The Origin of B-cells: Human Fetal B Cell Development and Implications for the Pathogenesis of Childhood Acute Lymphoblastic Leukemia

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Human B-lymphopoiesis is a dynamic life-long process that starts in utero by around six post-conception weeks. A detailed understanding of human fetal B-lymphopoiesis and how it changes in postnatal life is vital for building a complete picture of normal B-lymphoid development through ontogeny, and its relevance in disease. B-cell acute lymphoblastic leukemia (B-ALL) is one of the most common cancers in children, with many of the leukemia-initiating events originating in utero. It is likely that the biology of B-ALL, including leukemia initiation, maintenance and progression depends on the developmental stage and type of B-lymphoid cell in which it originates. This is particularly important for early life leukemias, where specific characteristics of fetal B-cells might be key to determining how the disease behaves, including response to treatment. These cellular, molecular and/or epigenetic features are likely to change with age in a cell intrinsic and/or microenvironment directed manner. Most of our understanding of fetal B-lymphopoiesis has been based on murine data, but many recent studies have focussed on characterizing human fetal B-cell development, including functional and molecular assays at a single cell level. In this mini-review we will give a short overview of the recent advances in the understanding of human fetal B-lymphopoiesis, including its relevance to infant/childhood leukemia, and highlight future questions in the field.

Keywords: B-lymphopoiesis, human fetal, childhood, infant, leukemia, B-ALL, B-cell

INTRODUCTION

Unraveling the details of human hematopoietic development during embryogenesis is crucial for both basic and medical science. Relative contributions of different progenitor compartments and downstream lineage specificity vary during human ontogeny. Detailed immunophenotyping of fetal hematopoietic tissues from 6 to 20 weeks post conception (pcw) has identified that a much higher proportion of fetal bone marrow (FBM) cells are B-lymphoid than fetal liver (FL) and adult bone marrow (ABM) (1). In keeping with this, the changing lymphoid/myeloid specification in aging bone marrow has been described (2–4). Secondly, a switch from multipotent to largely oligo/unipotent stem cells is also known to occur between fetal and adult life (5). Thirdly, differences in the proliferative capacity of human fetal and postnatal hematopoietic stem and progenitor cells (HSPC) have been demonstrated using functional and molecular studies, with a marked and progressive increase in stem cell quiescence evident during physiological aging.
(6–9). In addition, some fetal gene expression programs are inherently oncogenic (10–12), and high mutation rates are seen both in hematopoietic and non-hematopoietic fetal stem cells when compared to postnatal tissues (13, 14). Therefore, understanding how hematopoiesis changes through human ontogeny is crucial if we are to understand the site- and stage-specific variation in HSPC throughout the human lifetime and the role it plays in hematological disorders/diseases.

Fetal hematopoiesis is of particular interest in understanding childhood blood disorders that originate before birth. Significantly all infant leukemia and much of childhood acute lymphoblastic leukemia (ALL) originate before birth (15, 16).

ALL is the most common childhood malignancy, and 80% of childhood-ALL are of the B-lymphoid lineage. Early onset B-ALL can be divided into infant ALL (iALL) presenting at age <12 months or childhood-ALL presenting at age >12 months. While outcomes for childhood-ALL have improved dramatically over the past few years to reach an overall survival (OS) rate of >90% (17); the OS rate is only ~60% in infants (18). The reasons for such disparate outcomes is not clear, but the clues might lie in the developmental origins of infant and childhood-ALL.

Advances in understanding fetal hematopoiesis and prenatal oncogenic events, have been limited by a number of factors. The scarcity of human fetal biological samples is compounded by the difficulty in working with very small numbers of HSPC that can be obtained from each sample. Thus, majority of our understanding of early hematopoiesis development has come from murine studies. Neither these, nor adult human models can be used as a faithful surrogate for human fetal hematopoiesis (5, 19, 20). This in turn leads to difficulties in making developmentally relevant model systems for human leukemia (21, 22).

In this review we will focus on recent advances in our understanding of human B-lymphopoiesis during ontogeny, especially in fetal life, and review progenitor compartments therein which may align to the origin of iALL and childhood-ALL.

**HUMAN B-LYMPHOPOIESIS**

Hematopoiesis has traditionally been described as a hierarchical process with hematopoietic stem cells (HSCs) at the apex; these divide and differentiate into progressively restricted progenitors that subsequently give rise to the mature cell types of the hematopoietic and immune system (23, 24).

