REVIEW ARTICLE

Reframing leukemia-niche interactions: the emerging role of the marrow adipocyte lineage

Bexultan Kazybay,[1,2] Mauricio N. Ferrao Blanco,[1] Olaf Heidenreich[1,3] and Hermann Josef Vormoor[1,3]

[1]Princess Máxima Center for Pediatric Oncology; [2]Utrecht University and [3]University Medical Center Utrecht, Utrecht, the Netherlands

Correspondence: H.J. Vormoor
H.Vormoor@prinsesmaximacentrum.nl

Received: March 3, 2026.
Accepted: June 26, 2026.
Early view: July 2, 2026.

https://doi.org/10.3324/haematol.2026.300800

©2026 Ferrata Storti Foundation
Published under a CC BY-NC license

Supplementary Table 1. Characterization of adipogenic lineage population in murine bone via single-cell RNA sequencing studies

Species of origin	Source	Isolation approach	Adipogenic lineage populations	Markers	Additional markers	Hematopoietic support factors
Mouse	Tikhonova et al., 2019 [1]	Bones were flushed and digested by Liberase and DNase I. Samples were sorted for VE-Cad$^+$, LEPR$^+$ and COL2.3$^+$ cells.	Adipocyte-biased perivascular LEPR+	*Cxcl12, Lepr Lpl, Adipoq, Apoe, Gas6, Esm1*	(*Cd63, Cd200*)-low (*Alpl, Spp1, Wif1, Bglap, Sp7, Runx2*)*-low/neg *Mgp*✳ –	*Cxcl12, Scf, Vcam1, Il7, Csf1, Il15, Il34, Ccl2, Ccl19, Bmp4*
	Baryawno et al., 2019 [2]	The bones were flashed, crushed and digested by STEMxyme1 and Dispase II. Samples were further sorted for Ter119-CD71-Lin-.	Lepr-MSCs	*Cxcl12, Lepr Lpl, Cebpa, Adipoq, Apoe, Grem1*	(*Thy1, Ly6a*)-neg, *Cd73, Cd105 Sp7*, Alpl*, Runx2** (*Nes*, *Cspg4*)⏚ -neg	*Cxcl12, Scf, Vcam1, Angpt1*
	Wolock et al., 2019 [3]	Crushed bones were digested using Collagenase/Dispase and sorted for CD45-Ter119-CD31-.	adipocyte progenitor	*Cxcl12, Lepr Pparg, Cebpb, Adipoq*	*Nt5e* (*Runx2, Sp7, Alpl*)*-low and (*Bglap, Col1a1, Col1a2, Dmp1*)*-neg	*Cxcl12, Scf, Il7, Il6, Il34, Ccl2, Bmp4*
			pre-adipocyte	*Cxcl12, Lepr Pparg, Cebpb, Adipoq*	*(Fosb, Junb)******	
	Baccin et al., 2019 [4]	Crushed bones were either enzymatically digested (Collagenase II and Dispase) or used without digestion. They were further sorted for Lin-Cd45-Cd71- cells.	Adipo-CAR (Cxcl12-abundant-reticular) cells	*Cxcl12, Lepr Lpl, Cebpb, Adipoq, Apoe*	*CD51, CD200*-mid, *CD61*-low (*Bglap, Sp7, Alpl*)*-neg	*Cxcl12, Scf, Vcam1, Il7, Csf1*
