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Review

Relevance of AKT and RAS Signaling Pathways for Antibody–Drug Conjugate Immunotherapies in Acute Lymphoblastic Leukemia

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Abstract

Acute lymphoblastic leukemia is the most common cause of cancer-related death in children and represents a poor prognosis for patients in high-risk groups. Current treatment protocols are based on intensive polychemotherapy, which is associated with a significant toxicity profile. Due to their higher specificity and lower toxicity, immunotherapies based on monoclonal antibodies, in particular antibody–drug conjugates (ADCs), are revolutionizing cancer therapy. However, reports on the potential efficacy of ADC-targeted therapy in ALL and its subgroups are limited. Gene expression data suggest that potentially new ADC antigens are highly abundant in ALL subgroups and represent promising targets for cancer therapy. In addition, the PI3K/AKT and RAS/MAPK signaling pathways are often persistently activated in ALL and recent data showed that active feedback loops following inhibition of these pathways can lead to redundancy of cell surface receptors that can potentially serve as antigens for ADC treatment. Therefore, we provide here an overview of the most interesting receptors of the various ALL subgroups and discuss the influence that feedback loops of the PI3K/AKT and RAS/MAPK signaling pathways may have on increasing protein expression of the aforementioned receptors, which could lead to targeted combination therapy approaches in the future.

Keywords: PI3K/AKT-signaling; RAS/MAPK-signaling; acute lymphoblastic leukemia; drug response profiling; antibody–drug conjugates; immunotherapy

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1. Introduction

Antibody-Based Immunotherapies and Their Great but Underutilized Potential in ALL

1.1. Current Challenges in ALL Treatment

Despite improved overall prognosis, the treatment of ALL (acute lymphocytic leukemia) remains a serious clinical challenge, as 5-year and long-term survival rates decline with increasing age. While the survival rate in children (<15 years) is still comparatively high (90–95%), it drops significantly in young adults (15–39 years; approximately 70–80%) and especially in adults. Therefore, depending on the risk group, these patients only achieve a long-term survival rate of 40–70% [1–5].

Thereby, some subgroups are associated with a particularly poor prognosis, but each ALL subtype brings its own challenges (prognosis, risk of relapse, infestation of the central nervous system) [5]. For example, BCR-ABL1 (breakpoint cluster region/Abelson murine leukemia viral oncogene homolog 1)-positive ALL is present in 3% of pediatric B-ALL and

25% of adult B-ALL cases and is linked to poor outcome and a higher proportion of relapses. KMT2A (Histone-lysine N-methyltransferase 2A) gene rearrangements are found in 70% of infants and 15% of adults and confer a very poor prognosis. Moreover, therapy options for relapsed/refractory (r/r) T-cell-ALL (T-ALL) are limited [6]. In summary, both children and adults with a KMT2A-rearrangement, hypodiploidy, the presence of the BCR-ABL1 fusion gene, the Ph-like subtype (which has a similar genetic profile to the Ph-positive subtype without carrying the BCR-ABL1 fusion gene) and T-ALL frequently have a poor prognosis, thus requiring additional therapeutic options. However, other subtypes, such as the ETV6-RUNX1 subtype, also pose challenges, as up to 20% of patients may relapse [7]. Current ALL treatment protocols are essentially based on intensive polychemotherapy and associated with severe side effects, the occurrence of secondary tumors and r/r-disease.

1.2. Role of Antibody–Drug Conjugates

Compared to conventional chemotherapy, antibody-based therapy options (e.g., antibody–drug conjugates; ADCs) have a wider therapeutic window. ADCs combine a monoclonal antibody, a cytotoxic drug (payload) and a chemical linker to deliver chemotherapy specifically to cancer cells. In the treatment of B-ALL, standard chemotherapy leads to significantly worse results than the new immunotherapies and combinations. This has been proven by international, randomized studies [8,9]. Small-molecule inhibitors and humanized monoclonal antibodies directed against RTKs (receptor tyrosine kinases) are among the most effective targeted therapies in the clinic [10]. To date, immunotherapy approaches targeting the B cell antigen CD19 (blinatumomab), CD22 (inotuzumab ozogamicin) and CD20 (rituximab) were successfully included into treatment of B-ALL [11]. Of importance, immunotherapy may partly overcome high risk genotypes as highlighted by the imposing result of blinatumomab in KMT2A-r infants [12].

Up to now, 12 ADCs (tisotumab vedotin, loncastuximab tesirine, belantamab mafodotin, sacituzumab govitecan, trastuzumab deruxtecan, enfortumab vedotin, polatuzumab vedotin, inotuzumab ozogamicin, trastuzumab emtasine, brentuximab vedotin and gemtuzumab ozogamicin) have been approved for treatment of hematological and solid tumors, along with more than 150 novel ADCs in clinical development [13]. The CD22-directed ADC inotuzumab ozogamicin (InO) received approval for r/r B-ALL. However, not all patients benefit from InO therapy and therapy failure due to downregulation or alternative splicing of the CD22 antigen is commonly observed [14]. Reports on potential efficacy of ADC-targeted therapy in ALL and its subgroups beyond CD22-targeted therapy are limited [15]. CD19-targeted therapy is a promising approach, since CD19 is expressed on a variety of B cells and has a broader expression profile than that of other B-cell specific antigens like CD20 and CD22. However, the emergence of B-cell antigen-loss tumor escape variants (e.g., CD19) after treatment demonstrates that additional target antigens are required [16].

ADCs selectively deliver potent cytotoxic substances to tumor cells by binding to their target on the tumor cells. One of the key challenges for ADC design and clinical success is the selection of a suitable target for the specific tumor. Furthermore, the choice of the highly potent payload and the design of the linker for effective drug delivery must be carefully considered. The optimal target for ADC development should exhibit both high and uniform expression in tumor cells while precluding expression in normal and healthy cells [17]. However, ADC targets, which are currently under development, exhibit a broad expression profile in both tumor and normal cells. Some studies have already very successfully carried out the identification process of ADC targets for solid tumors [17–19]. The lack of validated suitable secondary target antigens for ALL is also a crucial reason for

the failure of treatment of resistant cells. Therefore, the identification of a broad repertoire of diverse target antigens is essential.

1.3. Key Signaling Pathways and Feedback Loops

Here, we utilize transcriptomics, proteomics, immunohistochemistry and cell surface membrane data from publicly available datasets and databases for evidence-based filtering to identify ADC targets with improved tumor selectivity. This review aims to provide a more detailed characterization of the different genetic subtypes of ALL. To this end, we discuss subgroup-specific cell surface markers that may serve as novel targets for ADC treatment of ALL cells. In addition, we explain that PI3K/AKT and RAS/MAPK signaling pathways play an important role in the regulation of cell surface receptors and why combination therapy with PI3K/AKT (phosphoinositide 3-kinase/protein kinase B) and RAS/MAPK (rat sarcoma/mitogen-activated protein kinase) pathway inhibitors can improve patient response to ADC immunotherapy.

2. The AKT and MAPK Pathway—Important Intracellular Regulatory Nodes

2.1. The AKT Pathway

AKT (Protein kinase B) belongs to the superfamily of AGC kinases (cAMP dependent protein kinase A/G/C), which also includes protein kinase A and C (PKA and PKC). AKT was identified as a viral oncogene of the transforming retrovirus AKT8 and as a homolog of PKA and PKC [20,21]. In mammalian cells, three AKT isoforms, AKT1, AKT2 and AKT3, have been identified, which are encoded by three different genes with partially different phenotypes and functions [22,23]. AKT1-null mice show growth retardation and increased lethality [24]. AKT2 knockout mice show altered glucose metabolism and insulin-resistant diabetes [25]. In contrast, AKT3 knockout mice have reduced brain size, combined with smaller neuronal cells [26]. AKT isoform-specific knockdown leads to increased phosphorylation of the other remaining AKT isoforms [27].

The activation of the PI3K/AKT signaling pathway starts with the binding of a ligand to the RTK. After RTK activation, the PI3K recruits to the plasma membrane, interacts with the phosphotyrosine residues of the receptor via the SH2 (src homology 2) domain of its p85 subunit and undergoes a conformational change with activation of its catalytic p110 subunit. Subsequently, the p110 subunit converts PtdIns(4,5)P2 to PtdIns(3,4,5)P3. AKT can bind to PtdIns(3,4,5)P3 with its N-terminal PH (pleckstrin homology) domain and becomes phosphorylated after conformational change at threonine residue 308 by PDK (phosphoinositide-dependent protein kinase-1) and for full activation at serine residue 473 by mTORC2 (mechanistic target of rapamycin complex 2). Phosphorylation of AKT at serine residue 473 also correlates with AKT kinase activity [28]. AKT regulates numerous substrates and thereby inhibits apoptosis, increases proliferation and, through the activation of mTOR, increases translation. While AKT itself is a crucial regulator in translation, mTORC1 is often considered the most important protein mediating translation.

A recurrent point mutation in the PH domain (E17K) of AKT isoform 1 has been identified in different tumors and leads to a conformational change in the PH domain, which allows AKT to bind to the membrane even when no PtdIns(3,4,5)P3 is present there. This subsequently leads to constitutive activation of AKT. In an animal model, the AKT1 (E17K) mutation leads to leukemia development with a 60% probability [29]. Constitutive activation of AKT is observed in 87% of patients with T-ALL and in over 80% of patients with B-ALL [30–32]. In addition, it was shown that the overexpression of AKT2 correlates with the aggressiveness of cancer and a poor survival rate [33,34]. Capivasertib, a selective AKT inhibitor, was approved together with fulvestrant for patients with ER-positive and HER2-negative breast cancer whose tumors harbored PIK3CA (catalytic

subunit alpha)/AKT1/PTEN (phosphatase and tensin homolog) alterations [35]. Recent data have shown that active feedback loops following inhibition of these pathways can lead to redundancy of cell surface receptors that can potentially serve as antigens for ADC treatment.

2.2. The MAPK Pathway

RAS belongs to the Ras superfamily, which includes over 150 small GTPases (guanosine triphosphateases) divided into five distinct subfamilies (RAS, RHO/RAC, RAN, RAB and ARF GTPases). Members of the RAS GTPases family encode different protein isoforms: HRAS, KRAS and NRAS with partially different transformation potential in different cellular contexts. In addition, KRAS4A and KRAS4B arise from alternative splicing of exon 4 of the KRAS locus [36,37]. The RAS proteins continuously cycle between active (GTP-bound) and inactive (GDP-bound) conformational states. To this end, RAS proteins interact with negative (RAS-GAP; GTPase-activating proteins) and positive (RAS-GEF; guanine nucleotide exchange factor) cellular regulators. Members of the RAS GTPase family play an important role in human malignancies by regulating cell growth, differentiation and survival through downstream signaling cascades, including the RAF/MEK/ERK (rapidly accelerated fibrosarcoma/mitogen-activated protein kinase/extracellular signal-related kinase) and PI3K/AKT pathways.

The importance of Ras signaling in tumorigenesis is underscored by the deregulation of many of its activator and effector pathways. Activation of RTKs by extracellular ligands leads to tyrosine phosphorylation of their cytoplasmic domains. These phosphorylation sites serve as a docking site for the SH2 domain-containing GRB2 (growth factor receptor-bound 2) adaptor protein. SOS (son of sevenless) can bind to GRB2 and then phosphorylate tyrosine-residues of the activated receptor. Subsequently, activated SOS promotes the exchange of GDP for GTP from RAS via its GEF activity. The active, GTP-bound RAS subsequently activates the RAF-MEK-ERK axis. ERK kinases can translocate to the nucleus and activate various transcription factors. Negative regulators of this pathway include members of the DUSP (dual specificity phosphatase), SPRY (sprouty) and SPRED (sprouty-related protein with EVH-1 domain) families, which are able to suppress this signaling. RAS family members are frequently activated by point mutations in human cancers, leading to constitutive activation of their downstream signaling pathways. Oncogenic mutations at position 12, 13 or 61 of RAS family member genes are among the most common genetic lesions in human cancers [38]. These mutations result in significant impairment of the GTPase activity of RAS proteins, locking them in a constitutively activated state, even in the absence of extracellular stimuli.

RAS mutations have been reported to make B-ALL cells more susceptible to relapse, as reflected by a higher relapse frequency. NRAS mutations, in particular, are overrepresented in children with ALL [39,40]. Overall, more than 50% of relapsed pediatric ALL patients have been shown to harbor mutations in the RAS pathway (KRAS, NRAS, NF1, EPOR) and recent studies on RAS mutations show a prevalence of 25.2% in newly diagnosed and 38.9% in relapsed children with ALL [40]. Several potent KRAS-G12C small-molecule inhibitors have been discovered, including AMG-510, MRTX849 and ARS-1620 [41–43]. However, NRAS-mutated cancer cells are resistant to KRAS-G12C-targeted inhibitors [42,43], highlighting the limitations and specificity of RAS isoform-targeted therapy. Furthermore, studies using MEK inhibitors (e.g., selumetinib) to treat leukemia patients with NRAS mutations do not lead to satisfactory responses due to the complex RAS downstream signaling and its compensatory effects [44].