The traditional human B-lymphoid developmental hierarchy in adult life demonstrates the following lineage progression in ABM: HSC, multi-potent progenitors (MPP), lymphoid-primed multi-potent progenitors (LMPP) (25, 26), multi-lymphoid progenitors (MLP) (27, 28), common lymphoid progenitors (CLP) (29), ProB-progenitors, PreB-cells and finally mature B-cells (30–32) (Figure 1). Lineage commitment is a multi-stage process defined by transcription factors and their related gene regulatory networks, influenced both by cell intrinsic factors and extracellular signals from the microenvironment (29, 33–35). CD19 expression is the hallmark of B-lineage commitment, with ProB-progenitors being the first CD19+ cells in ABM that also initiate immunoglobulin heavy chain VH-DH-JH rearrangement (31, 36). In recent years, single cell approaches have been extensively applied to delineate cellular hierarchies and molecular pathways in hematopoiesis (37, 38). However, the majority of studies have been done in human cord blood (5, 39) or adult tissues (38, 40, 41).

Recent studies have begun to leverage sophisticated transcriptomic and functional assays to identify B-lymphoid progenitor compartments in the fetus that are not represented in the adult. These, and/or their microenvironment, are hypothesized to be important for the pathogenesis of infant and childhood leukemias, and perhaps also adult malignancies with *in utero* origins (15, 42).

**HUMAN FETAL B-LYMPHOPOIESIS**

The timings and sites of fetal hematopoiesis have been broadly mapped out in humans. Hematopoiesis is initiated at day 18 post conception in the yolk sac, independently definitive HSC emerge from the aorta-gonad-mesonephros (AGM) at 4 pcw and subsequently migrate to the FL and then bone marrow, which remains the main site of hematopoiesis after birth (43–47). HSCs colonize the FL from 5th pcw, and they are detectable later in the long bones at 10–12 pcw (1, 48).

In humans, the first evidence of onset of embryonic lymphopoiesis is in the FL at 6 pcw, with multi-potent progenitors (HSC, MPP, LMPP) and fetal-specific oligo-potent early lymphoid progenitors (ELP) detectable. B-progenitors and B-cells are seen in FL by 7 pcw (9, 30, 49, 50). From 2nd trimester the FBM takes over from the FL as the main site of B-lymphopoiesis (1, 51).

**Fetal Lymphoid Progenitors**

Interestingly, in murine models immune restricted cells with lymphoid potential are observed in the yolk sac (YS), preceding the first HSCs found in FL; these have potential to produce lymphocytes and granulocyte macrophage progenitors (52) and express Il7 receptor (Il7-r/CD127). Transcriptomic data suggests that such lymphoid progenitors may also be present in human YS (9) but these have not been systematically characterized yet. In humans a potentially analogous cell has been identified in the FL, from 6 pcw; (CD34+CD19−IL7R+)(1, 50, 53, 54). Similar IL7R+ progenitors have been described in human FBM (1). FL and FBM CD34+CD127+CD19−CD10−ELP have been characterized by functional and transcriptomic assays, and shown to generate B, T and NK cells while retaining some residual myeloid output. These fetal-specific ELP are very rare in postnatal life (1, 54). There has therefore, been considerable interest in these cells as potential target cells for childhood-ALL.

**Fetal B-Progenitors**

From 7 pcw the presence of two committed CD19+ B-progenitors downstream of ELP has been confirmed in human FL samples; PreProB (CD34+CD19+CD10−) and ProB (CD34+CD19+CD10+) progenitors; differing in their CD10
expression (1, 50, 54). Similar progenitors have been described in cord blood (55, 56). PreProB-progenitors account for ~2.5% and ProB-progenitors ~8% of FL CD34+ cells, and these frequencies remain fairly stable in FL between 7 and 20 pcw. These cells have also been identified by single cell transcriptomic approaches in the human FL (9).

PreProB and ProB-progenitors are also present and markedly expanded in human FBM (1). Both B-progenitor compartments undergo marked expansion in the early stages of colonization of FBM, to account for up to around 20% and 11% of FBM CD34+ cells, respectively, at 11 pcw. Later in the second trimester PreProB-progenitors plateau while ProB-progenitors expand further to >30% of CD34+ cells in FBM. By contrast, ABM CD34+ compartment was found to have only 0.5% PreProB-progenitors and 14% ProB-progenitors (1).

