Adhesion Molecules Involved in Stem Cell Niche Retention During Normal Haematopoiesis and in Acute Myeloid Leukaemia

Julien M. P. Grenier, Céline Testut, Cyril Fauriat, Stéphane J. C. Mancini† and Michel Aurrand-Lions*

Aix-Marseille Université, Centre National de la Recherche Scientifique (CNRS), Institut National de la Santé et de la Recherche Médicale (INSERM), Institut Paoli Calmettes, Centre de Recherche en Cancérologie de Marseille (CRCM), Equipe Labellisée Ligue Nationale Contre le Cancer 2020, Marseille, France

In the bone marrow (BM) of adult mammals, haematopoietic stem cells (HSCs) are retained in micro-anatomical structures by adhesion molecules that regulate HSC quiescence, proliferation and commitment. During decades, researchers have used engraftment to study the function of adhesion molecules in HSC’s homeostasis regulation. Since the 90’s, progress in genetically engineered mouse models has allowed a better understanding of adhesion molecules involved in HSCs regulation by BM niches and raised questions about the role of adhesion mechanisms in conferring drug resistance to cancer cells nested in the BM. This has been especially studied in acute myeloid leukaemia (AML) which was the first disease in which the concept of cancer stem cell (CSC) or leukemic stem cells (LSCs) was demonstrated. In AML, it has been proposed that LSCs propagate the disease and are able to replenish the leukemic bulk after complete remission suggesting that LSC may be endowed with drug resistance properties. However, whether such properties are due to extrinsic or intrinsic molecular mechanisms, fully or partially supported by molecular crosstalk between LSCs and surrounding BM micro-environment is still matter of debate. In this review, we focus on adhesion molecules that have been involved in HSCs or LSCs anchoring to BM niches and discuss if inhibition of such mechanism may represent new therapeutic avenues to eradicate LSCs.

Keywords: adhesion, haematopoietic stem cell, leukemic stem cell, haematopoiesis, bone marrow, acute myeloid leukaemia

INTRODUCTION

Haematopoiesis takes place in the bone marrow of adult mammals and is the process leading to the formation of blood components throughout life. Haematopoietic stem cells (HSCs) are at the apex of the haematopoietic hierarchy and are able to self-renew and to differentiate into all blood cell types. The balance between differentiation and self-renewal is controlled by intrinsic properties of HSC and extrinsic cues delivered by the bone marrow microenvironment in micro-anatomical sites called “niches”.

Frontiers in Immunology | www.frontiersin.org
November 2021 | Volume 12 | Article 756231

doi: 10.3389/fimmu.2021.756231
The concept of niche has been formulated by R. Schofield in 1978 who proposed that stem cell association with other cells prevents maturation while its progeny proliferate and differentiate, unless they can occupy a similar ‘niche’ (1). Although this working hypothesis turned to be true, its formal proof has long time been hampered by the lack of methods allowing precise localization of un-manipulated HSC within their niche (2, 3). In addition, because HSC activity has been essentially studied in transplantation assays, it has been difficult to decipher whether experimental assays were measuring intrinsic HSC stemness of engrafted cells or their ability to find a supportive niche in which they can self-renew (4, 5). The development of constitutive knock-out mouse models in the early 90’s, and conditional or inducible models later on, has represented a breakthrough to study the contribution of niche components to mammalian haematopoiesis (6, 7). Accordingly, a bibliographic search using combination of the words “haematopoiesis, adhesion and niche” reveals that only seven publications combine such words between 1989 and 2000, while more than hundred papers have been published thereafter. This likely indicates that adhesion was initially considered as an intrinsic property of HSC, while it has been integrated to the niche concept later on. This review is focused on adhesion molecules implicated in HSC or acute myeloid LSC interaction with the BM microenvironment (Figure 1).

ADHESION MOLECULES INVOLVED IN HSC RETENTION IN THE BONE MARROW

With the exception of CD44, haematopoietic adhesion molecules belong to the immunoglobulin superfamily (Ig Sf), the cadherin family, the selectin family or the integrin family. Adhesion molecules promote cell/cell or cell/extracellular-matrix (ECM) interactions and deliver survival signals to haematopoietic cells. Reciprocally, stromal and endothelial cells express adhesion molecules interacting with haematopoietic cells or ECM contributing to the maintenance of bone marrow architecture.

Integrins

Integrins are non-covalent heterodimers of α and β chains. In mammals, 18 α and 8 β subunits form 24 different integrin heterodimers involved in embryonic development and maintenance of tissue homeostasis. α/β chain pairing and integrin interaction with ECM, cell surface molecules or soluble factors have been extensively reviewed in the past and will not be described in further details here (8–11).

One key property of integrins is that they can be expressed in inactive, activated or clustered state on the surface. The switch between inactive and active state results in increased ligand affinity as a consequence of inside-out or outside-in signalling. Integrin clustering further induces cytoskeleton rearrangement and enhanced cell signalling (Figure 2).

Among α4β1, α5β1, α6β1, α6β4 and α9β1 integrins that have been involved in interaction of HSC with bone marrow microenvironment (12–18), α4β1 is the most studied. The integrins α4β1 and α5β1 are activated by inside-out signalling that involves cytokines and divalent cations present in the bone marrow microenvironment, suggesting that they are essential for HSC retention in the bone marrow (19, 20). Accordingly, HSPC mobilization using G-CSF is correlated to decreased α4 integrin expression (21) and deletion or inhibition of α4β1 integrin result in accumulation of HSC in the blood circulation (22–25). Similar results were obtained using antibody against VCAM-1, suggesting a central role of α4β1/VCAM-1 axis in HSC retention in the bone marrow (26). This is consistent with the finding...
that β1 null HSC fail to engraft in irradiated recipient and that β1 null HSC from chimeric embryos are unable to seed foetal liver (27, 28).

Along this line, β7-deficient mice do not have defects in HSCs function (29), while interaction between α4β7 and MadCAM-1 (mucosal addressin cell adhesion molecule-1) accounts for half of the α4-integrin mediated homing activity to the bone marrow (30, 31). Therefore, it seems that β1 integrin heterodimers play a prominent role in bone marrow HSC retention as further supported by the fact that the dual α9β1/α4β1 inhibitor BOP ((N-(benzenesulfonyl)-L-prolyl-L-O-(1-pyrrolidinylcarbonyl) tyrosine) induces a rapid mobilization of HSCs including those that are located in the endosteal region which bind thrombin-cleaved osteopontin with high affinity (32). This is also supported by the finding that patients treated with natalizumab, an anti-α4 integrin antibody, present increased levels of circulating CD34+ progenitor cells associated with a higher migratory profile as compared to GM-CSF mobilization (33, 34).

