Front. Med. 2021, 15(3): 347–371
https://doi.org/10.1007/s11684-020-0821-6

REVIEW

Emerging molecular subtypes and therapeutic targets in B-cell precursor acute lymphoblastic leukemia

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Abstract **B-cell precursor acute lymphoblastic leukemia (BCP-ALL) is characterized by genetic alterations with high heterogeneity. Precise subtypes with distinct genomic and/or gene expression patterns have been recently revealed using high-throughput sequencing technology. Most of these profiles are associated with recurrent non-overlapping rearrangements or hotspot point mutations that are analogous to the established subtypes, such as *DUX4* rearrangements, *MEF2D* rearrangements, *ZNF384/ZNF362* rearrangements, *NUTM1* rearrangements, *BCL2*/*MYC* and/or *BCL6* rearrangements, *ETV6-RUNX1*-like gene expression, PAX5alt (diverse *PAX5* alterations, including rearrangements, intragenic amplifications, or mutations), and hotspot mutations PAX5 (p.Pro80Arg) with biallelic *PAX5* alterations, IKZF1 (p.Asn159Tyr), and ZEB2 (p.His1038Arg). These molecular subtypes could be classified by gene expression patterns with RNA-seq technology. Refined molecular classification greatly improved the treatment strategy. Multiagent therapy regimens, including target inhibitors (e.g., imatinib), immunomodulators, monoclonal antibodies, and chimeric antigen receptor T-cell (CAR-T) therapy, are transforming the clinical practice from chemotherapy drugs to personalized medicine in the field of risk-directed disease management. We provide an update on our knowledge of emerging molecular subtypes and therapeutic targets in BCP-ALL.**

Keywords BCP-ALL; subtypes; translocation; aneuploidy; sequence mutations

Introduction

B-cell precursor acute lymphoblastic leukemia (BCP-ALL) is a blood cancer that originates from B-lymphoid progenitors [1,2]. Genetic susceptibility and somatic clonal expansion (tumor acquired) are the hallmarks and biological basis of BCP-ALL. The enrichment of chromosomal alterations, including genomic translocations and entire chromosome losses or gains (aneuploidy), DNA copy number variations (CNVs), and sequence mutations, are common in leukemic blast cells of BCP-ALLs [3–7]. In the past few years, numerous molecular subtypes with distinct genetic abnormalities and clinical significance have been identified in multicenter, global collaboration cohort studies of patients with BCP-ALL [8–12]. A recognition of these multifaceted genetic alterations contributing to leukemogenesis is vital in ensuring a precise risk stratification of the disease, which can then lead to improvements to cure rates in both adults and children with BCP-ALL [5,12–26]. Before the 1980s, with the combined effectiveness of health-care systems and the absence of actionable risk stratification factors, the five-year overall survival rate was only approximately 50% in children patients with BCP-ALL [27–29]. In recent years, the released data from multiple large-cohort clinical trials indicate a five-year overall survival rate that is higher than 90% in children [29–42]. In addition, the rapid advancement in new drugs and agents, including target inhibitors, i.e., tyrosine kinase inhibitors (TKIs) and epigenetic inhibitors, immunomodulators, monoclonal antibodies, and chimeric antigen receptor T-cells (CAR-T), may further improve the prognosis of relapsed or refractory (R/R) BCP-ALL [13,43].

Received August 7, 2019; accepted September 4, 2020
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Overview of well-established molecular subtypes in BCP-ALL

The translocation t(9;22)(q34;q11.2) resulting in *BCR-ABL1* (Philadelphia, Ph) fusion accounted for 15%–25% of adults and 2%–5% of children with BCP-ALL[8,9,44]. *BCR-ABL1* fusion proteins are considered to be signaling regulators and can trigger kinase pathway activation [45–48]. Targeted treatments with TKIs have significantly improved the prognosis of patients with *BCR-ABL1* [8,9,13,49,50]. *KMT2A* (*MLL*) rearrangements account for 3%–4% of children with BCP-ALL, particularly in infants (< 1 year old), and in 4%–10% of adult patients, mainly > 30 years old, with BCP-ALL [8,9,18,24,51,52]. Additionally, this rearrangement is typically associated with poor prognosis [24,52,53]. The translocations t(4;11)(q21;q23), t(11;19)(q23;p13.3), and t(9;11)(p21;q23) resulting in *KMT2A-AFF1*, *KMT2A-MLLT1*, and *KMT2A-MLLT3*, respectively, account for more than 90% of *KMT2A* fusions in BCP-ALL [8,9]. The translocation t(12;21)(p13;q22) resulting in *ETV6-RUNX1* (also known as *TEL-AML1*) comprises approximately 15%–25% of children with BCP-ALL [8,9,17,18]. However, adults (< 1%) and patients with *ETV6-RUNX1* rarely have the same sensitivity to chemotherapy, and relapse and death events are less common [5,8,9,17,54,55]. In addition, *ETV6-RUNX1* fusion is detectable in 5% healthy newborns based on DNA-based genomic inverse PCR for exploration of ligated breakpoint screening, but most never transform to BCP-ALL [56]. Transcription factor 3 (*TCF3*) is frequently involved in two types of translocations, namely, t(1;19)(q23;p13) and t(17;19)(q22;p13), which result in *TCF3-PBX1* and *TCF3-HLF* fusions, respectively. *TCF3-PBX1* accounts for approximately 4%–7% of children patients and 2%–5% of adult patients with BCP-ALL and is associated with intermediate outcomes [8,9,12,54]. *TCF3-HLF* is a rare gene fusion (< 1% of ALL), and relapse and death events are common [25,57]. *HLF* is also involved in translocation t(18;19)(q21;p13), thereby resulting in *TCF4-HLF*. Both *TCF3-HLF* and *TCF4-HLF* fusions retain the bZIP_2 domain and accompany the overexpression of *HLF* [8,9,25]. The complex intrachromosomal amplification of chromosome 21 (iAMP21), which was first reported in 2003, helped to define a distinct cytogenetic subgroup [58,59]. This amplification occurs in approximately 2%–3% of children with B-lineage ALL, especially in adolescence [5,9,12]. This condition was originally considered a rare, high-risk subtype of BCP-ALL, but current intensive therapy has greatly improved its outcome [59,60]. High hyperdiploidy with a gain of at least five chromosomes is another independent predictor (along with *ETV6-RUNX1*) of favorable outcomes and accounts for approximately 15%–25% of patients with childhood BCP-ALL. However, high hyperdiploidy is rare in adults (< 1%) [8,9]. Conversely, hypodiploid (< 44 chromosomes) is uncommon (2%–3%) and associated with inferior outcomes compared with high hyperdiploidy BCP-ALL. In addition, hypodiploid (< 44 chromosomes) is heterogeneous with distinct genetic abnormalities and gene expression profiles consisting of near-haploid BCP-ALL (25–29 chromosomes), low hypodiploid (32–39 chromosomes), and high hypodiploid (40–43 chromosomes) (Table 1) [5,12,23].

The well-established molecular subtypes of BCP-ALL have been mostly integrated into the guidance of therapy options (e.g., dose and times of chemotherapy and types of targeted drugs) [13]. Their integration has significantly improved the long-term survival of both adult and children patients. However, subtypes with poor/intermediate prognosis, including *BCR-ABL1*, *KMT2A* fusions, *TCF3-PBX1*, *HLF* fusions, and low hypodiploid, are needed in intensive chemotherapy [5]. *BCR-ABL1* and *KMT2A* fusions not only occur in BCP-ALL but also in other types of acute or chronic leukemia, including acute myeloid leukemia (AML), mixed phenotype acute leukemia (MPAL), and chronic myeloid leukemia [61–63]. A potential supposition is that the fusion of genes may occur at different stages of hematopoietic stem cell development.

Emerging molecular subtypes in BCP-ALL

DUX4, *MEF2D*, and *ZNF384* gene fusions

Three new subtypes of adult and childhood BCP-ALL have been described recently [16,18,20–22,64]. The subtypes are involved in the rearrangements of DNA binding factors, including double homeobox 4 gene (*DUX4*), myocyte enhancer factor 2D (*MEF2D*), and zinc finger protein 384 (*ZNF384*), which separately account for approximately 4%–7%, 2%–4%, and 3%–5% of childhood BCP-ALL and 4%–7%, 2%–7%, and 3%–8% of adult BCP-ALL [8,9,15–18,20–22,26,65–67]. *DUX4-r*, *ZNF384-r*, and *MEF2D-r* BCP-ALL are associated with favorable, intermediate, and poor diagnoses, respectively. In most patients, *DUX4* overexpression is the consequence of *DUX4* fusion, typically *IGH* but rarely *ERG* [17,20,21]. By contrast, the partner genes of *MEF2D* and *ZNF384* are complex and diverse. A total of 9 genes (*BCL9*, *SS18*, *FOXJ2*, *CSF1R*, *DAZAP1*, *STAT6*, *HNRNPUL1*, *HNRNPH1*, and *HNRNPM*) and 11 genes (*EP300*, *TCF3*, *TAF15*, *CREBBP*, *EWSR1*, *ARID1B*, *SMARCA2*, *SMARCA4*, *SYNRG*, *NIPBL*, and *CLTC*) have been reported as fusion partners of *MEF2D* and *ZNF384* [8,15–18,20,22,66–68], respectively. Translocations t(1;1)(q21;q22) and t(1;19)(q22;q13) resulting in *MEF2D-BCL9* and *MEF2D-HNRNPUL1*, respectively, are the top two items in *MEF2D-r* BCP-ALL, accounting for 70% and 15% of the cases. *EP300*, *TCF3*, and *TAF15* are the most common 5′ genes rearranged to *ZNF384* with

translocations t(12;22)(p13;q13), t(12;19)(p13;p13), and t(12;17)(p13;q11), representing approximately 50%, 10%–20%, and 10% of *ZNF384* fusion-positive cases.

DUX4, located within a D4Z4 repeat array in the subtelomeric region of chromosome 4, is a key transcription factor regulating embryonic development and is not expressed in normal B-cells. DUX4 can bind a large percentage of activated genes in early developing embryos and improve the accessibility of genes as early as the 2- to 4-cell stages [20,21,69,70]. Intragenic deletions of *ERG* were previously reported in approximately 5% of children with BCP-ALLs, but they were designated as the biological feature in *DUX4-r* cases [5,21]. Functional studies show that *DUX4* rearrangements, as an early initiating event in leukemogenesis, can bind to an intragenic region of *ERG* and cause the overexpression of ERGalt with a noncanonical first exon and transcript. Aberrant ERGalt preserves the DNA binding and transactivating domains and encodes a truncated C-terminal *ERG* protein. The transcriptional activity of wild-type *ERG* is inhibited by the ERGalt protein-transforming leukemic blast cells [5,20,21,71]. Interestingly, despite the presence of approximately 40%–50% of genetic alterations in *IKZF1* deletions related to poor outcomes in other subtypes with BCP-ALL [72], *DUX4-r* BCP-ALL can achieve excellent outcome [5,12,17,18,21]. Recent studies have reported that *IGH-DUX4* translocation occurs on the silenced IGH allele, thereby reducing the oncogenic stress of *DUX4*'s high-level expression. The *ERG* deletions have a positive impact on the prognosis (*ERG* deletion positive/negative: five-year EFS 93%/68%, $P = 0.022$; five-year OS 97%/75%, $P = 0.029$) [73,74].

MEF2D is a transcription factor that can specifically bind to the myocyte-specific enhancer factor 2 (MEF2) element 5′-YTA[AT](4)TAR-3′. It belongs to the MEF2 gene family that contributes to the differentiation of muscle and neural cells, cardiac morphogenesis, formation of blood vessels, growth factor responsiveness, survival of neuronal cells, and acute leukemia [75,76]. As a member of the MEF2 gene family, *MEF2C* is an activated oncogene in early T-cell precursor ALL, a subtype of high risk T-lineage ALL [12,77–82]. In 2005, *MEF2D-DAZAP1* was reported in the TS-2 cell line, as established from a three-year-old girl with ALL; it was found to contain t(1;19)(q23;p13.3) but was lacking the *TCF3-PBX1* fusion [83]. In 2016, multiple research groups who used RNA-seq recognized simultaneously the *MEF2D* fusion in a subgroup of patients with BCP-ALL [16,18,20,64]. These studies determined that *MEF2D* fusions can retain the MADS box domain required to mediate DNA binding with enhanced *MEF2D* transcriptional activity. The heterogeneous nuclear ribonucleoproteins, including HNRNPUL1, HNRNPH1, and HNRNPM, are involved in *MEF2D-r* ALL [8,9,15]. These proteins can bind RNA and are associated with pre-mRNA processing in the nucleus. Histone deacetylase 9 (*HDAC9*), a target gene of *MEF2D*, is significantly upregulated in *MEF2D-r* patients, providing an optional therapeutic strategy by using histone deacetylase inhibitors, such as panobinostat [5,16,18]. Staurosporine and venetoclax have recently been reported to be effective in inducing the caspase-dependent proteolysis of MEF2D-fusion proteins and apoptosis in MEF2D-fusion$^+$ ALL cells [84].

ZNF384, also called *CIZ* or *NMP4*, can encode a C2H2-type zinc finger protein, whose function remains largely elusive, although it may function as a transcription factor. *ZNF384* fusions are often diagnosed as BCP-ALLs with an expression of cell surface markers of myeloid lineage (CD13 and CD33) or as B/myeloid (B/M) MPAL comprising approximately 50% of B/M MPAL [63]. In 2002, seven cases with *ZNF384-r* acute leukemia and recurrent *EWSR1-ZNF384* and *TAF15-ZNF384* were reported [85]. On the basis of large-cohort RNA-seq data analysis, *ZNF384*-positive patients with BCP-ALL were identified as a prognostic subtype with distinct gene expression features [8,9,16–18,20,22,65,66,86,87]. All *ZNF384* fusions keep their entire coding region. Cell apoptotic response, MAPK signaling, and JAK-STAT signaling pathways are significantly upregulated in this subtype [8,22]. Cardiotrophin-like cytokine factor 1 (*CLCF1*) is one of the most upregulated genes in *ZNF384-r* BCP-ALL that can bind to *CRLF1* to form a compound cytokine, thereby ultimately activating the JAK-STAT signaling pathway and B-cell proliferation *in vivo* [22,88]. In addition, up to 60% of patients with *ZNF384* fusions also show alterations in their signaling molecules, such as *NRAS* and *FLT3*, and 40% have epigenetic mutations, particularly *SETD1B*, *CREBBP*, and *EZH2*.

"Like" or "phenocopy" subtypes in BCP-ALL

Somatic mutations in the coding region and gene expression profile can help us recognize "like" or "phenocopy" subtypes that share similar gene expression features but lack consistent biomarkers. In recent years, several multi-omics and large-cohort studies have identified such subtypes, including Ph-like, *ETV6-RUNX1*-like, *KMT2A*-like, and *ZNF384*-like [8,9]. Integrated datasets showed that Ph-like and *ETV6-RUNX1*-like account for approximately 6%–15% and 2%–3% of children patients and 20%–25% and $< 1\%$ of adult patients with BCP-ALL. However, both *KMT2A*-like and *ZNF384*-like are rare ($< 1\%$). Ph-like and *ETV6-RUNX1*-like are associated with poor and intermediate outcomes. The prognoses of *KMT2A*-like and *ZNF384*-like remain unclear because of limitation of sample size [8,9,12].

The Ph-like subtype is *BCR-ABL1* negative, but its gene expression feature is similar to that of *BCR-ABL1*-positive patients [89–93]. The Ph-like subtype was registered in the

2016 revision to the WHO classification of myeloid neoplasms and acute leukemia [19]. Rearrangements of *CRLF2* (e.g., *IGH-CRLF2* and *P2RY8-CRLF2* atapproximately 30%–50%), *ABL1*/*ABL2* (10%), *JAK2* (10%), the erythropoietin receptor gene (*EPOR*, 5%–10%), and *PDGFRB* (5%) are the major chromosomal markers. Sequence mutations of signaling molecules, such as JAK-STAT signaling and Ras signaling (e.g., *NRAS*, *KRAS*, *JAK2*, and *PTPN11*), account for up to 15%–20% of Ph-like cases [8,9]. *BCR-ABL1* and Ph-like are associated with poor response to chemotherapy but are sensitive to TKIs, such as imatinib and dasatinib.

The *ETV6-RUNX1*-like subtype was defined as *ETV6-RUNX1* fusion negative and coexists with other *ETV6* and *IKZF1* alterations [17], accounting for approximately 10%–20% of the *ETV6-RUNX1*/-like subtype. The *ETV6-RUNX1*-like subtype is also significantly enriched in children patients, and more than 80% of cases of *ETV6-RUNX1*-like subtype are children [8,9].

The *KMT2A*-like and *ZNF384*-like are recently defined subtypes, accounting for 5%–15% and 7%–10% of the *KMT2A*/-like and *ZNF384*/-like [8,9]. Rare fusions, such as *MED12-HOXA9* and *AFF1-TMEM156*, are found in *KMT2A*-like cases. Notably, *HOXA9* is deregulated in *KMT2A* fusion-positive patients, and *AFF1* is the most common partner gene in *KMT2A* fusions [8,9]. Recurrent *ZNF362* fusions (*SMARCA2-ZNF362* and *TAF15-ZNF362*) are found in *ZNF384*-like ALL. The fusion partner genes, including *SMARCA2* and *TAF15*, and the sequence mutations of *ZEB2*, *CREBBP*, and *SETD1B*, are found in both *ZNF384-r* and *ZNF362-r* BCP-ALL. The zinc finger domains are retained in both fusion proteins [8].

The Ph-like subtype can successfully exemplify significant improvements in prognosis by seeking the phenocopied events. However, extra effort is required to identify other possible phenocopied subtypes (e.g., *HLF* fusion-like and hypodiploid-like subtypes) [8]. Moreover, the natural history and cell-of-origin of these "like" or "phenocopy" subtypes are still largely elusive. These gaps may prevent researchers from understanding the potential prognostic factors. A comprehensive comparison of the subtypes sharing similar gene expression profiles in many other aspects, such as cancer cell population, inherited or *de novo* variants within a noncoding region, aberrant splicing, bacterial and viral infections, chromatin accessibility, and/or epigenetics alterations, may provide more hints [27,87,94–105].

PAX5-driven subtypes: PAX5alt and PAX5 p.Pro80Arg

Paired box 5 (*PAX5*) is a member of the paired box (PAX) family and is an early B-lineage-specific transcriptional activator protein. Genetic alterations of *PAX5*, including DNA CNVs, sequence mutations, and chromosomal translocations, are common in patients with BCP-ALL [106]. CNVs and non-silent sequence mutations of *PAX5* occur in about 30% and 5%–9% of all BCP-ALL patients [8,9,18]. Chromosomal translocations of *PAX5*, which result in fusion genes, account for approximately 5%–7% of children and 2%–4% of adults with BCP-ALL [8,107]. *PAX5* fusions are highly heterogeneous and complex. At least 24 partner genes (e.g., *PAX5-JAK2*, *PAX5-ETV6*, and *PAX5-NOL4L*) of *PAX5* fusions are involved in *PAX5* rearrangements, thereby resulting in the expression of chimeric in-frame fusion transcript [9]. Furthermore, 15%–25% of patients with *PAX5* fusions have presented Ph-like subtype characteristics, mainly those of *PAX5-JAK2* and *PAX5-ZCCHC7*. Nearly 20% of *PAX5* fusions coexist with other chromosomal alterations, including *CRLF2* fusions, *ETV6-RUNX1*, *TCF3-PBX1*, *KMT2A*, *BCR-ABL1*, and iAMP21. For instance, *CRLF2* fusions coexist in up to 10% of all *PAX5* fusions, such as *PAX5-NOL4L*, *PAX5-AUTS2*, *PAX5-NCOA5*, and *P2RY8-CRLF2* pairs. Notably, these fusions have shown different gene expression profiles compared with the *CRLF2* fusions clustered to the *BCR-ABL1*/Ph-like subtype and account for up to 20% of all *CRLF2* fusions [8,9].