Both PreProB and ProB-progenitors lie downstream of ELP and generate exclusively B-lymphoid progeny in vitro and in vivo. Functional and molecular studies have established that FBM PreProB-progenitors lie upstream of ProB-progenitors, and are therefore the earliest B-lymphoid restricted progenitors in the fetal B-cell developmental hierarchy (1).

B cell maturation, defined by B cell receptor diversification, commences in B-lymphoid progenitors in fetal life. Fetal ELP and PreProB-progenitors show partial (D-H-J) IgH rearrangement (1, 54), whereas the more mature ProB-progenitors demonstrate complete V-H-D-J rearrangement (1).

### Fetal B-Cells

CD19+ B-cells have been reported in FL and FBM by many groups (30, 48, 49, 57–59), and recently been characterized in greater detail (1, 9, 60, 61). Evidence of B cell maturation is demonstrable in human fetal life, with polyclonal CD19+IgM+ B-cells (60–63). Although FL and FBM immunoglobulin heavy chain repertoires are equally diversified, FL appears to be the main source of IgM natural immunity during the 2nd trimester, and this correlates with the majority of B-cells in 2nd trimester FBM being CD34−CD19+CD10−IgM/D− PreB-cells with a relative lack of more downstream immature and transitional B-cells (60).

### B1 B-Cells and their Putative Progenitors

B cells can be further divided into B1 B-cells of the innate immune system and “conventional” B2 B-cells of the adaptive immune system. This division is well-established in mice, where slgM+CD11b+CD5+ B1a B-cells were first identified (64, 65) through the search for, the still elusive, cell of origin of adult human CLL (42, 66). B1b B-cells (slgM+CD11b+CD5−) were subsequently described (67); both these subtypes are seen predominantly in serous cavities. Further characterization of splenic B1 cells have identified them to be CD5+/−CD19hiCD1dmidCD23−CD43+IgMhiIgDlo (68). Murine B1 B-cell progenitors are found in the yolk sac (69) prior to the emergence of the first definitive HSCs in the FL, which have both B1 and B2 B-cell output (70). The B-cell output skews toward B2 B-cells over ontogeny, with B1 B-cell output being exceedingly rare in ABM (65, 71).

Human B1 B-cells and their upstream progenitors have been proposed as the in utero cell of origin for infant and childhood-ALL (72) and as having a role in auto-immune disease (73, 74). In humans, B1 B-cells were described in
umbilical cord blood and adult peripheral blood. These cells were CD20⁺CD27⁺CD43⁺CD38lo/int and functioned in line with murine counterparts, including spontaneous IgM secretion, constitutional BCR receptor activity and ability to induce allogeneic T cell proliferation (75). Putative B1 B-cells have also been described in human fetal hematopoiesis, with greatest frequencies in 10 pcw FL, decreasing as FBM is colonized (59). After birth, estimates of B1 B-cell populations range from 1 to 10% circulating B-cells, this frequency falls as age increases (76–78).

The progenitors of B1 B-cells in humans remain elusive and contentious. Two theories posit either a lineage (or layered) model where different subtypes arise from different progenitors or a selection model whereby there is interconversion between B1 and B2 B-cells. In humans, CD27 (one of the cell surface markers of B1 B-cells) expression in ABM ProB-cells coincides with LIN28B expression levels similar to that seen in FL. These cells mature preferentially to B1-like B-cells compared to their CD27⁻ counterparts. It is not clear whether this relates to a separate lineage or alternative differentiation potential (79).

In summary, human fetal B-lymphopoiesis starts around 6 pcw in FL, with B-cell production happening simultaneously in FL and FBM from 2nd trimester. Hematopoiesis in the FBM is skewed toward B-lymphopoiesis in 2nd trimester. In addition there are fetal-specific B-lymphoid progenitors (ELP and PreProB-progenitors), B-cells (B1 B-cells) and developmental pathways that are different from human adult life (Figure 1).