The expression of the HRAS, NRAS and KRAS genes is nearly ubiquitous and largely conserved across species. However, there are specific differences in expression and activa-

tion status in certain tumor types and their developmental stages, often due to mutations, suggesting that the different RAS members have distinct biological characteristics with specific downstream signaling and transcriptional networks [45]. For example, NRAS mutations occur in a high percentage of acute leukemias, whereas HRAS and KRAS mutations are significantly less common [46–48]. Interestingly, several syndromes are associated with aberrant RAS signaling (such as Noonan or LEOPARD syndrome) [49,50]. This is frequently due to mutations in the PTPN11 gene, which encodes SHP2, a negative regulator of the RAS signaling pathway [49]. Moreover, patients with Noonan syndrome (NS) have a predisposition to leukemia and certain solid tumors [51] and would therefore also benefit from ADCs against targets upregulated by the constitutively activated RAS signaling pathway.

3. Feedback Signaling of the PI3K/AKT and RAS/MAPK Pathways Influence the Regulation of Cell Surface Markers

ALL risk groups are defined by alterations in tyrosine kinases and transcription factors, particularly those involved in lymphoid development. As a result, an aberrantly altered phosphorylation cascade or transcription leads to altered gene expression, including receptors.

Recent results show that the B-cell-specific transcription factor EBF1 (early B-cell factor1) is a key regulator of CD22 expression and thus influences the response to the CD22-specific ADC inotuzumab ozogamicin [52]. These risk subgroups often respond poorly to standard chemotherapy. While remission can usually be achieved in approximately 75% of cases after induction of chemotherapy, overall survival in all risk groups across ALL drops to 50% [53]. The identification of genetic subgroups in recent years has increased the likelihood of response to targeted therapy.

Activated cell surface receptors, for example, receptor tyrosine kinases (RTKs), recruit adaptor proteins to trigger a cascade of protein interactions between intracellular effectors, ultimately leading to altered gene expression as well as protein function and thus strongly influence critical cellular processes such as proliferation and survival. This downstream signaling includes effectors such as RAS/MAPK or PI3K/AKT pathway proteins. Genetic alterations of RTKs, such as gene rearrangements or amplifications, lead to constitutively active signaling of these pathways. Attempts to inhibit individual downstream molecules of these signaling pathways frequently result in complex feedback mechanisms that redirect cell signaling back to RTKs or result to cross talk between these pathways [10,54]. In particular, the PI3K/AKT and RAS/MAPK signaling pathways can compensate for each other in promoting cell proliferation and survival [55].

The PI3K/AKT/mTOR signaling pathway is constitutively activated in various solid cancers and the majority of hematological malignancies, including ALL [56]. Genetic alterations of RTKs (B-ALL: 4–10% and T-ALL: 2–23%) and aberrantly activated tyrosine kinases (BCR-ABL) are one of the main causes of constitutive activation of AKT. Despite the knowledge of the therapeutic significance of the AKT signaling pathway, monotherapy with inhibitors targeting various components of the PI3K/AKT/mTOR pathway was shown to be ineffective and often led to resistance [57,58]. Consequently, increased AKT activation in patients with pre-B-ALL correlates with poor response to chemotherapy and is also associated with poor overall survival [59]. For example, AKT is responsible for the development of therapy resistance in T-ALL cells to glucocorticoids [60]. Furthermore, imatinib-resistant Ph-positive ALL cells show upregulation of the PI3K/AKT/mTOR and RAS/MAPK signaling pathways. However, it was shown that inhibition of constitutively activated AKT helps to overcome chemotherapy resistance in cancer cells [61].

Activation of the PI3K/AKT signaling pathway in tumors is modulated by negative feedback, including mTORC1-mediated inhibition of upstream signaling proteins. In turn,

AKT inhibition has been shown to induce the expression and activation of several receptor tyrosine kinases in a wide range of tumor types, including HER3 (human epidermal growth factor receptor 3), IGF-1R (insulin-like growth factor 1 receptor) and the insulin receptor [62,63]. The PI3K/AKT signaling pathway is a crucial regulator and orchestrates its downstream effectors FOXO (forkhead box class O), mTOR, GSK3 and S6K via phosphorylation, ultimately leading to a complex cascade of cellular events (Figure 1A). Inhibition of mTORC1 leads to inhibition of S6 kinase (S6K), a mediator of many transcriptional responses downstream of PI3K and AKT.

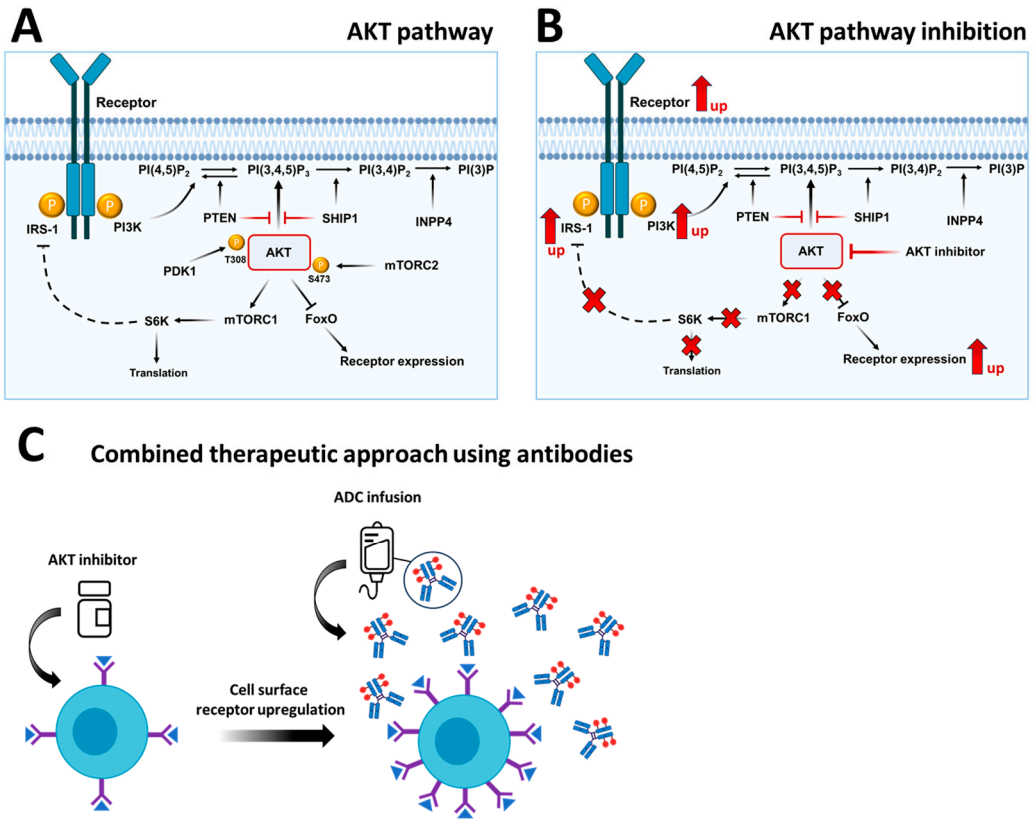

Figure 1. Inhibitory and feedback mechanisms of the PI3K/AKT/mTOR signaling pathway. (**A**) AKT and mTOR are two important proteins that serve as hubs in the regulation of PI3K/AKT/mTOR signaling. mTOR regulates translation via S6 kinase and adaptor proteins such as IRS-1. AKT regulates receptor expression through transcription factors such as FOXO. (**B**) AKT inhibition leads to the loss of negative feedback in the pathway and thus to increased receptor expression. It also leads to the inhibition of mTOR. mTOR inhibition leads to the stabilization of IRS-1 and thus to increased receptor and PI3K activation. (**C**) Schematic representation of the combined therapeutic approach consisting of an AKT inhibitor that upregulates receptor expression on the cell surface and an antibody–drug conjugate that binds to the upregulated receptor and specifically transports the conjugated cytotoxin into the cell by subsequent endocytosis.

S6K-mediated negative IRS (insulin receptor substrate)-dependent feedback also increases the expression and activity of receptor tyrosine kinases and thus the PI3K/AKT signaling pathway [64]. Furthermore, AKT can directly regulate transcription factors, including the FOXO family members. Inhibition of AKT leads to a FOXO-dependent activation of receptor expression (Figure 1B). Consequently, inhibition of mTOR or AKT leads to increased AKT phosphorylation and upregulation of IRS-1 and FOXO, which subsequently leads to increased expression and activity of receptor tyrosine kinases in approximately 70% of primary AML cells [65]. Moreover, tumors in which AKT suppresses HER3 expression respond more effectively to combined inhibition of AKT and HER3 than

to inhibition of either inhibitor alone [63]. In addition, HER2 (human epidermal growth factor receptor 2) inhibition (e.g., trastuzumab) abrogates PI3K/AKT signaling, thereby activating FOXO3A-mediated ERBB3 transcription. Elevated ERBB3 levels thus provide compensatory input for PI3K/AKT signaling and offer the potential to protect cancer cells from HER2-targeted therapies [66]. Inhibition of AKT or mTOR alone showed insufficient results to stop the growth of B-ALL cells [27].

The observed effects can be explained by a pronounced feedback mechanism and increased phosphorylation and activation of signaling molecules downstream of the receptor-PI3K-AKT-mTOR axis. However, the combination of mTOR and AKT inhibitors inhibits the phosphorylation of S6, as a readout signal for mTOR pathway activation, more effectively. In turn, the knockdown of AKT leads to the increase in the activity of several receptor tyrosine kinases in ALL, including ERBB2/3/4, EPHA1/2/3/4/5 (ephrin type-A receptor 1/2/3/4/5), EGFR (epidermal growth factor receptor), RET, MERTK, AXL, INSRR (insulin receptor related receptor), ROS1, TRKB (tropomyosin receptor kinase B), DDR1/2 (discoidin domain receptor 1/2), FGFR2/3 (fibroblast growth factor receptor 2/3) and VEGFR (vascular endothelial growth factor receptor) [27]. Overall, a combined therapeutic approach consisting of an AKT inhibitor that upregulates receptor expression on the cell surface and an antibody–drug conjugate that binds the upregulated receptor and specifically transports the conjugated cytotoxin into the cell represents a stringent therapy approach (Figure 1C).

The RAS/MAPK pathway represents a second important cellular signaling pathway that transduces signals from receptors into the nucleus and subsequently activates various transcription factors, including members of the FOXO family, SOX10 (SRY-related HMG-box 10), MYC or HIF1/2 (hypoxia inducible factor 1/2), that can alter receptor expression at the cell surface [67–69] (Figure 2A). Inhibition of MEK (e.g., by trametinib) leads to feedback activation of cell surface receptors, including the IGF1 receptor, which in turn leads to increased activation and signaling of RAS, PI3K and IRS proteins (Figure 2B) [70–72]. MEK or RAF inhibition has been shown to upregulate the expression of several RTKs by suppressing the transcription factor SOX10.

MYC, a transcriptional suppressor of ERBB2 and ERBB3, is stabilized by ERK-mediated phosphorylation. Inhibition of MEK, upstream of ERK, reduces ERK activity and leads to dephosphorylation and degradation of MYC in the nucleus. The lack of MYC suppression, in turn, leads to increased transcription of ERBB2 and ERBB3 and upregulation of their protein expression [73].

In addition, negative feedback can also be conveyed by ERK-mediated phosphorylation of inhibitory phosphorylation sites on EGFR (tyrosine 669) or ERBB2 (tyrosine 677) [74]. CDC25C (cell division cycle 25C) is a phosphatase that negatively regulates EGFR. ERK signaling activates CDC25C function, but CDC25C becomes inactive after BRAF inhibition [75].

FRS2 (fibroblast growth factor receptor substrate 2) is a membrane-anchored docking protein that links EGFR and FGFR receptors to the MAPK signaling cascade by recruiting Grb2/SOS. Upon receptor stimulation with FGF, FRS2 is phosphorylated not only at tyrosine residues but also at several threonine residues by ERK. Threonine phosphorylation of FRS2 is associated with reduced tyrosine phosphorylation of the docking protein and reduced Grb2 recruitment. Preventing threonine phosphorylation (e.g., by ERK inhibition) leads to enhanced tyrosine phosphorylation of FRS2 and increased MAPK stimulation [76].