In recent studies, two new subtypes (PAX5-driven) with specific *PAX5* alterations have been defined in BCP-ALL. The first subtype is PAX5alt with rearrangements, intragenic amplifications, or sequence mutations of *PAX5* [8,9]. The second subtype is the hotspot mutation PAX5 p.Pro80Arg (P80R) and biallelic *PAX5* alterations [8,9,65,86]. PAX5alt and PAX5 P80R occur in 7%–10% and 3%–4% of childhood and 4%–8% and 1% of adult patients with BCP-ALL. Moreover, both subtypes are associated with intermediate outcomes. Additionally, compared with adults with PAX5alt, adults with PAX5 P80R had more superior outcomes [8,9].

Diverse *PAX5* alterations were found in approximately 75% of patients in the PAX5alt subtype. The alterations include *PAX5* rearrangements (*PAX5-ETV6*, *PAX5-NOL4L*, *PAX5-AUTS2*, *PAX5-CBFA2T3*, *PAX5-DACH1*, *PAX5-FOXP1*, and *PAX5-ZNF521*), sequence mutations (PAX5 p.Pro32Ser (P32S), p.Pro34Leu (P34L), p.Arg38Cys (R38C)/p.Arg38His (R38H), and p.Arg140Leu (R140L)/p.Arg140Gln (R140Q)), and CNVs (mainly one copy loss and focal intragenic amplification of *PAX5*). The ratio of CNVs that is positive for PAX5alt showed lesser frequency than that of other subtypes, but focal intragenic amplification (8/10) of *PAX5* (PAX5amp) was observed [9]. Apart from *PAX5* alterations, other common genetic alterations in the PAX5alt subtype are the signaling molecules (e.g., *NRAS*, *KRAS*, and *FLT3*), cell-cycle regulator *CDKN2A* deletions, B-cell development (*IKZF1* and *VPREB1* deletions), transcriptional factors (*ZFP36L2* and *ETV6*), and epigenetics modifier (*KDM6A*). The gene expression data showed that cytokine receptor genes (e.g., *PDGFRB* and *FLT3*) are enriched in PAX5alt, which is in line with the activation mutations in signaling pathways [8,9].

Point mutations of PAX5 P80R in the DNA binding can affect the ability of *PAX5* to bind DNAs and regulate expressions. These mutations represent the first molecular subtype defined on the basis of homogeneous hotspot mutations and gene expression profiles [8,9,65,86,108,109]. Most patients with PAX5 P80R presented distinct gene expression profiles and uniform genetic alterations. PAX5 P80R patients can promote the biallelic alteration of *PAX5 in vivo*, and this alteration frequently coexists with the hemizygous loss of *PAX5*. This scenario results in a higher mutation allele frequency compared with that of other *PAX5* point mutations [9]. Hemizygous PAX5 P80R without the deletion of the wild-type *PAX5* allele may present gene expression features in other subtypes, such as the Ph-like and PAX5alt. Activating mutations in signaling (Ras and JAK/STAT pathways), including *PTPN11* and *IL7R*, and inactivating mutations in epigenetic factor *SETD2* are the most common genetic alterations coexisting with PAX5 P80R [8,9,65,86].

PAX5-driven subtypes showed high heterogeneity in genetics, such as diverse patterning genes involved in *PAX5* fusions, and sequence mutations scattered on the coding region of *PAX5*. This characteristic may further require diverse therapy agents, including a combination of chemotherapy and multi-inhibitors, and possibly immunotherapy. Additionally, different prognoses between adult and childhood PAX5alt indicates the presence of additional age-dependent factors that may affect the vitality, aggressiveness, and drug responsiveness of leukemic cells in this BCP-ALL subtype [9].

NUTM1 gene fusion

The NUT midline carcinoma family member 1 (*NUTM1*), also called nuclear protein in the testis, is located within chromosome 15q14. Previously, *NUTM1* fusions were mainly reported as translocations t(15;9)(q14;q34) and t(15;19)(q14;p13) that could result in *BRD3-NUTM1* and *BRD4-NUTM1* [110–113]. In recent years, rearrangements of *NUTM1* involving *ACIN1* (14q11), *CUX1* (7q22), *AFF1* (4q21), *BRD9* (5p15), *ZNF618* (9q32), *IKZF* (7p12), and *SLC12A6* (15q14) have been identified as a specific subtype (1%–2%) in BCP-ALL. This subtype is preliminarily considered a subtype of BCP-ALL associated with a favorable prognosis [8,9,16–18,114,115]. The *HOXA* gene family, particularly *HOXA9*, is upregulated in the *NUTM1-r* ALL, which has not been described in NUT midline carcinoma [8]. *KMT2A* fusions can regulate leukemogenic gene expressions, particularly the *HOXA* gene family, by modulating the acetylation of H3K27 and disturbing the telomeric silencing 1-like histone 3 lysine 79 (H3K79) methyltransferase DOT1L [51,116]. *HOXA9* can cooperate with the JAK/STAT signaling pathway and drive leukemia development [117]. The molecular mechanism of *NUTM1-r* ALL is still largely unknown and thus needs further study. Both *NUTM1* and *KMT2A* fusions may drive leukemogenesis by disturbing epigenetic status and upregulating the *HOXA* gene family.

Other gene fusions and point mutations

Rearrangements of BCL2/MYC and/or BCL6

Translocations t(14;18)(q32;q21), t(8;14)(q24;q32), and t(3;14)(q27;q32) that result in *BCL2-IGH*, *MYC-IGH*, and/or *BCL6-IGH* fusions occur in approximately 2% of adults (mostly $>$ 30 years old) with BCP-ALL and are less common in children. These translocations are associated with consistently poor responses in early treatment [9]. Low levels of circulating t(14;18)-positive cells can be found in approximately 50%–70% of healthy individuals but never develop into a disease [118–121]. Chromosomal alterations in *BCL2*, *MYC*, and/or *BCL6* have been frequently reported in chronic lymphocytic leukemia and double- or triple-hit lymphoma, which are rare in ALL with a B-cell-precursor immunophenotype [16,121–133]. The promoter regions of *BCL2*, *MYC*, and *BCL6* are usually affected by *IGH* translocations, causing an overexpression of the rearranged allele compared with the germline allele. This characteristic can dramatically activate the proliferation of leukemogenic blast cells [123]. At present, patients with the abovementioned alterations cannot be well cured because of the development of chemotherapy resistance [9,121]. This limitation poses a great challenge to patient treatment. The inhibition of cyclin-dependent kinase 7 (CDK7) has been reported as an optional target for reducing the resistance of BCL-2 in B-cell lymphoma models [133]. The developed therapeutic agents in B-cell lymphoma may also be effective in BCP-ALL. Additional functional assays and clinical tests are urgently needed to improve the survival rate in the *BCL2*/*MYC* and/or *BCL6-r* BCP-ALL.

ZEB2 p.His1038Arg (H1038R) and IGH-CEBPE gene fusion

Zinc finger E-box binding homeobox 2 (*ZEB2*), a member of the Zfh1 family of 2-handed zinc finger/homeodomain proteins, is a nuclear protein that can bind DNA and repress its transcriptional activity; this protein interacts with activated SMAD, a DNA binding protein, and recognizes an 8-bp palindromic sequence (GTCTAGAC) called the Smad binding element [134]. CCAAT enhancer binding protein epsilon (CEPBE) is a bZIP transcription factor that binds to certain DNA regulatory regions by means of homodimer formation. In a recent study, a hotspot mutation of ZEB2 p.His1038Arg (H1038R) and

translocation t(14;14) (q11;q32), which results in *IGH-CEBPE* with a truncation of the 3′ UTR, is defined as a rare subtype (< 1%) sharing similar gene expression features. The rs2239630 G > A at the promoter of *CEBPE* is associated with the *IGH-CEBPE* translocated ALL with increased *CEBPE* expression [135]. More than 50% of patients in this subtype also have *NRAS* sequence mutations. The leukemic oncogene *LMO1* is significantly upregulated in this subtype and is an important component of a transcriptional complex that includes TAL1, TCF12/HEB, TCF3/E2A, MYB, RUNX1, GATA3, and LDB1. This transcription complex can form a positive interconnected autoregulatory circuit that impacts the transformation in approximately 60% of patients with T-cell ALL (T-ALL) [77,136]. In addition, *SMAD1* and *BMP2* are significantly downregulated in this subtype; these genes can regulate the signals of the bone morphogenetic proteins and are involved in a range of biological activities, including morphogenesis, cell growth, apoptosis, development, and immune responses [137–140]. Preliminarily, *ZEB2* mutation is associated with poor event-free survival and high relapse in patients with BCP-ALL [141]. The clinical implications of ZEB2 p.His1038Arg (H1038R) and *IGH-CEBPE* gene fusion subtype are still largely unclear. Much larger sample sizes and functional tests are needed for this BCP-ALL subtype.

IKZF1 p.Asn159Tyr (N159Y)

IKZF1, also known as IKAROS, is a critical transcription factor related to the differentiation and maturation of the B-cell precursor. Somatic alterations of *IKZF1* are a hallmark of high-risk BCP-ALL with poor response to therapy [72,109,142]. Point mutations of IKZF1 p.Asn159Tyr (N159Y) were recently recognized as a rare subtype (< 1%) in BCP-ALL. In light of the limitation of sample size, the outcomes of IKZF1 N159Y are still undermined. IKZF1 N159Y, which is located in the DNA binding domain, may impact its capability for DNA binding and gene transcription regulation. Sequence mutations of *KRAS* are recurrent in patients with IKZF1 N159Y but lack extra copy number alterations. The gene expression data showed that the transcriptional coactivator *YAP1* is significantly upregulated, which can drive *KRAS*-induced transformation through rescued cell viability in *KRAS*-dependent cells [143]. The chromatin remodeling *SALL1* and the signaling factor *ARHGEF28* are also significantly upregulated in IKZF1 N159Y-positive patients. Meanwhile, the B-cell receptor signaling and JAK-STAT signaling pathways (e.g., *FLT3*, *FLT4*, and *STAT5*) are down-regulated in patients with IKZF1 N159Y. These two pathways are commonly activated in other BCP-ALLs [8,9,144–146]. At present, the public data show that IKZF1 N159Y-positive cases are still below 10. One case of IKZF1 N159T was reported in the chronic myelomonocytic leukemia cohort [147]. Surprisingly, *de novo* germline mutations, including IKZF1 N159S (n = 6) and IKZF1 N159T (n = 1), could exist at the same IKZF1 amino acid N159, which then would cause T-, B-, and myeloid cell-combined immunodeficiency, and a patient would develop T-ALL [148]. *Pneumocystis jirovecii* pneumonia is positive in all of patients with N159S or N159T mutations. A patient died at 2 years old without leukemia phenotype although the child received hematopoietic stem cell transplants [148]. Multi-center collaboration may accelerate the collection of patient data in this subtype for the further evaluation of its clinical significance (Table 1; Fig. 1A and 1B).

Table 1 Overview of biological subtypes of adult and childhood BCP-ALL

Subtype	Adult	Childhood	Key features	Molecular targeting agents	Outcomes
Ph	15%–25%	2%–5%	Gene fusion of *BCR-ABL1* (Ph), mutation of *RUNX1*, and common deletions of *PAX5*, *IKZF1*, and *CDKN2A/2B*	TKI; JAK/STAT, BTK/BCR, PD-1/PD-L1, CDK8, Aurora kinase A/B/C inhibitors	Poor outcome and improved with TKI
Ph-like	20%–25%	6%–15%	Gene fusions of *CRLF2*, *ABL1/ABL2*, *JAK2*, *EPOR, PDGFRB*, and *CSF1R* and mutations of *NRAS*, *KRAS*, *JAK2*, and *PTPN11*	TKI; JAK/STAT, BCL2 inhibitors	Poor outcome and amenable to TKI therapy
KMT2A	4%–10%	3%–4%	Gene fusions of *KMT2A* fused to *AFF1*, *MLLT1*, *MLLT3*, *MLLT10*, and *EPS15* and mutations of *NRAS*, *KRAS*, and *FLT3*; de-regulated gene expression of *HOXA* gene family, particularly *HOAX9*	DOT1L, HDAC, CDK4/6, BCL2, MEN1 inhibitors	Poor outcome
KMT2A-like	<1%	<1%	Gene fusions of *MED12-HOXA9* and *AFF1-TMEM156*	/	Poor outcome
ETV6-RUNX1	<1%	15%–25%	Gene fusion of *ETV-RUNX1* and mutations of *WHSC1*, *KRAS*, and *NRAS*	/	Favorable outcome

(*Continued*)

Subtype	Adult	Childhood	Key features	Molecular targeting agents	Outcomes
ETV6-RUNX1-like	<1%	2%–3%	Co-existing *ETV6* and *IKZF1* aberrations; CD27 positive, CD44 low to negative	/	Intermediate outcome
TCF3-PBX1	2%–5%	4%–7%	Gene fusion of *TCF3-PBX1* and mutations of *TP53*	CDK4/6 inhibitors	Intermediate outcome with intensive therapy, and association with CNS relapse
HLF	<1%	<1%	Gene fusions of *TCF3-HLF* and *TCF4-HLF*	CDK4/6, TKI, BCL2, BCR/BCL6 inhibitors	Poor outcome
DUX4	4%–7%	4%–7%	Gene fusions of *IGH-DUX4* and *ERG-DUX4*; de-regulated gene expression of ERGalt; CD2 and CD371 positive	/	Favorable outcome with *ERG* deletions; intermediate outcome without *ERG* deletions
MEF2D	2%–7%	2%–4%	Gene fusions of *MEF2D* fused to *BCL9, SS18, FOXJ2, CSF1R, DAZAP1, STAT6, HNRNPUL1, HNRNPH1, and HNRNPM*; de-regulated gene expression of *HDAC9;* CD10 negative and CD38 positive	HDAC inhibitors	Poor outcome
ZNF384	3%–8%	3%–5%	Gene fusions of *ZNF384* fused to *EP300*, *TCF3*, *TAF15*, *CREBBP*, *EWSR1*, *ARID1B*, *SMARCA2*, *SMARCA4*, *SYNRG*, and *NIPBL* and mutations of *NRAS*, *KRAS*, *FLT3*, *PTPN11*, *SETD1B*, *ZEB2*, *EZH2*, *KMT2D*, and *CREBBP*; mixed-phenotype	FLT3 inhibitors	Intermediate outcome
ZNF384-like	<1%	<1%	Gene fusions of *ZNF362* fused to *SMARCA2* and *TAF15*	/	/
PAX5alt	4%–8%	8%–10%	Gene fusions of *PAX5* fused to *ETV6*, *NOL4L*, *FOXP1*, *AUTS2*, *CBFA2T2/3*, *P2RY8-CRLF2*, deletions of *PAX5*, and mutations of *PAX5*, *NRAS*, *KRAS*, *FLT3*, and *JAK1*	TKI	Intermediate outcome
BCL/MYC	1%–2%	<1%	Gene fusions of *IGH-BCL2*, *IGH-MYC*, and *IGH-BCL6*	CDK7 inhibitors; BCL2 inhibitors	Poor outcome
NUTM1	<1%	1%–2%	Gene fusions of *NUTM1* fused to *ACIN1*, *CUX1*, *AFF1*, *BRD9*, *ZNF618*, *SLC12A6*, and *IKZF1*	Bromodomain inhibitors	Favorable outcome
High hyperdiploidy	<1%	15%–25%	>50 chromosomes, mutations of *NRAS*, *KRAS*, *FLT3*, *PTPN1*, *KMT2D*, and *CREBBP*	/	Favorable outcome
Near-haploid	<1%	2%–3%	25–29 chromosomes, mutations of *NRAS*, *FLT3*, and *PAX5*, and inactivation of *IKZF3* and *PAG1*	BCL2 inhibitors	Poor outcome
Low hypodiploid	1%–2%	10%–15%	32–39 chromosomes, mutations of *TP53*, deletions of *CDKN2A/2B* and *RB2*, and inactivation of *IKZF2*	BCL2 inhibitors	Poor outcome
High hypodiploid	<1%	<1%	40–43 chromosomes	/	Poor outcome
iAMP21	<1%	2%–3%	Complex structural alterations of chromosome 21	/	Intermediate outcome

(*Continued*)

Subtype	Adult	Childhood	Key features	Molecular targeting agents	Outcomes
PAX5 P80R	3%–4%	<1%	Hotspot mutations of *PAX5* p.Pro80Arg (P80R) and activating-mutations of *NRAS*, *KRAS*, *FLT3*, and *PTPN11*	TKI	Intermediate outcome
IKZF1 N159Y	<1%	<1%	Hotspot mutations of *IKZF1* p.Asn159Tyr (N159Y)	/	/
ZEB2 H1038R/ *IGH-CEBPE*	<1%	<1%	Gene fusion of *IGH-CEBPE* and mutations of *ZEB2* p.His1038Arg (H1038R), *NRAS*, *KMT2D*, *KRAS*, *KMT2A*, and *CDKN2A*	/	/

Percentages may not add up to 100% because of rounding. NA, not available.
Abbreviations: TKI, tyrosine kinase inhibitor.

Diagnosis and molecular classification of BCP-ALL based on RNA-seq

Genetic variations with clinical significance in BCP-ALL are structurally heterogeneous [18]. Multiple high-throughput sequencing approaches are highly recommended, as they can be utilized to accurately recognize the prognostic factors (e.g., fusion genes, gene expression-dependent subtypes, small sequence variants, and genomic duplications and deletions) and determine the strategic therapy [149]. RNA-seq is a single and comprehensive platform for BCP-ALL diagnosis and genomic classification in the laboratory and clinical settings [9,43,150–152]. For example, most of the known fusion genes (e.g., *BCR-ABL1*, *ETV6-RUNX1*, and *TCF3-PBX1*) and new fusion genes (e.g., *TCF3*/*4-HLF*, *NUTM1*, *DUX4*, *ZNF384*/*ZNF362*, and *MEF2D* fusions) in BCP-ALL can be detected by RNA-seq [149,153]. These newly identified recurrent *DUX4*, *ZNF384*, *MEF2D*, and *NUTM1* fusions have distinct clinical features [8,9,15,16,18,22,64]. Notably, RNA-seq is also a reliable technology for simultaneously identifying the positive-fusion gene and the gene expression-dependent subtypes, including Ph-like, *ETV6-RUNX1*-like, *ZNF384*-like, and *KMT2A*-like. Small sequence variants and genomic deletions (e.g., *IKZF1*) are also detectable by RNA-seq in BCP-ALL [8,9,77,149,151–154]. For instance, by re-analyzing the RNA-seq data from different BCP-ALL cohorts, the molecular subtypes characterized by hotspot mutations (e.g., PAX5 P80R and ZEB2 H1038R) could be identified [8]. Exon-level genomic deletions can cause differential transcripts expression (e.g., *IKZF1* exons 4–7, 2–7, 2–8, and 4–8) and thus can be used to predict genomic deletion events [153]. RNA-seq was also applied in AML diagnosis to accurately detect small sequence variants, *FLT3*-internal tandem duplication (ITD), and *KMT2A*-partial tandem duplication (PTD) events [155–157].

However, RNA-seq is more susceptible to bias factors originating from the samples, technology platform, and bioinformatics methodology (e.g., batch effect) compared with the DNA-based methods. Additional systematic benchmarks and further refinement of the methodology as a means of reducing the bias are needed to improve the stability and reducibility of the RNA-based methods [149,158,159].