MOLECULAR PROFILE OF FETAL B CELL PROGENITORS

Recent studies suggest that the ontogenic switch of B1 to B2 B-cells in murine B-cell lineage fate of progenitor cells is determined by a combination of intrinsic fetal gene expression programs (Lin28b) (80) and extrinsic FL environmental factors (81). Whole transcriptome profiling of murine fetal and adult B cell progenitors showed distinct differences between B-1 and B-2 B-cells as well as between fetal and adult progenitors (82). Although it is well-accepted that human fetal and adult B-lymphopoiesis differ significantly, very few studies have directly compared the molecular pathways underlying these differences. However, both human adult (35, 41, 83) and fetal (1, 9, 84) RNA-seq data sets across many hematopoietic subpopulations have been produced separately and are publicly available for such analyses.

The advent of single cell sequencing technology has allowed the transcriptome of hematopoietic cells to be investigated in unprecedented detail. Recent single-cell transcriptome profiling of human FL and FBM hematopoiesis has demonstrated the transcriptomic changes that drive differentiation in the fetal B cell hierarchy from HSC to mature B-cells; with upregulation of genes such as SPIB, SP100 and CTSS at HSC/MPP to B-lymphoid transition, followed by gradual upregulation of B-cell specific genes such as MS4A1, CD79B, and DNTT (1, 9).

Although fetal PreProB-progenitors are functionally identical to ProB-progenitors in being restricted to a B-lineage output; these two progenitor subtypes are molecularly distinct in their gene expression and chromatin accessibility patterns, with many myeloid (MPO, CSF1R), T-cell (CD7, CD244) and stem cell (SPINK2, PROM1) genes being accessible and expressed in PreProB-progenitors (1). In addition, when transcriptomes of iALL blasts are compared with different fetal HSPC populations, they most closely match the two fetal-specific progenitor populations, ELP and PreProB-progenitors (1) implicating these cells as potential targets for leukemic transformation.

Direct comparisons focusing on human B-progenitors showed that although adult and fetal counterparts were functionally similar, they did exhibit ontogeny-related transcriptomic differences at a single cell level, with fetal B-progenitors expressing high levels of genes involved in DNA recombination (DNTT, RAG1), as well as myeloid genes and known fetal-specific genes such as LIN28B (1, 80).

Previous studies have also shown that B cell receptor (BCR) development differs in fetal life, in particular with respect to VH-DH-JH joining (85). Fetal BCR have a shorter CDR3 length, and show preferential usage of VH6, DHQ52 and the JH3 and JH4 loci compared to postnatal B-cells (60, 86–89).

RELEVANCE TO CHILDHOOD-ALL

The practical importance of characterizing human fetal B-lymphopoiesis is to understand the origins of childhood B-ALL, many of which are initiated before birth. This has led to the suggestion that fetal specific B1 B-cells and their progenitors could be the target cells for leukemia initiation in many subtypes of childhood leukemia. Gene expression signatures from mice which distinguish B1 and B2 B-cells have been mapped to human orthologs; application of these signatures to human pediatric ALL transcriptomic datasets separates B1 B-cell-like ALL subtypes including ETV6-RUNX1 ALL, from B2 B-cell-like subtypes such as BCR-ABL1, hyperdiploid, and KMT2A ALL subtypes (90). Intriguingly, in murine models BCR-ABL transduction into B1 B-progenitors yields greater tumor burden in resulting murine leukemia than B2 B-progenitors (91).

These data suggest that it is likely that the biology of different types of infant/childhood Precursor B-ALL depends on the developmental stage specific characteristics of the leukemia-initiating cell although this remains to be demonstrated directly. Nevertheless, it is likely that this is particularly relevant for iALL, which invariably originates in utero and presents as a rapid onset aggressive leukemia within the 1st year of life.

Clinical and Biological Features of Infant and Childhood-ALL

The clinical course and molecular features of iALL are distinct from childhood-ALL. iALL remains a disease with dismal event-free survival (EFS) (18, 92–94), although recent risk-stratified treatment protocols suggest that outcomes could be improved (95). In iALL, blasts are predominantly CD19⁺CD10⁻, often with aberrant myeloid cell surface markers suggestive of an immature B-progenitor, as opposed to a CD19⁺CD10⁺ Pre-B phenotype in childhood-ALL (18, 96). KMT2A gene
rearrangements (KMT2A-r) is the main genetic driver for 70–80% iALL cases, as opposed to only 2–5% of childhood-ALL cases (97, 98).