It has been previously reported that inhibition of the RAS/MAPK signaling pathway can cause the upregulation and activation of several RTKs, including PDGFRB (platelet-derived growth factor receptor B), FGFR1, IGF1R, KDR (kinase insert domain receptor), AXL, ERBB2/3, EGFR and DDR1/2, as well as their ligands, in various tumor identi-

ties. Activation of these RTKs, in turn, is associated with increased AKT and ERK signaling [10,77,78]. The complex network of PI3K/AKT and RAS/MAPK signaling can mutually compensate for each other and promote cell proliferation and survival, in part through the same key downstream effectors, including mTOR/S6K/MYC and FOXO, as shown in Figure 2C. A common mechanism for tumors to evade RTK pathway inhibition is to activate and increase expression of alternative RTKs. For example,

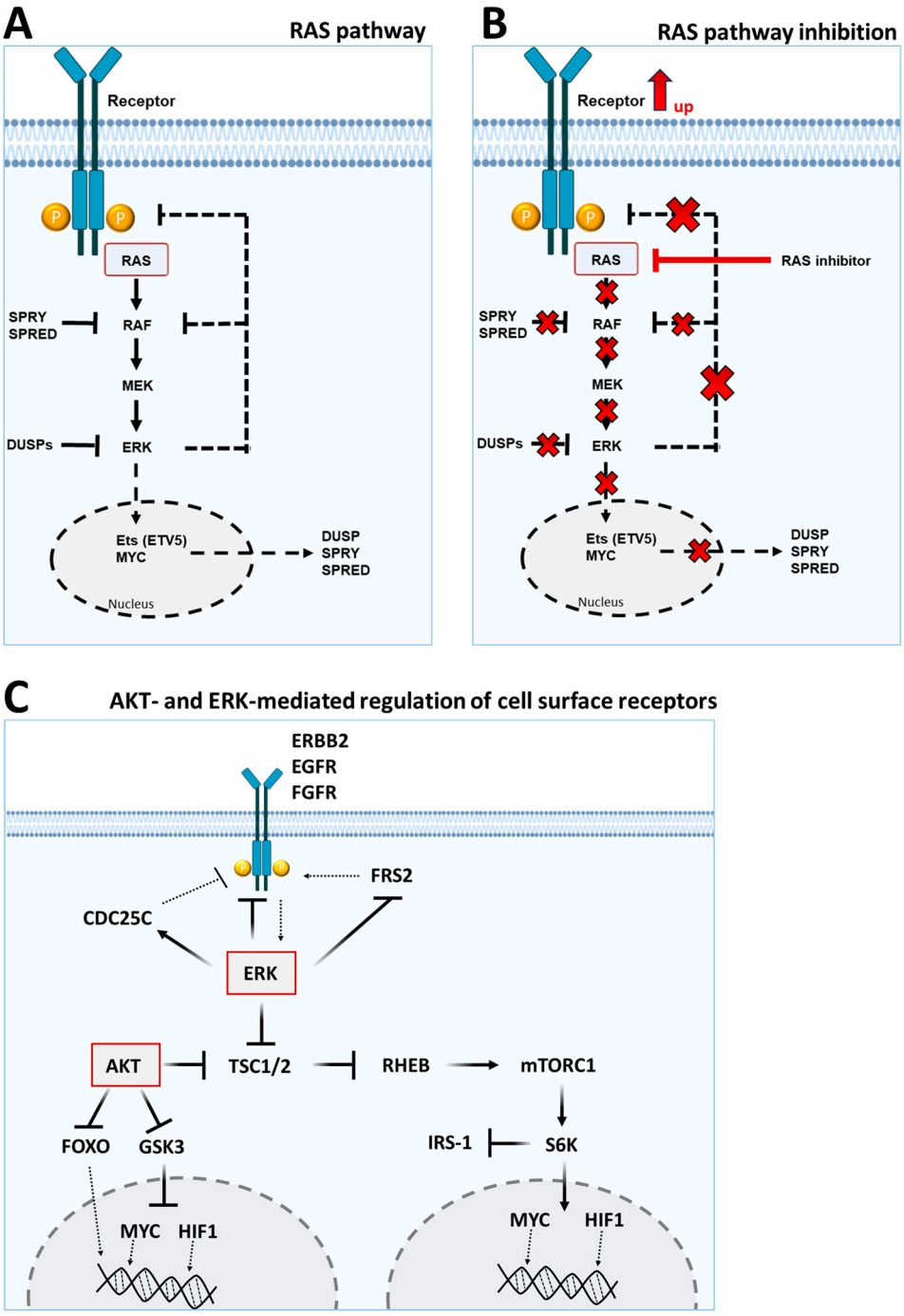

Figure 2. Inhibitory and feedback mechanisms of the RAS/MAPK signaling pathway. (**A**) Receptor tyrosine kinases (RTKs) at the plasma membrane are activated by extracellular ligands. Binding of the ligand to the receptor facilitates the activation of the tyrosine kinase activity of the cytoplasmic domain of the receptor. The tyrosine phosphorylated receptor serves as docking site for the SH2-domain containing GRB2 adapter protein. SOS, in turn, can bind to GRB2 and becomes activated.

Activated SOS, via its GEF activity, promotes the exchange of GDP for GTP from a member of the RAS subfamily. GTP bound and active RAS then activates RAF kinases. RAF kinases phosphorylate and activate MEK kinases. MEK kinases phosphorylate and activate ERK kinases. ERK kinases can translocate into the nucleus of the cell and can activate different transcription factors, which among others, upregulates its own negative regulators of the DUSP, SPRY and SPRED family. High ERK activity leads to feedback mechanism and in consequence to reduced expression and/or lower activity of the initiating RTK through various mechanisms. (**B**) RAS/MAPK pathway inhibition leads to the loss of negative feedback in the pathway and thus to increased receptor expression, which in turn can again activate the mitogen-activated protein kinase pathway. (**C**) AKT- and ERK-mediated regulation of cell surface receptors. AKT and ERK control cellular transcription and activation of cell surface receptors, in part, through MYC, HIF1 and FOXO. AKT and ERK phosphorylate and inhibit TSC1/2 thus activating mTORC1 by relieving inhibition of RHEB. The S6K is a downstream target of mTORC1 and can activate MYC and HIF1 or inhibit the receptor adaptor protein IRS-1. AKT can also inhibit FOXO, MYC and HIF1, partly by inhibiting GSK3. GSK3-mediated phosphorylation of MYC and HIF1 targets their proteasomal degradation. ERK can also influence the expression and activation of receptors directly by phosphorylation or by phosphorylation of mediators such as CDC25C and FRS2.

EGFR inhibition upregulates PDGFRB, MET and AXL expression [79–81]. However, it is reported that not only RTKs are upregulated by inhibition of the PI3K/AKT and RAS/MAPK signaling pathways. There are several reports describing MYC-, FOXO-, or HIF1/2-dependent regulation of non-RTKs cell surface markers (e.g., CSPG4, GLUT1/3, NOTCH3, CD20, PTPRZ1, CD146; F3, CNR1, VIPR2) [82–93]. Thus, treatment of tumor cells with PI3K/AKT (Figure 1) or RAS/MAPK pathway (Figure 2) inhibitors may lead to upregulation of receptor tyrosine kinases or other cell surface markers proteins, improving accessibility to ADC immunotherapeutics. In the next section, we therefore discuss the identification of novel potential antibody targets.

4. Identification of ALL Subgroup-Specific Expression of Cell Surface Markers

The exponential growth of large transcriptome data opens a new dimension in molecular biology by analyzing the entire spectrum of RNA transcripts in a cell. Large transcriptome datasets from ALL samples from major studies [94–96] provide important information and have led to groundbreaking discoveries. To explore novel cell surface targets from publicly available transcriptome datasets of ALL patient samples, we first selected protein-coding genes using Ensembl BioMart (Ensembl release 115; EMBL-EBI, Hinxton, UK). In the next step, we selected plasma membrane genes using an annotation list consisting of datasets from "the in silico human surfaceome" database, the Human Protein Atlas (HPA; subcellular location: selected for plasma membrane and cell junctions), the Gene Ontology database (GO:0009986; cell surface) and an "immune inhibitory receptor" dataset by Sing and colleagues (Figure 3) [97–102].

To increase the probability of true expression from background noise, we selected the receptors based on significance, expression level and subgroup-specific expression profile (Table S1). To minimize potential side effects of ADC targeting on healthy cells, we considered the removal of genes with high expression in hematopoietic stem cells and progenitor cells and thus prioritized cell surface targets with high expression on tumor cells.

The absence of targetable antigens on hematopoietic stem cells offers an advantage, as normal blood cells can be replenished from hematopoietic stem cells after transient ADC-induced depletion. Genes were carefully reviewed for their location on the outer cell membrane for their accessibility to immunotherapeutics using the STRING database analysis function and manual analysis of different datasets (UniProt keywords: KW-0472/membrane; UniProt keywords: KW-1133/transmembrane helix; Gene Ontology—

cellular component: GO:0005886/plasma membrane; Gene Ontology—cellular component: GO:0071944/cell periphery; Gene Ontology—cellular component: GO:0016021/integral component of membrane and HPA—predicted location) [103] (Table S2) as well as prioritized based on their protein expression using immunohistochemical (IHC) data [104] (Table S3). The three most promising candidates for each B-ALL subgroup and T-ALL cells were listed (Table 1).

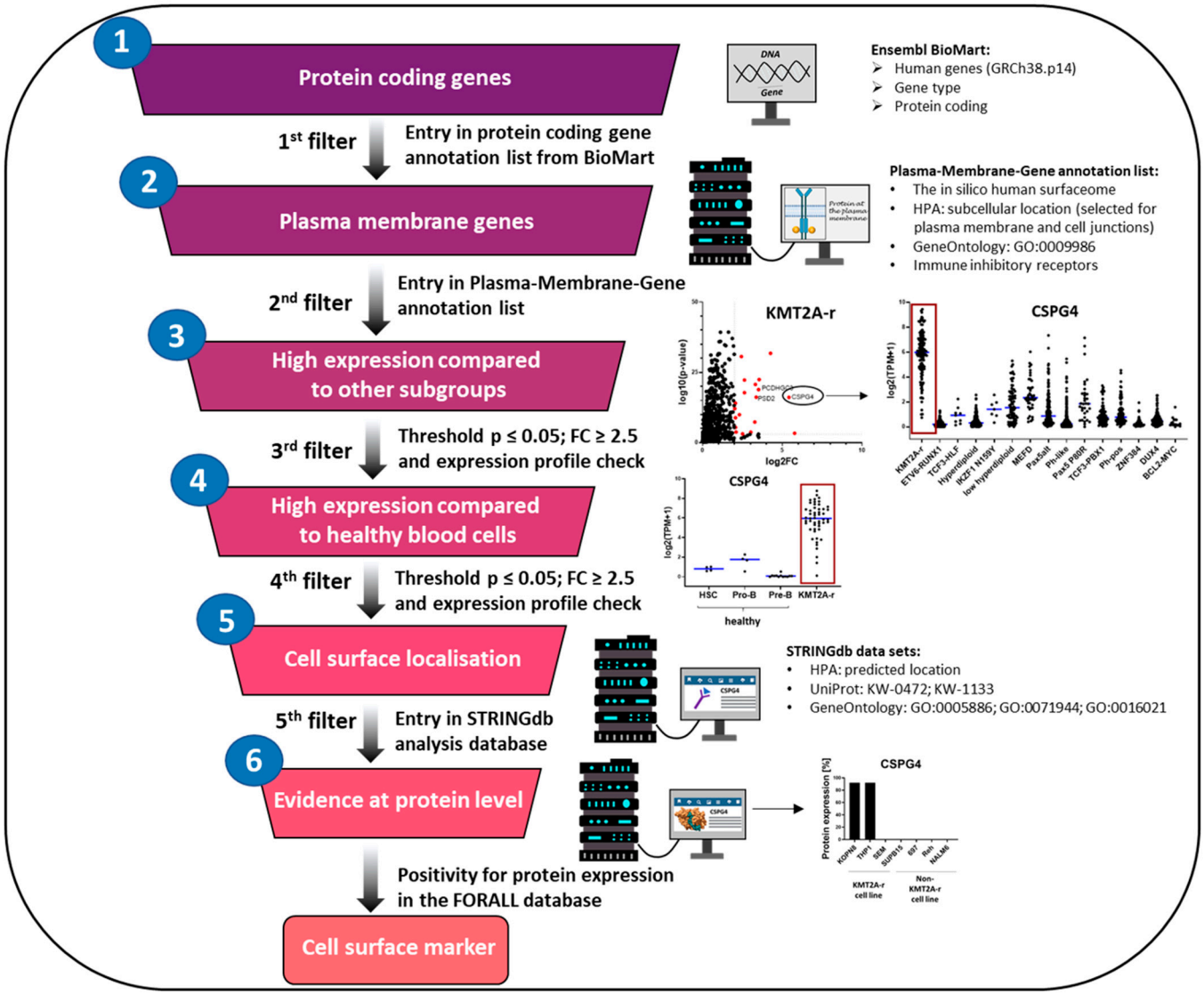

Figure 3. Cell surface marker identification workflow. Workflow depicting approach used for identification of new targets for the treatment of ALL patients divided into different ALL subgroups. Starting from all protein-coding genes from patient material in the publicly available datasets, we first selected for genes located at the plasma membrane. In the next step, we selected these genes for each B-ALL subgroup based on significance, expression level and subgroup-specific expression profile. We then eliminated genes that exhibited high expression in hematopoietic stem cells and progenitor cells. Genes exhibiting a leukemia subgroup-specific profile were thoroughly examined for their localization on the outer cell membrane and thus their accessibility to immunotherapy. Genes that met these criteria were analyzed for their protein expression in corresponding leukemia cell databases. The three most promising candidates for each B-ALL subgroup and T-ALL cells were listed. HPA: human protein atlas; GO: gene ontology; UniProt: universal protein database; FC: fold change; STRINGdb: STRING database; FORALL: functional omics resource of acute lymphoblastic leukemia.