New therapeutic targets and agents in BCP-ALL

Intensive chemotherapy and allogeneic hematopoietic cell transplantation were the core options of BCP-ALL treatment in the past [27]. Treatment toxicity with relapsed events induced by chemotherapy drugs has been one of the most critical concerns awaiting further resolution in BCP-ALL [13,27]. The advent of emerging inhibitors/antagonists and immunotherapeutic has launched a new era of target therapy in several molecular subtypes or unselected BCP-ALL patients (Table 2). This ongoing transformation may continuously reduce the use of chemotherapy drugs and consequently achieve less treatment-induced resistance events [160]. Molecular target therapy and cellular immunotherapy in BCP-ALL are mainly dependent on the specific genetics and gene expression markers of the patients' leukemic cells in various molecular subtypes (e.g., *BCR-ABL1*, Ph-like, and *KMT2A* fusions) or the shared or unselected cell surface marker (e.g., CD19 and CD22) (Fig. 2). Several molecular subtypes in BCP-ALL, including R/R subtypes, have benefited from the new therapeutic targets and agents, although a large number of biomarkers are still rarely used as therapy targets.

BCR-ABL1 and Ph-like (e.g., *BCR-ABL1*-negative with fusions or mutations involved in *ABL1*/*ABL2*, *PDGFRA*/*B*, *EPOR*, and *CSF1R*) have benefited from TKIs, including imatinib and/or dasatinib [91]. The combination of dasatinib and c-JUN N-terminal kinase (JNK) inhibitor, i.e., JNK-IN-8, can significantly improve the survival of the *BCR-ABL1*-positive mice model [161]. The cyclin-dependent kinases 8 (CDK8) inhibitor, YKL-06-101,

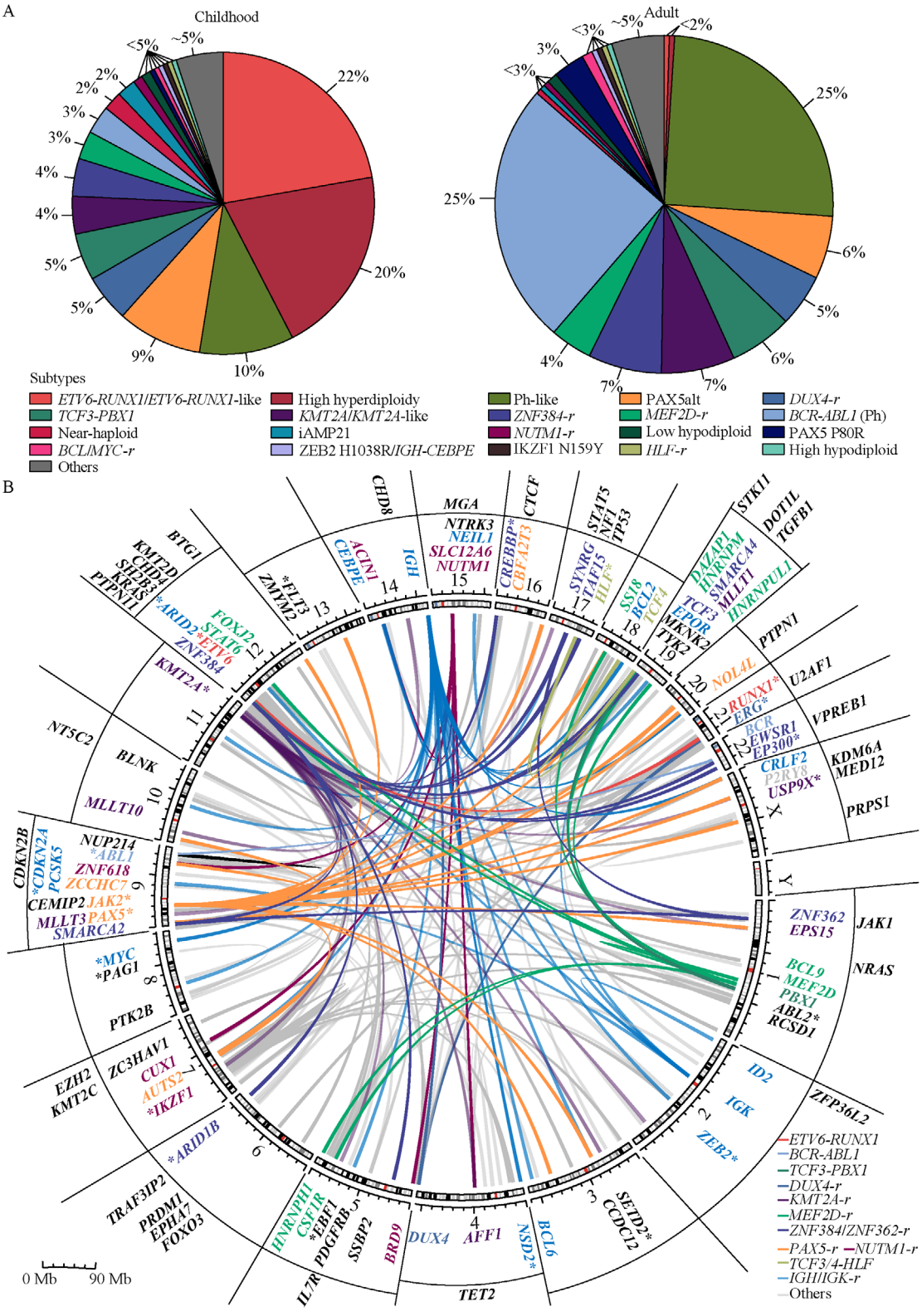

Fig. 1 Estimated percentage of major molecular subtypes and the genomic landscape of genetic mutations. (A) Pie plot represents the percentage of molecular subtypes in adult and children patients with BCP-ALL. (B) Cycle plot indicates the genomic landscape of major genetic alterations, including gene fusions, sequence mutations, and DNA CNVs. Chromosomes are separately arranged from chromosome 1 to X. Gene fusions are linked by ribbons, and the fusions involving *ETV6-RUNX1*, *BCR-ABL1*, *TCF3-PBX1*, *TCF3/4-HLF*, *IGH*, *KMT2A*, *MEF2D*, *ZNF384*, *NUTM1*, and *PAX5* are highlighted. Genes affected by sequence mutations and DNA CNVs are listed at the external lines according to chromosome location. * Genes affected by different types of variations, i.e., fusion genes, CNVs, and sequence mutations.

Table 2 Summary of known and potential therapy targets in BCP-ALL

Therapy targets	Classification	Agents	PubMed ID	ClinicalTrials.gov identifier	Associated subtype
CD19	Immunotherapy	Blinatumomab; denintuzumab; SGN19a (denintuzumab mafodotin); SAR3419 (coltuximab ravtansine); AFM11; ADCT-42; KTE-C19 (autologous CD19 CAR T); CART-19 (autologous); UCART19 (allogeneic); C-CAR-011; iC9-CAR19 (autologous); CD19CAR-4-1BB-CD3zeta-EGFR-texpressing T lymphocytes (autologous); CART-19 (autologous); 4SCAR19 (autologous); CTL019 T-cells; CTL019 autologous T-cells (with tocilizumab); CD19CAT-41BBZ CAR T-cells (autologous); huCART19 (autologous); iC9/CAR.19/IL15-transduced CB-NK cells (umbilical and cord-blood derived); PCAR-019 (autologous); CD19 CAR-NK cells (allogeneic)	16352804, 20424114, 21849486, 22592608, 23307031, 24731302, 26041741, 26516065, 26907630, 27460500, 27846391, 27887660, 27571406, 28249141, 28202953, 28490811, 28698205, 28827408, 29385376, 30728140	NCT00450944, NCT01860937, NCT01864889, NCT01865617, NCT01974479, NCT01974479, NCT02003222, NCT02028455, NCT02030847, NCT02101853, NCT02143414, NCT02185781, NCT02228096, NCT02374333, NCT02412306, NCT02443831, NCT02454270, NCT02456350, NCT02458014, NCT02614066, NCT02669264, NCT02746952, NCT02772198, NCT02799550, NCT02807883, NCT02810223, NCT02819583, NCT02848911, NCT02851589, NCT02877303, NCT02879695, NCT02892695, NCT02906371, NCT02924753, NCT02935257, NCT02935543, NCT02968472, NCT02975687, NCT02997761, NCT03016377, NCT03018093, NCT03027739, NCT03056339, NCT03064269, NCT03076437, NCT03103971, NCT03109093, NCT03110640, NCT03114865, NCT03937544, NCT04012879	/
CD20	Immunotherapy	Rituximab; ofatumumab; REGN1979; CD20-CAR transduced T-cells (autologous)	18381448, 18780832, 18971949, 20628151, 21298738	NCT01363128, NCT02419469, NCT02651662, NCT01735604	/
CD22	Immunotherapy	Epratuzumab; inotuzumab; BL22 and moxetumomab pasudotox; CART22 cells (autologous)	21869836, 22128838, 23243285, 24579885, 25484043, 25552705, 25728039, 28152223, 28449314, 29155426, 31110217	NCT01371630, NCT01925131, NCT02311998, NCT02650414, NCT03094611, NCT03104491	/
CD19/CD20	Immunotherapy	CD19/20-CAR transduced T-cells (autologous or allogeneic)	28515942	NCT03097770	/
CD19/CD22	Immunotherapy	Combotox; deglycosylated ricin A chain conjugated CD19/CD22 immunotoxins; DT2219ARL	10803517, 12592332, 17706771, 19327829, 21732928, 29155426, 30581986, 31182121	NCT01408160, NCT03330691, NCT04094766	/
CD19/CD28	Immunotherapy	CAR T (autologous; CD19, CD28)	10048973, 20424114, 23515080, 28039295	NCT02146924	/
CD19/CD28/ CD137	Immunotherapy	CD19.CAR/28 and CD19.CAR/28.137 T-cells (autologous)	27887866	NCT01853631, NCT02685670	/
CD19/CD133	Immunotherapy	Tandem CAR (TanCAR) of CD19 and CD133	30046161	/	/
CD19/CD137	Immunotherapy	Second generation CAR T (CD19, CD137)	27887866	NCT02965092	/
CD20/CD22	Immunotherapy	Hexavalent antibodies (HexAbs); Bs20x22	18025153, 20628151, 21347809	/	/
CD28/CD137	Immunotherapy	Third generation CAR T (CD28, CD137)	14961035, 27887866	NCT02186860	/
CD25	Immunotherapy	ADCT-301	25337274	NCT02588092	/
CD38	Immunotherapy	Isatuximab	26631114, 28483761, 30858549, 30862646	NCT03860844	/
CD52	Immunotherapy	Alemtuzumab	28123068, 29264111	NCT00773149	
CD123	Immunotherapy	XmAb14045	19454491, 27571406	NCT02730312	/
Integrin alpha4	Immunotherapy	Chemotherapy combined with natalizumab	23319569	/	/
ROR1	Immunotherapy	ROR1 CAR-specific T lymphocytes (autologous)	21813176, 29476010, 29849118, 30631148	NCT02706392	/
EPHA3	Immunotherapy	IIIA4	27922598	/	

(*Continued*)

Therapy targets	Classification	Agents	PubMed ID	ClinicalTrials.gov identifier	Associated subtype
PD-1/PD-L1	Inhibitors	Nivolumab; pembrolizumab; REG2810	/	NCT02651662, NCT02767934, NCT02819804	Ph
CTLA-4	Inhibitors	Ipilimumab	/	NCT00060372, NCT02879695	/
CDK4/6	Inhibitors	Palbociclib; ribociclib; PD0332991	17537993, 24736461, 25744718, 25813205, 26637365, 27099147, 29408328	NCT02310243, NCT03472573, NCT03515200, NCT03132454, NCT03792256	*KMT2A*, *TCF3-PBX1*, *TCF3/4-HLF*
CDK7	Inhibitors	THZ1	31085176	/	*BCL/MYC*
CDK8	Inhibitors	YKL-06-101	31628323	/	*BCR-ABL1*
Tyrosine kinase	Inhibitors	Dasatinib, PLX3397, nilotinib, sunitinib, sorafenib, ponatinib; ABL001 (asciminib)	17068151, 17077147, 19322212, 20807819, 22297722, 22897847, 23861246, 23974192, 24711557, 24464015, 24828076, 25049327, 25207766, 25759025, 26872634, 26773044, 27919910, 28329763, 28461505, 28408464, 28555080, 28819281, 29348129, 29681510, 29997224	NCT01620216, NCT02081378, NCT02390752, NCT02883049	Ph, Ph-like, *HLF*, PAX5alt, PAX5 P80R
BTK/BCR	Inhibitors	Ibrutinib	28031181	NCT02815059, NCT02997761, NCT02997761, NCT03267186, NCT03267186	Ph
FLT3, PI3K/mTOR pathway	Inhibitors	PKC412; idelalisib; sirolimus; quizartinib; crenolanib; dactolisib; rapamycin; CCI-779; TGR-1202	16195324, 17942929, 18704194, 22705992, 22955920, 27461063, 27784673, 28424165	NCT00651261, NCT00866281, NCT01162551, NCT01756118, NCT02779283, NCT03742323	*ZNF384*
JAK/STAT	Inhibitors	Ruxolitinib; AZD1480, CHZ868	20018760, 22955920, 25049327, 26175414, 26500062, 27860260, 28331226, 28369050, 28461505, 29907650	NCT01914484, NCT02420717, NCT02494882, NCT02723994	Ph
MEK1/2, RAS, B-Raf	Inhibitors	MEK162, trametinib, selumetinib; trametinib/sorafenib	27054332, 32220889	NCT02089230	/
SYK	Inhibitors	Entospletinib; PRT318; PRT260607	24948121, 26847027	NCT02404220	/
SRC	Inhibitors	/	24625531, 28804122		/
Aurora kinase A/B/C	Inhibitors	Danusertib		EudraCT number 2007-004070-18	Ph
PYST1 (Erk activation)	Inhibitors	BCI	26073130, 28804122	/	/
JNK	Inhibitors	SP600125; JNK-IN-8	26310606, 26310606, 32552902	/	/
Casein Kinase II (CK2)	Inhibitors	CX-4945	32396934	/	/
VEGFR	Inhibitors	Axitinib	25686603	NCT02551718	/
LEPR	Inhibitors	1-day fasting	27941793		/
HSP90	Inhibitors	PU-H71	22271575, 26443624, 28619753	/	/
DRD2	Inhibitors	ONC201	29533922, 31127149	NCT02392572	/
MDM2	Inhibitors	DS302-b; RG7112; Nutlin-3	19421231, 19710698, 21986948, 29653964, 21986948	NCT02319369	/
MEN1	Inhibitors	VTP50469	31821784	/	*KMT2A*
HER2	Inhibitors	Trastuzumab	15531467, 18971949, 22267607	NCT00724360	/
PARP	Inhibitors	Talazoparib	24856976, 28634224	NCT02116777	/
Hedgehog	Inhibitors	PF-04449913	30487223, 31030089	NCT01841333	/

(*Continued*)

Therapy targets	Classification	Agents	PubMed ID	ClinicalTrials.gov identifier	Associated subtype
CXCR-4	Inhibitors	BL-8040; plerixafor (BKT140); AMD3100; LY2510924	12835717, 24502926, 26031918, 26398122, 27071778, 27307990, 28409853, 28280274, 30254339	NCT01352650, NCT02605460, NCT02763384	/
DNA methyl-transferases (DNMT1/ DNMT3A/ DNMT3B)	Inhibitors	Decitabine; azacitidine; pinometostat	19179467, 28171800, 29728108, 30841886	NCT00075010, NCT00349596, NCT01861002, NCT02141828, NCT02458235	/
Histone deacetylases (HDACs)	Inhibitors	Vorinostat; panobinostat; romidepsin; entinostat; chidamide; givinostat (ITF2357)	27428428, 27824051, 28331226, 30171027, 31439580, 31969338	NCT00217412, NCT00462605, NCT01132573, NCT01321346, NCT01422499, NCT02551718, NCT02553460, NCT03117751, NCT03564470, NCT03564704	*MEF2D*, *KMT2A*
DOT1L	Inhibitors	EPZ-5676	23801631, 24993360, 28428443, 29724899	NCT01684150, NCT02141828, NCT03724084, NCT03701295	*KMT2A*
c-Myc	Inhibitors	Shikonins, TGR-1202, JQ1	21949397, 21986948, 22904298, 27784673	/	
BCL2/BCL-X_L	Inhibitors	Venetoclax (ABT-199); ABT-737; navitoclax (ABT-263)	23788110, 26214592, 27054332, 28122742, 28974549, 30631148, 30862722	NCT03181126, NCT03236857, NCT03319901, NCT03504644, NCT03576547, NCT03808610, NCT03181126, NCT03826992, NCT04029688	*KMT2A*, Ph-like, *HLF*, *BCL/MYC*, near-haploid, low hypodiploid
BCL-6	Inhibitors	PRT062607; RI-BPI	23107779, 26214592, 25759025, 25780007	/	/
Proteasome	Inhibitors	Ixazomib; bortezomib; carfilzomib; CX-4945	23357978, 26593250	NCT02228772, NCT02293109, NCT02535806, NCT02578511	/
BIRC5 (survivin)	Inhibitors	YM155	25895498, 30991025	/	/
Retinoid X receptor	Inhibitors	Bexarotene, carbacyclin, ATRA, 9- and 13-cis RA	26321221	/	/
Reactive oxygen species	Inhibitors	Verteporfin	26774450, 30563887, 31109083	/	/
Bromodomain	Inhibitors	BMS-986158	30723300	NCT03936465	*NUTM1*
TP53	Agonist	SB225002	19710698, 23334668, 28600336, 28557976, 29300620, 30657737	/	/
IL-15	Agonist	ALT-803	23644531, 25896649, 29365313, 29463563, 26980764	NCT01885897, NCT02890758	/
Fas	Agonist	Rimiducid (AP1903)	25977584, 28697888, 30514753	NCT03016377, NCT03056339	/