Finally, it has recently been reported in zebrafish that VCAM-1+ patrolling macrophages can interact with HSCs in an α4β1 dependent manner and contribute to their retention in the niche (35). This study confirms earlier findings in mouse models showing that macrophages contribute to HSC retention within niches through integrin-mediated interactions (36–38).

Selectins
The selectin family encompasses three members: E- (Endothelial), P- (Platelets) and L- (Leukocyte) selectins expressed by endothelial cells (E- and P- selectins), platelets (P-Selectin) and leukocytes (L-Selectin). They have been initially involved in the rolling of haematopoietic cells along vessels in flowing blood (39–41).

The minimal requirements for Ca2+-dependent ligand binding to selectins are the tetra-saccharides Sialyl Lewis X (SleX) and Sialyl Lewis A (SleA) (42, 43). As reviewed elsewhere (44), SleX and SleA synthesis requires several enzymes including α(1→3)-fucosyltransferase activities as illustrated by defective selectin-dependent leucocyte trafficking in FucT-VII deficient mice (45). This is reminiscent of the phenotype of P-Selectin deficient mice that harbour elevated number of circulating neutrophils, loss of leucocyte rolling in mesenteric venules and delayed leucocyte recruitment in peritonitis model (46). In contrast, E-selectin deficient mice have no defect in neutrophils trafficking suggesting a compensatory mechanism mediated by P-selectin (47).

The study of double knockout mice for E- and P-selectin has revealed defect in haematopoiesis with increased extramedullary erythropoiesis and reduced haematopoietic progenitor cell homing in irradiated deficient mice upon transplantation (41, 48). However, such functions were mostly attributed to HSPC homing and it is only in 2012 that E-selectin was shown to mediate HSC proliferation at the expense of self-renewal (49).

In contrast to E- and P-Selectin, early haematopoietic defects in L-Selectin-deficient mice have not been reported so far (50).

Cadherins
Cadherins are transmembrane glycoproteins characterized by tandemly repeated sequence motifs in their extracellular segments that allow homophilic interactions in a Ca2+-dependent manner (51). N-cadherin is not only expressed by neural cells but also by HSCs and spindle shaped osteoblastic cells lining the bones, called “Spindle-shaped N-cadherin”CD45+ Osteoblastic” (SNO) in the original publication. Because conditional inactivation of BMP receptor type IA (BMPRIA) led to expansion of both SNO and HSC, with asymmetric N-Cadherin distribution between SNO and HSC adjacent cells, it has been proposed that N-cadherin-mediated adhesion contributes to HSCs maintenance in endosteal niche (52). This concept was further supported by the fact that the knock-out of
N-cadherin in LSK cells impairs long term engraftment in the bone marrow but not in the spleen (53). However, the latter demonstration used LSK cells, a compartment in which less than 20% of the cells are HSCs. Therefore, the function of N-cadherin mediated adhesion in HSC maintenance has been challenged in several studies. First, it was demonstrated that N-cadherin is not expressed on purified HSCs and that osteoblasts are dispensable for HSC maintenance (54). Second, the conditional deletion of N-cadherin in HSC using Mx1-Cre did not affect haematopoiesis, nor did its specific deletion in osteoblasts (55–57). Therefore, the controversial function of N-cadherin in HSC maintenance has been revisited in the light of the methodology used to study its function (engraftment versus knock-out) and with respect to heterogeneous expression of N-cadherin by HSC subsets (58, 59). This led to the most recent concept that N-cadherin-mediated adhesion of HSC to BM stromal progenitor cells (BMSPC) may only be revealed during emergency haematopoiesis such as the one needed by “reserve” HSC to survive chemotherapy (60).

**Ig Sf Adhesion Molecules**

Several Ig Sf adhesion molecules such as ALCAM (CD166), ESAM, JAM-A or JAM-C are expressed by HSPCs and BM stromal or endothelial cells (61–64). Some others such as ICAM-1 or VCAM-1 are expressed in the BM microenvironment and interact with integrins expressed by HSPCs or contribute to more complex adhesive networks involving IgSf/Integrin as well as IgSf/IgSf interactions such as the JAM family members (65–68). Therefore, early haematopoietic defects reported for IgSf deficient animals have to be interpreted with caution unless specific conditional knock-out mouse models are combined with orthogonal methods such as long-term engraftment. Defects in early haematopoiesis following knockout have been reported for ALCAM, ESAM, VCAM-1, JAM-C, JAM-B and ICAM-1 (Table 1).

**ADHESION MOLECULES INVOLVED IN LSC RETENTION IN THE BONE MARROW**

Similar to HSCs, LSCs are retained into specialized microanatomical sites by adhesive interactions. Indeed, AML development originates from LSC which share with HSCs the ability to self-renew (79, 80). After disease initiation, acute myeloid leukemic burst is accompanied by a remodelling of bone marrow niches that alters the physiological adhesive network of HSC (81–83). Whether adhesive remodelling occurs already at disease initiation in immunocompetent context remains to be addressed, but several adhesive Ligand/Receptor pairs have been involved in AML development in mouse models. Among them, only a limited number of Ligand/Receptor pairs that cross barrier species have been validated as putative therapeutic targets in preclinical setting using patient derived xenograft (PDX) models. This has encouraged some clinical trials targeting LSC adhesion to the niche in order to sensitize these cells to chemotherapy as recently reviewed by A. Villatoro et al. (84). In the next section, we will discuss the adhesion molecules known to contribute to LSC stemness maintenance that belong to the emerging class of adjuvant therapies for LSC eradication in AML.