	Matsushita et al., 2020 [5]	Bone epiphyseal growth plates were cut off and the remaining part was digested by liberase and pronase followed by grinding. CD45/Ter119/CD31- tdTomato+ Cxcl12(GFP)+ cells were sorted.	Reticular Adipoq+ cells	*Cxcl12, Lepr Cebpb, Adipoq*	*Col1a1**-low (*Bglap, Spp1, Alpl, Postn*)*-neg	*Cxcl12, Scf, Fgf7, and Il7*
	Zhong et al., 2020 and 2021 [6, 7]	The epiphyses were cut off and the central bone marrow was flashed. The metaphyseal bone fragments were digested by proteases and sorted for endosteal Td$^+$bone marrow cells.	Marrow adipogenic lineage precursors (MALPs)	*Cxcl12, Lepr Lpl, Cebpa, Pparg, Adipoq, Apoe, Grem1, Klf2, Ebf1, Ebf2, Ebf3*	(*Plin1*-neg, *Fabp4*-low)✳✳ (*Lep*-neg, *Hoxc8*-low, *Hoxc9*-low)✳✳✳ (*Ucp1*-neg, *Cidea*-low, *Cox7a1*-low, *Zic1*-low)† (*Tnfrsf9*-neg, *Cited1*-low, *Shox2*-low, *Tbx1*-low) †† *Pdgfrb**** , *Lamb1**** (*Vegfa*, *Vegfc*, *Angpt4*, *Rspo3*) †††	*Cxcl12, Scf, Vcam1, Il7, Angpt1 Csf1*
	Dolgalev and Tikhonova, 2021 [8] Inoue et al., 2023 [9]♦	Data from Baccin et al. [4], Baryawno et al. [2], Tikhonova et al. [1], Wolock et al.[3], and Zhong et al. [6] were integrated and re-analysed.	Adipo-primed mesenchymal stem and progenitor cells (MSPC-Adipo)	*Cxcl12, Lepr Lpl, Cebpa, Pparg, Adipoq, Apoe, Grem1*	(*Bglap*, *Postn*)*-neg (*Sp7*, *Alpl, Col1a1, Wif1, Dmp1, and Bglap*)*-low/neg *Runx2**, *Spp1**	*Cxcl12, Scf, Vcam1, Il7, Csf1, Il15, Il34, Ccl2, Ccl19, Bmp4*
	Sivaraj et al., 2021 [10]	Bones were crushed and digested using Collagenase type II and I. CD45/CD117-neg *Pdgfrb-CreERT2 GFP*+ cells were sorted.	Lepr+ Esm1+ diaphyseal bone marrow stromal cells	*Cxcl12, Lepr Lpl, Cebpa, Cebpb, Pparg, Adipoq, Apoe, Gas6, Esm1*	(*Alpl*, *Sp7*, *Bglap2*, *Col11a2*)*-neg *Pdgfrb****	*Cxcl12, Scf*
	Ye et al., 2022 [11]	Bones were crushed and digested by Collagenase I and Dispase. Samples were sorted for Lin$^-$CD45/Ter119−VDO$^+$ to produce in house data which was further integrated with data from Tikhonova et al.[1] and Baryawno et al.[2]	Early mesenchymal cells (adipo-lineage committed cells)	*Cxcl12, Lepr Adipoq*	(*Bglap*, *Alpl*)*-neg, *Col1a1**-low	*Cxcl12, Vcam1*
	Pisterzi et al., 2023 [12]	Bones were crushed and digested using Collagenase. Samples were sorted for either lin$^-$ CD45$^-$ Ter119$^-$ CD31$^+$ or lin$^-$ CD45$^-$ Ter119$^-$ CD31$^-$ Sca-1$^+$ CD51$^+$ cells.	Lepr+ cells	*Cxcl12, Lepr Lpl, Adipoq, Apoe*	*Runx2**, *Spp1**	*Cxcl12, Scf*