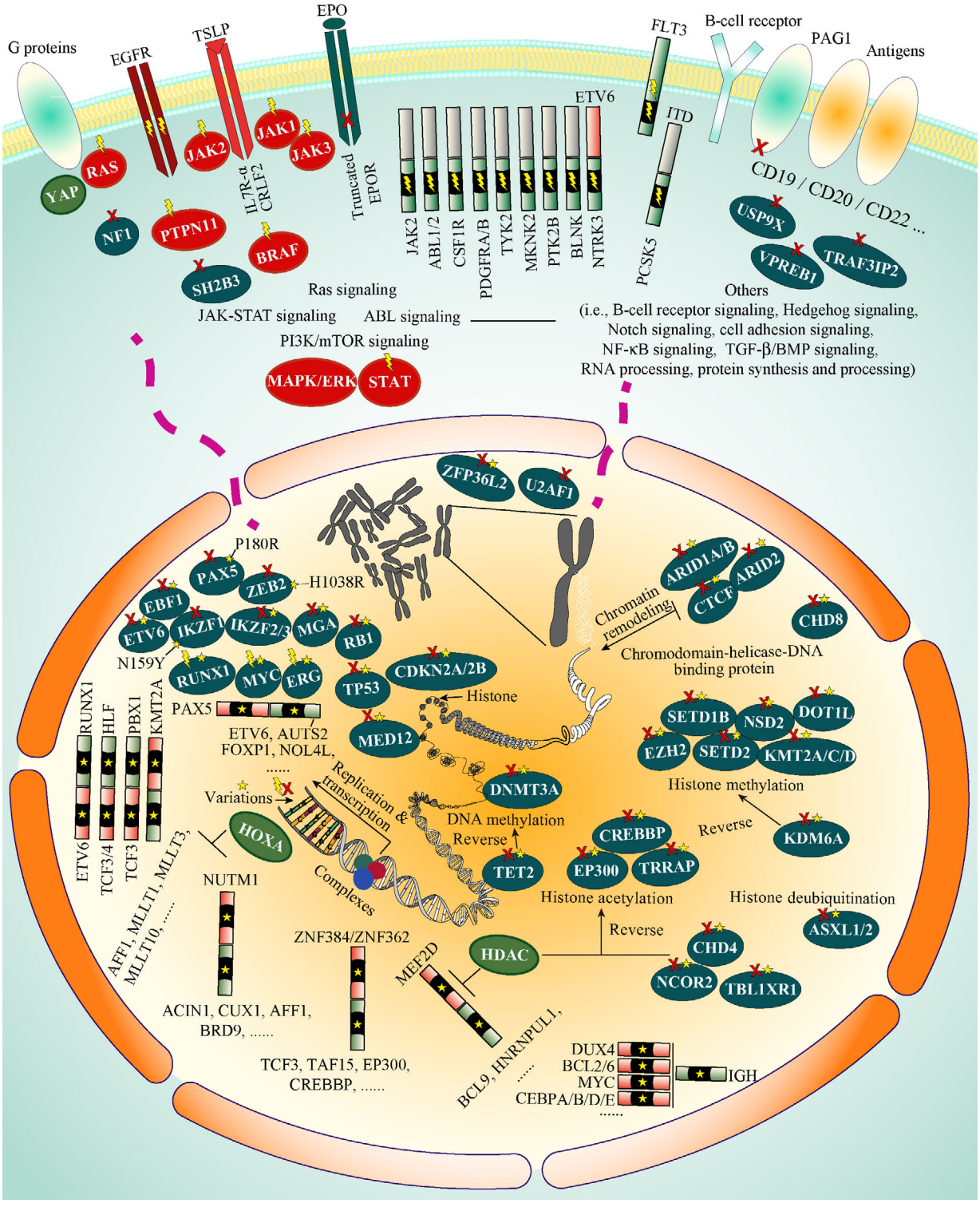

Fig. 2 Schematic of the candidate therapy pathways and targets from the cell surface to the nucleus of leukemic blast cells of patients with BCP-ALL. Signaling pathways (e.g., Ras signaling and JAK-STAT signaling) are mutant or/and activated in most subtypes of BCP-ALL. Other cytokine receptors and signaling pathways (e.g., Hedgehog signaling and Notch signaling in *NUTM1* fusions; CRLF2, IL-7, and EPOR in Ph-like subtype; and PAG1 in near-haploid) are enriched in specific subtypes. Cell surface antigens, including CD19, CD20, and CD22, are the most promising CAR-T therapy targets. De-regulated tumor suppressors or cell cycle regulators (e.g., *TP53* and *CDKN2A*/*2B*), transcription factors (e.g., *PAX5*, *IKZF1*, and *ERG*), epigenetic modification (DNA methylation, histone acetylation, methylation, and deubiquitylation), and chromatin remodeling (e.g., *CTCF* and *ARID1A*/*B*) are the hallmarks of BCP-ALL in the nucleus.

combined with the mTOR inhibitor can induce cell death of human *BCR-ABL1* leukemic cells [162]. Besides, both CDK4/6 inhibitors and Bcl-2 inhibitor are two types of molecular inhibitors that have been tested in R/R BCP-ALL [13,163], such as CDK4/6 inhibitors palbociclib (NCT02310243, NCT03472573, NCT03515200, NCT03132454, and NCT03792256) and Bcl-2 inhibitor venetoclax (NCT03826992, NCT03319901, NCT03181126, NCT04029688, NCT03808610, and NCT03504644). *KMT2A* fusions, *HLF* fusions, and other R/R BCP-ALL may benefit from the inhibition of the cell cycle and apoptosis pathways. De-regulated DNA methylation or histone deacetylation has been found in several BCP-ALL subtypes (e.g., *KMT2A* and *MEF2D* fusions). DOT1L inhibitors (e.g., pinometostat/EPZ-5676) have been tested in phase I trials (NCT01684150 and NCT02141828) for *KMT2A-r* leukemia [164], and the phase 1b/2 trials (NCT03724084 and NCT03701295) are currently recruiting patients. HDAC inhibitors (e.g., vorinostat and panobinostat) have also been proposed to be benefiting several BCP-ALL subtypes (NCT02553460), including *MEF2D* fusions and R/R BCP-ALL [16,18,64,165]. A newly proposed bioavailable Menin (*MEN1*)-*KMT2A* interaction inhibitor, VTP50469, showed that it can improve survival in patient-derived tumor xenograft mouse models of *KMT2A-r* BCP-ALL by suppressing a subset of *KMT2A* fusion target genes [166]. Other activated critical cellular pathways regulating cell proliferation and apoptosis (i.e., pre-B/B-cell receptor, RAS, JAK-STAT, and mTOR/PI3K) [13] are also promising targeted pathways. Numerous clinical trials have been registered. The test combining multiple molecular compounds or agents are still in progress. Nonetheless, additional work is required to verify whether the intensive dose of chemotherapy drugs can be reduced reasonably.

Apart from the inhibitors/antagonists, immunotherapeutic agents, such as CAR-T and monoclonal antibodies, are another promising strategy for targeting specific cell surface markers overexpressed in leukemic cells. Immunotherapeutic agents can be used in the therapy of most children and adults with R/R BCP-ALL. The cell membrane antigens CD19, CD20, and CD22 are the three most promising targets of immunotherapeutic agents for BCP-ALL [167–174]. Other bispecific agents (e.g., Combobox for CD19/CD22) are becoming the next-generation CAR-T treatment options. As one of the hottest fields in BCP-ALL, a series of clinical trials of CAR-T for R/R BCP-ALL is ongoing (e.g., NCT03330691, NCT03937544, NCT00450944, NCT04012879, and NCT04094766). The immunotherapeutic agents inotuzumab and blinatumomab were approved by the United States Food and Drug Authority for the therapy of adults with R/R BCP-ALL, which can help to improve in the future the overall survival of both children and adults with BCP-ALL. In addition, the combination of the TKIs imatinib or dasatinib with multiagent chemotherapy is currently used in multiple clinical trials of R/R BCP-ALL. This treatment has markedly improved the outcome in BCP-ALL subset, as the five-year overall survival of patients has increased to 75% from less than 50% [12,175]. Controlling early death, reducing therapy-induced resistance mutations, and comprehensive clinical management of adult patients are the potential key issues of medical precision in BCP-ALL treatment (Table 2) [5,8,9,12,13,25,40,60,61,160,167,169,176–182].

Conclusions

Through decades of collaboration, more than 95% of patients with BCP-ALL have been classified and labeled using detectable genetic alterations, including distinct translocations of chromosomes, aneuploidy, DNA copy number alterations, sequence mutations, and gene expression patterns [8–12,183]. Refined risk stratification and the approval of new drugs and agents, including target inhibitors, monoclonal antibodies, and immunomodulators, and CAR-T, have resulted in an excellent five-year event-free survival and a five-year overall survival in children with BCP-ALL. However, the development of resistance and early death during treatments continue to pose daunting challenges for some subtypes of BCP-ALL, including hypodiploid (< 44 chromosomes), *HLF*-arranged, *BCL2*/*MYC-r*, *BCR-ABL1*/Ph-like, *KMT2A-r*, and *MEF2D-r* BCP-ALL. Additionally, single-cell-based traces of cancer cell populations, chromatin accessibility, epigenetic alterations, genome-wide germline mutations, functional non-coding and synonymous mutations, and other abnormalities at the non-genomic levels, such as protein and metabolic levels, are still poorly understood. Information on these aspects can help in drug discovery and improvement in the prognoses of leukemia patients, including BCP-ALLs [103–105,183–188]. Through the comprehensive identification of prognostic biomarkers and the development of new techniques in diagnosis and target treatment, we can further improve the survival time and life quality of patients with BCP-ALL.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Nos. 82070147, 81570122, and 81770205), the National Key Research and Development Program (No. 2016YFC0902800), the Shanghai Municipal Education Commission-Gaofeng Clinical Medicine Grant Support (No. 20161303), the Innovation Foundation for Doctoral Students of Shanghai Jiao Tong University School of Medicine (Research Grant BXJ201815), and the Center for HPC at Shanghai Jiao Tong University. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Compliance with ethical guidelines

Jianfeng Li, Yuting Dai, Liang Wu, Ming Zhang, Wen Ouyang, Jinyan Huang, and Saijuan Chen declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

References

1. Hunger SP, Mullighan CG. Acute lymphoblastic leukemia in children. N Engl J Med 2015; 373(16): 1541–1552
2. Pui CH. Genomic and pharmacogenetic studies of childhood acute lymphoblastic leukemia. Front Med 2015; 9(1): 1–9
3. Huang KL, Mashl RJ, Wu Y, Ritter DI, Wang J, Oh C, Paczkowska M, Reynolds S, Wyczalkowski MA, Oak N, Scott AD, Krassowski M, Cherniack AD, Houlahan KE, Jayasinghe R, Wang LB, Zhou DC, Liu D, Cao S, Kim YW, Koire A, McMichael JF, Hucthagowder V, Kim TB, Hahn A, Wang C, McLellan MD, Al-Mulla F, Johnson KJ; Cancer Genome Atlas Research Network, Lichtarge O, Boutros PC, Raphael B, Lazar AJ, Zhang W, Wendl MC, Govindan R, Jain S, Wheeler D, Kulkarni S, Dipersio JF, Reimand J, Meric-Bernstam F, Chen K, Shmulevich I, Plon SE, Chen F, Ding L. Pathogenic germline variants in 10,389 adult cancers. Cell 2018; 173(2): 355–370.e14
4. Stadler ZK, Schrader KA, Vijai J, Robson ME, Offit K. Cancer genomics and inherited risk. J Clin Oncol 2014; 32(7): 687–698
5. Iacobucci I, Mullighan CG. Genetic basis of acute lymphoblastic leukemia. J Clin Oncol 2017; 35(9): 975–983
6. Genovese G, Kähler AK, Handsaker RE, Lindberg J, Rose SA, Bakhoum SF, Chambert K, Mick E, Neale BM, Fromer M, Purcell SM, Svantesson O, Landén M, Höglund M, Lehmann S, Gabriel SB, Moran JL, Lander ES, Sullivan PF, Sklar P, Grönberg H, Hultman CM, McCarroll SA. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. N Engl J Med 2014; 371(26): 2477–2487
7. Vijayakrishnan J, Qian M, Studd JB, Yang W, Kinnersley B, Law PJ, Broderick P, Raetz EA, Allan J, Pui CH, Vora A, Evans WE, Moorman A, Yeoh A, Yang W, Li C, Bartram CR, Mullighan CG, Zimmerman M, Hunger SP, Schrappe M, Relling MV, Stanulla M, Loh ML, Houlston RS, Yang JJ. Identification of four novel associations for B-cell acute lymphoblastic leukaemia risk. Nat Commun 2019; 10(1): 5348
8. Li JF, Dai YT, Lilljebjörn H, Shen SH, Cui BW, Bai L, Liu YF, Qian MX, Kubota Y, Kiyoi H, Matsumura I, Miyazaki Y, Olsson L, Tan AM, Ariffin H, Chen J, Takita J, Yasuda T, Mano H, Johansson B, Yang JJ, Yeoh AE, Hayakawa F, Chen Z, Pui CH, Fioretos T, Chen SJ, Huang JY. Transcriptional landscape of B cell precursor acute lymphoblastic leukemia based on an international study of 1,223 cases. Proc Natl Acad Sci USA 2018; 115(50): E11711–E11720
9. Gu Z, Churchman ML, Roberts KG, Moore I, Zhou X, Nakitandwe J, Hagiwara K, Pelletier S, Gingras S, Berns H, Payne-Turner D, Hill A, Iacobucci I, Shi L, Pounds S, Cheng C, Pei D, Qu C, Newman S, Devidas M, Dai Y, Reshmi SC, Gastier-Foster J, Raetz EA, Borowitz MJ, Wood BL, Carroll WL, Zweidler-McKay PA, Rabin KR, Mattano LA, Maloney KW, Rambaldi A, Spinelli O, Radich JP, Minden MD, Rowe JM, Luger S, Litzow MR, Tallman MS, Racevskis J, Zhang Y, Bhatia R, Kohlschmidt J, Mrózek K, Bloomfield CD, Stock W, Kornblau S, Kantarjian HM, Konopleva M, Evans WE, Jeha S, Pui CH, Yang J, Paietta E, Downing JR, Relling MV, Zhang J, Loh ML, Hunger SP, Mullighan CG. PAX5-driven subtypes of B-progenitor acute lymphoblastic leukemia. Nat Genet 2019; 51(2): 296–307
10. Pui CH, Tang JY, Yang JJ, Chen SJ, Chen Z. International collaboration to save children with acute lymphoblastic leukemia. J Glob Oncol 2019; 5(5): 1–2
11. Pui CH, Yang JJ, Bhakta N, Rodriguez-Galindo C. Global efforts toward the cure of childhood acute lymphoblastic leukaemia. Lancet Child Adolesc Health 2018; 2(6): 440–454
12. Teachey DT, Pui CH. Comparative features and outcomes between paediatric T-cell and B-cell acute lymphoblastic leukaemia. Lancet Oncol 2019; 20(3): e142–e154
13. Bassan R, Bourquin JP, DeAngelo DJ, Chiaretti S. New approaches to the management of adult acute lymphoblastic leukemia. J Clin Oncol 2018; 36(35): 3504 – 3519
14. Li B, Li H, Bai Y, Kirschner-Schwabe R, Yang JJ, Chen Y, Lu G, Tzoneva G, Ma X, Wu T, Li W, Lu H, Ding L, Liang H, Huang X, Yang M, Jin L, Kang H, Chen S, Du A, Shen S, Ding J, Chen H, Chen J, von Stackelberg A, Gu L, Zhang J, Ferrando A, Tang J, Wang S, Zhou BB. Negative feedback-defective PRPS1 mutants drive thiopurine resistance in relapsed childhood ALL. Nat Med 2015; 21(6): 563–571
15. Ohki K, Kiyokawa N, Saito Y, Hirabayashi S, Nakabayashi K, Ichikawa H, Momozawa Y, Okamura K, Yoshimi A, Ogata-Kawata H, Sakamoto H, Kato M, Fukushima K, Hasegawa D, Fukushima H, Imai M, Kajiwara R, Koike T, Komori I, Matsui A, Mori M, Moriwaki K, Noguchi Y, Park MJ, Ueda T, Yamamoto S, Matsuda K, Yoshida T, Matsumoto K, Hata K, Kubo M, Matsubara Y, Takahashi H, Fukushima T, Hayashi Y, Koh K, Manabe A, Ohara A, Tokyo Children's Cancer Study Group (TCCSG). Clinical and molecular characteristics of *MEF2D* fusion-positive B-cell precursor acute lymphoblastic leukemia in childhood, including a novel translocation resulting in *MEF2D-HNRNPH1* gene fusion. Haematologica 2019; 104(1): 128–137

16. Gu Z, Churchman M, Roberts K, Li Y, Liu Y, Harvey RC, McCastlain K, Reshmi SC, Payne-Turner D, Iacobucci I, Shao Y, Chen IM, Valentine M, Pei D, Mungall KL, Mungall AJ, Ma Y, Moore R, Marra M, Stonerock E, Gastier-Foster JM, Devidas M, Dai Y, Wood B, Borowitz M, Larsen EE, Maloney K, Mattano LA Jr, Angiolillo A, Salzer WL, Burke MJ, Gianni F, Spinelli O, Radich JP, Minden MD, Moorman AV, Patel B, Fielding AK, Rowe JM, Luger SM, Bhatia R, Aldoss I, Forman SJ, Kohlschmidt J, Mrózek K, Marcucci G, Bloomfield CD, Stock W, Kornblau S, Kantarjian HM, Konopleva M, Paietta E, Willman CL, Loh ML, Hunger SP, Mullighan CG. Genomic analyses identify recurrent MEF2D fusions in acute lymphoblastic leukaemia. Nat Commun 2016; 7: 13331
17. Lilljebjörn H, Henningsson R, Hyrenius-Wittsten A, Olsson L, Orsmark-Pietras C, von Palffy S, Askmyr M, Rissler M, Schrappe M, Cario G, Castor A, Pronk CJ, Behrendtz M, Mitelman F, Johansson B, Paulsson K, Andersson AK, Fontes M, Fioretos T. Identification of ETV6-RUNX1-like and DUX4-rearranged subtypes in paediatric B-cell precursor acute lymphoblastic leukaemia. Nat Commun 2016; 7(1): 11790
18. Liu YF, Wang BY, Zhang WN, Huang JY, Li BS, Zhang M, Jiang L, Li JF, Wang MJ, Dai YJ, Zhang ZG, Wang Q, Kong J, Chen B, Zhu YM, Weng XQ, Shen ZX, Li JM, Wang J, Yan XJ, Li Y, Liang YM, Liu L, Chen XQ, Zhang WG, Yan JS, Hu JD, Shen SH, Chen J, Gu LJ, Pei D, Li Y, Wu G, Zhou X, Ren RB, Cheng C, Yang JJ, Wang KK, Wang SY, Zhang J, Mi JQ, Pui CH, Tang JY, Chen Z, Chen SJ. Genomic profiling of adult and pediatric B-cell acute lymphoblastic leukemia. EBioMedicine 2016; 8: 173–183
19. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Cazzola M, Vardiman JW. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016; 127(20): 2391–2405
20. Yasuda T, Tsuzuki S, Kawazu M, Hayakawa F, Kojima S, Ueno T, Imoto N, Kohsaka S, Kunita A, Doi K, Sakura T, Yujiri T, Kondo E, Fujimaki K, Ueda Y, Aoyama Y, Ohtake S, Takita J, Sai E, Taniwaki M, Kurokawa M, Morishita S, Fukayama M, Kiyoi H, Miyazaki Y, Naoe T, Mano H. Recurrent DUX4 fusions in B cell acute lymphoblastic leukemia of adolescents and young adults. Nat Genet 2016; 48(5): 569–574
21. Zhang J, McCastlain K, Yoshihara H, Xu B, Chang Y, Churchman ML, Wu G, Li Y, Wei L, Iacobucci I, Liu Y, Qu C, Wen J, Edmonson M, Payne-Turner D, Kaufmann KB, Takayanagi SI, Wienholds E, Waanders E, Ntziachristos P, Bakogianni S, Wang J, Aifantis I, Roberts KG, Ma J, Song G, Easton J, Mulder HL, Chen X, Newman S, Ma X, Rusch M, Gupta P, Boggs K, Vadodaria B, Dalton J, Liu Y, Valentine ML, Ding L, Lu C, Fulton RS, Fulton L, Tabib Y, Ochoa K, Devidas M, Pei D, Cheng C, Yang J, Evans WE, Relling MV, Pui CH, Jeha S, Harvey RC, Chen IL, Willman CL, Marcucci G, Bloomfield CD, Kohlschmidt J, Mrózek K, Paietta E, Tallman MS, Stock W, Foster MC, Racevskis J, Rowe JM, Luger S, Kornblau SM, Shurtleff SA, Raimondi SC, Mardis ER, Wilson RK, Dick JE, Hunger SP, Loh ML, Downing JR, Mullighan CG, St. Jude Children's Research Hospital–Washington University Pediatric Cancer Genome Project. Deregulation of DUX4 and ERG in acute lymphoblastic leukemia. Nat Genet 2016; 48(12): 1481–1489
22. Qian M, Zhang H, Kham SK, Liu S, Jiang C, Zhao X, Lu Y, Goodings C, Lin TN, Zhang R, Moriyama T, Yin Z, Li Z, Quah TC, Ariffin H, Tan AM, Shen S, Bhojwani D, Hu S, Chen S, Zheng H, Pui CH, Yeoh AE, Yang JJ. Whole-transcriptome sequencing identifies a distinct subtype of acute lymphoblastic leukemia with predominant genomic abnormalities of EP300 and CREBBP. Genome Res 2017; 27(2): 185–195
23. Holmfeldt L, Wei L, Diaz-Flores E, Walsh M, Zhang J, Ding L, Payne-Turner D, Churchman M, Andersson A, Chen SC, McCastlain K, Becksfort J, Ma J, Wu G, Patel SN, Heatley SL, Phillips LA, Song G, Easton J, Parker M, Chen X, Rusch M, Boggs K, Vadodaria B, Hedlund E, Drenberg C, Baker S, Pei D, Cheng C, Huether R, Lu C, Fulton RS, Fulton LL, Tabib Y, Dooling DJ, Ochoa K, Minden M, Lewis ID, To LB, Marlton P, Roberts AW, Raca G, Stock W, Neale G, Drexler HG, Dickins RA, Ellison DW, Shurtleff SA, Pui CH, Ribeiro RC, Devidas M, Carroll AJ, Heerema NA, Wood B, Borowitz MJ, Gastier-Foster JM, Raimondi SC, Mardis ER, Wilson RK, Downing JR, Hunger SP, Loh ML, Mullighan CG. The genomic landscape of hypodiploid acute lymphoblastic leukemia. Nat Genet 2013; 45(3): 242–252
24. Andersson AK, Ma J, Wang J, Chen X, Gedman AL, Dang J, Nakitandwe J, Holmfeldt L, Parker M, Easton J, Huether R, Kriwacki R, Rusch M, Wu G, Li Y, Mulder H, Raimondi S, Pounds S, Kang G, Shi L, Becksfort J, Gupta P, Payne-Turner D, Vadodaria B, Boggs K, Yergeau D, Manne J, Song G, Edmonson M, Nagahawatte P, Wei L, Cheng C, Pei D, Sutton R, Venn NC, Chetcuti A, Rush A, Catchpoole D, Heldrup J, Fioretos T, Lu C, Ding L, Pui CH, Shurtleff S, Mullighan CG, Mardis ER, Wilson RK, Gruber TA, Zhang J, Downing JR, St. Jude Children's Research Hospital–Washington University Pediatric Cancer Genome Project. The landscape of somatic mutations in infant MLL-rearranged acute lymphoblastic leukemias. Nat Genet 2015; 47(4): 330–337
25. Fischer U, Forster M, Rinaldi A, Risch T, Sungalee S, Warnatz HJ, Bornhauser B, Gombert M, Kratsch C, Stütz AM, Sultan M, Tchinda J, Worth CL, Amstislavskiy V, Badarinarayan N, Baruchel A, Bartram T, Basso G, Canpolat C, Cario G, Cavé H, Dakaj D, Delorenzi M, Dobay MP, Eckert C, Ellinghaus E, Eugster S, Frismantas V, Ginzel S, Haas OA, Heidenreich O, Hemmrich-Stanisak G, Hezaveh K, Höll JI, Hornhardt S, Husemann P, Kachroo P, Kratz CP, Te Kronnie G, Marovca B, Niggli F, McHardy AC, Moorman AV, Panzer-Grümayer R, Petersen BS, Raeder B, Ralser M, Rosenstiel P, Schäfer D, Schrappe M, Schreiber S, Schütte M, Stade B, Thiele R, von der Weid N, Vora A, Zaliova M, Zhang L, Zichner T, Zimmermann M, Lehrach H, Borkhardt A, Bourquin JP, Franke A, Korbel JO, Stanulla M, Yaspo ML. Genomics and drug profiling of fatal TCF3-HLF-positive acute lymphoblastic leukemia identifies recurrent mutation patterns and therapeutic options. Nat Genet 2015; 47(9): 1020–1029
26. Zaliova M, Stuchly J, Winkowska L, Musilova A, Fiser K, Slamova M, Starkova J, Vaskova M, Hrusak O, Sramkova L, Stary J, Zuna J, Trka J. Genomic landscape of pediatric B-other acute lymphoblastic leukemia in a consecutive European cohort. Haematologica 2019; 104(7): 1396–1406
27. Pui CH, Nichols KE, Yang JJ. Somatic and germline genomics in paediatric acute lymphoblastic leukaemia. Nat Rev Clin Oncol 2019; 16(4): 227–240
28. Bonaventure A, Harewood R, Stiller CA, Gatta G, Clavel J, Stefan DC, Carreira H, Spika D, Marcos-Gragera R, Peris-Bonet R,