**CD44**

CD44 is a class I transmembrane glycoprotein that does not belong to an adhesion molecular family and that interacts with ECM ligands such as a as osteopontin, fibronectin or hyaluronan (HA). When CD44 is sialo-fucosylated and bears SleX glycan, it is called HCELL and interacts with E- and L-selectin (85, 86). In addition, several isoforms of CD44 are generated by alternative splicing and associated with different cellular processes (87). CD44 isoforms are widely expressed on AML cells and expression of the CD44-6v isoform has been associated with poor prognosis (88, 89). Functionally, CD44 has been involved in AML cell adhesion to bone marrow stromal cells (90, 91) and ligation of CD44 with HA or activating antibodies such as H90 has been shown to reverse differentiation blockage in AML cells (92). The same H90 activating antibody inhibited homing of AML-LSC to microenvironmental niches reducing the leukemic burden in a PDX setting. This was attributed to opposing effects of the H90 antibody which increases adhesion of normal CD34+CD38− cells to HA but inhibits adhesion of CD34+CD38+ AML blasts to HA (93).

**Integrins**

Overexpression of the integrins α4β1 (CD11b/Mac1), α5, α6 and αv,β3 by AML cells has been associated with poor prognosis (94–96). Indeed, it has early been shown that both β1 and β2 integrin chains are necessary for AML blast adhesion to BM stromal cells (97).

Among the β1 integrins, α4β1 seems to play the most prominent role through its interaction with fibronectin (FN) and VCAM-1. Interaction of integrin α4β1 with FN protects AML cells from chemotheraphy and is associated with the maintenance of minimal residual disease (MRD). Treatment with a blocking antibody against α4β1 abrogates chemoresistence and MRD in mice (98). Similarly, integrin α4β1 interaction with VCAM-1 contributes to drug resistance by activating NF-kB pathway in BM stromal cells which is essential to promote chemoresistence in leukemic cells as demonstrated by inhibition of NF-kB signalling (99). This study illustrates the reciprocal crosstalk between LSC and stromal cells since NF-kB activation in stromal cells upregulates VCAM-1 which serves as a positive feedback loop for leukemic cell adhesion to stromal cells.

More recently, the interaction between the integrin α3β1 and collagen has been shown to confer doxorubicin chemoresistance via the inhibition of Rac-1 (100). This protective effect is reversed by anti-α3β1. Although these studies show the therapeutic potential of integrin inhibition in AML, they do not formally prove that LSC are more addicted to integrin-mediated adhesion than normal HSC. To find such differential adhesive cues, Ebert and collaborators have used results from pooled in vivo shRNA screens. They have found that the integrin α3β1 is essential for leukemic initiation and maintenance but dispensable for normal HSPC activity (101). This was attributed to constitutive...
activation of Syk, a candidate therapeutic target in AML, that is phosphorylated upon engagement of surface receptors including not only $\alpha_\beta_3$ integrin, but also $\beta_3$ integrins (102, 103). In summary, integrin signalling converging toward specific activation pathway such as NF-kB or Syk may represent attractive therapeutic targets.

**E-Selectin**

E- and P-Selectins are constitutively expressed by bone marrow endothelial cells and play a role in HSPC rolling on micro vessels (39, 104, 105). However, they induce contrasting effects in HSPC upon interaction in vitro (86, 106–108). The study of early haematopoiesis in E-Selectin deficient mice (Sele$^{-/-}$) has revealed that inhibition of E-Selectin in vivo increases dormancy and self-renewal of HSC (49). This is not mediated by the conventional ligands of E-Selectin since HSC isolated from mice deficient for P-selectin glycoprotein ligand-1 (Psgl-1 encoded by Selpg), HCELL (Cd44) or both do not present increased dormancy. In contrast, LSC of AML make a different selectin receptor usage that promotes AML cell survival. Indeed, leukemic cells present alterations in glycosylation which leads to expression of fucosylated ligands such as PSLG-1 (CD162) that activate PI3K/Akt survival pathway (109, 110). Even more interesting is the fact that inhibition of E-selectin interaction with its ligands using a glycomimetic stimulates proliferation of AML blast while dampening HSC cycling. Since these finding have been confirmed in preclinical mouse models, this led to the opening of phase II/III clinical trials combining inhibition of E-selectin with conventional chemotherapy in AML (NCT03616470, NCT03701308).

**Ig Sf Adhesion Molecules**

Most of the Ig Sf molecules expressed by normal HSC are also expressed by LSCs in AML, however only few of them allows enrichment of cells with leukemic initiating activity associated to poor prognosis. We have shown that JAM-C is expressed by a fraction of LSCs presenting high activation of Src kinase family and enriched for leukaemia initiating activity. Increased frequencies of JAM-C expressing cells identify AML patients with poor disease outcome (111). This has been confirmed in an independent study on a large cohort of AML patients (112, 113). The "CD34$^+$ CD38$^{low}$ CD123$^+$ CD41$^+$" JAM-C$^+$ cells are enriched tenfold for LSCs as compared to cells lacking JAM-C expression within the same compartment suggesting that JAM-C may play a cell-autonomous signalling function at the transition between healthy HSC and LSC. This would be consistent with results showing that PDX or AML cell line engraftment of JAM-C expressing cells is only partially dependent on JAM-B expression by recipient mice and with results showing that silencing JAM-C expression is sufficient to decrease Src family kinase activation (111). This could be due to promiscuous cis-interactions between JAM-C and the integrin $\alpha_4\beta_1$ since JAM-B has been shown to bind $\alpha_4\beta_1$ when interaction is facilitated by the simultaneous engagement with JAM-C (67).

NCAM1(CD56) is another Ig Sf molecules whose expression is correlated with poor overall survival in AML with t(8;21) (q22; q22) and highly expressed by LSC in mouse AML models using MLL-AF9 or Hoxa9-Meis1 as driver translocations (114). NCAM1 expression confers drug resistance to AML cells and knockdown of NCAM1 sensitizes blasts to genotoxic agents (115). This is likely due to constitutive activation of the MEK-ERK pathway, similar to what has been reported during neural development (116). These two examples pave the way for the use of Ig Sf molecule expression to stratify patients eligible to treatments targeting downstream signalling pathways such as Src or Mek/Erk.

