurora B kinase, preventing mitotic progression	Preclinical	2nd (Llombart, 2022)
	Palbociclib	CDK4/6 inhibitors, prevent phosphorylation of the retinoblastoma protein (pRB), inducing cell cycle arrest before S-phase	Phase I (**NCT03132454**[4], **NCT03515200**[2a], **NCT03792256**[6], **NCT04996160**[a]) Clinical Trials	5th (Pikman, 2017; Raetz, 2023)
	Ribociclib		Phase I (**NCT03740334**[4]) Clinical Trial	
Epigenetic Modulators	5-Azacytidine	DNMT inhibitors, induce DNA hypomethylation, transcriptional activation, and cytotoxicity	Phase I/II (**NCT05740449**[7b]) and Phase II (NCT05376111[1], NCT06686108[1]) Clinical Trials	3rd
	Decitabine		Phase I/II (**NCT01483690**[2c]) and Phase II (NCT06686108[1]) Clinical Trials	3rd
	GSK3685032	DNMT1-selective inhibitor, induces DNA hypomethylation and transcriptional activation	Preclinical	3rd (Pappalardi, 2021)
	Panobinostat	HDAC inhibitor, induces apoptosis	Phase II (**NCT02518750**[2d]) Clinical Trial	3rd (Waibel, 2018)
	Vorinostat	HDAC1,2,3,6 inhibitor, induces cell cycle arrest and/or apoptosis	Phase I/II (**NCT01483690**[2c]) Clinical Trial	3rd (Waibel, 2018)
RNA splicing modulators	E7107	SF3B1 inhibitor, alters mRNA splicing	Preclinical	4th (Han, 2022)
	Indisulam	RBM39 degradation via DCAF15, modulates RNA splicing	Preclinical	4th (Ji, 2024)
Signal Transduction Inhibitors	BMS-906024	Gamma secretase inhibitor, blocks Notch receptor activation, leading to cell cycle arrest	Phase I (NCT01363817[6]) Clinical Trial	5th
	MK-0752		Phase I (**NCT00100152**[2e]) Clinical Trial	5th
	Dactolisib	PI3K/mTOR dual inhibitor, blocks survival signaling	Preclinical	5th (Yang, 2019)
	Dasatinib	ABL and SRC family tyrosine kinase inhibitor, inhibits proliferation	Phase I/II (**NCT05751044**[5]) and Phase II (NCT06390319[1]) Clinical Trials	5th (Saygin, 2023)
	Duvelisib	PI3Kδ/γ inhibitors, block survival signaling	Preclinical	5th (Yang, 2019)
	Idelalisib		Preclinical	5th (Yang, 2019)
	Everolimus	mTORC1 inhibitors, induce cell growth arrest and apoptosis	Phase I (**NCT03328104**[6]) and Phase I/II (**NCT00081874**[6]) Clinical Trials	5th (Yang, 2019)
	Temsirolimus		Phase I (**NCT01614197**[6], **NCT01403415**[6]) Clinical Trials	5th
	Imatinib	ABL tyrosine kinase inhibitor, inhibits proliferation and induces apoptosis	Phase I (ALLTogether 1[1]) and Phase III (NCT03007147[4]) Clinical trial	5th (Moorman, 2020)
	Ruxolitinib	JAK1/2 inhibitor, suppresses cytokine and growth factor signaling	Phase I/II (**NCT05745714**[5], NCT05075681[1]) Clinical Trials	5th (Courtois, 2023)
	Tofacitinib	JAK1/3 inhibitor, suppresses cytokine and growth factor signaling	Preclinical	5th