Piñeros M, Sant M, Kuehni CE, Murphy MFG, Coleman MP, Allemani C, CONCORD Working Group. Worldwide comparison of survival from childhood leukaemia for 1995–2009, by subtype, age, and sex (CONCORD-2): a population-based study of individual data for 89 828 children from 198 registries in 53 countries. Lancet Haematol 2017; 4(5): e202–e217

29. Yeoh AE, Ariffin H, Chai EL, Kwok CS, Chan YH, Ponnudurai K, Campana D, Tan PL, Chan MY, Kham SK, Chong LA, Tan AM, Lin HP, Quah TC. Minimal residual disease-guided treatment deintensification for children with acute lymphoblastic leukemia: results from the Malaysia–Singapore acute lymphoblastic leukemia 2003 study. J Clin Oncol 2012; 30(19): 2384–2392
30. Vora A, Goulden N, Mitchell C, Hancock J, Hough R, Rowntree C, Moorman AV, Wade R. Augmented post-remission therapy for a minimal residual disease-defined high-risk subgroup of children and young people with clinical standard-risk and intermediate-risk acute lymphoblastic leukaemia (UKALL 2003): a randomised controlled trial. Lancet Oncol 2014; 15(8): 809–818
31. Toft N, Birgens H, Abrahamsson J, Griškevičius L, Hallböök H, Heyman M, Klausen TW, Jónsson OG, Palk K, Pruunsild K, Quist-Paulsen P, Vaitkeviciene G, Vettenranta K, Åsberg A, Frandsen TL, Marquart HV, Madsen HO, Norén-Nyström U, Schmiegelow K. Results of NOPHO ALL2008 treatment for patients aged 1–45 years with acute lymphoblastic leukemia. Leukemia 2018; 32(3): 606–615
32. Pui CH, Pei D, Coustan-Smith E, Jeha S, Cheng C, Bowman WP, Sandlund JT, Ribeiro RC, Rubnitz JE, Inaba H, Bhojwani D, Gruber TA, Leung WH, Downing JR, Evans WE, Relling MV, Campana D. Clinical utility of sequential minimal residual disease measurements in the context of risk-based therapy in childhood acute lymphoblastic leukaemia: a prospective study. Lancet Oncol 2015; 16(4): 465–474
33. Pui CH, Pei D, Campana D, Cheng C, Sandlund JT, Bowman WP, Hudson MM, Ribeiro RC, Raimondi SC, Jeha S, Howard SC, Bhojwani D, Inaba H, Rubnitz JE, Metzger ML, Gruber TA, Coustan-Smith E, Downing JR, Leung WH, Relling MV, Evans WE. A revised definition for cure of childhood acute lymphoblastic leukemia. Leukemia 2014; 28(12): 2336–2343
34. Place AE, Stevenson KE, Vrooman LM, Harris MH, Hunt SK, O'Brien JE, Supko JG, Asselin BL, Athale UH, Clavell LA, Cole PD, Kelly KM, Laverdiere C, Leclerc JM, Michon B, Schorin MA, Welch JJ, Lipshultz SE, Kutok JL, Blonquist TM, Neuberg DS, Sallan SE, Silverman LB. Intravenous pegylated asparaginase versus intramuscular native *Escherichia coli* L-asparaginase in newly diagnosed childhood acute lymphoblastic leukaemia (DFCI 05-001): a randomised, open-label phase 3 trial. Lancet Oncol 2015; 16(16): 1677–1690
35. Pieters R, de Groot-Kruseman H, Van der Velden V, Fiocco M, van den Berg H, de Bont E, Egeler RM, Hoogerbrugge P, Kaspers G, Van der Schoot E, De Haas V, Van Dongen J. Successful therapy reduction and intensification for childhood acute lymphoblastic leukemia based on minimal residual disease monitoring: Study ALL10 From the Dutch Childhood Oncology Group. J Clin Oncol 2016; 34(22): 2591–2601
36. Hunger SP, Lu X, Devidas M, Camitta BM, Gaynon PS, Winick NJ, Reaman GH, Carroll WL. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. J Clin Oncol 2012; 30(14): 1663–1669
37. Domenech C, Suciu S, De Moerloose B, Mazingue F, Plat G, Ferster A, Uyttebroeck A, Sirvent N, Lutz P, Yakouben K, Munzer M, Röhrlich P, Plantaz D, Millot F, Philippet P, Dastugue N, Girard S, Cavé H, Benoit Y, Bertrandfor Y, Children's Leukemia Group (CLG) of European Organisation for Research and Treatment of Cancer (EORTC). Dexamethasone (6 mg/m^2/day) and prednisolone (60 mg/m^2/day) were equally effective as induction therapy for childhood acute lymphoblastic leukemia in the EORTC CLG 58951 randomized trial. Haematologica 2014; 99 (7): 1220–1227
38. Conter V, Bartram CR, Valsecchi MG, Schrauder A, Panzer-Grümayer R, Möricke A, Aricò M, Zimmermann M, Mann G, De Rossi G, Stanulla M, Locatelli F, Basso G, Niggli F, Barisone E, Henze G, Ludwig WD, Haas OA, Cazzaniga G, Koehler R, Silvestri D, Bradtke J, Parasole R, Beier R, van Dongen JJ, Biondi A, Schrappe M. Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study. Blood 2010; 115(16): 3206–3214
39. Pui CH, Campana D, Pei D, Bowman WP, Sandlund JT, Kaste SC, Ribeiro RC, Rubnitz JE, Raimondi SC, Onciu M, Coustan-Smith E, Kun LE, Jeha S, Cheng C, Howard SC, Simmons V, Bayles A, Metzger ML, Boyett JM, Leung W, Handgretinger R, Downing JR, Evans WE, Relling MV. Treating childhood acute lymphoblastic leukemia without cranial irradiation. N Engl J Med 2009; 360(26): 2730–2741
40. Pedrosa F, Coustan-Smith E, Zhou Y, Cheng C, Pedrosa A, Lins MM, Pedrosa M, Lucena-Silva N, Ramos AML, Vinhas E, Rivera GK, Campana D, Ribeiro RC. Reduced-dose intensity therapy for pediatric lymphoblastic leukemia: long-term results of the Recife RELLA05 pilot study. Blood 2020; 135(17): 1458–1466
41. Eckert C, Groeneveld-Krentz S, Kirschner-Schwabe R, Hagedorn N, Chen-Santel C, Bader P, Borkhardt A, Cario G, Escherich G, Panzer-Grümayer R, Astrahantseff K, Eggert A, Sramkova L, Attarbaschi A, Bourquin JP, Peters C, Henze G, von Stackelberg A, ALL-REZ BFM Trial Group. Improving stratification for children with late bone marrow B-cell acute lymphoblastic leukemia relapses with refined response classification and integration of genetics. J Clin Oncol 2019; 37(36): 3493–3506
42. Winick N, Martin PL, Devidas M, Shuster J, Borowitz MJ, Paul Bowman W, Larsen E, Pullen J, Carroll A, Willman C, Hunger SP, Carroll WL, Camitta BM. Randomized assessment of delayed intensification and two methods for parenteral methotrexate delivery in childhood B-ALL: Children's Oncology Group Studies P9904 and P9905. Leukemia 2020; 34(4): 1006–1016
43. Coccaro N, Anelli L, Zagaria A, Specchia G, Albano F. Next-generation sequencing in acute lymphoblastic leukemia. Int J Mol Sci 2019; 20(12): 2929
44. Churchman ML, Low J, Qu C, Paietta EM, Kasper LH, Chang Y, Payne-Turner D, Althoff MJ, Song G, Chen SC, Ma J, Rusch M, McGoldrick D, Edmonson M, Gupta P, Wang YD, Caufield W, Freeman B, Li L, Panetta JC, Baker S, Yang YL, Roberts KG, McCastlain K, Iacobucci I, Peters JL, Centonze VE, Notta F, Dobson SM, Zandi S, Dick JE, Janke L, Peng J, Kodali K, Pagala V, Min J, Mayasundari A, Williams RT, Willman CL, Rowe J, Luger S, Dickins RA, Guy RK, Chen T, Mullighan CG. Efficacy of

retinoids in IKZF1-mutated BCR-ABL1 acute lymphoblastic leukemia. Cancer Cell 2015; 28(3): 343–356

45. Gu S, Sayad A, Chan G, Yang W, Lu Z, Virtanen C, Van Etten RA, Neel BG. SHP2 is required for BCR-ABL1-induced hematologic neoplasia. Leukemia 2018; 32(1): 203–213
46. Pfeifer H, Cazzaniga G, van der Velden VHJ, Cayuela JM, Schäfer B, Spinelli O, Akiki S, Avigad S, Bendit I, Borg K, Cavé H, Elia L, Reshmi SC, Gerrard G, Hayette S, Hermanson M, Juh A, Jurcek T, Chillón MC, Homburg C, Martinelli G, Kairisto V, Lange T, Lion T, Mueller MC, Pane F, Rai L, Damm-Welk C, Sacha T, Schnittger S, Touloumenidou T, Valerhaugen H, Vandenberghe P, Zuna J, Serve H, Herrmann E, Markovic S, Dongen JJMV, Ottmann OG. Standardisation and consensus guidelines for minimal residual disease assessment in Philadelphia-positive acute lymphoblastic leukemia (Ph^+ ALL) by real-time quantitative reverse transcriptase PCR of ela2 BCR-ABL1. Leukemia 2019; 33(8): 1910–1922
47. Baccarani M, Castagnetti F, Gugliotta G, Rosti G, Soverini S, Albeer A, Pfirrmann M, International BCR-ABL Study Group. The proportion of different BCR-ABL1 transcript types in chronic myeloid leukemia. An international overview. Leukemia 2019; 33 (5): 1173–1183
48. Su Z, Wu F, Hu W, Liu X, Wu S, Feng X, Cui Z, Yang J, Wang Z, Guan H, Zhao H, Wang W, Zhao C, Peng J. Philadelphia chromosome-positive acute myeloid leukemia with masses and osteolytic lesions: finding of 18F-FDG PET/CT. Front Med 2017; 11(3): 440–444
49. Mullighan CG, Miller CB, Radtke I, Phillips LA, Dalton J, Ma J, White D, Hughes TP, Le Beau MM, Pui CH, Relling MV, Shurtleff SA, Downing JR. BCR-ABL1 lymphoblastic leukaemia is characterized by the deletion of Ikaros. Nature 2008; 453(7191): 110–114
50. Lou Y, Ma Y, Li C, Suo S, Tong H, Qian W, Mai W, Meng H, Yu W, Mao L, Wei J, Xu W, Jin J. Efficacy and prognostic factors of imatinib plus CALLG2008 protocol in adult patients with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia. Front Med 2017; 11(2): 229–238
51. Chen CW, Koche RP, Sinha AU, Deshpande AJ, Zhu N, Eng R, Doench JG, Xu H, Chu SH, Qi J, Wang X, Delaney C, Bernt KM, Root DE, Hahn WC, Bradner JE, Armstrong SA. DOT1L inhibits SIRT1-mediated epigenetic silencing to maintain leukemic gene expression in MLL-rearranged leukemia. Nat Med 2015; 21(4): 335–343
52. Meyer C, Hofmann J, Burmeister T, Gröger D, Park TS, Emerenciano M, Pombo de Oliveira M, Renneville A, Villarese P, Macintyre E, Cavé H, Clappier E, Mass-Malo K, Zuna J, Trka J, De Braekeleer E, De Braekeleer M, Oh SH, Tsaur G, Fechina L, van der Velden VH, van Dongen JJ, Delabesse E, Binato R, Silva ML, Kustanovich A, Aleinikova O, Harris MH, Lund-Aho T, Juvonen V, Heidenreich O, Vormoor J, Choi WW, Jarosova M, Kolenova A, Bueno C, Menendez P, Wehner S, Eckert C, Talmant P, Tondeur S, Lippert E, Launay E, Henry C, Ballerini P, Lapillone H, Callanan MB, Cayuela JM, Herbaux C, Cazzaniga G, Kakadiya PM, Bohlander S, Ahlmann M, Choi JR, Gameiro P, Lee DS, Krauter J, Cornillet-Lefebvre P, Te Kronnie G, Schäfer BW, Kubetzko S, Alonso CN, zur Stadt U, Sutton R, Venn NC, Izraeli S, Trakhtenbrot L, Madsen HO, Archer P, Hancock J, Cerveira N, Teixeira MR, Lo Nigro L, Möricke A, Stanulla M, Schrappe M, Sedék L, Szczepański T, Zwaan CM, Coenen EA, van den Heuvel-Eibrink MM, Strehl S, Dworzak M, Panzer-Grümayer R, Dingermann T, Klingebiel T, Marschalek R. The MLL recombinome of acute leukemias in 2013. Leukemia 2013; 27(11): 2165–2176
53. Sanjuan-Pla A, Bueno C, Prieto C, Acha P, Stam RW, Marschalek R, Menéndez P. Revisiting the biology of infant t(4;11)/MLL-$AF4^+$ B-cell acute lymphoblastic leukemia. Blood 2015; 126(25): 2676–2685
54. Burmeister T, Gökbuget N, Schwartz S, Fischer L, Hubert D, Sindram A, Hoelzer D, Thiel E. Clinical features and prognostic implications of TCF3-PBX1 and ETV6-RUNX1 in adult acute lymphoblastic leukemia. Haematologica 2010; 95(2): 241–246
55. Papaemmanuil E, Rapado I, Li Y, Potter NE, Wedge DC, Tubio J, Alexandrov LB, Van Loo P, Cooke SL, Marshall J, Martincorena I, Hinton J, Gundem G, van Delft FW, Nik-Zainal S, Jones DR, Ramakrishna M, Titley I, Stebbings L, Leroy C, Menzies A, Gamble J, Robinson B, Mudie L, Raine K, O'Meara S, Teague JW, Butler AP, Cazzaniga G, Biondi A, Zuna J, Kempski H, Muschen M, Ford AM, Stratton MR, Greaves M, Campbell PJ. RAG-mediated recombination is the predominant driver of oncogenic rearrangement in ETV6-RUNX1 acute lymphoblastic leukemia. Nat Genet 2014; 46(2): 116–125
56. Schäfer D, Olsen M, Lähnemann D, Stanulla M, Slany R, Schmiegelow K, Borkhardt A, Fischer U. Five percent of healthy newborns have an *ETV6-RUNX1* fusion as revealed by DNA-based GIPFEL screening. Blood 2018; 131(7): 821–826
57. Inaba T, Roberts WM, Shapiro LH, Jolly KW, Raimondi SC, Smith SD, Look AT. Fusion of the leucine zipper gene HLF to the E2A gene in human acute B-lineage leukemia. Science 1992; 257 (5069): 531–534
58. Harewood L, Robinson H, Harris R, Al-Obaidi MJ, Jalali GR, Martineau M, Moorman AV, Sumption N, Richards S, Mitchell C, Harrison CJ. Amplification of AML1 on a duplicated chromosome 21 in acute lymphoblastic leukemia: a study of 20 cases. Leukemia 2003; 17(3): 547–553
59. Harrison CJ. Blood spotlight on iAMP21 acute lymphoblastic leukemia (ALL), a high-risk pediatric disease. Blood 2015; 125(9): 1383–1386
60. Moorman AV, Robinson H, Schwab C, Richards SM, Hancock J, Mitchell CD, Goulden N, Vora A, Harrison CJ. Risk-directed treatment intensification significantly reduces the risk of relapse among children and adolescents with acute lymphoblastic leukemia and intrachromosomal amplification of chromosome 21: a comparison of the MRC ALL97/99 and UKALL2003 trials. J Clin Oncol 2013; 31(27): 3389–3396
61. Wylie AA, Schoepfer J, Jahnke W, Cowan-Jacob SW, Loo A, Furet P, Marzinzik AL, Pelle X, Donovan J, Zhu W, Buonamici S, Hassan AQ, Lombardo F, Iyer V, Palmer M, Berellini G, Dodd S, Thohan S, Bitter H, Branford S, Ross DM, Hughes TP, Petruzzelli L, Vanasse KG, Warmuth M, Hofmann F, Keen NJ, Sellers WR. The allosteric inhibitor ABL001 enables dual targeting of BCR-ABL1. Nature 2017; 543(7647): 733–737
62. Bullinger L, Döhner K, Döhner H. Genomics of acute myeloid leukemia diagnosis and pathways. J Clin Oncol 2017; 35(9): 934–946
63. Alexander TB, Gu Z, Iacobucci I, Dickerson K, Choi JK, Xu B, Payne-Turner D, Yoshihara H, Loh ML, Horan J, Buldini B, Basso G, Elitzur S, de Haas V, Zwaan CM, Yeoh A, Reinhardt D,