**OUTLOOK**

Recent studies have shown that HSC niches are altered during AML development with strong coordinated changes of the osteolineage and endothelial compartments, and alterations of the mesenchymal compartment occurring early during leukemic development. Whether such alterations depend on adhesive interaction of

---

**TABLE 1 | Knock-out mice of Ig Sf molecules presenting haematopoietic defects.**

| Adhesion molecule | Year | Ligands | Altered phenotype | Haematopoietic phenotype | References |
|-------------------|------|---------|-------------------|-------------------------|-----------|
| ICAM-1            | 1994 | $\alpha_4\beta_2$ | cardiovascular, cellular, digestive/alimentary, growth/size/body, haematopoietic, homeostasis, immune, mortality/aging, neoplasm, vision/eye | Expansion of Lt-HSC compartment associated with impaired quiescence and myeloid expansion (69, 70) |
| VCAM-1            | 1995 | $\alpha_4\beta_1$ | cardiovascular, embryonic, growth/size/body, homeostasis, mortality/aging, immune | Increased frequencies of circulating progenitors (65, 71) |
| ESAM              | 2003 | ESAM    | cardiovascular, cellular, growth/size/body, haematopoietic, immune | Increased HSCs frequency and proliferation compared to wild-type mice (63, 72) |
| ALCAM (CD166)     | 2004 | ALCAM   | nervous system, vision/eye, haematopoietic CD6 | Defects in Lt-HSC engraftment although no differences in absolute numbers of HSCs were observed (61, 73, 74) |
| JAM-C             | 2004 | JAM-C   | behaviour, cardiovascular, cellular, craniofacial, digestive/alimentary, endocrine/exocrine, growth/size/body, haematopoietic, immune, integument, mortality/aging, endocrine/exocrine | Increased number of CMOs (75-77) |
| JAM-B             | 2011 | JAM-B   | $\alpha_4\beta_2$ | Loss of quiescent HSCs and exacerbated response to mobilizing agent (78) |
leukemic initiating cells with BM microenvironment resulting in localization of LSCs in specific sites remain to be defined, but it seems that LSC take advantage of pre-existing adhesive pathways in the niche to maintain survival signals and dormancy that protect them from chemotherapies. Therefore, the selective disruption of LSC from their niche by targeting single adhesion molecule remains a major limitation for current therapies. A better knowledge of the differences between LSC/Niche and HSC/Niche integrated adhesive networks will help refining specificity of therapeutic strategies directed against adhesive cues.

All authors contributed to the article and approved the submitted version.

**FUNDING**

JG was supported by a grant from the French Society of Haematology (SFH). CT was supported by a grant from the ligue nationale contre le cancer. The work was supported by the Ligue Nationale Contre le Cancer, ELN2020.

**REFERENCES**

1. Schofield R. The Relationship Between the Spleen Colony-Forming Cell and the Haemopoietic Stem Cell. *Blood Cells* (1978) 4:7–25.
2. Pinho S, Frenette PS. Haematopoietic Stem Cell Activity and Interactions With the Niche. *Nat Rev Mol Cell Biol* (2019) 20:303–20. doi: 10.1038/s41580-019-0103-9
3. Crane GM, Jeffery E, Morrison SJ. Adult Haematopoietic Stem Cell Niches. *Nat Rev Immunol* (2017) 17:573–90. doi: 10.1038/nri.2017.53
4. Lemischka IR. Clonal, In Vivo Behavior of the Totipotent Hematopoietic Stem Cell. *Semin Immunol* (1991) 3:349–55.
5. Mielcarek M, Reems J, Tokor-Storb B. Extrinsic Control of Stem Cell Fate: Practical Considerations. *Stem Cells* (1997) 15(Suppl 1):229–232; discussion 233–236. doi: 10.1002/stem.5530150831
6. Chen KG, Johnson KR, Robey PG. Mouse Genetic Analysis of Bone Marrow Stem Cell Niches: Technological Pitfalls, Challenges, and Translational Considerations. *Stem Cell Rep* (2017) 9:1343–58. doi: 10.1016/j.stemcr.2017.09.014
7. Joseph C, Quach JM, Walkley CR, Lane SW, Lo Celso C, Purton LE. Deciphering Hematopoietic Stem Cell Niches in Their Niche: A Critical Appraisal of Genetic Models, Lineage Tracing, and Imaging Strategies. *Stem Cells* (2013) 13:520–33. doi: 10.1002/stem.2013.10.010
8. Samarzija I, Dekanić A, Humphries JD, Paradzik M, Stojanović N, Humphries MJ, et al. Integrin Crosstalk Contributes to the Complexity of Signalling and Unpredictable Cancer Cell Fates. *Cancers (Basel)* (2020) 12: E1910. doi: 10.3390/cancers12071910
9. Hynes RO. Integrins: Versatility, Modulation, and Signaling in Cell Adhesion. *Cell* (1992) 69:11–25. doi: 10.1016/0092-8674(92)90115-s
10. Humphries JD, Byron A, Humphries MJ, Integrin Ligands at a Glance. *J Cell Sci* (2006) 119:3901–3. doi: 10.1242/jcs.03098
11. Harburger DS, Calderwood DA. Integrin Signalling at a Glance. *J Cell Sci* (2009) 122:159–63. doi: 10.1242/jcs.018093
12. Grassinger J, Haylock DN, Storan MJ, Haines GO, Williams B, Whitty GA, et al. Thrombin-Cleaved Osteopontin Regulates Hemopoietic Stem and Progenitor Cell Functions Through Interactions With Alpha4Beta1 and AlphasBeta1 Integrins. *Blood* (2009) 114:49–59. doi: 10.1182/blood-2009-01-197988
13. Hertz B, Volkman T, Irle S, Loechelt C, Neubauer A, Brendel C. α4 Integrin Levels on Mobilized Peripheral Blood Stem Cells Predict Rapidity of Engraftment in Patients Receiving Autologous Stem Cell Transplantation. *Blood* (2011) 118:2362–5. doi: 10.1182/blood-2011-02-331918
14. Qian H, Tryggvason K, Jacobsen SE, Ekblom M. Contribution of Alpha6 Integrins to Hematopoietic Stem and Progenitor Cell Homing to Bone Marrow and Collaboration With Alpha4 Integrins. *Blood* (2006) 107:3503–10. doi: 10.1182/blood-2005-10-3932
15. Schreiber TD, Steinl C, Esil M, Abele H, Geiger K, Müller CA, et al. The Integrin Alpha4Beta1 on Hematopoietic Stem and Progenitor Cells: Involvement in Cell Adhesion, Proliferation and Differentiation. *Haematologica* (2009) 94:1493–501. doi: 10.3324/haematol.2009.06072
16. Notta F, Doulavos S, Laurenti E, Poeppl A, Jurisica I, Dick JE. Isolation of Single Human Hematopoietic Stem Cells Capable of Long-Term Multilineage Engraftment. *Science* (2011) 333:218–21. doi: 10.1126/science.1201219
17. Huntsman HD, Bat T, Cheng H, Cash A, Cherukuv P, Fu J-F, et al. Human Hematopoietic Stem Cells From Mobilized Peripheral Blood can be Purified Based on CD49f Integlin Expression. *Blood* (2015) 126:1631–3. doi: 10.1182/blood-2015-07-660670
18. Soligo D, Schirò R, Luksch R, Manara G, Quirici N, Parravicini C, et al. Expression of Integrins in Human Bone Marrow. *Br J Haematol* (1990) 76:323–32. doi: 10.1111/j.1365-2141.1990.tb06363.x
19. Takamatsu Y, Simmons PJ, Lévesque JP. Dual Control by Divalent Cations and Mitogenic Cytokines of Alpha 4 Beta 1 and Alpha 5 Beta 1 Integrin Avidity Expressed by Human Hemopoietic Cells. *Cell Adhes Commun* (1998) 5:349–66. doi: 10.3109/15419069809010781
20. Lévesque JP, Leavesey DJ, Niutta S, Vadas M, Simmons PJ. Cytokines Increase Human Hemopoietic Cell Adhesiveness by Activation of Very Late Antigen (VLA)-4 and VLA-5 Integrins. *J Exp Med* (1995) 181:1805–15. doi: 10.1084/jem.181.5.1805
21. Prosper F, Stonecek D, McCarthy JB, Verfaillie CM. Mobilization and Homing of Peripheral Blood Progenitors Is Related to Reversible Downregulation of Alpha4Beta1 Integrin Expression and Function. *J Clin Invest* (1998) 101:2456–67. doi: 10.1172/JCI18188
22. Arroyo AG, Yang JT, Bayburn H, Hynes RO. Differential Requirements for Alpha4 Integrins During Fetal and Adult Hematopoiesis. *Cell* (1996) 85:997–1008. doi: 10.1016/s0092-8674(96)01301-x
23. Scott LM, Priestley GV, Papayannopoulos T. Deletion of Alpha4 Integrins From Adult Hematopoietic Cells Reveals Roles in Homeostasis, Regeneration, and Homing. *Blood Cells* (2003) 23:9349–60. doi: 10.1128/MCB.23.24.9349-9360.2003
24. Papayannopoulos T, Nakamoto B. Peripheralization of Hemopoietic Progenitors in Primates Treated With Anti-VLA4 Integrin. *Proc Natl Acad Sci U.S.A.* (1993) 90:3937–8. doi: 10.1073/pnas.90.20.39374
25. Ramirez P, Rettig MP, Uy GL, Deych E, Holt MS, Ritchey JK, et al. BI035192, a Small Molecule Inhibitor of VLA-4, Mobilizes Hematopoietic Stem and Progenitor Cells. *Blood* (2009) 114:1340–3. doi: 10.1182/blood-2008-10-184721
26. Papayannopoulos T, Craddock C, Nakamoto B, Priestley GV, Wolf NS. The VLA4/VCAM-1 Adhesion Pathway Defines Contrasting Mechanisms of Lodgement of Transplanted Murine Hemopoietic Progenitors Between Bone Marrow and Spleen. *Proc Natl Acad Sci USA* (1995) 92:9647–51. doi: 10.1073/pnas.92.21.9647