For each target, we then examined the literature evidence regarding its potential role in tumor biology by assigning it to the biologically important PI3K/AKT or RAS/MAPK signaling pathway and investigated whether antibodies had already been generated for each target (Table 2). For 12 of the 46 targets on our list, ADCs have already been tested preclinically or clinically, including ERBB2 and F3. This underscores the validity and potential of the depicted antigens in this review. In contrast, we introduce 34 additional targets that, to our knowledge, have not yet been used for ADC development.

However, there are some potential candidates for which an unconjugated antibody has already been generated. One potential target candidate in this list is the OSM receptor (oncostatin M), for which a fully human monoclonal antibody (vixarelimab) has already been developed. The antibody is already being used in clinical trials for the treatment of pruritus in prurigo nodularis [105]. Preclinical data show that overexpression of OSMR leads to adverse outcomes in a variety of tumor types [106,107]. In summary, these cell surface markers may have the potential to be developed into ADCs to target specific antigens for each ALL subgroup.

Table 1. Information of new putative ADC target structures.

Subtype	Gene 1	Protein ID	Normal Tissue Expression	Pathway	Gene 2	Protein ID	Normal Tissue Expression	Pathway	Gene 3	Protein ID	Normal Tissue Expression	Pathway
KMT2A-r	*CSPG4*	CSPG-4	Intestine	MAPK; AKT	*PSD2*	PSD-2	Brain	n.a.	*PCDHGC3*	PCDH-gamma-C3	Brain	MAPK
ETV6-RUNX1	*DSC3*	DSC-3	Esophagus, Skin	MAPK; AKT	*LRRC4B*	NGL-3	Brain, Cervix, Pituitary gland	MAPK; AKT	*PTPRK*	R-PTP-kappa	Low tissue specificity	n.a.
TCF3-HLF	*CLSTN2*	CLSTN2	Brain, Ovary	n.a.	*LPAR1*	LPA-1	Brain	MAPK; AKT	*F3*	TF/CD142	Low tissue specificity	MAPK; AKT
Hyperdiploid (HeH)	*EFNB1*	Ephrin-B1	Low tissue specificity	MAPK	*IL3RA*	IL-3R-alpha/CD123	Low tissue specificity	MAPK; AKT	*IL13RA1*	IL-13R-alpha/CD213a1	Low tissue specificity	MAPK; AKT
IKZF1-N159Y	*TRPC4*	TrpC4	Endometrium, Seminal vesicle, Smooth muscle	MAPK; AKT	*ATP1A2*	ATP1A2	Brain, Skeletal muscle, Tongue	n.a.	*CACNG4*	TARP gamma-4	Brain	n.a.
Low hyper-diploid (L-HD)	*PDGFRB*	PDGF-R-beta/CD140B	Low tissue specificity	MAPK; AKT	*SLC6A9*	GlyT-1	Brain, Skin	n.a.	*DDR2*	CD167b	Low tissue specificity	MAPK; AKT
MEF2D	*PTPRZ1*	R-PTP-zeta	Brain	AKT	*TNFRSF13B*	CD267	Intestine, Lymphoid tissue, Skeletal muscle	n.a.	*DCHS2*	Cadherin-27	Brain, Intestine	n.a.
PAX5alt	*ERBB2*	HER2/CD340	Low tissue specificity	MAPK; AKT	*VIPR2*	VIP-R-2	Low tissue specificity	MAPK; AKT	*MS4A1*	CD20	Lymphoid tissue	MAPK; AKT
Ph-like	*CRLF2*	CRLF-2	Bone marrow, Gallbladder, Lymphoid tissue	AKT	*TTYH2*	hTTY2	Brain	n.a.	*CHRNA1*	CHRNA-1	Skeletal muscle	n.a.

Table 1. *Cont.*

Subtype	Gene 1	Protein ID	Normal Tissue Expression	Pathway	Gene 2	Protein ID	Normal Tissue Expression	Pathway	Gene 3	Protein ID	Normal Tissue Expression	Pathway
PAX5-P80R	*MEGF10*	MEGF-10	Brain, Retina	n.a.	*TNFRSF13B*	CD267	Intestine, Lymphoid tissue, Skeletal muscle	n.a.	*PDGFRB*	PDGF-R-beta/CD140B	Low tissue specificity	MAPK; AKT
TCF3-PBX1	*LRRC15*	LRRC-15	Lymphoid tissue, Skin	n.a.	*ITGA8*	ITG-alpha-8	Prostate	AKT	*SLAMF1*	IPO-3/CD150	Lymphoid tissue	AKT
Ph-pos	*IL2RA*	CD25	Adipose tissue, Lymphoid tissue, Urinary bladder	MAPK; AKT	*TSPAN15*	Tspan-15	Low tissue specificity	MAPK	*OSMR*	IL31RB	Low tissue specificity	MAPK; AKT
ZNF384	*XKR3*	XKR-3	Testis	n.a.	*SLC2A3*	GLUT-3	Bone marrow	MAPK; AKT	*CD226*	DNAM-1/CD226	Lymphoid tissue, Parathy-roid gland	MAPK; AKT
DUX4	*PTPRM*	R-PTP-mu	Low tissue specificity	MAPK; AKT	*MCAM*	MUC18/CD146	Low tissue specificity	MAPK; AKT	*CLEC12B*	CLEC-12B	Bone marrow, Skin, Testis	MAPK; AKT
BCL2-MYC	*CNR1*	CB-1	Adipose tissue, Pituitary gland	MAPK; AKT	*CD70*	CD70	Lymphoid tissue	MAPK; AKT	*BEST3*	Bestrophin-3	Skeletal muscle, Tongue	MAPK
T-ALL	*CD1B*	CD1b	Lymphoid tissue	n.a.	*NOTCH3*	Notch-3	Low tissue specificity	MAPK; AKT	*CCR9*	CCR-9/CD199	Lymphoid tissue	MAPK; AKT

n.a.: not available; normal tissue expression taken from HPA [97].

Table 2. Antibody–drug conjugates for novel cell surface receptors in ALL.

Subtype	Gene 1	ADC	Reference	Gene 2	ADC	Reference	Gene 3	ADC	Reference
KMT2A-r	*CSPG4*	anti-CSPG4-(PDD); anti-CSPG4(scFv)-SNAP-AURIF	[108,109], experimental	*PSD2*	No		*PCDHGC3*	No	
ETV6-RUNX1	*DSC3*	No		*LRRC4B*	No		*PTPRK*	No	
TCF3-HLF	*CLSTN2*	No		*LPAR1*	No		*F3*	Tisotumab vedotin	[110], approved
Hyperdiploid (HeH)	*EFNB1*	No		*IL3RA*	BAY-943	[111], experimental	*IL13RA1*	No	
IKZF1-N159Y	*TRPC4*	No		*ATP1A2*	No		*CACNG4*	No	
Low hyperdiploid (L-HD)	*PDGFRB*	No		*SLC6A9*	No		*DDR2*	No	
MEF2D	*PTPRZ1*	No		*TNFRSF13B*	anti-TNFRSF13B (Tabalumab)-MC-Vc-PAB-MMAE	CreativeBiolabs, CAT#ADC-W-1907 experimental	*DCHS2*	No	
PAX5alt	*ERBB2*	Trastuzumab deruxtecan; Trastuzumab emtansine	[112,113], approved	*VIPR2*	No		*MS4A1*	MRG001	[114], NCT05155839 (Phase 1)
Ph-like	*CRLF2*	No		*TTYH2*	No		*CHRNA1*	No	
PAX5-P80R	*MEGF10*	No		*TNFRSF13B*	anti-TNFRSF13B (Tabalumab)-MC-Vc-PAB-MMAE	CreativeBiolabs, CAT#ADC-W-1907 experimental	*PDGFRB*	No	
TCF3-PBX1	*LRRC15*	ABBV-085	[115], NCT02565758 (Phase 1)	*ITGA8*	No		*SLAMF1*	No	

Table 2. *Cont.*

Subtype	Gene 1	ADC	Reference	Gene 2	ADC	Reference	Gene 3	ADC	Reference
Ph-pos	*IL2RA*	Camidanlumab tesirine	[116], NCT04052997 (Phase 2)	*TSPAN15*	No		*OSMR*	No	
ZNF384	*XKR3*	No		*SLC2A3*	anti-SLC3A2 ADC (19G4-MMAE);	[117], experimental	*CD226*	No	
DUX4	*PTPRM*	No		*MCAM*	AMT-253	[118], NCT06209580 (Phase 1/2)	*CLEC12B*	No	
BCL2-MYC	*CNR1*	No		*CD70*	PRO1160; Vorsetuzumab mafodotin (SGN-75)	[119], NCT05721222 (Phase 1/2), NCT01015911 (Phase 1)	*BEST3*	No	
T-ALL	*CD1B*	No		*NOTCH3*	PF-06650808	[120], NCT02129205 (Phase 1)	*CCR9*	No	

Trial identifier/NCT number from ClinicalTrials.gov; accessed on 27 September 2025.

5. Introduction of New ADC Target Genes

In this review, we highlight ALL subgroup-specific cell surface markers as potential candidates for immunotherapies. To identify novel ALL subgroup-specific candidates, we explored publicly available expression data and compared the gene expression of the different ALL subgroups (Table S1). The detailed functions of the different genes per subgroup, including ADC availability/development status (see also Table S4) and PI3K/AKT and RAS/MAPK pathway affiliation, are listed in the following section (see Figure 4 for overview).

5.1. KMT2A-r (CSPG4, PSD2, PCDHGC3)

CSPG4: Chondroitin sulfate proteoglycan 4 is a membrane-bound proteoglycan and was originally identified as a tumor antigene on the surface of melanoma cells with restricted distribution in normal tissue [121]. However, it is expressed on malignant cells, including cancer-initiating cells in various types of solid tumors. It was also shown that CSPG4 is aberrantly expressed on the leukemic blasts of a subset of AML (acute myeloid leukemia) and ALL patients, but absent from the surface of healthy hematopoietic cells [122]. In AML, CSPG4 expression has been shown to correlate with KMT2A rearrangement, but was not dependent on specific fusion partner genes of KMT2A [122]. However, CSPG4 expression was shown to correlate with the monocytic morphology status of blasts [122,123]. CSPG4-mediated activation of the FAK (focal adhesion kinase) integrin signaling pathway increases chemotherapy resistance through sustained activation of the AKT signaling pathway [124]. Furthermore, CSPG4 activates RAS/MAPK signaling via RTK-dependent and -independent mechanisms [125,126]. CSPG4 has been shown to play an important role in tumor cell growth, migration and metastasis [124,127]. An ADC targeting CSPG4 has been developed, containing a single-chain antibody fragment conjugated to auristatin F. This ADC was developed for triple-negative breast cancer [109]. Another ADC comprises an anti-CSPG4 antibody linked to pyrridinobenzodiazepine (PDD). Anti-CSPG4-PDD inhibited the growth and colony formation of CSPG4-expressing melanoma cells and induced apoptosis at low concentrations without off-target toxicity [108].