	Selumetinib	MEK1/2 inhibitor, suppresses MAPK/ERK signaling pathway, reduces cell proliferation and promotes pro-apoptotic signaling	Preclinical	5th (Matheson, 2019)
	Trametinib	MEK1/2 inhibitor, suppresses MAPK/ERK signaling pathway, decreases cell proliferation and induces apoptosis	Phase I/II (**NCT05658640**[1]) Clinical Trial	5th
Apoptosis Regulators	LP-118	Dual BCL-2/BCL-XL inhibitor, induces BAK activation, cytochrome C release and apoptosis	Phase I (**NCT04771572**[1]) and Phase I/II (NCT06207123[1*]) Clinical Trials	1st (Ravikrishnan, 2025)
	Venetoclax	Selective BCL-2 inhibitor, promotes apoptosis	Phase I/II (**NCT05751044**[5], **NCT05745714**[5]) and Phase II (NCT06390319[1]) Clinical Trials	1st, 5th (Pullarkat, 2021)
Folate Metabolism Inhibitors	SHIN1 (RZ-2994)	SHMT1/2 inhibitor, induces S/G2 cell cycle arrest	Preclinical	6th (Pikman, 2022)
	SHIN2		Preclinical	6th (Pikman, 2022)
Chemotherapy	Nelarabine	Purine nucleoside analog; disrupts DNA synthesis in T-cells	Phase I/II (**NCT00981799**[2d]) and Phase III (NCT00408005[6]) Clinical Trials	8th (Dunsmore, 2020)
Adoptive cell therapy	Anti-CCR9 CAR-T cells	Engineered T cells targeting CCR9-expressing leukemia cells	Preclinical	9th (Maciocia, 2022)
	Anti-CD1a CAR-T cells	Engineered T cells targeting CD1a-expressing leukemia cells	Phase I (**NCT05679895**[1], **NCT05745181**) Clinical Trials	9th (Sánchez-Martínez, 2019)
	Anti-CD5 CAR-T cells	Engineered T cells targeting CD5-expressing leukemia cells	Phase I (**NCT05032599**[2f], **NCT06633354**[1], **NCT05596266**[1]) and phase I/II Clinical Trials (**NCT06316856**[1])	9th (Pan, 2024)
	Anti-CD7 CAR-T cells	Engineered T cells targeting CD7-expressing leukemia cells	Phase I (**ChiCTR2000034762**[3], **NCT05397184**[1], **NCT04264078**[3], **NCT04823091**[3], **NCT04984356**[6], **NCT05043571**[1]) Clinical Trials	9th (Tan, 2023; Chiesa, 2023; Huang, 2020; Zhang, 2023; Ghobadi, 2024)
	Dual anti-CCR9/CD1a CAR-T cells	Engineered T cells targeting CCR9/CD1a-expressing leukemia cells	Preclinical	9th (Tirado, 2025)
Monoclonal antibodies	Daratumumab	Anti-CD38 monoclonal antibody, induces antibody-dependent cellular cytotoxicity and phagocytosis	Phase II (**NCT03384654**[6], NCT05289687[1a]) Clinical Trials	9th (Bhatla, 2024)
	Isatuximab		Phase II (**NCT02999633**[2g], **NCT03860844**[2h]) Clinical Trials	9th (Bride, 2018)
	Lusvertikimab	Anti-IL7R monoclonal antibody, induces immune-mediated cellular cytotoxicity	Preclinical	9th (Lenk, 2024)