**AUTHOR CONTRIBUTIONS**

JG wrote and revised the manuscript. CT, CF, and SM revised the manuscript and MA-L supervised the work.

**ACKNOWLEDGMENTS**

We apologize for colleagues whose work has not been cited due to space limitation. Figures 1, 2 were created by JG with BioRender.com.
Grenier et al. Adhesion Molecules in Niche Retention

33. Jing D, Oelschlaegel U, Ordemann R, Hölig K, Ehninger G, Reichmann H, Zohren F, Toutzaris D, Klärner V, Hartung H-P, Kieseier B, Haas R. The

42. Tvaros

30. Murakami JL, Xu B, Franco CB, Hu X, Galli SJ, Weissman IL, et al. Evidence

27. Potocnik AJ, Brakebusch C, Fassler R. Fetal and Adult Hematopoietic Stem Cells Require Beta1 Integrin Function for Colonizing Fetal Liver, Spleen, and Bone Marrow. Immunity (2000) 12:653–63. doi: 10.1016/S1074-7613(00)00216-2

28. Hirsch E, Iglesias A, Potocnik AJ, Hartmann U, Fässler R. Impaired Recruitment Into Bone Marrow Following Transplantation. Blood (2004) 104:2020–6. doi: 10.1182/blood-2003-12-4157

29. Bungartz G, Stiller S, Bauer M, Müller W, Schippers A, Wagner N, et al. Adult Murine Hematopoiesis can Proceed Without Beta1 and Beta7 Integrins. Blood (2006) 108:1857–64. doi: 10.1182/blood-2005-07-006758

30. Murakami JL, Xu B, Franco CB, Hu X, Galli SJ, Weissman IL, et al. Evidence That β7 Integrin Regulates Hematopoietic Stem Cell Homing and Engraftment Through Interaction With MAdCAM-1. Stem Cells Dev (2016) 25:18–26. doi: 10.1089/scd.2014.0551

31. Katayama Y, Hidalgo A, Peired A, Fenretre PS, Inteegrin alpha4beta2 and Its Counterreceptor MADCAM-1 Contribute to Hematopoietic Progenitor Recruitment Into Bone Marrow Following Transplantation. Blood (2004) 108:2020–6. doi: 10.1182/blood-2003-12-4157

32. Cao B, Zhang Z, Grassinger J, Williams B, Heazlewood CK, Churches QI, et al. Therapeutic Targeting and Rapid Mobilization of Endostate HSC Using a Small Molecule Integrin Antagonist. Nat Commun (2016) 7:11100. doi: 10.1038/ncomms11107