*Osteogenic markers
***Pericyte markers
*****Stress-related transcription factors
✳ Chondrogenic markers
✳✳ Mature adipocyte markers
✳✳✳ White adipocyte markers
† Brown adipocyte markers
†† Beige adipocyte markers
††† Angiogenic markers
⏚ Perivascular MSC markers
♦[9] Reanalyzed data from [13] and [8]

Supplementary Table 2. Classification of stromal cell populations based on single-cell RNA sequencing studies.

		Early Mesenchymal Progenitor	Adipogenic progenitor	Adipo-derived osteogenic progenitor	Osteo - chondrogenic progenitor	Osteogenic progenitor	Osteoblast	Chondrogenic progenitor	Chondrocyte
Stromal markers	*CD81*	+++ 14-17	++ *13, 15, 16, 18*	++ 15, 16	+ 16	+ 15, 16	+ 15		+ 18
	LEPR	++ 16, 17	+++ 11, 13-16, 18, 19	+++ 15, 16	undetectable 16	++ 16	undetectable 15		+ 18
	CXCL12	++ 16, 17	+++ 11, 13-16, 18, 19	+++ 15, 16	undetectable 16	++ 16			+ 18
	KITLG (SCF)	undetectable 14	+++ 11, 14, 15, 18, 19	++ 15, 16	undetectable 16	++ 15, 16	+ 15		+ 18
	ANGPT1	++ 16, 17	+++ 11, 14-16, 18, 19	+++ 15, 16	undetectable 16	undetectable 15	undetectable 15		+ 18
Adipogenic markers	*LPL*	+ 14, 16	+++ 11, 13-16, 18, 19	++ 15, 16	undetectable 16	+ 15	+ 15		+ 18
	CSF1	+ 15-17	+++ 11, 15, 16	++ 15, 16	undetectable 16	+ 13, 16			+ 18
	VCAM1	undetectable 14	+++ 11, 13, 15, 16, 18	++ 15, 16	undetectable 16	++ 16			+ 18
	IL-7	undetectable 14	+++ 11, 15, 16, 19	++ 15, 16	undetectable 16	undetectable 16			+ 18
	PPARG	++ 15, 16	+++ 11, 14-16, 18	++ 15, 16	undetectable 16	undetectable 16	undetectable 15		+ 18
	FABP4	undetectable 14-16	+++ 16	++ 16	undetectable 16	undetectable 16			+ 18
	ADIPOQ	undetectable 16	++ 13, 16, 19	undetectable 16	undetectable 16	undetectable 16			+ 18
	GAS6	+ 14	++ 11, 14-16, 18, 19	++ 15, 16	undetectable 16	+ 15, 16			++ 18
	CEBPA	undetectable 16	+ 11, 15	+++ 16	undetectable 16	undetectable 16			+ 18
	CEBPB	++ 15, 17	++ 11, 15, 18	+ 15, 16	undetectable 16	+ 16			+ 18
	CEBPD	+ 15, 17	+ 11, 15, 18	+ 15, 16	undetectable 16	++ 15, 16	+ 15		+ 18
	PLIN1	undetectable 16	+ 13, 15, 18	+ 15, 16	undetectable 16	undetectable 16			+ 18
	CD36	undetectable 16	++ 11, 19	undetectable 16	undetectable 16	undetectable 15, 16			+ 18
Osteogenic markers	*COL1A1*	++ 15	++ 11, 14, 15, 18	++ 16	undetectable 16	++ 18	+++ 18	+ 13	++ 18
	COL1A2	++ 15, 16	++ 14-16, 18	+++ 15, 16	+++ 16	++ 13, 15-17	+++ 18	+ 13	++ 18
	ALPL	undetectable 14, 17	++ 11, 14-16, 18	++ 15, 16	undetectable 16	++ 13, 17	+++ 17, 18		+ 18
	BGLAP	undetectable 14, 16	undetectable 14, 16	undetectable 16	+++ 16	++ 15	+++ 15	++ 13	+ 18
	SPP1	undetectable 15, 16	undetectable 16	undetectable 16	+++ 16	undetectable 15	+++ 15	++ 13	+ 18
	POSTN	undetectable 16	undetectable 16	undetectable 16	++ 17	undetectable 16			+ 18
	CDH11	+ 14, 15	++ 14	++ 15, 16	+++ 16	+++ 15, 16	+++ 15, 16	+ 13	++ 18
	NCAM1	undetectable 14, 16	undetectable 16	undetectable 16	+++ 13, 16	+++ 15, 16	+++ 15, 16	+++ 13	+ 18
	OMD	+ 15	undetectable 16	undetectable 16	undetectable 16	+++ 15	+++ 15	+++ 13	+ 18
	RUNX2	undetectable 14	++ 11, 14, 15, 18	++ 16	+++ 16	+++ 15	+++ 15	++ 13	++ 18
	TGFb1	undetectable 15, 16	undetectable 15	undetectable 16	undetectable 16	+ 15	++ 15		+ 18
Chondrogenic markers	*WIF1*	undetectable 16	undetectable 15, 16	undetectable 16	+++ 16, 17	++ 15, 17	++ 15	+++ 13	++ 18
	ACAN	+ 15						++ 17	+++ 18
	MMP13	++ 17	undetectable 16	undetectable 16	+++ 16	+++ 17		+++ 13, 17	
	CHAD	undetectable 14, 16	undetectable 14, 16	undetectable 16	+++ 16	+ 15	++ 15		+++ 18
	COL2A1							+++ 17	+++ 18
	COL9A2/3	undetectable 16	undetectable 16	undetectable 16	undetectable 16	undetectable 16			+++ 18
	MGP	++ 15-17	++ 13, 15, 16, 18	++ 15, 16	++ 18	+ 16	+ 17	+++ 17	+++ 18
	SOX9	+ 14	undetectable 14	undetectable 16		+ 15		+ 13, 17	+++ 18

Marker gene expression levels are indicated as follows: "undetectable" denotes genes that were specifically examined but showed no detectable expression signal; "+" indicates low-level expression; "++" represents moderate expression; "+++" signifies high expression levels.