PSD2: Pleckstrin and Sec7 domain-containing 2 is a guanine nucleotide exchange factor for ADP-ribosylation factor 6 (ARF6) that regulates membrane trafficking of small G proteins [128]. The 5′ end of the PSD gene contains five CpG islands, so that its expression can be controlled by epigenetic modification. In addition, PSD mRNA correlates positively with its methylation status and in gastric cancer PSD was shown to be silenced by epigenetic modification. However, it has recently been implicated in the progression of various other cancers [129].

PCDHGC3: Protocadherin gamma-C3 is a putative calcium-dependent cell adhesion protein and member of the PCDH cluster. In cancer, clustered PCDHs are subject to epigenetic silencing through hypermethylation [130]. Hypermethylation and suppressed expression of PCDHGC3 were detected in 17 of 28 (~61%) carcinomas [131]. Interestingly, this epigenetic alteration was detected in primary tumors that developed metastases several years later. Downregulation of PCDHGC3 leads to metastasis-promoting capabilities by increasing cell proliferation, migration and invasion [132]. Knockout of PCDHGC3 leads to an increased migration rate of cerebral microvascular endothelial cells, mediated by RAS/MAPK, β-catenin/Wnt and mTOR signaling pathways [133]. Overexpression of PCDHGC3 in colon cancer cell lines resulted in reduced cell proliferation and colony-forming capacity [131]. Furthermore, PCDHGC3 is highly expressed in glioblastoma and its high expression is associated with longer progression-free survival of patients [134].

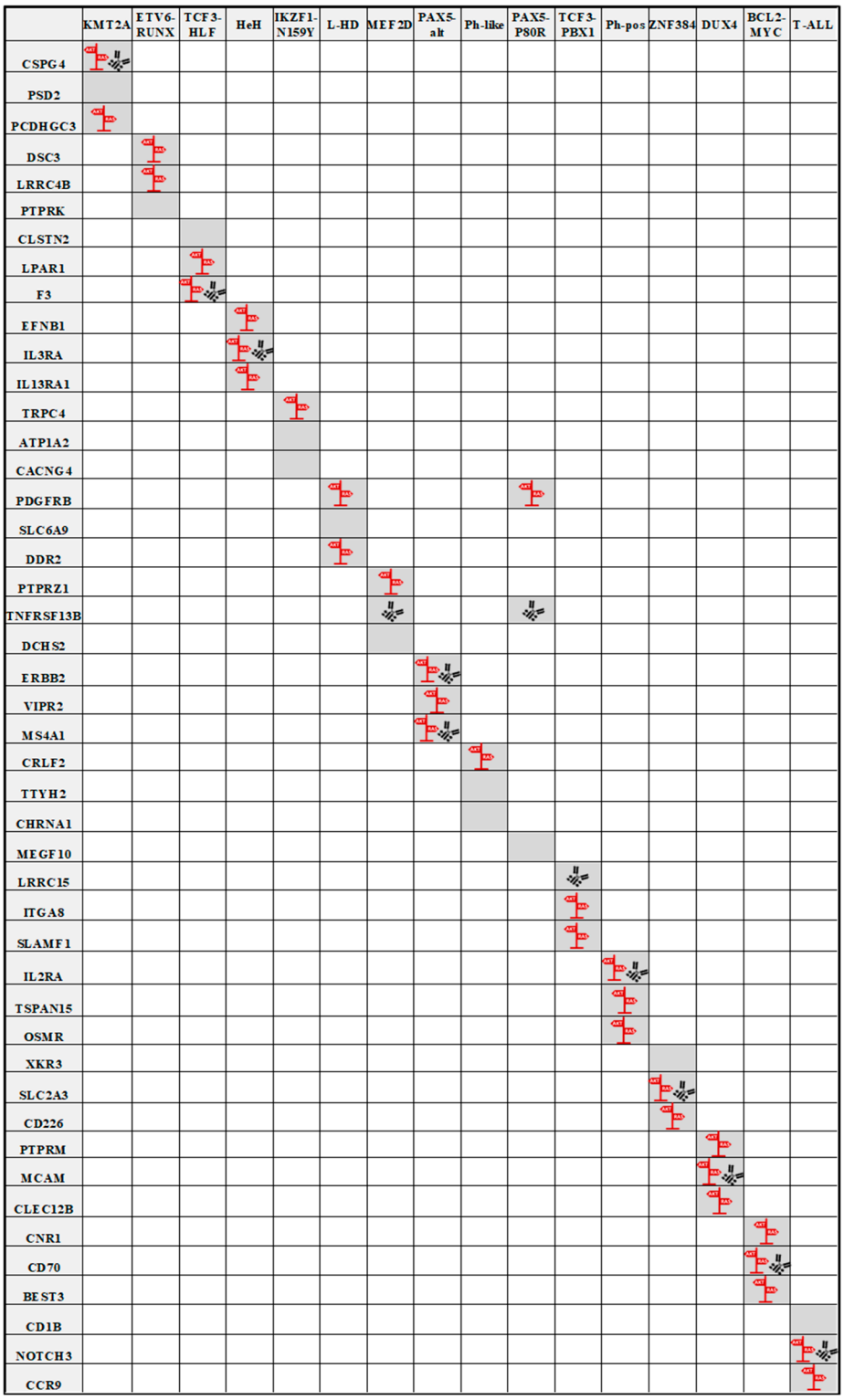

Figure 4. Visual overview of ALL subgroup-specific cell surface markers as potential candidates for immunotherapies. The diagram shows the cell surface markers and the different ALL subgroups. The most relevant markers (according to their expression) in the respective subgroup are highlighted in gray. The antibody symbol (black) indicates all targets for which ADCs are already being used preclinically or clinically. The signpost symbol (red) indicates all targets for which there is evidence of involvement in the AKT or RAS signaling pathway.

5.2. ETV6-RUNX1 (DSC3, LRRC4B, PTPRK)

DSC3: Desmocollin-3 belongs to the cadherin superfamily and is an integral component of the intercellular desmosome junctions. Methylation of DSC3 has been detected in 41% of colorectal cancer samples, which is associated with a poor prognosis. Furthermore, DSC3 has been reported to be hypomethylated in patients with ETV6-RUNX1 (ETS variant transcription factor 6/runt-related transcription factor 1) subtype compared to other B-ALL subtypes [135]. In the hyperdiploid B-ALL subtype (HeH), DSC3 was hypermethylated and downregulated compared to non-leukemic controls [136]. It has also been shown to be regulated by p53 [137]. DSC3, in turn, inhibits EGFR/MAPK and AKT signaling [138,139].

LRRC4B (NGL-3): Leucine-rich repeat protein C4 belongs to the leucine-rich repeat protein family and has been shown to be expressed in brain tissue [140]. It is a synaptic adhesion protein that regulates the formation of excitatory synapses. LRRC4 inhibits glioblastoma cell proliferation, migration, invasion and angiogenesis by downregulating the expression and response of pleiotropic cytokines. LRRC4 negatively regulates the ERK, AKT and STAT3 (signal transducer and activator of transcription 3) signaling pathways [141,142]. Furthermore, LRRC4 induces cell cycle delay in the late G1 phase by affecting the expression of various cell cycle-regulating proteins (e.g., p21 and p27). Overall, LRRC4 plays an important role in maintaining normal functions and suppressing tumorigenesis in the central nervous system [143].

PTPRK (R-PTP-kappa): Receptor-type tyrosine-protein phosphatase kappa belongs to the R2B family (PTPRT, PTPRM, PTPRK and PTPRU). The MAM domain of PTPRK contributes to the homophilic adhesion of PTPRK and PTPRM while preventing the interaction of PTPRK with PTPRM [144,145]. PTPRK is stabilized by transhomophilic interactions at cell–cell contact at the plasma membrane and regulates processes involving cell contact and adhesion, such as growth control, tumor invasion and metastasis. PTPRK acts as a negative regulator of EGFR signaling [146]. PTPRK was found methylated in 27 of 57 (47%) primary ALL samples. Methylation of the PTPRK promoter was associated with increased cell proliferation, decreased apoptosis and reduced overall survival [147]. Methylation was reversible with decitabine and histone deacetylase inhibitors [147]. Reduced PTPRK expression activates AKT, ERK1/2 and the β-catenin/Wnt signaling pathway and influences the stabilization of the E-cadherin complex at the cell membrane to promote cell–cell adhesion [147,148].

5.3. TCF-HLF (CLSTN2, LPAR1, F3)

CLSTN2: Calsyntenin-2 modulates calcium-mediated postsynaptic signaling. CLSTN2 showed strong expression in ALL cells with TCF3-HLF (transcription factor 3/hepatic leukemia factor) translocation compared to other ALL subtypes. After knockout of TCF3-HLF in HAL-01 cells, CLSTN2 was one of the significantly differentially expressed genes [149]. CLSTN2 was found hypermethylated in the hyperdiploid subtype of pediatric B-ALL cases [150].

LPAR1 (LPA-1): Lysophosphatidic acid receptor 1 is a G protein-coupled receptor for lysophosphatidic acid (LPA) binding. LPA and LPA receptors are integral components of signaling pathways involved in cell proliferation, migration, survival, vascular homeostasis, stromal remodeling, lymphocyte trafficking and immune regulation [151,152]. In accordance, LPAR1 has been shown to promote metastasis and tumor motility and abnormal LPAR1 expression has been observed in various cancers [151,153]. In B cells, LPA acts as a growth factor that promotes cell proliferation and inhibits apoptosis by triggering PLC (phospholipase C), RAS/MAPK and PI3K/AKT signaling [152,154]. In contrast, knockdown of LPAR1 reduced the expression levels of phosphorylated ERK, JNK (Jun N-terminal kinase) and AKT [155].

F3 (TF/CD142): F3/Tissue factor is a cell-associated receptor that initiates the blood coagulation cascade by forming a complex with circulating factor VII or VIIa. The [F3:VIIa] complex activates factors IX or X through specific, limited proteolysis. At the same time, F3 is also known as a mediator of intracellular signaling events that, as a cytokine-like receptor, can alter gene expression patterns and cell behavior. It regulates coagulation-independent processes such as tumor growth, angiogenesis and inflammatory regulation [156]. F3 upregulation is frequently observed on cancer cells as well as on tumor-associated endothelial cells or inflammatory cells [157,158]. In different cell types F3 can stimulate the transcription of VEGF (vascular endothelial growth factor A). Conversely, VEGF, a key factor in angiogenesis, can induce F3 expression in endothelial cells and further promote angiogenesis [159]. F3 regulates the RAS/MAPK and PI3K/AKT signaling pathways, as F3 knockdown reduced protein levels of phosphorylated ERK and AKT [160]. Tisotumab vedotin (Tivdak) is an approved antibody–drug conjugate for the treatment of adult patients with recurrent or metastatic cervical cancer whose disease progression occurs during or after chemotherapy. It consists of a fully human monoclonal antibody specific for F3 that is conjugated to monomethyl auristatin E (MMAE) [110]. Recent studies suggest that F3 is a useful surface target for the treatment of patients with triple-negative breast cancer [161].

5.4. Hyperdiploid (EFNB1, IL3RA, IL13RA)

EFNB1 (Ephrin-B1): EFNB1 represents a cell-surface transmembrane ligand for Eph receptors. Eph receptors constitute the largest known subfamily of receptor protein tyrosine kinases and are critical for migration and adhesion during neuronal, vascular and epithelial development [162]. Since both ephrin ligands and Eph receptors are membrane-bound proteins, binding and activation of intracellular Eph/ephrin signaling pathways can only occur via direct cell–cell interaction. EFNB1 has been reported to contribute to tumor progression in various cancers and high EFNB1 expression is significantly associated with a poor prognosis in human DLBCL (diffuse large B-cell lymphoma) and gliomas [163,164]. EFNB1 levels were significantly associated with the cell of origin in B cell neoplasms [163]. EFNB1 can activate mTOR, p38 MAPK and ERK signaling pathways in medulloblastoma [165].

IL3RA (CD123): The interleukin-3 receptor subunit alpha is a cytokine receptor that is overexpressed in various hematological malignancies, including AML and ALL. In detail, IL3RA is overexpressed in approximately 97% of Ph-positive and 86% of Ph-negative B-ALL cases. Within the Ph-negative cohort, IL3RA was frequently expressed in cases with Ph-like signature [166]. Furthermore, IL3RA expression in B-ALL correlated with poor overall survival and is associated with a high risk of relapse [167,168]. The high expression of IL3RA on leukemia cells and its low expression on normal hematopoietic stem cells make IL3RA an attractive target for therapy [169]. After IL-3 binding to IL3RA, IL-3R heterodimerization promotes the stable formation of the IL-3/IL-3R complex, leading to the activation of JAK (janus kinase)/STAT, RAS/MAPK and PI3K/AKT signaling [170–172]. IMGN632 is an IL3RA-targeting antibody–drug conjugate consisting of a humanized anti-IL3RA antibody coupled to a DNA-monoalkylating cytotoxic payload with limited toxicity in normal myeloid progenitor cells [173]. In addition, the ADC BAY-943 consists of a humanized anti-IL3RA antibody conjugated to a kinesin spindle protein inhibitor and demonstrates efficacy in preclinical models of hematological malignancies (e.g., AML) [111].