33. Jung D, Oelschlaegel U, Ordemann R, Hölig K, Ehnheimer G, Reichmann H, et al. CD49d Blockade by Natalizumab in Patients With Multiple Sclerosis Affects Steady-State Hematopoiesis and Mobilizes Progenitors With a Distinct Phenotype and Function. Bone Marrow Transplant (2010) 45:1499–96. doi: 10.1038/bmt.2009.381

34. Zohren F, Toutzaris D, Klärner V, Hartung H-P, Kieseier B, Haas R. The Monoclonal Anti-VLA-4 Antibody Natalizumab Mobilizes CD34+ Hematopoietic Progenitor Cells in Humans. Blood (2008) 113:3893–5. doi: 10.1182/blood-2007-10-123039

35. Li D, Xue W, Li L, Dong M, Wang J, Wang X, et al. VCAM-1+ Macrophages Guide the Homing of HSPCs to a Vascular Niche. Nature (2018) 564:119–24. doi: 10.1038/s41586-018-0709-7

36. Jacobsen RN, Forristal CE, Raggatt LJ, Nowlan B, Barbier V, Kaur S, et al. Mobilization With Granulocyte Colony-Stimulating Factor Blocks Medullar Dormancy, Self Renewal and Chemoresistance. Nat Med (2012) 18:1651–7. doi: 10.1038/nm.2969

37. Arbonés ML, Ord DC, Ley K, Rateh H, Maynard-Curry C, Otten G, et al. Lymphocyte Homing and Leukocyte Rolling and Migration Are Impaired in L-Selectin-Deficient Mice. Immunity (1994) 1:247–60. doi: 10.1016/1074-7613(94)90076-0

38. Hatta K, Nose A, Nagafuchi A, Takeichi M. Cloning and Expression of cDNA Encoding a Nuclear Calcium-Dependent Cell Adhesion Molecule: Its Identity in the Cadherin Gene Family. J Cell Biol (1998) 106:873–81. doi: 10.1083/jcb.106.3.873

39. Zhang J, Niu C, Ye L, Huang H, He X, Tong W-G, et al. Identification of the Haematopoietic Stem Cell Niche and Control of the Niche Size. Nature (2003) 425:836–41. doi: 10.1038/nature02041

40. Hosokawa K, Arai F, Yoshihara H, Iwasaki H, Nakamura Y, Gomei Y, et al. Knockdown of N-Cadherin Suppresses the Long-Term Engraftment of Hematopoietic Stem Cells. Blood (2010) 116:5534–6. doi: 10.1182/blood-2009-05-224887

41. Kiel MJ, Radice GL, Morrison SJ. Lack of Evidence That Hematopoietic Stem Cells Depend on N-Cadherin-Mediated Adhesion to Osteoblasts for Their Maintenance. Cell Stem Cell (2007) 1:204–17. doi: 10.1016/j.stem.2007.06.001

42. Kiel MJ, Acar M, Radice GL, Morrison SJ. Hematopoietic Stem Cells Do Not Depend on N-Cadherin to Regulate Their Maintenance. Cell Stem Cell (2009) 4:170–9. doi: 10.1016/j.stem.2008.10.005

43. Bromberg O, Frisch BJ, Weber JM, Porter RL, Civitelli R, Calvi LM. Osteoblastic N-Cadherin is Not Required for Microenvironmental Support and Regulation of Hematopoietic Stem and Progenitor Cells. Blood (2012) 120:303–13. doi: 10.1182/blood-2011-09-377853

44. Greenbaum AM, Revollo LD, Wolosynek JRF, Civitelli R, Link DC. N-Cadherin in Osteolineage Cells Is Not Required for Maintenance of Hematopoietic Stem Cells. Blood (2012) 120:295–302. doi: 10.1182/blood-2011-09-377457

45. Ari A, Hosokawa K, Toyama H, Matsumoto Y, Suda T. Role of N-Cadherin in the Regulation of Hematopoietic Stem Cells in the Bone Marrow Niche. Ann N Y Acad Sci (2012) 1256:72–7. doi: 10.1111/j.1749-6632.2012.06576.x

46. Haug JS, He XC, Grindley JC, Wunderlich JP, Gaudenz K, Ross JT, et al. N-Cadherin Expression Level Distinguishes Reserved Versus Primed States of Hematopoietic Stem Cells. Cell Stem Cell (2008) 2:567–79. doi: 10.1016/j.stem.2008.01.017

47. Zhao M, Tao F, Venkataraman A, Li Z, Smith SE, Unruh J, et al. N-Cadherin-Expressing Bone and Marrow Stromal Progenitor Cells Maintain Reserve Hematopoietic Stem Cells. Cell Rep (2019) 26:652–669.e6. doi: 10.1016/j.celrep.2018.12.093

48. Chitteti BR, Kobayashi M, Cheng Y, Zhang H, Poteat BA, Brockmeier HE, et al. CD166 Regulates Human and Murine Hematopoietic Stem Cells and the Hematopoietic Niche. Blood (2014) 124:519–29. doi: 10.1182/blood-2014-03-565721

49. Ooi AGL, Karsunky H, Majeti R, Butz S, Vestweber D, Ishida T, et al. The Adhesion Molecule Esam is a Novel Hematopoietic Stem Cell Marker. Stem Cells (2009) 27:653–61. doi: 10.1634/stemcells.2008-0824

50. Yokota T, Oritani K, Butz S, Kowake K, Kincade PW, Miyata T, et al. The Endothelial Antigen ESAM Marks Primitive Hematopoietic Progenitors Throughout Life in Mice. Blood (2009) 113:2914–23. doi: 10.1182/blood-2008-07-167106
64. Sugano Y, Takeuchi M, Hirata A, Matsushita H, Kitamura T, Tanaka M, et al. Junctional Adhesion Molecule-A, JAM-A, Is a Novel Cell-Surface Marker for Long-Term Repopulating Hematopoietic Stem Cells. *Blood* (2008) 111:1167–72. doi: 10.1182/blood-2007-03-081554

65. Ulyanova T, Scott LM, Priestley GV, Jiayi J, Nakamoto B, Koni PA, et al. VCAM-1 Expression in Adult Hematopoietic and Nonhematopoietic Cells Is Controlled by Tissue-Inductive Signals and Reflects Their Developmental Origin. *Blood* (2005) 106:86–94. doi: 10.1182/blood-2004-09-3147