Current evidence suggests that iALL (particularly KMT2A-r ALL) originates in utero and has been traced back to its fetal origin through retrospective detection of the fusion gene in neonatal blood spots (99), as well as studies in monozygotic twins with ALL (100, 101). A characteristic feature of iALL is the fact that a single hit (KMT2A-r) before birth seems to be sufficient to induce a rapidly-proliferating, therapy-resistant leukemia without the need for additional mutations (102).

Unlike iALL, many cases of childhood-ALL also originate in utero but only develop into full-blown leukemia after a second post-natal hit (15, 16). Several subtypes of childhood B-ALL have been shown to arise in utero including those characterized by KMT2A-r (103, 104), ETV6-RUNX1 (105–107), BCR-ABL (108), TCF3-PBX1 (109), TCF3-ZNF384 (110) gene fusions and high hyperdiploid ALL (111, 112) (Figure 2).

There are several properties of fetal hematopoietic cells that may underlie the pathogenesis of iALL and childhood-ALL. Firstly, fetal HSPC are more proliferative (may underlie the pathogenesis of iALL and childhood-ALL. Current evidence suggests that iALL (particularly KMT2A-r ALL) originates in utero and has been traced back to its fetal origin through retrospective detection of the fusion gene in neonatal blood spots (99), as well as studies in monozygotic twins with ALL (100, 101). A characteristic feature of iALL is the fact that a single hit (KMT2A-r) before birth seems to be sufficient to induce a rapidly-proliferating, therapy-resistant leukemia without the need for additional mutations (102).

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There are several properties of fetal hematopoietic cells that may underlie the pathogenesis of iALL and childhood-ALL. Firstly, fetal HSPC are more proliferative (5, 7) and have better long term repopulating ability in xenograft models (8, 113–115). Fetal-specific gene expression programs such as the LIN28B-LET-7-HMGA2 axis (79, 80, 116, 117) have been shown to drive self-renewal (118) and oncogenesis (10–12, 119). Activation of LIN28B, in particular, has been demonstrated in several cancers and results in suppression of LET-7 micro-RNAs and subsequent de-repression of an array of oncogenes including MYC, RAS, BLIMP1, ARID3A and HMGA2 (10, 120). ARID3A is necessary for fetal B lymphopoiesis and B1 cell division (121, 122), and has also been shown to promote cancers by driving higher MYC expression (123, 124). HMGA2 is a fetal-specific transcription factor that is re-expressed in many cancers. It promotes cell proliferation, and the Lin28-Let-7-HMGA2 axis maintains cancers in an undifferentiated state (125). The expression of oncogenes such as LIN28B in fetal HSPC, may therefore play a role in leukemia initiation and transformation of fetal target cells, and in particular the development of aggressive leukemias in infancy and early childhood.

Secondly, there is a higher proportion of B-progenitors in fetal life compared to adults (1, 2). B-lymphopoiesis itself changes through the human lifetime with a switch in the ratio of B-progenitors to more mature B-cells (30, 49). Regardless of the mechanism, hematopoiesis in the human FBM is skewed toward the B-lymphoid lineage with the presence of a very high frequency of B-progenitors (1, 126) thus expanding the pool of target cells for malignant transformation.

**Developmental Origins of iALL**

It is also possible that the fetal cell of origin for iALL and childhood-ALL are different (Figure 2). We suggest that an attractive hypothesis is that iALL arises in a unique B-progenitor found only in fetal life. Of particular interest are fetal-specific IL7R+ ELP (1, 50, 53, 54) and PreProB-progenitors (1, 50, 55, 56) that share immunophenotypic, transcriptomic and IgH rearrangement patterns with iALL blasts (1, 96). Compared to ABM counterparts, fetal PreProB-progenitors uniquely express known oncogenic genes such as LIN28B, as well as genes implicated in KMT2A-r iALL, such as KLRK1 and PPP1R14A (127, 128) that have not previously been recognized as being fetal-specific (1). Fetal ELP/PreProB-progenitors also demonstrate features that could account for lineage plasticity such as an accessible chromatin pattern, together with residual expression, of myeloid and stem cell genes (1). In addition, iALL can switch to a myeloid lineage at relapse, especially after B-lymphoid directed treatment (129–132). This could either be a feature of residual preleukemic primitive progenitors that are capable of giving rise to both myeloid and lymphoid leukemia, or because of plasticity and/or reprogramming of leukemia early B-lymphoid progenitors (130, 133). For example, KMT2A-r, the most frequent genetic driver of iALL, may drive leukemogenesis by binding to accessible genes in permissive fetal progenitors; or indeed alter the chromatin accessibility and gene expression patterns of target genes. KMT2A is a lysine methyltransferase, and KMT2A-r is thought to promote leukemogenesis by activating key target genes such as HOXA9 and MEIS1 (134, 135). Although there is some heterogeneity in KMT2A-r ALL based on the specific fusion partner gene, most KMT2A-fusion proteins drive and maintain leukemia via a protein complex involving AF4/ENL/AF9/PTEF-B. KMT2A-fusion proteins bind directly to gene targets where they aberrantly upregulate gene expression, partly by increasing histone-3-lysine-79 dimethylation through DOT1L (135).