IL13RA1 (CD213a1): The interleukin-13 receptor subunit alpha-1 is a glycosylated protein that binds IL-13 with low affinity. However, in combination with IL4RA, it forms a functional IL-13 receptor for high-affinity binding of IL-13. On human B cells, IL13RA1 expression is modulated by CD40 ligands or surface immunoglobulins [174]. IL-13RA1 contains a proline-rich box-1 region that binds JAK1, JAK3 and TYK2 (tyrosine kinase 2) and in response to IL-13, receptor heterodimers induce phosphorylation of Janus tyro-

sine kinases [175,176]. IL-4, another cytokine that binds to the IL-13 receptor, has been shown to induce strong tyrosine phosphorylation of IRS-1/2 and increase RAS/MAPK and PI3K/AKT activity [177,178].

5.5. IKZF1-N159Y (TRPC4, ATP1A2, CACNG4)

TRPC4: The short transient receptor potential channel 4 forms a receptor-activated, non-selective, calcium-permeant cation channel and thus functions as a cell–cell contact-dependent endothelial calcium entry channel. The TRPC subfamily comprises seven members, TRPC1 to TRPC7. Heteromultimers can be formed between TRPC1, 4 and 5 on the one hand, and between TRPC3, 6 and 7 on the other [179]. After stimulation of G protein-coupled receptors or receptor tyrosine kinases, the PLC signaling pathway regulates the formation of TRPC4 and TRPC5 cation channels [180]. Knockdown of TRPC4 suppressed the activation of ERK and AKT signaling in endothelial cells [181].

ATP1A2: The sodium/potassium-transporting ATPase subunit alpha-2 belongs to the family of P-type cation-transporting ATPases and the subfamily of Na^+/K^+ ATPases. ATP1A2 is an integral membrane protein that catalyzes the hydrolysis of ATP and simultaneously facilitates the exchange of sodium and potassium ions across the plasma membrane. This creates the electrochemical gradient of sodium and potassium, which provides the energy for the active transport of various nutrients. Together with the small glycoprotein subunit beta, the large catalytic alpha-ATP1A2 subunit forms the enzyme. Mutations in this gene can lead to familial basilar or hemiplegic migraine, as well as to alternating hemiplegia of childhood [182].

CACNG4 (TARP gamma-4): The voltage-dependent calcium channel gamma-4 subunit regulates the activity of L-type calcium channels that contain CACNA1C as a pore-forming subunit. Downregulation of CACNG4 modulates the channels to maintain their active/open state, leading to higher intracellular calcium levels. CACNG4 thus acts by closing the channel pore and inhibiting calcium influx. Subsequently, CACNG4 alters calcium signaling and influences AKT signaling. CACNG4 expression is elevated in patients with breast cancer associated with poor prognosis [183]. CACNG4 was one of ten genes significantly overexpressed in erlotinib-resistant glioblastoma cells [184].

5.6. Low Hyperdiploid (PDGFRB, SLC6A9, DDR2)

PDGFRB (CD140B): Platelet-derived growth factor receptor beta is a tyrosine-protein kinase that acts as a cell-surface receptor for homodimeric PDGFB and PDGFD, as well as for heterodimers of PDGFA and PDGFB. PDGFRB possesses five extracellular immunoglobulin-like domains, a single membrane-spanning helix domain, an intracellular juxtamembrane domain, a tyrosine kinase domain and a carboxyl tail. Upon binding to the PDGF ligand, dimerization of the receptor releases inhibitory conformations through autophosphorylation of regulatory tyrosine residues. Activated PDGFRB regulates the PI3K/AKT and RAS/MAPK signaling pathways, including a negative feedback loop to PDGFRB, particularly in mTOR-activated cells [185,186]. PDGFRB plays an essential role in the regulation of embryonic development, cell proliferation, cell survival, cell differentiation and migration. PDGFRB gene fusions (e.g., with EBF1; early B cell factor 1) are frequently found in B-ALL cases with Ph-like subtype. PDGFRB fusion partners often contain dimerization domains to enhance the kinase activity of PDGFRB [187].

SLC6A9 (GlyT-1): The sodium- and chloride-dependent glycine transporter 1 inhibits glycine signaling by rapidly removing glycine from the synaptic cleft, as glycine acts as an inhibitory neurotransmitter in the central nervous system [188]. The SLC6A transporter has been reported to associate with the NMDA receptor [189]. To date, no specific role

for SLC6A9 in hematological malignancies has been described. Therefore, further efforts should be made to further characterize this protein in the disease of ALL.

DDR2 (CD167b): Discoidin domain-containing receptors, including DDR1 and DDR2, form a unique class of receptor tyrosine kinases. They are activated by fibrillar collagens at the cell–matrix interface and are involved in the regulation of tissue remodeling and bone development [190,191]. Furthermore, DDR2 regulates extracellular matrix remodeling through upregulation of collagenases, cell differentiation, migration and proliferation. Inhibition of DDR2 (e.g., by dasatinib) has been shown to enhance tumor responses to anti-PD-1 immunotherapy [192]. Binding of collagen to DDR2 activates RAS/MAPK and PI3K/AKT signaling pathways as well as the transcription factor RUNX2 [193,194]. Furthermore, knockdown of AKT3 activates DDR kinases in bone-seeking breast cancer cells [195].

5.7. MEF2D (PTPRZ1, TNFRSF13B, DCHS2)

PTPRZ1 (R-PTP-zeta): Receptor-type tyrosine-protein phosphatase zeta belongs to the R5 receptor tyrosine phosphatase subfamily and negatively regulates the proliferation of oligodendrocyte precursor cells in the embryonic spinal cord. It is therefore required for the differentiation of precursor cells into mature, fully myelinating oligodendrocytes and PTPRZ1 expression is associated with cancer stem cell development in glioblastoma. In consequence, knockdown of PTPRZ altered the expression levels of the transcription factors SOX2 (SRY-box transcription factor 2) and POU3F2 (POU class 3 homeobox 2), which are responsible for stem cell development [196]. Previous studies showed that several members of the protein tyrosine phosphatase family, including PTPRZ1, were methylated and silenced in CLL (chronic lymphocytic leukemia) [197,198]. PTPRZ1 has been shown to negatively regulate AKT kinase activity in ovarian cells [199].

TNFRSF13B (TACI/CD267): TNFRSF13B encodes the tumor necrosis factor superfamily member 13B, a transmembrane receptor of lymphocytes that binds members of the tumor necrosis ligand family (APRIL/TNFSF13 and BAFF) and heparan sulfate chains [200]. Binding of BAFF and APRIL to the receptor activates TNFR-associated factors (TRAF 2, 5 and 6), which in turn activate NF-kB (nuclear factor kappa-light-chain-enhancer of activated B-cells), c-Jun and AP-1 (activator protein 1) [201,202]. On B cells, APRIL can bind to the receptors TNFRSF17 (BCMA) and TNFRSF13B, leading to the survival of plasma cells in the bone marrow. Moreover, CLL cells with high TNFRSF13B expression showed improved survival when cultured with BAFF and/or APRIL [203]. APRIL signaling via TNFRSF13B has also been shown to mediate immunosuppression by regulatory T cells in multiple myeloma [204]. Anti-TNFRSF13B (tabalumab)-MC-Vc-PAB-MMAE is a monoclonal anti-TNFRSF13B antibody conjugated to MMAE via an MC-Vc linker [205].

DCHS2 (CDH27/PCDH23): Protein dachsous homolog 2 is a large protein encoded in humans by the DCHS2 gene. It belongs to the calcium-dependent cell adhesion proteins and contains multiple cadherin domains. FAT4 (FAT atypical cadherin 4) in the stroma binds to DCHS1/2 to inhibit the self-renewal of nephron progenitor cells. DCHS2 and its paralog DCHS1 function partially redundantly to regulate the number of nephron progenitor cells [206]. Nothing is known about its role in leukemia, so far.

5.8. PAX5alt (ERBB2, VIPR2, MS4A1)

ERBB2 (HER2/CD340): The ErbB/HER family of receptor tyrosine kinases consists of four cell surface glycoproteins: ERBB1 (EGFR), ERBB2, ERBB3 and ERBB4 [207]. Ligands for HER2 have not yet been identified. ERBB2 is part of several cell surface receptor complexes and requires a coreceptor for ligand binding. HER2 can heterodimerize with any of the other three family members [208]. Dimerization leads to the autophosphorylation of tyrosine residues within the cytoplasmic domain of the receptors and initiates various

signaling pathways, such as the RAS/MAPK and PI3K/AKT pathway. Signaling via the ERBB receptor family promotes cell proliferation and counteracts apoptosis. ERBB2 is expressed in approximately 30% of B-ALL cases and 56% of Ph (philadelphia)-positive ALL cases show elevated HER2 activity [209]. Furthermore, HER2 is one of the most highly phosphorylated tyrosine kinase receptors in AKT-knockdown cells [27]. Accordingly, ERBB2 overexpression leads to the activation of multiple signaling pathways, such as the PI3K/AKT and RAS/MAPK pathways [210,211]. Two HER2-targeting ADCs, trastuzumab emtansine (Kadcyla) and trastuzumab deruxtecan (Enhertu), are approved as second-line treatment after trastuzumab taxane-based therapy in patients with HER2-positive breast cancer [112,113].

VIPR2: Vasoactive intestinal peptide (VIP) receptor 2 is a G protein-coupled receptor linked to adenylyl cyclase via the Gαs protein. VIP stimulation leads to cAMP (cyclic adenosine monophosphate) production, activation of protein kinase A and ERK signaling [212]. VIPR2 also interacts with the Gαi and Gαq proteins to regulate PI3K/AKT and PKC signaling and VIPR2 signaling via the RAS/MAPK and PI3K/AKT pathways, regulates cyclin D1 levels to control cell proliferation and migration [213,214].

MS4A1 (CD20): The B lymphocyte antigen MS4A1 is a B lymphocyte-specific membrane protein involved in the regulation of cellular calcium influx, which is necessary for the development, differentiation and activation of B lymphocytes. It represents a storage-gated calcium channel component that promotes calcium influx after activation by the B cell receptor. MS4A1 is induced by CXCR4/SDF1 (C-X-C chemokine receptor type 4/stromal cell-derived factor 1) chemokine signaling. It consists of four hydrophobic transmembrane domains [215]. MS4A1 is expressed by the majority of B cells, starting with late pre-B lymphocytes, and is lost in terminally differentiated plasmablasts and plasma cells [216]. Thus, anti-CD20 monoclonal antibodies have revolutionized the treatment of lymphomas [217]. MS4A1 upregulation has been frequently observed in high-risk patients, patients with high minimal residual disease (MRD) at the end of the induction phase and in relapsed patients [218]. Immunotherapy with rituximab inhibits the constitutively activated survival signaling pathways ERK1/2, p38 MAPK, NF-kappaB and AKT [219]. MRG001 is an anti-MS4A1 antibody–drug conjugate for patients with r/r advanced non-Hodgkin lymphoma. It consists of a chimeric monoclonal anti-MS4A1 antibody conjugated to monomethyl auristatin E (MMAE) via a valine-citrulline linker. In preclinical studies, the ADC showed significant inhibition of tumor growth in rituximab-resistant non-Hodgkin lymphoma models [114].

5.9. Ph-like (CRLF2, TTYH2, CHRNA1)

CRLF2: Cytokine receptor-like factor 2 belongs to the type I cytokine receptor family and forms a functional complex with TSLP (thymic stromal lymphopoietin) and IL7R (interleukin 7 receptor), which can stimulate cell proliferation by activating the JAK/STAT signaling pathway. Thus, CRLF2 (cytokine receptor-like factor 2) is involved in the development of the hematopoietic system. In the Ph-like B-ALL subtype, CRLF2 was overexpressed in 75% of cases [220]. Patients with high-risk ALL with CRLF2 overexpression show high relapse rates and poor overall survival. Furthermore, chromosomal breaks and fusion of CRLF2 with IGH@ (immunoglobulin heavy locus) or the G protein-coupled purinergic receptor gene P2Y8 (P2Y receptor family member 8) have been demonstrated [221]. The fusion to both genes place CRLF2 under alternative transcriptional control, leading to CRLF2 overexpression [221]. Furthermore, CRLF2 alterations are strongly associated with JAK mutations [222]. In addition, increased activation of the AKT/mTOR/S6 axis can be observed in a large number of primary CRLF2-altered ALL samples [223].