66. Balzano M, De Grandis M, Vu Manh T-P, Chasson L, Bardin F, Farina A, et al. Nidogen-1 Contributes to the Interaction Network Involved in Pro-B Cell Retention in the Peri-Sinusoidal Hematopoietic Stem Cell Niche. *Cell Rep* (2019) 26:3257–3271.e8. doi: 10.1016/j.celrep.2019.02.065

67. Cunningham SA, Rodriguez JM, Arrate MP, Tran TM, Brock TA. JAM2 Interacts With Alpha5beta1. *Facultative Niche Retention in AML*. *J Biol Chem* (2002) 277:27589–92. doi: 10.1074/jbc.C200331200

68. Lamagna C, Meda P, Mandicourt G, Brown J, Gilbert RJC, Jones EY, et al. DISRUPTION OF ENDOTHELIAL CELL-SELECTIVE ADHESION MOLECULE INHIBITS ANGIOGENIC PROCESSES. *In Vito* and In Vivo. *J Biol Chem* (2003) 278:34598–604. doi: 10.1074/jbc.M304980200

69. Xu H, Gonzalez JA, St Pierre Y, Williams JR, Kupper TS, Cotran RS, et al. LEUKCYTOSIS AND RESISTANCE TO SEPTIC SHOCK IN INTERCELLULAR ADHESION MOLECULE 1-DEFICIENT MICE. *J Exp Med* (1994) 180:95–109. doi: 10.1084/jem.180.1.95

70. Kwee L, Burns DK, Rumberger JM, Norton C, Wolitzky B, Terry R, et al. Creation and Characterization of E-Selectin- and VCAM-1-Deficient Mice. *Ciba Found Symp* (1995) 189:17–28; discussion 28-34, 77–78. doi: 10.1002/9780470514719.ch3

71. Ishida T, Kundra RK, Yang E, Hirata K, Ho Y-D, Quertermous T. Targeted Disruption of Endothelial Cell-Selective Adhesion Molecule Inhibits Angiogenic Processes *In Vivo* and In Vivo. *J Biol Chem* (2003) 278:34598–604. doi: 10.1074/jbc.M304980200

72. Weiner JA, Koo SJ, Nicolas S, Fraboulet S, Pfaff SL, Pouquet O, et al. Axon Fasciculation Defects and Retinal Dysplasias in Mice Lacking the Immunoglobulin Superfamily Adhesion Molecule BEN/ALCAM/Sc1. *Mol Cell Neurosci* (2004) 27:59–69. doi: 10.1016/j.mcn.2004.06.005

73. Jeannet R, Cai Q, Liu H, Vu H, Kuo Y-H. Alcam Regulates Long-Term Marrow Niche Impairs Quiescence and Repopulation of Hematopoietic Stem Cells. *Stem Cell Rep* (2018) 11:258–73. doi: 10.1016/j.stemcr.2018.05.016

74. Praetor A, McBride JM, Chiu H, Rangell L, Cabote L, Lee WP, et al. GENETIC DELETION OF JAM-C REVEALS A ROLE IN MYELOID PROGENITOR GENERATION. *Blood* (2009) 113:1919–24. doi: 10.1182/blood-2008-10-180526

75. Lapidot T, Sirard C, Vormoor J, Murdoch B, Hoang T, Caceres-Cortes J, et al. INTEGRATION OF OMICS UNVEIL THE BONE-MARROW NICHE AS INITIATING CELLS. *Cell Rep* (2019) 29:560–71. doi: 10.1016/j.celrep.2019.02.065

76. Beltrán M, Cai Q, Kuo Y-H, Li J, Cardona AB, et al. INTEGRATION OF OMICS UNVEIL THE BONE-MARROW NICHE AS INITIATING CELLS. *Cell Rep* (2019) 26:3257–3271.e8. doi: 10.1016/j.celrep.2019.02.065

77. Baryawno N, Przybylski D, Kowalczyk MS, Kfox Y, Severe N, Gustafsson K, et al. A TUMOR CELL PREPARED BY THE PARENTAL Tumor CELLS/initiates differentiation and reduces the export of the derived Cells. *Cell Rep* (2019) 35:109119. doi: 10.1016/j.celrep.2021.109119

78. Duarte D, Hawkins ED, Akinduro O, Ang H, De Filippo K, Kong JY, et al. INHIBITION OF ENDOSTEAL VASCULAR NICHE REMODELING RESCUES HEMATOPOIETIC STEM CELL LOSS IN AML. *Cell Stem Cell* (2018) 22:64–77.e6. doi: 10.1016/j.stem.2017.11.006

79. Villatoro A, Konieczny J, Cuminetti V, Arranz L. Leukemia Stem Cell Release From the Stem Cell Niche to Treat Acute Myeloid Leukemia. *Front Cell Dev Biol* (2020) 8:607. doi: 10.3389/fcell.2020.00607

80. Zoller M. CD44, Hyaluronan, the Hematopoietic Stem Cell, and Leukemia-Initiating Cells. *Front Immunol* (2015) 6:235. doi: 10.3389/fimmu.2015.00325

81. Bonnet D, Dick JE. Human Acute Myeloid Leukemia Is Organized as a Hierarchy That Originates From a Primitive Hematopoietic Cell. *Nat Med* (2003) 9:1158–64. doi: 10.1097/01.nhm.2003.05.016

82. M. CD44, Hyaluronan, the Hematopoietic Stem Cell, and Leukemia-Initiating Cells. *Front Immunol* (2015) 6:235. doi: 10.3389/fimmu.2015.00325

83. Duarte D, Hawkins ED, Akinduro O, Ang H, De Filippo K, Kong JY, et al. INHIBITION OF ENDOSTEAL VASCULAR NICHE REMODELING RESCUES HEMATOPOIETIC STEM CELL LOSS IN AML. *Cell Stem Cell* (2018) 22:64–77.e6. doi: 10.1016/j.stem.2017.11.006

84. Zoller M. CD44, Hyaluronan, the Hematopoietic Stem Cell, and Leukemia-Initiating Cells. *Front Immunol* (2015) 6:235. doi: 10.3389/fimmu.2015.00325

85. Villatoro A, Konieczny J, Cuminetti V, Arranz L. Leukemia Stem Cell Release From the Stem Cell Niche to Treat Acute Myeloid Leukemia. *Front Cell Dev Biol* (2020) 8:607. doi: 10.3389/fcell.2020.00607