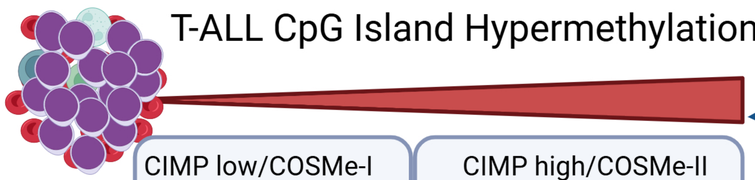
Histone modification

Ac acetylation

Me3 methylation

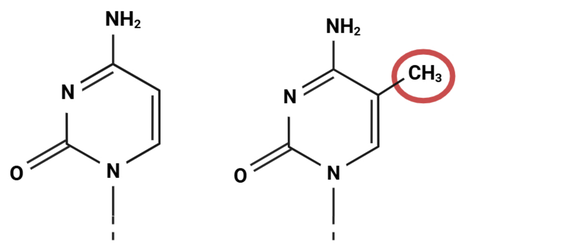
DNA modification

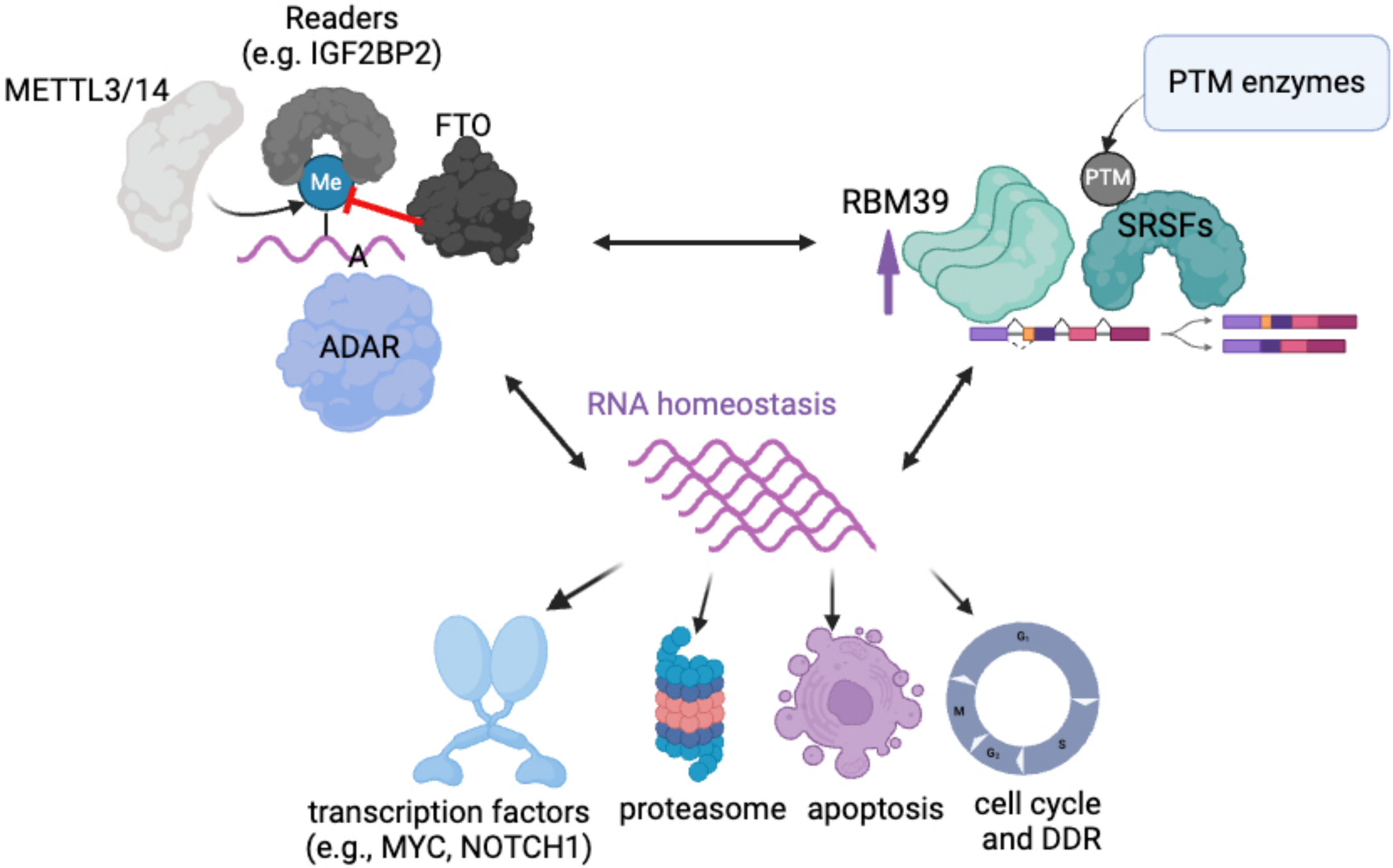
Me methylation



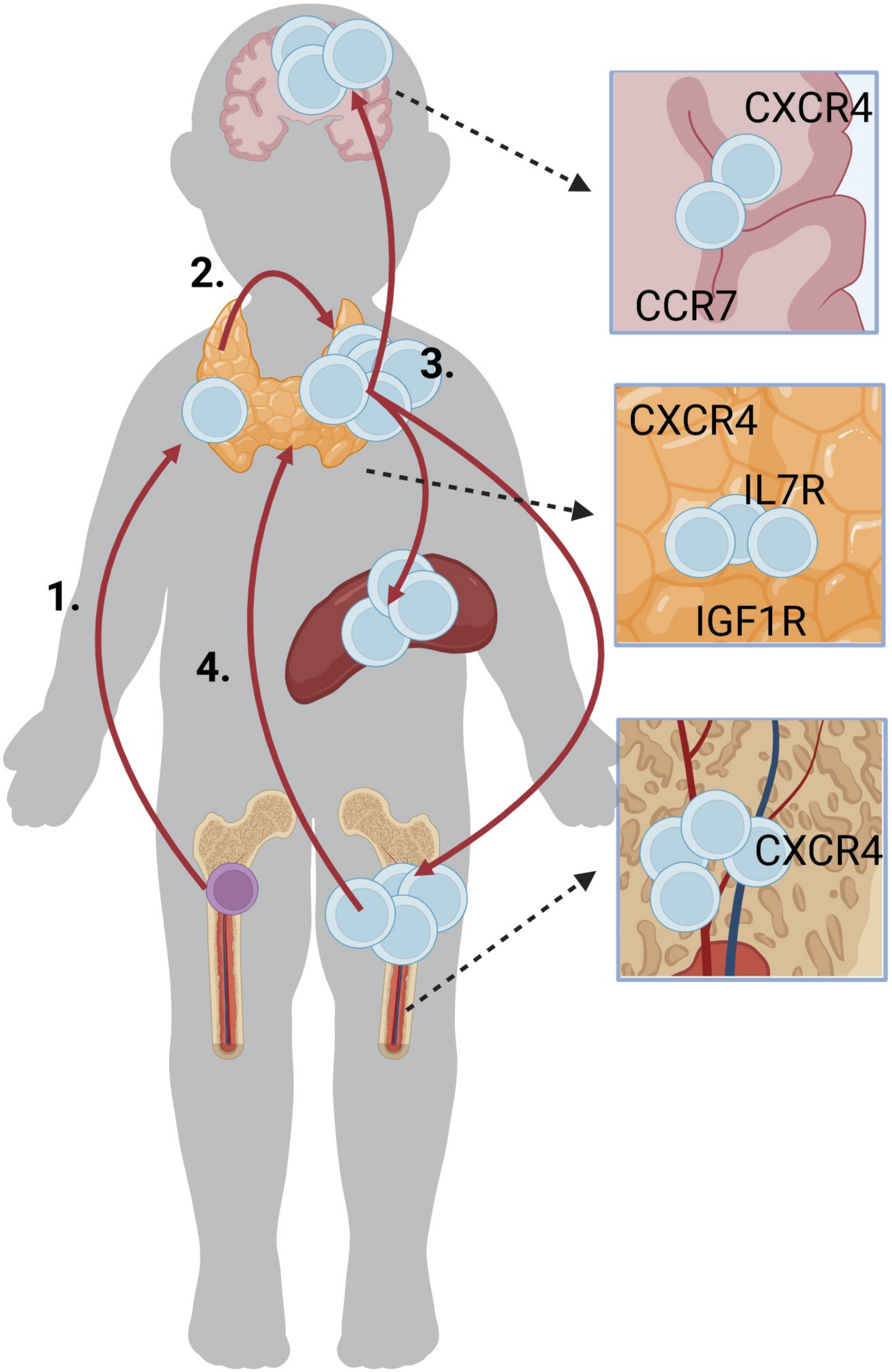
T-ALL CpG Island Hypermethylation

CIMP low/COSMe-I	CIMP high/COSMe-II
STIL-TAL1 translocation	*TLX3 overexpression*
PTEN aberrations	*NKX2-1 overexpression*
6q deletion	*HOXA overexpression*
	WT1 mutations
Worse prognosis	Better prognosis