TTYH2 (hTTY2): Tweety family member 2 is a cell surface protein with five transmembrane regions and represents a Ca^{2+}-activated chloride channel. TTYH2 gene expression is significantly upregulated in colon carcinomas and renal cell carcinomas [224]. The TTYH2 gene is thought to regulate both the proliferative and metastatic potential of colon carcinomas [225]. Furthermore, TTYH2 is among the genes whose gene expression profile was elevated in high-risk ALL cases and associated with poor outcome [226].

CHRNA1: Upon binding to acetylcholine, the acetylcholine receptor subunit alpha undergoes a comprehensive conformational change affecting all subunits and leading to the opening of an ion-conducting channel across the plasma membrane. In melanoma, CHRNA1 is highly expressed in metastatic samples compared to their primary tumor samples. CHRNA1 is strongly associated with CHRNB1 and CHRNG and together these genes are negatively involved in the survival of melanoma patients [227].

5.10. PAX5-P80R (MEGF10, PDGFRB, TNFRSF13B)

MEGF10: Multiple epidermal growth factor-like domain protein 10 is a membrane receptor involved in the phagocytosis of apoptotic cells by macrophages and astrocytes. MEGF10 recognizes C1q, an "eat-me" signal, on the surface of apoptotic cells [228]. MEGF10 interacts with ABCA1 (ATP-binding cassette transporter A1) in the process of phagocytosis. Moreover, MEGF10 belongs to a group of hypermethylated genes that were epigenetically repressed and showed significantly reduced expression in neuroblastoma cells. Low MEGF10 expression also correlates with reduced relapse-free survival. Knockdown of MEGF10 expression in neuroblastoma cells led to increased cell growth [229].

Information on PDGFRB and TNFRSF13B can be found in Section 5.6 or Section 5.7, respectively.

5.11. TCF-PBX1 (LRRC15, ITGA8, SLAMF1)

LRRC15: Leucine-rich repeat-containing protein 15 is involved in cell–cell and cell–matrix interactions and adheres to extracellular matrix components such as fibronectin and collagen [230]. LRRC15 exhibits high expression levels in solid tumors compared to normal tissue. High LRRC15 expression correlates with metastasis, poor response to chemotherapy and shortened overall survival in patients with osteosarcoma [231]. Furthermore, LRRC15 has been reported to be regulated by TGFB (transforming growth factor beta) [232]. ABBV-085 is a humanized anti-LRRC15 IgG1 antibody conjugated to the antimitotic MMAE payload via a protease-cleavable valine-citrulline linker [233]. In preclinical experiments it demonstrated efficacy in sarcomas and other advanced solid tumors [115].

ITGA8: The integrin family consists of cell adhesion receptors that are widely expressed in various cancer types. Integrins mediate tumor cell proliferation, migration and invasion [234]. Integrin alpha-8 interacts with FAK to activate the downstream PI3K/AKT/mTOR signaling pathway [235]. Recently, ITGA8 was observed to be highly expressed in multiple myeloma patients with early relapse [236].

SLAMF1 (IPO-3/CD150): The signaling lymphocytic activation molecule 1 belongs to the signaling lymphocytic activation molecule family. Like other receptors in this family, SLAMF1 is expressed in various hematopoietic cells and plays a role in the regulation and differentiation of immune cells. SLAM receptors are self-ligand receptors that are activated by homo- or heterotypic cell–cell interactions. SLAMF1 signaling leads to the activation of RAS/MAPK and PI3K/AKT signaling, thus influencing cytotoxicity, humoral immune responses, lymphocyte development, cell survival, cell growth and cell adhesion [237–239]. SLAMF receptors negatively regulate B cell receptor (BCR) signaling in CLL. Consequently, SLAMF1 was shown to be downregulated on CLL cells compared to their healthy counterparts [240].

5.12. Ph-pos (IL2RA, TSPAN15, OSMR)

IL2RA (CD25): The interleukin-2 receptor alpha subunit is one of three chains of the IL2 receptor and is involved in the regulation of immune tolerance by controlling the activity of regulatory T cells (TREGs). Accordingly, it is primarily expressed on T and NK cells and only the binding of IL-2 to the dimeric and trimeric IL-2Rs leads to downstream signaling via three main pathways: PI3K/AKT, JAK/STAT5 and RAS/MAPK [241,242]. However, IL2RA has also been found to be overexpressed in AML cells and has been associated with chemotherapy resistance and poor outcome [243]. ALL cells, particularly Ph-positive ALL cells, have been shown to aberrantly express IL2RA. While normal B cells have low levels of IL2RA, primary ALL cells and ALL cell lines highly overexpress IL2RA. High IL2RA expression levels were associated with poor clinical outcomes for patients with B-ALL, in contrast to favorable outcomes for lymphoma patients [244]. On B cells, IL2RA formed an inhibitory complex involving PKCδ as well as SHIP1 and SHP1 phosphatases for feedback control of oncogenic BCR signaling or its oncogenic mimics [245]. Silencing of IL2RA in primary ALL cells induces cell cycle arrest and apoptosis [246]. Furthermore, in Ph-positive ALL cells, aberrant DNA methylation patterns and gene expression profiles were shown to be centered around a cytokine network defined by high hypomethylation and strong overexpression of IL2RA [244]. Camidanlumab tesirine (ADCT-301) is an ADC consisting of a human anti-CD25 antibody conjugated to SG3199 via a cathepsin-cleavable valine-alanine linker and is used to treat AML and ALL cells [116].

TSPAN15: The tetraspanin family comprises 33 family members that interact with integrins, adhesion molecules and T cell receptors, forming dimers or heterodimers. Tetraspanin-15 regulates the maturation and transport of the transmembrane metalloprotease ADAM10 (ADAM metallopeptidase domain 10). Tspan15 is a marker for poor prognosis and is upregulated in certain cancers [247,248]. In a mouse model TSPAN15 promotes cancer progression [248]. Overexpression of TSPAN15 activates the PI3K/AKT and EGFR/MAPK signaling pathways, promoting tumor cell proliferation in hepatocellular carcinoma [247,249].

OSMR (IL31RB): The oncostatin M receptor belongs to the family of type I cytokine receptors and forms the IL31 receptor with IL31RA. Upon binding of IL31, the IL31 receptor complex activates STAT proteins. Oncostatin M (OSM) is an inflammatory cytokine of the interleukin-6 family produced by osteoblasts, bone marrow macrophages and neutrophils. OSM acts via a heterodimeric receptor, consisting of CD130 and the OSM receptor and induces the proliferation of hematopoietic stem and progenitor cells [250]. Thus, OSMR signaling can regulate tumor growth and metastasis and provide an advantage to cancer cells [107]. OSMR, as a member of the cytokine receptor family, is capable of activating signaling pathways such as JAK/STAT, RAS/MAPK and PI3K/AKT upon OSM ligand binding [106,251,252]. OSMR has been shown to be overexpressed in various cancer types and is associated with poor outcomes [106,107].

5.13. ZNF384 (XKR3, SLC2A3, CD226)

XKR3: XK-related protein 3 belongs to the XK family. XKR3 is a membrane transporter in the XK/Kell complex of the Kell blood group system. A NUP214-XKR3 fusion has been detected in a case of T-ALL [253]. But overall, not much is known about the functions of XKR33 in cancer.

SLC2A3 (GLUT3): Solute carrier family 2 member 3 represents a glucose transporter that mediates the uptake of various monosaccharides across the cell membrane. SLC2A3 is highly expressed in colorectal cancer (CRC) and negatively associated with disease progression in CRC patients. Mechanistically, low glucose status led to dramatic upregulation of SLC2A3 via the AMPK signaling pathway. Under glucose-limiting conditions, SLC2A3

accelerated CRC cell growth by upregulating glucose supply and promoting nucleotide synthesis. SLC2A3 has the highest affinity for glucose among all GLUT (glucose transporter) transporters and demonstrated a greater impact on cell growth than GLUT1 under glucose-limiting stress [254]. Following SLC2A3 silencing, the RAS/MAPK and PI3K/AKT signaling pathways were inactivated [255]. 19G4-MMAE is a SLC3A2-targeting antibody–drug conjugate that exhibits potent antitumor activity in head and neck squamous cell carcinoma with a favorable safety profile [117].

CD226 (DNAM-1): CD226 belongs to the immunoglobulin superfamily and functions as an adhesion molecule. It is involved in intercellular adhesion, lymphocyte signaling, cytotoxicity and lymphokine secretion mediated by cytotoxic T lymphocytes and NK cells. Upon binding to the NECTIN2 ligand, CD226 stimulates the activation and proliferation of CD8 T cells [256]. Another ligand of human CD226 is CD155, which is expressed at high levels in solid cancers and hematological malignancies [257]. CD226 influences intracellular metabolism and enhances the PI3K/AKT and RAS/MAPK signaling pathways [258].

5.14. DUX4 (PTPRM, MCAM, CLEC12B)

PTPRM (R-PTP-mu): Receptor-type tyrosine-protein phosphatase mu belongs to the R2B family (PTPRT, PTPRM, PTPRK and PTPRU). PTPRM is involved in cell–cell adhesion through homophilic interactions. PTPRM was found methylated in 36 of 57 (64%) primary ALL samples [147]. PTPRM expression positively correlates with the survival of breast cancer patients with BRCA mutation [144]. Knockdown of PTPRM in breast cancer cells also led to increased cell migration and invasion through regulation of the RAS/MAPK signaling pathway [145,259]. Furthermore, overexpression of PTPRM in cervical cancer has been shown to affect the SRC-AKT axis [144].

MCAM (MUC18/CD146): The melanoma cell adhesion molecule is a cell surface glycoprotein that plays a role in cell adhesion and the cohesion of the endothelial monolayer at intercellular junctions in vascular tissue. MCAM enables melanoma cells to interact with cellular elements of the vasculature, thus promoting hematogenous tumor spread. However, it has been found to be highly expressed in many tumors at every stage of cancer development and progression, particularly during metastasis. It serves as a receptor for various ligands, including growth factors and extracellular matrices such as galectins and laminins. As a coreceptor of VEGFR2 and PDGFRB, CD146 activates PI3K/AKT, RAS/MAPK and PLC to enhance pro-angiogenesis signaling, which promotes cell growth, proliferation, differentiation and survival [260,261]. The ADC AMT-253 consists of a humanized IgG1 antibody directed against MCAM conjugated to exatecan, a topoisomerase I inhibitor. AMT-253 was developed for the treatment of MCAM-positive solid tumors and was evaluated in a Phase I clinical trial [118].

CLEC12B: CLEC12B represents the C-Type lectin domain family 12 member B. It is an inhibitory cell surface receptor that protects target cells against lysis by natural killer cells. Thus, high expression of CLEC12B represents an important selective advantage for tumor cells. The extracellular domain of CLEC12B shows homology to the activating natural killer cell receptor NKG2D (natural killer group 2D). However, CLEC12B contains an immunoreceptor tyrosine-based inhibitory motif (ITIM) in its intracellular domain and can counteract NKG2D-mediated signals [262]. CLEC12B negatively regulates PI3K/AKT and RAS/MAPK signaling by recruiting SHP1/2 phosphatases to its ITIM.

5.15. BCL2-MYC (CNR1, CD70, BEST3)

CNR1 (CB-1): Cannabinoid receptor 1 belongs to the group of G protein-coupled receptors and is part of the endocannabinoid system. Cannabinoid receptors 1 and 2 are overexpressed in various malignancies and cannabinoids have an important influence on the vi-

ability and growth of tumor cells. In particular, overexpression of CNR1 and 2 (cannabinoid receptor 1/2) has been observed in CLL compared to healthy B cells [263]. CNR1 promotes embryonic development via PI3K/AKT and RAS/MAPK signaling pathways [264].

CD70: CD70 is a type 2 transmembrane glycoprotein and belongs to the tumor necrosis factor (TNF) ligand family. CD70 is expressed on activated antigen-presenting cells, including B cells, and binds to CD27 on T lymphocytes to induce T cell activation and proliferation. Binding of CD27 to CD70 activates PI3K/AKT and RAS/MAPK signaling pathways in lymphocytes [265]. CD70 has been shown to be a promising target in AML due to its expression on AML blasts and leukemia stem cells and its lack of expression on normal hematopoietic stem cells [266]. Increased CD70 expression was observed in relapsed acute myeloid leukemia cells after treatment with hypomethylating agents [267]. Furthermore, high CD70 surface expression has been observed on ALL cells compared to healthy controls [268]. PRO1160 is a human monoclonal antibody specific for CD70 and conjugated to exatecan via a protease-cleavable linker. This ADC is highly effective in cell-based xenograft models of renal cell carcinoma, non-Hodgkin lymphoma and nasopharyngeal carcinoma [119].