References

1. Tikhonova AN, Dolgalev I, Hu H, et al. The bone marrow microenvironment at single-cell resolution. Nature. 2019;569(7755):222-228.
2. Baryawno N, Przybylski D, Kowalczyk MS, et al. A Cellular Taxonomy of the Bone Marrow Stroma in Homeostasis and Leukemia. Cell. 2019;177(7):1915-1932.
3. Wolock SL, Krishnan I, Tenen DE, et al. Mapping Distinct Bone Marrow Niche Populations and Their Differentiation Paths. Cell Rep. 2019;28(2):302-311 e305.
4. Baccin C, Al-Sabah J, Velten L, et al. Combined single-cell and spatial transcriptomics reveal the molecular, cellular and spatial bone marrow niche organization. Nat Cell Biol. 2020;22(1):38-48.
5. Matsushita Y, Nagata M, Kozloff KM, et al. A Wnt-mediated transformation of the bone marrow stromal cell identity orchestrates skeletal regeneration. Nat Commun. 2020;11(1):332.
6. Zhong L, Yao L, Tower RJ, et al. Single cell transcriptomics identifies a unique adipose lineage cell population that regulates bone marrow environment. Elife. 2020;9:e54695.
7. Zhong L, Yao L, Seale P, Qin L. Marrow adipogenic lineage precursor: A new cellular component of marrow adipose tissue. Best Pract Res Clin Endocrinol Metab. 2021;35(4):101518.
8. Dolgalev I, Tikhonova AN. Connecting the Dots: Resolving the Bone Marrow Niche Heterogeneity. Front Cell Dev Biol. 2021;9:622519.
9. Inoue K, Qin Y, Xia Y, et al. Bone marrow Adipoq-lineage progenitors are a major cellular source of M-CSF that dominates bone marrow macrophage development, osteoclastogenesis, and bone mass. Elife. 2023;12:e82118.
10. Sivaraj KK, Jeong HW, Dharmalingam B, et al. Regional specialization and fate specification of bone stromal cells in skeletal development. Cell Rep. 2021;36(2):109352.
11. Ye J, Calvo IA, Cenzano I, et al. Deconvolution of the hematopoietic stem cell microenvironment reveals a high degree of specialization and conservation. iScience. 2022;25(5):104225.
12. Pisterzi P, Chen L, van Dijk C, et al. Resource: A Cellular Developmental Taxonomy of the Bone Marrow Mesenchymal Stem Cell Population in Mice. Hemasphere. 2023;7(2):e823.
13. Wang Z, Li X, Yang J, et al. Single-cell RNA sequencing deconvolutes the in vivo heterogeneity of human bone marrow-derived mesenchymal stem cells. Int J Biol Sci. 2021;17(15):4192-4206.
14. Ferrao Blanco MN, Kazybay B, Belderbos M, Heidenreich O, Vormoor HJ. Distinct stromal cell populations define the B-cell acute lymphoblastic leukemia microenvironment. Leukemia. 2025;39(11):2622-2639.
15. Bandyopadhyay S, Duffy MP, Ahn KJ, et al. Mapping the cellular biogeography of human bone marrow niches using single-cell transcriptomics and proteomic imaging. Cell. 2024;187(12):3120-3140.
16. Li H, Braunig S, Dhapolar P, et al. Identification of phenotypically, functionally, and anatomically distinct stromal niche populations in human bone marrow based on single-cell RNA sequencing. Elife. 2023;12:e81656.
17. Zhang P, Dong J, Fan X, et al. Characterization of mesenchymal stem cells in human fetal bone marrow by single-cell transcriptomic and functional analysis. Signal Transduct Target Ther. 2023;8(1):126.
18. Jardine L, Webb S, Goh I, et al. Blood and immune development in human fetal bone marrow and Down syndrome. Nature. 2021;598(7880):327-331.
19. Chen L, Pronk E, van Dijk C, et al. A Single-Cell Taxonomy Predicts Inflammatory Niche Remodeling to Drive Tissue Failure and Outcome in Human AML. Blood Cancer Discov. 2023;4(5):394-417.