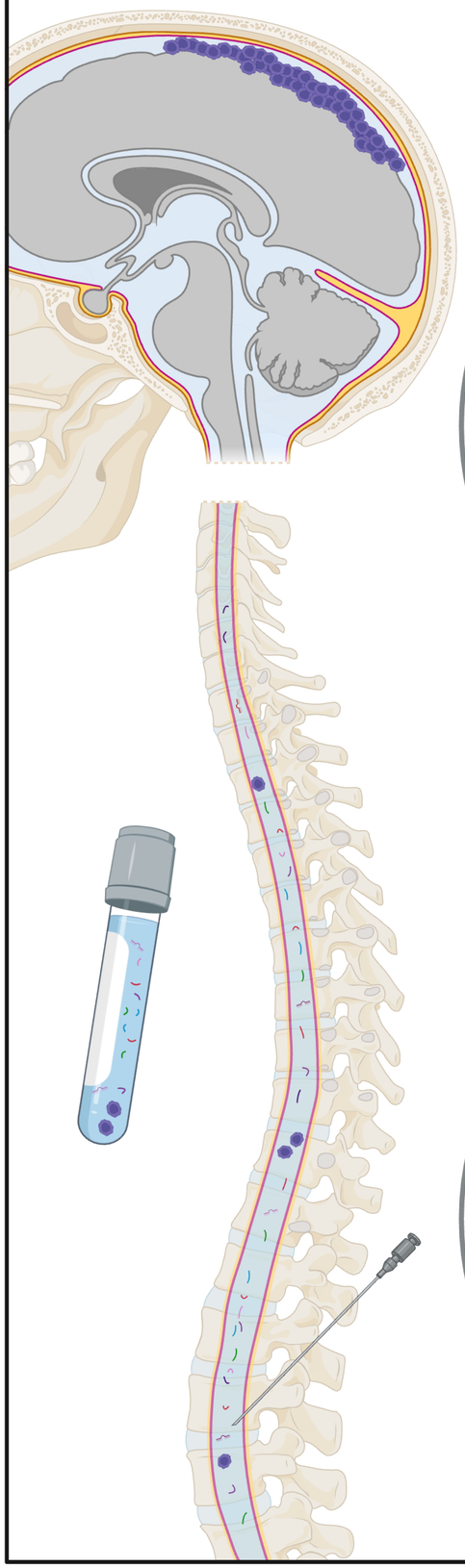



Readers
(e.g. IGF2BP2)
METTL3/14
FTO
Me
A
ADAR
PTM enzymes
PTM
RBM39
SRSFs
RNA homeostasis
transcription factors
(e.g., MYC, NOTCH1)
proteasome
apoptosis
cell cycle
and DDR

(pre)TCR
LAT
IL-7R
LCK
LCK
P
P
P
ZAP70
P
P
RAS
Ruxolinitib
Tofacitinib
JAK
P
P
PIP2
PIP3
PI3K
PTEN
PDK1
Dasatinib
RAF
P
STAT
P
STAT
Dactolisib
Idelasib
Duvelisib
mTORC2
P
Selumetinib
Trametinib
MEK
P
P
AKT
P
Everolimus
Temsirolimus
mTORC1
P
STAT
P
STAT
P
ERK
P
BCL2
Venetoclax
Cytoplasm
MYC, BCL2,
BCL2L1, CCND1
Nucleus