Tomizawa D, Kiyokawa N, Lammens T, De Moerloose B, Catchpoole D, Hori H, Moorman A, Moore AS, Hrusak O, Meshinchi S, Orgel E, Devidas M, Borowitz M, Wood B, Heerema NA, Carrol A, Yang YL, Smith MA, Davidsen TM, Hermida LC, Gesuwan P, Marra MA, Ma Y, Mungall AJ, Moore RA, Jones SJM, Valentine M, Janke LJ, Rubnitz JE, Pui CH, Ding L, Liu Y, Zhang J, Nichols KE, Downing JR, Cao X, Shi L, Pounds S, Newman S, Pei D, Guidry Auvil JM, Gerhard DS, Hunger SP, Inaba H, Mullighan CG. The genetic basis and cell of origin of mixed phenotype acute leukaemia. Nature 2018; 562(7727): 373–379

64. Suzuki K, Okuno Y, Kawashima N, Muramatsu H, Okuno T, Wang X, Kataoka S, Sekiya Y, Hamada M, Murakami N, Kojima D, Narita K, Narita A, Sakaguchi H, Sakaguchi K, Yoshida N, Nishio N, Hama A, Takahashi Y, Kudo K, Kato K, Kojima S. MEF2D-BCL9 fusion gene is associated with high-risk acute B-cell precursor lymphoblastic leukemia in adolescents. J Clin Oncol 2016; 34(28): 3451–3459
65. Bastian L, Schroeder MP, Eckert C, Schlee C, Tanchez JO, Kämpf S, Wagner DL, Schulze V, Isaakidis K, Lázaro-Navarro J, Hänzelmann S, James AR, Ekici A, Burmeister T, Schwartz S, Schrappe M, Horstmann M, Vosberg S, Krebs S, Blum H, Hecht J, Greif PA, Rieger MA, Brüggemann M, Gökbuget N, Neumann M, Baldus CD. PAX5 biallelic genomic alterations define a novel subgroup of B-cell precursor acute lymphoblastic leukemia. Leukemia 2019; 33(8): 1895–1909
66. McClure BJ, Heatley SL, Kok CH, Sadras T, An J, Hughes TP, Lock RB, Yeung D, Sutton R, White DL. Pre-B acute lymphoblastic leukaemia recurrent fusion, EP300-ZNF384, is associated with a distinct gene expression. Br J Cancer 2018; 118 (7): 1000–1004
67. Ping N, Qiu H, Wang Q, Dai H, Ruan C, Ehrentraut S, Drexler HG, MacLeod RA, Chen S. Establishment and genetic characterization of a novel mixed-phenotype acute leukemia cell line with EP300-ZNF384 fusion. J Hematol Oncol 2015; 8(1): 100
68. Prima V, Hunger SP. Cooperative transformation by MEF2D/DAZAP1 and DAZAP1/MEF2D fusion proteins generated by the variant t(1;19) in acute lymphoblastic leukemia. Leukemia 2007; 21(12): 2470–2475
69. Liu L, Leng L, Liu C, Lu C, Yuan Y, Wu L, Gong F, Zhang S, Wei X, Wang M, Zhao L, Hu L, Wang J, Yang H, Zhu S, Chen F, Lu G, Shang Z, Lin G. An integrated chromatin accessibility and transcriptome landscape of human pre-implantation embryos. Nat Commun 2019; 10(1): 364
70. Wu J, Xu J, Liu B, Yao G, Wang P, Lin Z, Huang B, Wang X, Li T, Shi S, Zhang N, Duan F, Ming J, Zhang X, Niu W, Song W, Jin H, Guo Y, Dai S, Hu L, Fang L, Wang Q, Li Y, Li W, Na J, Xie W, Sun Y. Chromatin analysis in human early development reveals epigenetic transition during ZGA. Nature 2018; 557(7704): 256–260
71. Dong X, Zhang W, Wu H, Huang J, Zhang M, Wang P, Zhang H, Chen Z, Chen SJ, Meng G. Structural basis of DUX4/IGH-driven transactivation. Leukemia 2018; 32(6): 1466–1476
72. Stanulla M, Dagdan E, Zaliova M, Möricke A, Palmi C, Cazzaniga G, Eckert C, Te Kronnie G, Bourquin JP, Bornhauser B, Koehler R, Bartram CR, Ludwig WD, Bleckmann K, Groeneveld-Krentz S, Schewe D, Junk SV, Hinze L, Klein N, Kratz CP, Biondi A, Borkhardt A, Kulozik A, Muckenthaler MU, Basso G, Valsecchi MG, Izraeli S, Petersen BS, Franke A, Dörge P, Steinemann D, Haas OA, Panzer-Grümayer R, Cavé H, Houlston RS, Cario G, Schrappe M, Zimmermann M, TRANSCALL Consortium; International BFM Study Group. IKZF1^{plus} defines a new minimal residual disease-dependent very-poor prognostic profile in pediatric B-cell precursor acute lymphoblastic leukemia. J Clin Oncol 2018; 36(12): 1240–1249
73. Zaliova M, Potuckova E, Hovorkova L, Musilova A, Winkowska L, Fiser K, Stuchly J, Mejstrikova E, Starkova J, Zuna J, Stary J, Trka J. ERG deletions in childhood acute lymphoblastic leukemia with *DUX4* rearrangements are mostly polyclonal, prognostically relevant and their detection rate strongly depends on screening method sensitivity. Haematologica 2019; 104(7): 1407–1416
74. Tian L, Shao Y, Nance S, Dang J, Xu B, Ma X, Li Y, Ju B, Dong L, Newman S, Zhou X, Schreiner P, Tseng E, Hon T, Ashby M, Li C, Easton J, Gruber TA, Zhang J. Long-read sequencing unveils IGH-DUX4 translocation into the silenced IGH allele in B-cell acute lymphoblastic leukemia. Nat Commun 2019; 10(1): 2789
75. Yang Q, She H, Gearing M, Colla E, Lee M, Shacka JJ, Mao Z. Regulation of neuronal survival factor MEF2D by chaperone-mediated autophagy. Science 2009; 323(5910): 124–127
76. Hirano D, Hayakawa F, Yasuda T, Tange N, Yamamoto H, Kojima Y, Morishita T, Imoto N, Tsuzuki S, Mano H, Naoe T, Kiyoi H. Chromosomal translocation-mediated evasion from miRNA induces strong MEF2D fusion protein expression, causing inhibition of PAX5 transcriptional activity. Oncogene 2019; 38 (13): 2263–2274
77. Chen B, Jiang L, Zhong ML, Li JF, Li BS, Peng LJ, Dai YT, Cui BW, Yan TQ, Zhang WN, Weng XQ, Xie YY, Lu J, Ren RB, Chen SN, Hu JD, Wu DP, Chen Z, Tang JY, Huang JY, Mi JQ, Chen SJ. Identification of fusion genes and characterization of transcriptome features in T-cell acute lymphoblastic leukemia. Proc Natl Acad Sci USA 2018; 115(2): 373–378
78. Homminga I, Pieters R, Langerak AW, de Rooi JJ, Stubbs A, Verstegen M, Vuerhard M, Buijs-Gladdines J, Kooi C, Klous P, van Vlierberghe P, Ferrando AA, Cayuela JM, Verhaaf B, Beverloo HB, Horstmann M, de Haas V, Wiekmeijer AS, Pike-Overzet K, Staal FJ, de Laat W, Soulier J, Sigaux F, Meijerink JP. Integrated transcript and genome analyses reveal NKX2-1 and MEF2C as potential oncogenes in T cell acute lymphoblastic leukemia. Cancer Cell 2011; 19(4): 484–497
79. Ma M, Wang X, Tang J, Xue H, Chen J, Pan C, Jiang H, Shen S. Early T-cell precursor leukemia: a subtype of high risk childhood acute lymphoblastic leukemia. Front Med 2012; 6(4): 416–420
80. Seki M, Kimura S, Isobe T, Yoshida K, Ueno H, Nakajima-Takagi Y, Wang C, Lin L, Kon A, Suzuki H, Shiozawa Y, Kataoka K, Fujii Y, Shiraishi Y, Chiba K, Tanaka H, Shimamura T, Masuda K, Kawamoto H, Ohki K, Kato M, Arakawa Y, Koh K, Hanada R, Moritake H, Akiyama M, Kobayashi R, Deguchi T, Hashii Y, Imamura T, Sato A, Kiyokawa N, Oka A, Hayashi Y, Takagi M, Manabe A, Ohara A, Horibe K, Sanada M, Iwama A, Mano H, Miyano S, Ogawa S, Takita J. Recurrent SPI1 (PU.1) fusions in high-risk pediatric T cell acute lymphoblastic leukemia. Nat Genet 2017; 49(8): 1274–1281
81. Zhang J, Ding L, Holmfeldt L, Wu G, Heatley SL, Payne-Turner D, Easton J, Chen X, Wang J, Rusch M, Lu C, Chen SC, Wei L, Collins-Underwood JR, Ma J, Roberts KG, Pounds SB, Ulyanov A, Becksfort J, Gupta P, Huether R, Kriwacki RW, Parker M,

McGoldrick DJ, Zhao D, Alford D, Espy S, Bobba KC, Song G, Pei D, Cheng C, Roberts S, Barbato MI, Campana D, Coustan-Smith E, Shurtleff SA, Raimondi SC, Kleppe M, Cools J, Shimano KA, Hermiston ML, Doulatov S, Eppert K, Laurenti E, Notta F, Dick JE, Basso G, Hunger SP, Loh ML, Devidas M, Wood B, Winter S, Dunsmore KP, Fulton RS, Fulton LL, Hong X, Harris CC, Dooling DJ, Ochoa K, Johnson KJ, Obenauer JC, Evans WE, Pui CH, Naeve CW, Ley TJ, Mardis ER, Wilson RK, Downing JR, Mullighan CG. The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. Nature 2012; 481(7380): 157–163

82. Liu Y, Easton J, Shao Y, Maciaszek J, Wang Z, Wilkinson MR, McCastlain K, Edmonson M, Pounds SB, Shi L, Zhou X, Ma X, Sioson E, Li Y, Rusch M, Gupta P, Pei D, Cheng C, Smith MA, Auvil JG, Gerhard DS, Relling MV, Winick NJ, Carroll AJ, Heerema NA, Raetz E, Devidas M, Willman CL, Harvey RC, Carroll WL, Dunsmore KP, Winter SS, Wood BL, Sorrentino BP, Downing JR, Loh ML, Hunger SP, Zhang J, Mullighan CG. The genomic landscape of pediatric and young adult T-lineage acute lymphoblastic leukemia. Nat Genet 2017; 49(8): 1211–1218
83. Prima V, Gore L, Caires A, Boomer T, Yoshinari M, Imaizumi M, Varella-Garcia M, Hunger SP. Cloning and functional characterization of MEF2D/DAZAP1 and DAZAP1/MEF2D fusion proteins created by a variant t(1;19)(q23;p13.3) in acute lymphoblastic leukemia. Leukemia 2005; 19(5): 806–813
84. Tange N, Hayakawa F, Yasuda T, Odaira K, Yamamoto H, Hirano D, Sakai T, Terakura S, Tsuzuki S, Kiyoi H. Staurosporine and venetoclax induce the caspase-dependent proteolysis of MEF2D-fusion proteins and apoptosis in MEF2D-fusion^{+} ALL cells. Biomed Pharmacother 2020; 128: 110330
85. Martini A, La Starza R, Janssen H, Bilhou-Nabera C, Corveleyn A, Somers R, Aventin A, Foà R, Hagemeijer A, Mecucci C, Marynen P. Recurrent rearrangement of the Ewing's sarcoma gene, EWSR1, or its homologue, TAF15, with the transcription factor CIZ/NMP4 in acute leukemia. Cancer Res 2002; 62(19): 5408–5412
86. Passet M, Boissel N, Sigaux F, Saillard C, Bargetzi M, Ba I, Thomas X, Graux C, Chalandon Y, Leguay T, Lengliné E, Konopacki J, Quentin S, Delabesse E, Lafage-Pochitaloff M, Pastoret C, Grardel N, Asnafi V, Lhéritier V, Soulier J, Dombret H, Clappier E, Group for Research on Adult ALL (GRAALL). PAX5 P80R mutation identifies a novel subtype of B-cell precursor acute lymphoblastic leukemia with favorable outcome. Blood 2019; 133 (3): 280–284
87. Bueno C, Tejedor JR, Bashford-Rogers R, González-Silva L, Valdés-Mas R, Agraz-Doblás A, Díaz de la Guardia R, Ribera J, Zamora L, Bilhou-Nabera C, Abermil N, Guermouche H, Gouache E, Leverger G, Fraga MF, Fernández AF, Ballerini P, Varela I, Menendez P. Natural history and cell of origin of *TCF3-ZNF384* and *PTPN11* mutations in monozygotic twins with concordant BCP-ALL. Blood 2019; 134(11): 900–905
88. Savin VJ, Sharma M, Zhou J, Gennochi D, Fields T, Sharma R, McCarthy ET, Srivastava T, Domen J, Tormo A, Gauchat JF. Renal and hematological effects of CLCF-1, a B-cell-stimulating cytokine of the IL-6 family. J Immunol Res 2015; 2015: 714964
89. Den Boer ML, van Slegtenhorst M, De Menezes RX, Cheok MH, Buijs-Gladdines JG, Peters ST, Van Zutven LJ, Beverloo HB, Van der Spek PJ, Escherich G, Horstmann MA, Janka-Schaub GE, Kamps WA, Evans WE, Pieters R. A subtype of childhood acute lymphoblastic leukaemia with poor treatment outcome: a genome-wide classification study. Lancet Oncol 2009; 10(2): 125–134
90. Roberts KG, Morin RD, Zhang J, Hirst M, Zhao Y, Su X, Chen SC, Payne-Turner D, Churchman ML, Harvey RC, Chen X, Kasap C, Yan C, Becksfort J, Finney RP, Teachey DT, Maude SL, Tse K, Moore R, Jones S, Mungall K, Birol I, Edmonson MN, Hu Y, Buetow KE, Chen IM, Carroll WL, Wei L, Ma J, Kleppe M, Levine RL, Garcia-Manero G, Larsen E, Shah NP, Devidas M, Reaman G, Smith M, Paugh SW, Evans WE, Grupp SA, Jeha S, Pui CH, Gerhard DS, Downing JR, Willman CL, Loh M, Hunger SP, Marra MA, Mullighan CG. Genetic alterations activating kinase and cytokine receptor signaling in high-risk acute lymphoblastic leukemia. Cancer Cell 2012; 22(2): 153–166
91. Roberts KG, Li Y, Payne-Turner D, Harvey RC, Yang YL, Pei D, McCastlain K, Ding L, Lu C, Song G, Ma J, Becksfort J, Rusch M, Chen SC, Easton J, Cheng J, Boggs K, Santiago-Morales N, Iacobucci I, Fulton RS, Wen J, Valentine M, Cheng C, Paugh SW, Devidas M, Chen IM, Reshmi S, Smith A, Hedlund E, Gupta P, Nagahawatte P, Wu G, Chen X, Yergeau D, Vadodaria B, Mulder H, Winick NJ, Larsen EC, Carroll WL, Heerema NA, Carroll AJ, Grayson G, Tasian SK, Moore AS, Keller F, Frei-Jones M, Whitlock JA, Raetz EA, White DL, Hughes TP, Guidry Auvil JM, Smith MA, Marcucci G, Bloomfield CD, Mrózek K, Kohlschmidt J, Stock W, Kornblau SM, Konopleva M, Paietta E, Pui CH, Jeha S, Relling MV, Evans WE, Gerhard DS, Gastier-Foster JM, Mardis E, Wilson RK, Loh ML, Downing JR, Hunger SP, Willman CL, Zhang J, Mullighan CG. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. N Engl J Med 2014; 371(11): 1005–1015
92. Hurtz C, Wertheim GB, Loftus JP, Blumenthal D, Lehman A, Li Y, Bagashev A, Manning B, Cummins KD, Burkhardt JK, Perl AE, Carroll M, Tasian SK. Oncogene-independent BCR-like signaling adaptation confers drug resistance in Ph-like ALL. J Clin Invest 2020; 130(7): 3637–3653
93. Sánchez R, Ribera J, Morgades M, Ayala R, Onecha E, Ruiz-Heredia Y, Juárez-Rufián A, de Nicolás R, Sánchez-Pina J, Vives S, Zamora L, Mercadal S, Coll R, Cervera M, García O, Ribera JM, Martínez-López J. A novel targeted RNA-Seq panel identifies a subset of adult patients with acute lymphoblastic leukemia with BCR-ABL1-like characteristics. Blood Cancer J 2020; 10(4): 43
94. Tong J, Flavell RA, Li HB. RNA m^6A modification and its function in diseases. Front Med 2018; 12(4): 481–489
95. Rheinbay E, Nielsen MM, Abascal F, Wala JA, Shapira O, Tiao G, Hornshøj H, Hess JM, Juul RI, Lin Z, Feuerbach L, Sabarinathan R, Madsen T, Kim J, Mularoni L, Shuai S, Lanzós A, Herrmann C, Maruvka YE, Shen C, Amin SB, Bandopadhayay P, Bertl J, Boroevich KA, Busanovich J, Carlevaro-Fita J, Chakravarty D, Chan CWY, Craft D, Dhingra P, Diamanti K, Fonseca NA, Gonzalez-Perez A, Guo Q, Hamilton MP, Haradhvala NJ, Hong C, Isaev K, Johnson TA, Juul M, Kahles A, Kahraman A, Kim Y, Komorowski J, Kumar K, Kumar S, Lee D, Lehmann KV, Li Y, Liu EM, Lochovsky L, Park K, Pich O, Roberts ND, Saksena G, Schumacher SE, Sidiropoulos N, Sieverling L, Sinnott-Armstrong N, Stewart C, Tamborero D, Tubio JMC, Umer HM, Uuskü la-Reimand L, Wadelius C, Wadi L, Yao X, Zhang CZ, Zhang J, Haber JE, Hobolth A, Imielinski M, Kellis M, Lawrence MS, von Mering C, Nakagawa H, Raphael BJ, Rubin MA, Sander C, Stein LD, Stuart JM, Tsunoda T, Wheeler DA, Johnson R, Reimand J, Gerstein M, Khurana E, Campbell PJ, López-Bigas N; PCAWG

Drivers and Functional Interpretation Working Group; PCAWG Structural Variation Working Group, Weischenfeldt J, Beroukhim R, Martincorena I, Pedersen JS, Getz G; PCAWG Consortium. Analyses of non-coding somatic drivers in 2,658 cancer whole genomes. Nature 2020; 578(7793): 102–111