These mechanisms of KMT2A-r mediated transformation are difficult to create without a bona fide model of iALL, which has been very difficult to generate. However, we have recently developed a novel iALL model derived by CRISPR-Cas9 mediated KMT2A-r in primary human FL HSPC (136). This demonstrates that a human fetal cell context is permissive, and indeed probably required; to give rise to an ALL that recapitulates key features of iALL. In this model, recruitment of fetal-specific genes by KMT2A-AF4 is demonstrated by KMT2A-N and AF4-C binding and H3K79me2 at these genes by ChIP-seq (136). Furthermore, maintenance of fetal-specific gene expression programs accounts for the unique molecular profile of iALL, suggesting that it is the specific fetal target cell(s) in which it arises that provide the permissive cellular context (136).

**Developmental Origins of Childhood-ALL**

It is possible that childhood-ALL on the other hand is likely to arise from a more mature CD19+CD10+ fetal B-progenitor such as ProB-progenitors or PreB-cells. These cell populations are found in abundance in FBM and expand rapidly throughout the second trimester. As in iALL, several genes that have been implicated in the pathogenesis of childhood-ALL are also important in fetal B lymphoid development. Some of these, such as PAX5, EBF1, TCF3, and IL7R (137, 138), are expressed at higher levels in fetal B-progenitors compared to postnatal counterparts (1). This is also true for the B-cell specific gene RAG1 that may play a role in driving childhood-ALL-associated chromosomal translocations such as ETV6-RUNX1 (139). In addition, childhood-ALL is characterized by multiple lesions affecting cell cycle and B-cell differentiation genes (138). It is hypothesized that the proliferative capacity and...
complementary epigenetic profile (such as greater chromatin accessibility of highly expressed genes) of the cell of origin provide the right substrate for leukemic transformation (35, 140). This permissive cell-state is likely to be present in FBM ProB-progenitors where their rapid proliferation at the expense of differentiation during a particular developmental time window may make them more susceptible to oncogenic hits. Others have hypothesized that it is the fetal/neonatal BM niche that drives the lymphoid-biased phenotype of KMT2A-r infant/childhood leukemia (141).

CONCLUSION

Recent advances in developmental hematopoiesis have allowed better characterization of human fetal B-lymphopoiesis using molecular and functional studies. This has revealed fetal-specific B-lymphoid progenitors and B-cell developmental pathways that can be distinguished from postnatal B-lymphopoiesis. Lineage specification of fetal progenitors, the enrichment of multi/oligopotent progenitors and their proliferative capacity is also likely to be driven by microenvironmental cues from the FL and FBM hematopoietic niche.

Studies directly comparing fetal B-lymphoid cells and their microenvironment with childhood and adult counterparts are crucial if we are to understand the site- and stage-specific variation in hematopoiesis throughout the human lifetime and the role it plays in normal and abnormal B-lymphopoiesis. This also has implications for using age-appropriate controls for studies of disorders of hematopoiesis, particularly in early life.

The lymphoid bias of normal fetal hematopoiesis may well be a key factor in the predominance of ALL among infants and children. A better understanding of the importance of the fetal context for leukemogenesis is likely to require models derived from human fetal HSPCs and/or niche. Using human fetal cells to develop faithful infant and childhood-ALL models will allow better understanding of disease pathogenesis and rational development and testing of therapeutics in the future.

AUTHOR CONTRIBUTIONS

TJ, RL, and AR drafted the manuscript. AR reviewed and edited the manuscript. All authors read and approved the final manuscript.
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Conflict of Interest: The authors 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.

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