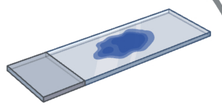

1.
2.
3.
4.
CXCR4
CCR7
CXCR4
IL7R
IGF1R
CXCR4

A

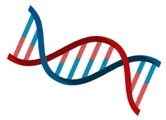


Diagnostic challenges

Low rates of cytospin positivity

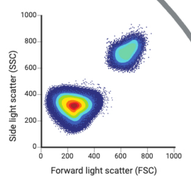


Insufficient material for mutational profile at relapse



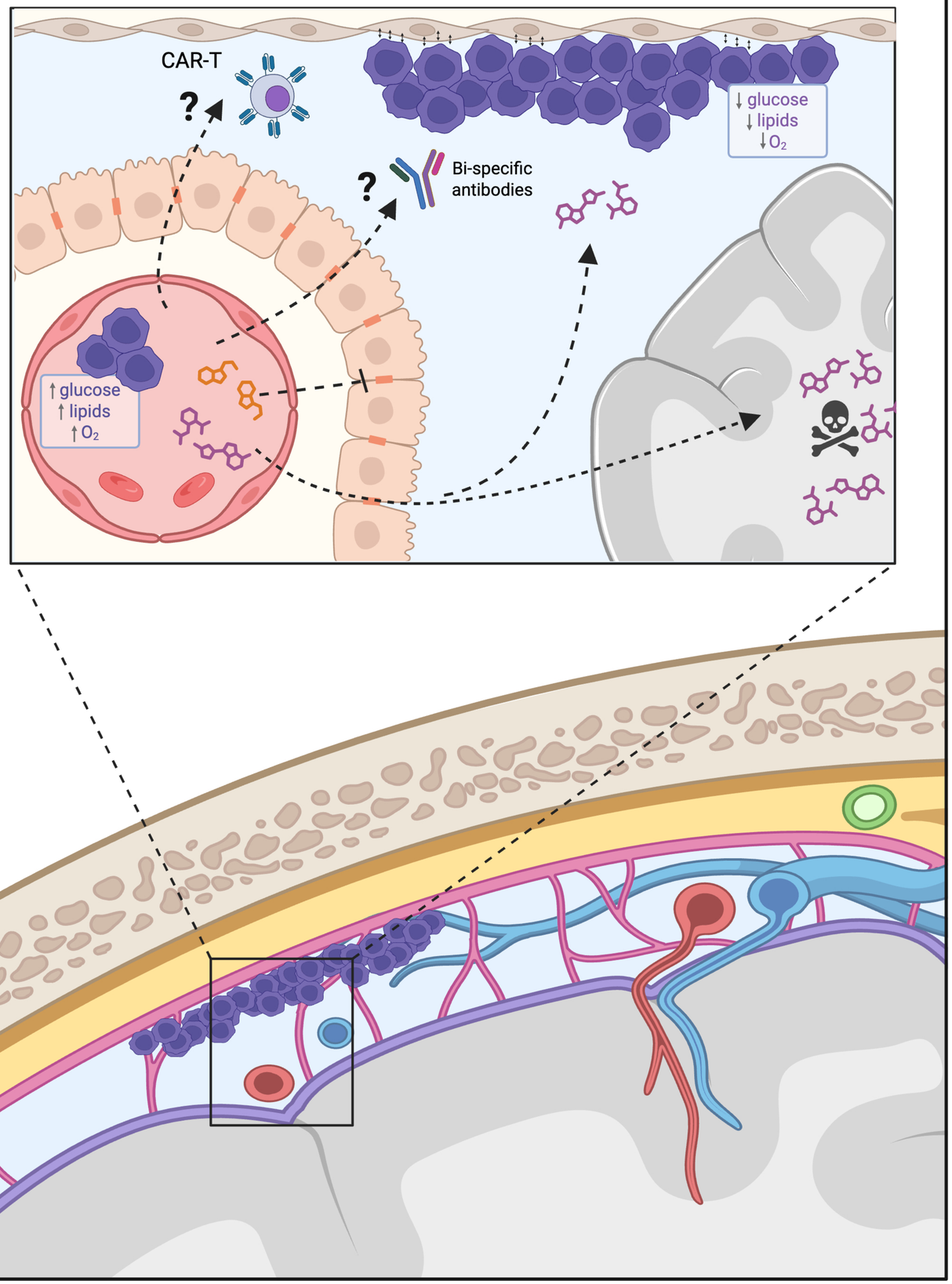
Diagnostic improvements

Potential enhanced detection by flow cytometry

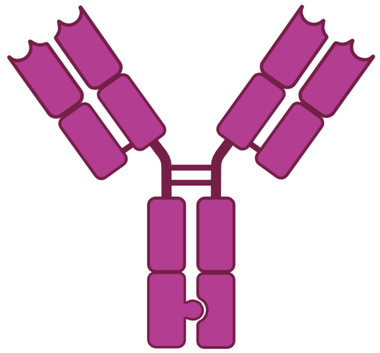


Discovery of soluble biomarkers