96. Calabrese C, Davidson NR, Demircioğlu D, Fonseca NA, He Y, Kahles A, Lehmann KV, Liu F, Shiraishi Y, Soulette CM, Urban L, Greger L, Li S, Liu D, Perry MD, Xiang Q, Zhang F, Zhang J, Bailey P, Erkek S, Hoadley KA, Hou Y, Huska MR, Kilpinen H, Korbel JO, Marin MG, Markowski J, Nandi T, Pan-Hammarström Q, Pedamallu CS, Siebert R, Stark SG, Su H, Tan P, Waszak SM, Yung C, Zhu S, Awadalla P, Creighton CJ, Meyerson M, Ouellette BFF, Wu K, Yang H; PCAWG Transcriptome Working Group, Brazma A, Brooks AN, Göke J, Rätsch G, Schwarz RF, Stegle O, Zhang Z; PCAWG Consortium. Genomic basis for RNA alterations in cancer. Nature 2020; 578(7793): 129–136
97. Miguel-Escalada I, Bonàs-Guarch S, Cebola I, Ponsa-Cobas J, Mendieta-Esteban J, Atla G, Javierre BM, Rolando DMY, Farabella I, Morgan CC, García-Hurtado J, Beucher A, Morán I, Pasquali L, Ramos-Rodríguez M, Appel EVR, Linneberg A, Gjesing AP, Witte DR, Pedersen O, Grarup N, Ravassard P, Torrents D, Mercader JM, Piemonti L, Berney T, de Koning EJP, Kerr-Conte J, Pattou F, Fedko IO, Groop L, Prokopenko I, Hansen T, Marti-Renom MA, Fraser P, Ferrer J. Human pancreatic islet three-dimensional chromatin architecture provides insights into the genetics of type 2 diabetes. Nat Genet 2019; 51(7): 1137–1148
98. Li Y, Roberts ND, Wala JA, Shapira O, Schumacher SE, Kumar K, Khurana E, Waszak S, Korbel JO, Haber JE, Imielinski M; PCAWG Structural Variation Working Group, Weischenfeldt J, Beroukhim R, Campbell PJ; PCAWG Consortium. Patterns of somatic structural variation in human cancer genomes. Nature 2020; 578(7793): 112–121
99. Gerstung M, Jolly C, Leshchiner I, Dentro SC, Gonzalez S, Rosebrock D, Mitchell TJ, Rubanova Y, Anur P, Yu K, Tarabichi M, Deshwar A, Wintersinger J, Kleinheinz K, Vázquez-García I, Haase K, Jerman L, Sengupta S, Macintyre G, Malikic S, Donmez N, Livitz DG, Cmero M, Demeulemeester J, Schumacher S, Fan Y, Yao X, Lee J, Schlesner M, Boutros PC, Bowtell DD, Zhu H, Getz G, Imielinski M, Beroukhim R, Sahinalp SC, Ji Y, Peifer M, Markowetz F, Mustonen V, Yuan K, Wang W, Morris QD; PCAWG Evolution & Heterogeneity Working Group, Spellman PT, Wedge DC, Van Loo P; PCAWG Consortium. The evolutionary history of 2,658 cancers. Nature 2020; 578(7793): 122–128
100. Yang M, Vesterlund M, Siavelis I, Moura-Castro LH, Castor A, Fioretos T, Jafari R, Lilljebjörn H, Odom DT, Olsson L, Ravi N, Woodward EL, Harewood L, Lehtiö J, Paulsson K. Proteogenomics and Hi-C reveal transcriptional dysregulation in high hyperdiploid childhood acute lymphoblastic leukemia. Nat Commun 2019; 10(1): 1519
101. Zhang Z, Pan Z, Ying Y, Xie Z, Adhikari S, Phillips J, Carstens RP, Black DL, Wu Y, Xing Y. Deep-learning augmented RNA-seq analysis of transcript splicing. Nat Methods 2019; 16(4): 307–310
102. van Galen P, Hovestadt V, Wadsworth Ii MH, Hughes TK, Griffin GK, Battaglia S, Verga JA, Stephansky J, Pastika TJ, Lombardi Story J, Pinkus GS, Pozdnyakova O, Galinsky I, Stone RM, Graubert TA, Shalek AK, Aster JC, Lane AA, Bernstein BE. Single-cell RNA-Seq reveals AML hierarchies relevant to disease progression and immunity. Cell 2019; 176(6): 1265–1281.e24
103. Liu Y, Li C, Shen S, Chen X, Szlachta K, Edmonson MN, Shao Y, Ma X, Hyle J, Wright S, Ju B, Rusch MC, Liu Y, Li B, Macias M, Tian L, Easton J, Qian M, Yang JJ, Hu S, Look AT, Zhang J. Discovery of regulatory noncoding variants in individual cancer genomes by using cis-X. Nat Genet 2020; 52(8): 811–818
104. Witkowski MT, Dolgalev I, Evensen NA, Ma C, Chambers T, Roberts KG, Sreeram S, Dai Y, Tikhonova AN, Lasry A, Qu C, Pei D, Cheng C, Robbins GA, Pierro J, Selvaraj S, Mezzano V, Daves M, Lupo PJ, Scheurer ME, Loomis CA, Mullighan CG, Chen W, Rabin KR, Tsirigos A, Carroll WL, Aifantis I. Extensive remodeling of the immune microenvironment in B cell acute lymphoblastic leukemia. Cancer Cell 2020; 37(6): 867–882.e12
105. Rodríguez-Hernández G, Opitz FV, Delgado P, Walter C, Álvarez-Prado AF, González-Herrero I, Auer F, Fischer U, Janssen S, Bartenhagen C, Raboso-Gallego J, Casado-García A, Orfao A, Blanco O, Alonso-López D, Rivas JL, Tena-Dávila SG, Müschen M, Dugas M, Criado FJG, Cenador MBG, Vicente-Dueñas C, Hauer J, Ramiro AR, Sanchez-Garcia I, Borkhardt A. Infectious stimuli promote malignant B-cell acute lymphoblastic leukemia in the absence of AID. Nat Commun 2019; 10(1): 5563
106. Dang J, Wei L, de Ridder J, Su X, Rust AG, Roberts KG, Payne-Turner D, Cheng J, Ma J, Qu C, Wu G, Song G, Huether RG, Schulman B, Janke L, Zhang J, Downing JR, van der Weyden L, Adams DJ, Mullighan CG. PAX5 is a tumor suppressor in mouse mutagenesis models of acute lymphoblastic leukemia. Blood 2015; 125(23): 3609–3617
107. Potter N, Jones L, Blair H, Strehl S, Harrison CJ, Greaves M, Kearney L, Russell LJ. Single-cell analysis identifies CRLF2 rearrangements as both early and late events in Down syndrome and non-Down syndrome acute lymphoblastic leukaemia. Leukemia 2019; 33(4): 893–904
108. Mullighan CG, Goorha S, Radtke I, Miller CB, Coustan-Smith E, Dalton JD, Girtman K, Mathew S, Ma J, Pounds SB, Su X, Pui CH, Relling MV, Evans WE, Shurtleff SA, Downing JR. Genome-wide analysis of genetic alterations in acute lymphoblastic leukaemia. Nature 2007; 446(7137): 758–764
109. Churchman ML, Qian M, Te Kronnie G, Zhang R, Yang W, Zhang H, Lana T, Tedrick P, Baskin R, Verbist K, Peters JL, Devidas M, Larsen E, Moore IM, Gu Z, Qu C, Yoshihara H, Porter SN, Pruett-Miller SM, Wu G, Raetz E, Martin PL, Bowman WP, Winick N, Mardis E, Fulton R, Stanulla M, Evans WE, Relling MV, Pui CH, Hunger SP, Loh ML, Handgretinger R, Nichols KE, Yang JJ, Mullighan CG. Germline genetic IKZF1 variation and predisposition to childhood acute lymphoblastic leukemia. Cancer Cell 2018; 33(5): 937–948.e8
110. Schram AM, Chang MT, Jonsson P, Drilon A. Fusions in solid tumours: diagnostic strategies, targeted therapy, and acquired resistance. Nat Rev Clin Oncol 2017; 14(12): 735–748
111. Le Loarer F, Watson S, Pierron G, de Montpreville VT, Ballet S, Firmin N, Auguste A, Pissaloux D, Boyault S, Paindavoine S, Dechelotte PJ, Besse B, Vignaud JM, Brevet M, Fadel E, Richer W, Treilleux I, Masliah-Planchon J, Devouassoux-Shisheboran M, Zalcman G, Allory Y, Bourdeaut F, Thivolet-Bejui F, Ranchere-Vince D, Girard N, Lantuejoul S, Galateau-Sallé F, Coindre JM, Leary A, Delattre O, Blay JY, Tirode F. SMARCA4 inactivation defines a group of undifferentiated thoracic malignancies transcriptionally related to BAF-deficient sarcomas. Nat Genet

2015; 47(10): 1200–1205

112. French C. NUT midline carcinoma. Nat Rev Cancer 2014; 14(3): 149–150
113. Alekseyenko AA, Walsh EM, Wang X, Grayson AR, Hsi PT, Kharchenko PV, Kuroda MI, French CA. The oncogenic BRD4-NUT chromatin regulator drives aberrant transcription within large topological domains. Genes Dev 2015; 29(14): 1507–1523
114. Hormann FM, Hoogkamer AQ, Beverloo HB, Boeree A, Dingjan I, Wattel MM, Stam RW, Escherich G, Pieters R, den Boer ML, Boer JM. NUTM1 is a recurrent fusion gene partner in B-cell precursor acute lymphoblastic leukemia associated with increased expression of genes on chromosome band 10p12.31-12.2. Haematologica 2019; 104(10): e455–e459
115. Pincez T, Landry JR, Roussy M, Jouan L, Bilodeau M, Laramée L, Couture F, Sinnett D, Gendron P, Hébert J, Oligny L, Rouette A, Tran TH, Wilhelm BT, Bittencourt H, Cellot S. Cryptic recurrent ACIN1-NUTM1 fusions in non-KMT2A-rearranged infant acute lymphoblastic leukemia. Genes Chromosomes Cancer 2020; 59 (2): 125–130
116. Godfrey L, Kerry J, Thorne R, Repapi E, Davies JO, Tapia M, Ballabio E, Hughes JR, Geng H, Konopleva M, Milne TA. MLL-AF4 binds directly to a BCL-2 specific enhancer and modulates H3K27 acetylation. Exp Hematol 2017; 47: 64–75
117. de Bock CE, Demeyer S, Degryse S, Verbeke D, Sweron B, Gielen O, Vandepoel R, Vicente C, Vanden Bempt M, Dagklis A, Geerdens E, Bornschein S, Gijsbers R, Soulier J, Meijerink JP, Heinäniemi M, Teppo S, Bouvy-Liivrand M, Lohi O, Radaelli E, Cools J. HOXA9 cooperates with activated JAK/STAT signaling to drive leukemia development. Cancer Discov 2018; 8(5): 616–631
118. Limpens J, Stad R, Vos C, de Vlaam C, de Jong D, van Ommen GJ, Schuuring E, Kluin PM. Lymphoma-associated translocation t(14;18) in blood B cells of normal individuals. Blood 1995; 85 (9): 2528–2536
119. Dölken G, Illerhaus G, Hirt C, Mertelsmann R. BCL-2/JH rearrangements in circulating B cells of healthy blood donors and patients with nonmalignant diseases. J Clin Oncol 1996; 14(4): 1333–1344
120. Schüler F, Dölken L, Hirt C, Kiefer T, Berg T, Fusch G, Weitmann K, Hoffmann W, Fusch C, Janz S, Rabkin CS, Dölken G. Prevalence and frequency of circulating t(14;18)-MBR translocation carrying cells in healthy individuals. Int J Cancer 2009; 124 (4): 958–963
121. Roulland S, Kelly RS, Morgado E, Sungalee S, Solal-Celigny P, Colombat P, Jouve N, Palli D, Pala V, Tumino R, Panico S, Sacerdote C, Quirós JR, Gonzáles CA, Sánchez MJ, Dorronsoro M, Navarro C, Barricarte A, Tjønneland A, Olsen A, Overvad K, Canzian F, Kaaks R, Boeing H, Drogan D, Nieters A, Clavel-Chapelon F, Trichopoulou A, Trichopoulos D, Lagiou P, Bueno-de-Mesquita HB, Peeters PH, Vermeulen R, Hallmans G, Melin B, Borgquist S, Carlson J, Lund E, Weiderpass E, Khaw KT, Wareham N, Key TJ, Travis RC, Ferrari P, Romieu I, Riboli E, Salles G, Vineis P, Nadel B. t(14;18) Translocation: a predictive blood biomarker for follicular lymphoma. J Clin Oncol 2014; 32 (13): 1347–1355
122. Johnson NA, Savage KJ, Ludkovski O, Ben-Neriah S, Woods R, Steidl C, Dyer MJ, Siebert R, Kuruvilla J, Klasa R, Connors JM, Gascoyne RD, Horsman DE. Lymphomas with concurrent BCL2 and MYC translocations: the critical factors associated with survival. Blood 2009; 114(11): 2273–2279
123. Puente XS, Beà S, Valdés-Mas R, Villamor N, Gutiérrez-Abril J, Martín-Subero JI, Munar M, Rubio-Pérez C, Jares P, Aymerich M, Baumann T, Beekman R, Belver L, Carrio A, Castellano G, Clot G, Colado E, Colomer D, Costa D, Delgado J, Enjuanes A, Estivill X, Ferrando AA, Gelpí JL, González B, González S, González M, Gut M, Hernández-Rivas JM, López-Guerra M, Martín-García D, Navarro A, Nicolás P, Orozco M, Payer AR, Pinyol M, Pisano DG, Puente DA, Queirós AC, Quesada V, Romeo-Casabona CM, Royo C, Royo R, Rozman M, Russiñol N, Salaverría I, Stamatopoulos K, Stunnenberg HG, Tamborero D, Terol MJ, Valencia A, López-Bigas N, Torrents D, Gut I, López-Guillermo A, López-Otín C, Campo E. Non-coding recurrent mutations in chronic lymphocytic leukaemia. Nature 2015; 526(7574): 519–524
124. Put N, Meeus P, Chatelain B, Rack K, Boeckx N, Nollet F, Graux C, Van Den Neste E, Janssens A, Madoe V, Van Hoof A, Bilhou-Nabera C, Wlodarska I, Vandenberghe P, Michaux L. Translocation t(14;18) is not associated with inferior outcome in chronic lymphocytic leukemia. Leukemia 2009; 23(6): 1201–1204
125. Niitsu N, Okamoto M, Miura I, Hirano M. Clinical features and prognosis of *de novo* diffuse large B-cell lymphoma with t(14;18) and 8q24/c-MYC translocations. Leukemia 2009; 23(4): 777–783
126. Leich E, Salaverria I, Bea S, Zettl A, Wright G, Moreno V, Gascoyne RD, Chan WC, Braziel RM, Rimsza LM, Weisenburger DD, Delabie J, Jaffe ES, Lister A, Fitzgibbon J, Staudt LM, Hartmann EM, Mueller-Hermelink HK, Campo E, Ott G, Rosenwald A. Follicular lymphomas with and without translocation t(14;18) differ in gene expression profiles and genetic alterations. Blood 2009; 114(4): 826–834
127. Le Gouill S, Talmant P, Touzeau C, Moreau A, Garand R, Juge-Morineau N, Gaillard F, Gastinne T, Milpied N, Moreau P, Harousseau JL, Avet-Loiseau H. The clinical presentation and prognosis of diffuse large B-cell lymphoma with t(14;18) and 8q24/c-MYC rearrangement. Haematologica 2007; 92(10): 1335–1342
128. Guo Y, Karube K, Kawano R, Yamaguchi T, Suzumiya J, Huang GS, Ohshima K. Low-grade follicular lymphoma with t(14;18) presents a homogeneous disease entity otherwise the rest comprises minor groups of heterogeneous disease entities with Bcl2 amplification, Bcl6 translocation or other gene aberrances. Leukemia 2005; 19(6): 1058–1063
129. Godon A, Moreau A, Talmant P, Baranger-Papot L, Geneviève F, Milpied N, Zandecki M, Avet-Loiseau H. Is t(14;18)(q32;q21) a constant finding in follicular lymphoma? An interphase FISH study on 63 patients. Leukemia 2003; 17(1): 255–259
130. Huang JZ, Sanger WG, Greiner TC, Staudt LM, Weisenburger DD, Pickering DL, Lynch JC, Armitage JO, Warnke RA, Alizadeh AA, Lossos IS, Levy R, Chan WC. The t(14;18) defines a unique subset of diffuse large B-cell lymphoma with a germinal center B-cell gene expression profile. Blood 2002; 99(7): 2285–2290
131. Ye BH, Lista F, Lo Coco F, Knowles DM, Offit K, Chaganti RS, Dalla-Favera R. Alterations of a zinc finger-encoding gene, BCL-6, in diffuse large-cell lymphoma. Science 1993; 262(5134): 747–750
132. Baron BW, Nucifora G, McCabe N, Espinosa R 3rd, Le Beau MM, McKeithan TW. Identification of the gene associated with the recurring chromosomal translocations t(3;14)(q27;q32) and t(3;22)(q27;q11) in B-cell lymphomas. Proc Natl Acad Sci USA 1993; 90 (11): 5262–5266