BEST3 (Bestrophin-3): Bestrophin-3 belongs to the bestrophin family and forms calcium-sensitive chloride channels. Bestrophins are transmembrane proteins and have a homology region with a high content of aromatic residues. BEST3 is predominantly expressed in the brain and gastrointestinal tract [97,269]. ERK-dependent upregulation of bestrophin-3 in renal epithelial cells has been shown to be part of an adaptive response to counteract endoplasmic reticulum stress-induced cell death [270].

5.16. T-ALL (CD1B, NOTCH3, CCR9)

CD1B: The T cell surface glycoprotein CD1B is an antigen-presenting protein that binds self and exogenous lipid and glycolipid antigens and presents them to T cell receptors on natural killer T cells [271]. Accordingly, CD1 is expressed on the surface of numerous different human antigen-presenting cells. Human CD1 molecules are divided into group 1 (CD1A and CD1C) and group 2 (CD1D). CD1B belongs to group 1 of the CD1 family of transmembrane glycoproteins. CD1B-autoreactive T cells recognize phospholipid antigens and contribute to antitumor immunity against CD1B-positive T cell lymphoma [272].

NOTCH3: The neurogenic locus notch homolog protein 3 acts as a receptor for the membrane-bound ligands Jagged1, Jagged2 and Delta1 on juxtaposing cells to regulate cell fate determination following conformational changes. Upon ligand binding, protease-mediated cleavage of the NOTCH receptor by the gamma-secretase complex and ADAM metalloproteases leads to release of the intracellular Notch domain (NICD) that translocates to the nucleus. NICD forms a transcriptional activator complex with RBPJ/RBPSUH and activates genes for differentiation, proliferation and apoptosis [273,274]. Furthermore, NOTCH3 has been shown to contribute to the growth of T-cell leukemia by regulating the unfolded protein response [275]. Activating NOTCH3 mutations were recently identified in T-ALL and are detectable even in the absence of activated NOTCH1 [276]. NOTCH3 activates downstream RAS/MAPK and AKT/mTOR signaling [277,278]. PF-06650808 is an anti-NOTCH3 antibody–drug conjugate that delivers an auristatin-based cytotoxic payload to target cells. In a phase I trial for treatment of patients with breast cancer and other advanced solid tumors, PF-06650808 demonstrated a manageable safety profile and antitumor activity [120].

CCR9 (CD199): The C-C chemokine receptor type 9 is a 7-pass transmembrane G-coupled receptor for the ligand CCL25 [279]. CCR9 is expressed in more than 70% of T-ALL cases, including more than 85% of cases of r/r disease and only on a small proportion (<5%) of normal T cells [280]. In cancer cells, CCR9/CCL25 upregulates AKT and ERK1/2

levels to exert antiapoptotic effects and chemoresistance [281–283]. CCL25/CCR9, as a member of CC chemokines and their receptors, is known to be involved in chemotactic cells, lymphocyte development, survival, proliferation and migration [284].

6. Discussion

The biological importance of an antibody target is underscored by its overexpression in cancer cells, its restricted expression in healthy and normal tissues and its key role in disease development. In particular, increased expression of the target on various other blood cell types can limit ADC accumulation at target tumor sites [285]. The results in this review are intended to guide the development of novel ADCs against surface targets, which, based on these data, appear to be of utmost importance for each individual ALL subgroup.

Of the novel targets described here, 12 ADC targets have already been evaluated in clinical trials (e.g., ERBB2 and F3) or are in preclinical testing, including NOTCH3 and IL3RA antibodies, demonstrating the validity of this approach. Nevertheless, further investigations are necessary to evaluate the internalization potential of these novel targets. For this purpose, a high-affinity monoclonal antibody must be developed, if none already exists. Furthermore, the choice of the highly potent payload (e.g., microtubule inhibitors, DNA-damaging agents or topoisomerase inhibitors), the drug-to-antibody ratio (DAR), and the design of the linker for effective drug delivery (cleavable or non-cleavable) must be carefully considered. In particular, the intracellular transport of an ADC plays an important role in drug discovery. Acid-soluble linkers are released in the early endosomes, while proteolytic linkers rely on the presence of proteases (e.g., cathepsin B) in the late endosomes or lysosomes [286].

However, resistance to various chemotherapeutic agents has been shown to be mediated by mutation or altered expression of the drug target topoisomerase, overexpression of drug transporter (ATP-binding cassette transporter such as MDR1 or MRP1), altered apoptotic mechanisms or signaling pathways as well as defects in ADC trafficking pathways (e.g., clathrin- or caveolin-dependent endocytosis) [287]. In particular, ATP-binding cassette (ABC) transporters can export the common payloads used in ADCs (MMAE, MMAF or calicheamicin) from the cell and mediate resistance.

ALL subgroups such as KMT2A-r, TCF3-HLF and hypodiploid karyotypes define rare subgroups with highly drug-resistant disease [288]. Heterogeneity within the tumor and the adaptive mechanisms that help cells survive under changing physiological conditions complicate the effective treatment of cancer with targeted therapies. Often, drug tolerance in these cells is driven by overexpression and increased receptor activity of redundant receptors.

However, protein degradation and methylation can influence transcriptomic results and can lead to reduced protein expression of these targets. One subgroup known for extensive methylation is the KMT2A-r subgroup. In these cases, a combinatorial therapy approach including DNA methyltransferase inhibitors (e.g., decitabine) along with ADCs may improve treatment. For example, it has already been shown that the expression of the established melanoma antigen CSPG4 can be induced in ovarian cancer cells by the hypomethylating activity of the FDA-approved drug decitabine. Treatment of CSPG4-negative SKOV-3 ovarian cancer cells with decitabine resulted in upregulation of CSPG4 in the majority of decitabine-treated SKOV-3 cells [289].

Of the genes discussed in this work, 12/46 (~26%) genes are known to be aberrantly methylated (CSPG4, PSD2, PCDHGC3, DSC3, PTPRK, CLSTN2, ERBB2, PTPRZ1, MEGF10, IL2RA, PTPRM and CD70), 33/46 (~72%) genes play a role in at least one pathway of the PI3K/AKT and RAS/MAPK signaling pathways (see Table 1), 3/46 (~7%) genes are RTKs (DDR2, PDGFRB and ERBB2), 43/46 (~93%) genes are non-RTK cell surface markers

and 13/46 (~28%) genes are regulated by at least one member of the FOXO, HIF or MYC family (CSPG4, CD1B, CD70, NOTCH3, CD20, CD226, PTPRZ1, CNR1, GLUT3, CD146, F3, DSC3 and VIPR2). For 12 of the 46 targets on our list, ADCs have already been tested preclinically or clinically (Table 2: CSPG4, F3/TF, IL3RA, TNFRSF13B, ERBB2/HER2, MS4A1/CD20, LRRC15, IL2RA/CD25, SLC2A3, MCAM, CD70 and NOTCH3). In addition, 13 of the 46 cell surface proteins are clinically relevant as they are already being investigated in clinical trials for the treatment of cancer (Table S4: CSPG4, PDGFRB, PTPRZ1, ERBB2/HER2, CRLF2, LRRC15, IL2RA/CD25, IL3RA, CD70, NOTCH3, F3/TF, DDR2 and MS4A1/CD20) [ClinicalTrials.gov; accessed on 27 September 2025]. In consequence, we are introducing 30 new targets that, to our knowledge, have not previously been used for ADC development or investigated in clinical trials for cancer treatment.

The identification of new cell surface markers that could serve as specific targets for targeted immunotherapy represents a further step in the development of new therapeutics for the treatment of leukemia. Testing the antileukemic efficacy of novel or approved ADCs in primary ALL samples to anticipate direct effects of antibody-based immunotherapy in a preclinically relevant manner can be performed by ex vivo drug response profiling (DRP). To examine if treatment with ADCs is effective in ALL patient samples or in cell lines, samples can be measured in high throughput in a 384-well format, as illustrated in Figure 5. For DRP, primary human leukemic cells can be co-cultured on hTERT (human telomerase catalytic subunit gene)-immortalized bone marrow stroma cells under serum-free conditions. After 72 h of incubation with the ADC, cellular viability can be measured by automated microscopy-based image analysis (live-cell imaging). The use of the antibody–drug conjugate inotuzumab ozogamicin for DRP screening of patient samples has been shown before [290], but DRP data for other promising ADCs for ALL treatment is missing so far. However, the development and establishment of an ADC involves several steps beyond design, internalization and high-throughput DRP. Nonspecific cytotoxicity must also be evaluated, for example, by additionally saturating the antigen binding site with an uncoupled antibody prior to ADC application. The ADC should then be tested in vivo for antitumor activity, distribution, half-life and stability in the organism as well as for toxicity.

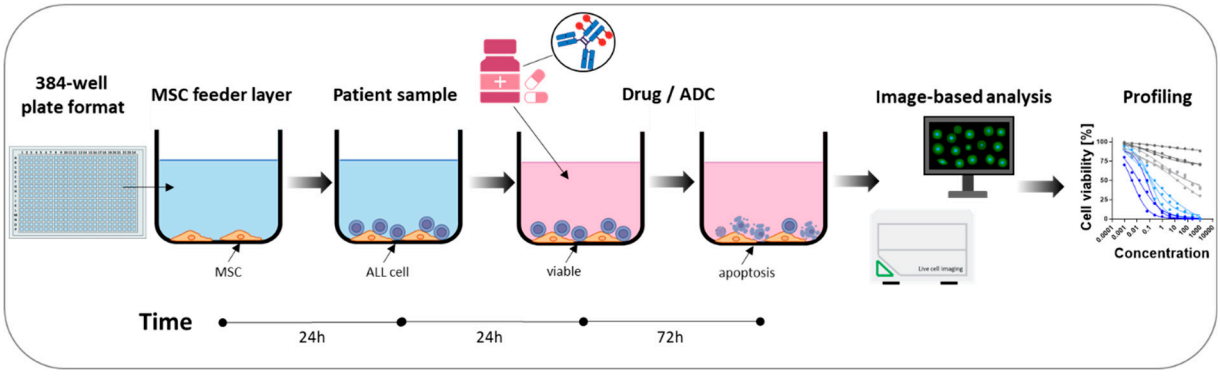

Figure 5. Setup of the drug response profiling platform. Drug profiling can be performed on ALL cells (patient material or cell lines) in co-culture with human bone marrow–derived stroma cells. Viability (based on intact DNA content) can be analyzed after 72 h of treatment with ADC compounds by quantifying viable ALL cells and furthermore to generate dose–response curves (IC50). This platform enables the identification of drug-response phenotypes in individual ALL patients, providing an additional layer of information to facilitate individual treatment approaches.

The expression of target antigens is often modulated according to the mutational profile of the tumor cells [291]. RAS mutations have a major impact on key cellular signaling pathways, which in turn can affect the protein expression of important surface markers. For example, it has already been shown that BRAF mutations lead to altered

expression levels of NECTIN4, a target molecule used to treat thyroid cancer with the approved antibody enfortumab vedotin [19].

In this study, we suggest clinically validated and novel immunotherapy targets against malignant cells of the different ALL subgroups. In addition, we describe a new strategy to overcome resistance of non-responsive ALL cells by combining RAS/MAPK or PI3K/AKT pathway inhibitors with ALL subgroup-specific ADCs.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/lymphatics3040033/s1, Table S1: Gene expression of novel cell surface structures in ALL subgroups; Table S2: Annotation of genes depending on their location according to occurrence in specified datasets; Table S3: Protein expression of novel cell surface structures in ALL subgroups; Table S4: Targets in clinical trials.

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Abbreviations

RAS/RAF/MEK/ERK, rat sarcoma/rapidly accelerated fibrosarcoma/mitogen-activated protein kinase/extracellular signal-related kinase; GEF, guanine nucleotide exchange factor; PI3-kinase, phosphoinositide 3-kinase/PI3K; AKT, protein kinase B/PKB; mTOR, mechanistic target of rapamycin; PTEN, phosphatase and tensin homolog; ADC, Antibody–drug Conjugate; DRP, Drug Response Profiling; ALL, Acute lymphoblastic leukemia; RTK, Receptor Tyrosine Kinase.

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