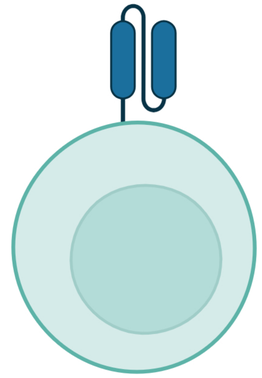
B



Monoclonal Antibodies



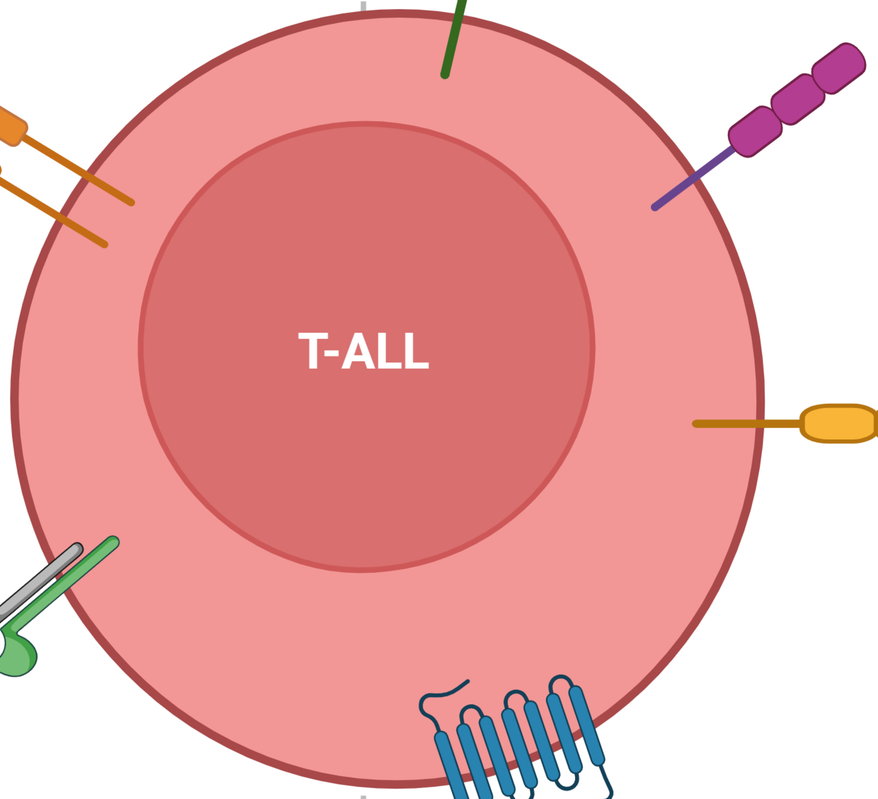
Chimeric Antigen Receptors



CD1a
NCT05679895
NCT05745181

CD38
Daratumumab
NCT03384654
NCT05289687

CD5
NCT05032599
NCT06633354
NCT05596266
NCT06316856



CD7
ChiCTR2000034762
ISRCTN15323014
NCT04264078
NCT04416984
NCT04823091
NCT04984356
NCT05043571

IL-7R
Lusvertikimab
Preclinical study in T-ALL
NCT03980080 in healthy subjects

CCR9
Preclinical study in T-ALL