133. Zhao X, Ren Y, Lawlor M, Shah BD, Park PMC, Lwin T, Wang X, Liu K, Wang M, Gao J, Li T, Xu M, Silva AS, Lee K, Zhang T, Koomen JM, Jiang H, Sudalagunta PR, Meads MB, Cheng F, Bi C, Fu K, Fan H, Dalton WS, Moscinski LC, Shain KH, Sotomayor EM, Wang GG, Gray NS, Cleveland JL, Qi J, Tao J. BCL2 amplicon loss and transcriptional remodeling drives ABT-199 resistance in B cell lymphoma models. Cancer Cell 2019; 35(5): 752–766.e9
134. Wu LM, Wang J, Conidi A, Zhao C, Wang H, Ford Z, Zhang L, Zweier C, Ayee BG, Maurel P, Zwijsen A, Chan JR, Jankowski MP, Huylebroeck D, Lu QR. Zeb2 recruits HDAC-NuRD to inhibit Notch and controls Schwann cell differentiation and remyelination. Nat Neurosci 2016; 19(8): 1060–1072
135. Studd JB, Yang M, Li Z, Vijayakrishnan J, Lu Y, Yeoh AE, Paulsson K, Houlston RS. Genetic predisposition to B-cell acute lymphoblastic leukemia at 14q11.2 is mediated by a CEBPE promoter polymorphism. Leukemia 2019; 33(1): 1–14
136. Li Z, Abraham BJ, Berezovskaya A, Farah N, Liu Y, Leon T, Fielding A, Tan SH, Sanda T, Weintraub AS, Li B, Shen S, Zhang J, Mansour MR, Young RA, Look AT. APOBEC signature mutation generates an oncogenic enhancer that drives LMO1 expression in T-ALL. Leukemia 2017; 31(10): 2057–2064
137. Moya IM, Umans L, Maas E, Pereira PN, Beets K, Francis A, Sents W, Robertson EJ, Mummery CL, Huylebroeck D, Zwijsen A. Stalk cell phenotype depends on integration of Notch and Smad1/5 signaling cascades. Dev Cell 2012; 22(3): 501–514
138. Fuentealba LC, Eivers E, Ikeda A, Hurtado C, Kuroda H, Pera EM, De Robertis EM. Integrating patterning signals: Wnt/GSK3 regulates the duration of the BMP/Smad1 signal. Cell 2007; 131 (5): 980–993
139. Bi Y, Ehirchiou D, Kilts TM, Inkson CA, Embree MC, Sonoyama W, Li L, Leet AI, Seo BM, Zhang L, Shi S, Young MF. Identification of tendon stem/progenitor cells and the role of the extracellular matrix in their niche. Nat Med 2007; 13(10): 1219–1227
140. Shi Y, Massagué J. Mechanisms of TGF-β signaling from cell membrane to the nucleus. Cell 2003; 113(6): 685–700
141. Zaliova M, Potuckova E, Lukes J Jr, Winkowska L, Starkova J, Janotova I, Sramkova L, Stary J, Zuna J, Stanulla M, Zimmermann M, Bornhauser B, Bourquin JP, Eckert C, Cario G, Trka J. Frequency and prognostic impact of ZEB2 H1038 and 1072 mutations in childhood B-other acute lymphoblastic leukemia. Haematologica 2020; [Epub ahead of print] doi: 10.3324/haematol.2020.249094
142. Katerndahl CDS, Heltemes-Harris LM, Willette MJL, Henzler CM, Frietze S, Yang R, Schjerven H, Silverstein KAT, Ramsey LB, Hubbard G, Wells AD, Kuiper RP, Scheijen B, van Leeuwen FN, Müschen M, Kornblau SM, Farrar MA. Antagonism of B cell enhancer networks by STAT5 drives leukemia and poor patient survival. Nat Immunol 2017; 18(6): 694–704
143. Shao DD, Xue W, Krall EB, Bhutkar A, Piccioni F, Wang X, Schinzel AC, Sood S, Rosenbluh J, Kim JW, Zwang Y, Roberts TM, Root DE, Jacks T, Hahn WC. KRAS and YAP1 converge to regulate EMT and tumor survival. Cell 2014; 158(1): 171–184
144. Lauberth SM, Rauchman M. A conserved 12-amino acid motif in Sall1 recruits the nucleosome remodeling and deacetylase corepressor complex. J Biol Chem 2006; 281(33): 23922–23931
145. Miller NL, Lawson C, Kleinschmidt EG, Tancioni I, Uryu S, Schlaepfer DD. A non-canonical role for Rgnef in promoting integrin-stimulated focal adhesion kinase activation. J Cell Sci 2013; 126(21): 5074–5085
146. Graczyk-Jarzynka A, Zagozdzon R, Muchowicz A, Siernicka M, Juszczynski P, Firczuk M. New insights into redox homeostasis as a therapeutic target in B-cell malignancies. Curr Opin Hematol 2017; 24(4): 393–401
147. Mason CC, Khorashad JS, Tantravahi SK, Kelley TW, Zabriskie MS, Yan D, Pomicter AD, Reynolds KR, Eiring AM, Kronenberg Z, Sherman RL, Tyner JW, Dalley BK, Dao KH, Yandell M, Druker BJ, Gotlib J, O'Hare T, Deininger MW. Age-related mutations and chronic myelomonocytic leukemia. Leukemia 2016; 30(4): 906–913
148. Boutboul D, Kuehn HS, Van de Wyngaert Z, Niemela JE, Callebaut I, Stoddard J, Lenoir C, Barlogis V, Farnarier C, Vely F, Yoshida N, Kojima S, Kanegane H, Hoshino A, Hauck F, Lhermitte L, Asnafi V, Roehrs P, Chen S, Verbsky JW, Calvo KR, Husami A, Zhang K, Roberts J, Amrol D, Sleaseman J, Hsu AP, Holland SM, Marsh R, Fischer A, Fleisher TA, Picard C, Latour S, Rosenzweig SD. Dominant-negative IKZF1 mutations cause a T, B, and myeloid cell combined immunodeficiency. J Clin Invest 2018; 128(7): 3071–3087
149. Rusch M, Nakitandwe J, Shurtleff S, Newman S, Zhang Z, Edmonson MN, Parker M, Jiao Y, Ma X, Liu Y, Gu J, Walsh MF, Becksfort J, Thrasher A, Li Y, McMurry J, Hedlund E, Patel A, Easton J, Yergeau D, Vadodaria B, Tatevossian RG, Raimondi S, Hedges D, Chen X, Hagiwara K, McGee R, Robinson GW, Klco JM, Gruber TA, Ellison DW, Downing JR, Zhang J. Clinical cancer genomic profiling by three-platform sequencing of whole genome, whole exome and transcriptome. Nat Commun 2018; 9 (1): 3962
150. Li Z, Jiang N, Lim EH, Chin WHN, Lu Y, Chiew KH, Kham SKY, Yang W, Quah TC, Lin HP, Tan AM, Ariffin H, Yang JJ, Yeoh AE. Identifying IGH disease clones for MRD monitoring in childhood B-cell acute lymphoblastic leukemia using RNA-Seq. Leukemia 2020; 34(9): 2418–2429
151. Hagiwara K, Ding L, Edmonson MN, Rice SV, Newman S, Easton J, Dai J, Meshinchi S, Ries RE, Rusch M, Zhang J. RNAIndel: discovering somatic coding indels from tumor RNA-Seq data. Bioinformatics 2020; 36(5): 1382–1390
152. Tian L, Li Y, Edmonson MN, Zhou X, Newman S, McLeod C, Thrasher A, Liu Y, Tang B, Rusch MC, Easton J, Ma J, Davis E, Trull A, Michael JR, Szlachta K, Mullighan C, Baker SJ, Downing JR, Ellison DW, Zhang J. CICERO: a versatile method for detecting complex and diverse driver fusions using cancer RNA sequencing data. Genome Biol 2020; 21(1): 126
153. Brown LM, Lonsdale A, Zhu A, Davidson NM, Schmidt B, Hawkins A, Wallach E, Martin M, Mechinaud FM, Khaw SL, Bartolo RC, Ludlow LEA, Challis J, Brooks I, Petrovic V, Venn NC, Sutton R, Majewski IJ, Oshlack A, Ekert PG. The application of RNA sequencing for the diagnosis and genomic classification of pediatric acute lymphoblastic leukemia. Blood Adv 2020; 4(5): 930–942
154. Yizhak K, Aguet F, Kim J, Hess JM, Kübler K, Grimsby J, Frazer R, Zhang H, Haradhvala NJ, Rosebrock D, Livitz D, Li X, Arich-Landkof E, Shoresh N, Stewart C, Segrè AV, Branton PA, Polak P,

Ardlie KG, Getz G. RNA sequence analysis reveals macroscopic somatic clonal expansion across normal tissues. Science 2019; 364 (6444): eaaw0726

155. Arindrarto W, Borràs DM, de Groen RAL, van den Berg RR, Locher IJ, van Diessen SAME, van der Holst R, van der Meijden ED, Honders MW, de Leeuw RH, Verlaat W, Jedema I, Kroes WGM, Knijnenburg J, van Wezel T, Vermaat JSP, Valk PJM, Janssen B, de Knijff P, van Bergen CAM, van den Akker EB, Hoen PAC, Kiełbasa SM, Laros JFJ, Griffioen M, Veelken H. Comprehensive diagnostics of acute myeloid leukemia by whole transcriptome RNA sequencing. Leukemia 2020; [Epub ahead of print] doi: 10.1038/s41375-020-0762-8
156. Gu M, Zwiebel M, Ong SH, Boughton N, Nomdedeu J, Basheer F, Nannya Y, Quiros PM, Ogawa S, Cazzola M, Rad R, Butler AP, Vijayabaskar MS, Vassiliou GS. RNAmut: robust identification of somatic mutations in acute myeloid leukemia using RNA-sequencing. Haematologica 2020; 105(6): e290–e293
157. Audemard EO, Gendron P, Feghaly A, Lavallée VP, Hébert J, Sauvageau G, Lemieux S. Targeted variant detection using unaligned RNA-Seq reads. Life Sci Alliance 2019; 2(4): e201900336
158. Kosugi S, Momozawa Y, Liu X, Terao C, Kubo M, Kamatani Y. Comprehensive evaluation of structural variation detection algorithms for whole genome sequencing. Genome Biol 2019; 20(1): 117
159. Wang C, Gong B, Bushel PR, Thierry-Mieg J, Thierry-Mieg D, Xu J, Fang H, Hong H, Shen J, Su Z, Meehan J, Li X, Yang L, Li H, Łabaj PP, Kreil DP, Megherbi D, Gaj S, Caiment F, van Delft J, Kleinjans J, Scherer A, Devanarayan V, Wang J, Yang Y, Qian HR, Lancashire LJ, Bessarabova M, Nikolsky Y, Furlanello C, Chierici M, Albanese D, Jurman G, Riccadonna S, Filosi M, Visintainer R, Zhang KK, Li J, Hsieh JH, Svoboda DL, Fuscoe JC, Deng Y, Shi L, Paules RS, Auerbach SS, Tong W. The concordance between RNA-seq and microarray datadepends on chemical treatment and transcript abundance. Nat Biotechnol 2014; 32(9): 926–932
160. Li B, Brady SW, Ma X, Shen S, Zhang Y, Li Y, Szlachta K, Dong L, Liu Y, Yang F, Wang N, Flasch DA, Myers MA, Mulder HL, Ding L, Liu Y, Tian L, Hagiwara K, Xu K, Zhou X, Sioson E, Wang T, Yang L, Zhao J, Zhang H, Shao Y, Sun H, Sun L, Cai J, Sun HY, Lin TN, Du L, Li H, Rusch M, Edmonson MN, Easton J, Zhu X, Zhang J, Cheng C, Raphael BJ, Tang J, Downing JR, Alexandrov LB, Zhou BS, Pui CH, Yang JJ, Zhang J. Therapy-induced mutations drive the genomic landscape of relapsed acute lymphoblastic leukemia. Blood 2020; 135(1): 41–55
161. Xiao X, Liu P, Li D, Xia Z, Wang P, Zhang X, Liu M, Liao L, Jiao B, Ren R. Combination therapy of BCR-ABL-positive B cell acute lymphoblastic leukemia by tyrosine kinase inhibitor dasatinib and c-JUN N-terminal kinase inhibition. J Hematol Oncol 2020; 13(1): 80
162. Menzl I, Zhang T, Berger-Becvar A, Grausenburger R, Heller G, Prchal-Murphy M, Edlinger L, Knab VM, Uras IZ, Grundschober E, Bauer K, Roth M, Skucha A, Liu Y, Hatcher JM, Liang Y, Kwiatkowski NP, Fux D, Hoelbl-Kovacic A, Kubicek S, Melo JV, Valent P, Weichhart T, Grebien F, Zuber J, Gray NS, Sexl V. A kinase-independent role for CDK8 in BCR-ABL1^{+} leukemia. Nat Commun 2019; 10(1): 4741
163. Khaw SL, Suryani S, Evans K, Richmond J, Robbins A, Kurmasheva RT, Billups CA, Erickson SW, Guo Y, Houghton PJ, Smith MA, Carol H, Roberts AW, Huang DC, Lock RB. Venetoclax responses of pediatric ALL xenografts reveal sensitivity of MLL-rearranged leukemia. Blood 2016; 128(10): 1382–1395
164. Stein EM, Garcia-Manero G, Rizzieri DA, Tibes R, Berdeja JG, Savona MR, Jongen-Lavrenic M, Altman JK, Thomson B, Blakemore SJ, Daigle SR, Waters NJ, Suttle AB, Clawson A, Pollock R, Krivtsov A, Armstrong SA, DiMartino J, Hedrick E, Löwenberg B, Tallman MS. The DOT1L inhibitor pinometostat reduces H3K79 methylation and has modest clinical activity in adult acute leukemia. Blood 2018; 131(24): 2661–2669
165. Stubbs MC, Kim W, Bariteau M, Davis T, Vempati S, Minehart J, Witkin M, Qi J, Krivtsov AV, Bradner JE, Kung AL, Armstrong SA. Selective inhibition of HDAC1 and HDAC2 as a potential therapeutic option for B-ALL. Clin Cancer Res 2015; 21(10): 2348–2358
166. Krivtsov AV, Evans K, Gadrey JY, Eschle BK, Hatton C, Uckelmann HJ, Ross KN, Perner F, Olsen SN, Pritchard T, McDermott L, Jones CD, Jing D, Braytee A, Chacon D, Earley E, McKeever BM, Claremon D, Gifford AJ, Lee HJ, Teicher BA, Pimanda JE, Beck D, Perry JA, Smith MA, McGeehan GM, Lock RB, Armstrong SA. A Menin-MLL inhibitor induces specific chromatin changes and eradicates disease in models of MLL-rearranged leukemia. Cancer Cell 2019; 36(6): 660–673.e11
167. Ying Z, Huang XF, Xiang X, Liu Y, Kang X, Song Y, Guo X, Liu H, Ding N, Zhang T, Duan P, Lin Y, Zheng W, Wang X, Lin N, Tu M, Xie Y, Zhang C, Liu W, Deng L, Gao S, Ping L, Wang X, Zhou N, Zhang J, Wang Y, Lin S, Mamuti M, Yu X, Fang L, Wang S, Song H, Wang G, Jones L, Zhu J, Chen SY. A safe and potent anti-CD19 CAR T cell therapy. Nat Med 2019; 25(6): 947–953
168. Pan J, Niu Q, Deng B, Liu S, Wu T, Gao Z, Liu Z, Zhang Y, Qu X, Zhang Y, Liu S, Ling Z, Lin Y, Zhao Y, Song Y, Tan X, Zhang Y, Li Z, Yin Z, Chen B, Yu X, Yan J, Zheng Q, Zhou X, Gao J, Chang AH, Feng X, Tong C. CD22 CAR T-cell therapy in refractory or relapsed B acute lymphoblastic leukemia. Leukemia 2019; 33(12): 2854–2866
169. Fry TJ, Shah NN, Orentas RJ, Stetler-Stevenson M, Yuan CM, Ramakrishna S, Wolters P, Martin S, Delbrook C, Yates B, Shalabi H, Fountaine TJ, Shern JF, Majzner RG, Stroncek DF, Sabatino M, Feng Y, Dimitrov DS, Zhang L, Nguyen S, Qin H, Dropulic B, Lee DW, Mackall CL. CD22-targeted CAR T cells induce remission in B-ALL that is naive or resistant to CD19-targeted CAR immunotherapy. Nat Med 2018; 24(1): 20–28
170. Kantarjian H, Stein A, Gökbuget N, Fielding AK, Schuh AC, Ribera JM, Wei A, Dombret H, Foà R, Bassan R, Arslan Ö, Sanz MA, Bergeron J, Demirkan F, Lech-Maranda E, Rambaldi A, Thomas X, Horst HA, Brüggemann M, Klapper W, Wood BL, Fleishman A, Nagorsen D, Holland C, Zimmerman Z, Topp MS. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med 2017; 376(9): 836–847
171. Curran KJ, Margossian SP, Kernan NA, Silverman LB, Williams DA, Shukla N, Kobos R, Forlenza CJ, Steinherz P, Prockop S, Boulad F, Spitzer B, Cancio MI, Boelens JJ, Kung AL, Szenes V, Park JH, Sauter CS, Heller G, Wang X, Senechal B, O'Reilly RJ, Riviere I, Sadelain M, Brentjens RJ. Toxicity and response after CD19-specific CAR T-cell therapy in pediatric/young adult relapsed/refractory B-ALL. Blood 2019; 134(26): 2361–2368
172. Mohty M, Gautier J, Malard F, Aljurf M, Bazarbachi A,

Chabannon C, Kharfan-Dabaja MA, Savani BN, Huang H, Kenderian S, Nagler A, Perales MA. CD19 chimeric antigen receptor-T cells in B-cell leukemia and lymphoma: current status and perspectives. Leukemia 2019; 33(12): 2767–2778

173. Chen H, Wang F, Zhang P, Zhang Y, Chen Y, Fan X, Cao X, Liu J, Yang Y, Wang B, Lei B, Gu L, Bai J, Wei L, Zhang R, Zhuang Q, Zhang W, Zhao W, He A. Management of cytokine release syndrome related to CAR-T cell therapy. Front Med 2019; 13(5): 610–617
174. Chen Z. Prospects of immunotherapy for cancer. Front Med 2019; 13(1): 1–2
175. Schultz KR, Carroll A, Heerema NA, Bowman WP, Aledo A, Slayton WB, Sather H, Devidas M, Zheng HW, Davies SM, Gaynon PS, Trigg M, Rutledge R, Jorstad D, Winick N, Borowitz MJ, Hunger SP, Carroll WL, Camitta B, Children's Oncology Group. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group study AALL0031. Leukemia 2014; 28(7): 1467–1471
176. Malard F, Mohty M. Acute lymphoblastic leukaemia. Lancet 2020; 395(10230): 1146–1162
177. Mikhael J, Richardson P, Usmani SZ, Raje N, Bensinger W, Karanes C, Campana F, Kanagavel D, Dubin F, Liu Q, Semiond D, Anderson K. A phase 1b study of isatuximab plus pomalidomide/dexamethasone in relapsed/refractory multiple myeloma. Blood 2019; 134(2): 123–133
178. Diaz-Flores E, Comeaux EQ, Kim KL, Melnik E, Beckman K, Davis KL, Wu K, Akutagawa J, Bridges O, Marino R, Wohlfeil M, Braun BS, Mullighan CG, Loh ML. Bcl-2 is a therapeutic target for hypodiploid B-lineage acute lymphoblastic leukemia. Cancer Res 2019; 79(9): 2339–2351
179. Li D, Hu Y, Jin Z, Zhai Y, Tan Y, Sun Y, Zhu S, Zhao C, Chen B, Zhu J, Chen Z, Chen S, Li J, Liu H. TanCAR T cells targeting CD19 and CD133 efficiently eliminate MLL leukemic cells. Leukemia 2018; 32(9): 2012–2016
180. Kim E, Hurtz C, Koehrer S, Wang Z, Balasubramanian S, Chang BY, Müschen M, Davis RE, Burger JA. Ibrutinib inhibits pre-BCR^{+} B-cell acute lymphoblastic leukemia progression by targeting BTK and BLK. Blood 2017; 129(9): 1155–1165
181. Tzoneva G, Dieck CL, Oshima K, Ambesi-Impiombato A, Sánchez-Martín M, Madubata CJ, Khiabanian H, Yu J, Waanders E, Iacobucci I, Sulis ML, Kato M, Koh K, Paganin M, Basso G, Gastier-Foster JM, Loh ML, Kirschner-Schwabe R, Mullighan CG, Rabadan R, Ferrando AA. Clonal evolution mechanisms in NT5C2 mutant-relapsed acute lymphoblastic leukaemia. Nature 2018; 553(7689): 511–514
182. Ohki K, Takahashi H, Fukushima T, Nanmoku T, Kusano S, Mori M, Nakazawa Y, Yuza Y, Migita M, Okuno H, Morimoto A, Yoshino H, Kato M, Hayashi Y, Manabe A, Ohara A, Hasegawa D, Inukai T, Tomizawa D, Koh K, Kiyokawa N, Tokyo Children's Cancer Study Group (TCCSG). Impact of immunophenotypic characteristics on genetic subgrouping in childhood acute lymphoblastic leukemia: Tokyo Children's Cancer Study Group (TCCSG) study L04–16. Genes Chromosomes Cancer 2020; 59 (10): 551–561
183. Greaves M. A causal mechanism for childhood acute lymphoblastic leukaemia. Nat Rev Cancer 2018; 18(8): 471–484
184. Meyer LK, Hermiston ML. The epigenome in pediatric acute lymphoblastic leukemia: drug resistance and therapeutic opportunities. Cancer Drug Resist 2019; 2:313–325
185. Fang DD, Wen D, Xu Y. Identification of cancer stem cells provides novel tumor models for drug discovery. Front Med 2012; 6(2): 112–121
186. Good Z, Sarno J, Jager A, Samusik N, Aghaeepour N, Simonds EF, White L, Lacayo NJ, Fantl WJ, Fazio G, Gaipa G, Biondi A, Tibshirani R, Bendall SC, Nolan GP, Davis KL. Single-cell developmental classification of B cell precursor acute lymphoblastic leukemia at diagnosis reveals predictors of relapse. Nat Med 2018; 24(4): 474–483
187. Tan Y, Liu H, Chen S. Mutant DNA methylation regulators endow hematopoietic stem cells with the preleukemic stem cell property, a requisite of leukemia initiation and relapse. Front Med 2015; 9(4): 412–420
188. James AR, Schroeder MP, Neumann M, Bastian L, Eckert C, Gökbuget N, Tanchez JO, Schlee C, Isaakidis K, Schwartz S, Burmeister T, von Stackelberg A, Rieger MA, Göllner S, Horstman M, Schrappe M, Kirschner-Schwabe R, Brüggemann M, Müller-Tidow C, Serve H, Akalin A, Baldus CD. Long non-coding RNAs defining major subtypes of B cell precursor acute lymphoblastic leukemia. J Hematol Oncol 2019; 12(1): 8