86. Zoller M. CD44, Hyaluronan, the Hematopoietic Stem Cell, and Leukemia-Initiating Cells. *Front Immunol* (2015) 6:235. doi: 10.3389/fimmu.2015.00325

87. Baryawno N, Przybylski D, Kowalczyk MS, Kfox Y, Severe N, Gustafsson K, et al. A TUMOR CELL PREPARED BY THE PARENTAL Tumor CELLS/initiates differentiation and reduces the export of the derived Cells. *Cell Rep* (2019) 35:109119. doi: 10.1016/j.celrep.2021.109119

88. Duarte D, Hawkins ED, Akinduro O, Ang H, De Filippo K, Kong JY, et al. INHIBITION OF ENDOSTEAL VASCULAR NICHE REMODELING RESCUES HEMATOPOIETIC STEM CELL LOSS IN AML. *Cell Stem Cell* (2018) 22:64–77.e6. doi: 10.1016/j.stem.2017.11.006

89. Villatoro A, Konieczny J, Cuminetti V, Arranz L. Leukemia Stem Cell Release From the Stem Cell Niche to Treat Acute Myeloid Leukemia. *Front Cell Dev Biol* (2020) 8:607. doi: 10.3389/fcell.2020.00607

90. Zoller M. CD44, Hyaluronan, the Hematopoietic Stem Cell, and Leukemia-Initiating Cells. *Front Immunol* (2015) 6:235. doi: 10.3389/fimmu.2015.00325
101. Miller PG, Al-Shahrouf F, Hartwell KA, Chu LP, Jaras M, Puram RV, et al. In Vivo RNAi Screening Identifies a Leukemia-Specific Dependence on Integrin α₃β₇ Signaling. Cancer Cell (2013) 24:45–58. doi: 10.1016/j.ccr.2013.05.004

102. Hahn CK, Berchuck JE, Ross KN, Kakoza RM, Clauser K, Schinzel AC, et al. Proteomic and Genetic Approaches Identify Syk as an AML Target. Cancer Cell (2009) 16:281–94. doi: 10.1016/j.ccr.2009.08.018

103. Oellerich T, Oellerich MF, Engelke M, Münch S, Nimz M, et al. β2 Integrin-Derived Signals Induce Cell Survival and Proliferation of AML Blasts by Activating a Syk/STAT Signaling Axis. Blood (2013) 121:3889–3899. doi: 10.1182/blood-2012-09-457887

104. Schweitzer KM, Dräger AM, van der Valk P, Thijsen SF, Zevenbergen A, Thijsmeijer AP, et al. Constitutive Expression of E-Selectin and Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) in Human CD34(+) Cell Interactions With Bone Marrow Endothelium Are Independent of PSGL-1. Blood (2004) 103:1685–92. doi: 10.1182/blood-2003-06-189972

105. Hidalgo A, Weiss LA, Frenette PS. Functional Selectin Ligands Mediating Human CD34(+) Cell Interactions With Bone Marrow Endothelium Are Enhanced Postnatally. JCI Invest (2002) 11:559–69. doi: 10.1172/JCI114047

106. Levesque JP, Zannettino AC,浦ney M, Niuota S, Haylock DN, Snapp KR, et al. PSGL-1-Mediated Adhesion of Human Hematopoietic Progenitors to P-Selectin Results in Suppression of Hematopoiesis. Immunity (1999) 11:369–78. doi: 10.1016/s1074-7613(00)80112-0

107. Winkler IG, Snapp KR, Simmons PJ, Levesque J-P, Adhesion to E-Selectin Promotes Growth Inhibition and Apoptosis of Human and Murine Hematopoietic Progenitor Cells Independent of PSGL-1. Blood (2004) 103:1685–92. doi: 10.1182/blood-2003-06-1924

108. Eto T, Winkler I, Purton LE, Levesque J-P. Contrast Effects of P-Selectin and E-Selectin on the Differentiation of Murine Hematopoietic Progenitor Cells. Exp Hematol (2005) 33:232–42. doi: 10.1016/j.exphem.2004.10.018

109. Barbier A, Erbani J, Fiveash C, Davies JM, Tay J, Tallack MR, et al. Endothelial E-Selectin Inhibition Improves Acute Myeloid Leukaemia Therapy by Disrupting Vascular Niche-Mediated Chemoresistance. Nat Commun (2020) 11:2042. doi: 10.1038/s41467-020-15817-5

110. Erbani J, Tay J, Barbier V, Levesque J-P, Winkler IG. Acute Myeloid Leukemia Chemo-Resistance Is Mediated by E-Selectin Receptor CD162 in Bone Marrow Niches. Front Cell Dev Biol (2020) 0:668. doi: 10.3389/fcell.2020.00668

111. De Grandis M, Bardin F, Fauriat C, Zemmour C, El-Kaoutari A, Serpé A, et al. JAM-C Identifies Src Family Kinase-Activated Leukemia-Initiating Cells and Predicts Poor Prognosis in Acute Myeloid Leukemia. Cancer Res (2017) 77:6627–40. doi: 10.1158/0008-5472.CAN-17-1223

112. von Bonin M, Moll K, Kramer M, Oeschlagel U, Wermke M, Röllig C, et al. JAM-C Expression as a Biomarker to Predict Outcome of Patients With Acute Myeloid Leukemia-Letter. Cancer Res (2018) 78:6339–41. doi: 10.1158/0008-5472.CAN-18-0642

113. De Grandis M, Mancini SJ, Vey N, Aurand-Lions M. JAM-C Expression as a Biomarker to Predict Outcome of Patients With Acute Myeloid Leukemia-Response. Cancer Res (2018) 78:6342–3. doi: 10.1158/0008-5472.CAN-18-0834

114. Baer MR, Stewart CC, Lawrence D, Arthur DC, Byrd JC, Davey FR, et al. Expression of the Neural Cell Adhesion Molecule CD56 Is Associated With Short Remission Duration and Survival in Acute Myeloid Leukemia With T (8;21)(Q22;Q22). Blood (1997) 90:1643–8. doi: 10.1182/blood.V90.4.1643

115. Sasca D, Szybinski J, Schüler A, Shah V, Heidelberger J, Hazan P, et al. NCAM1 (CD56) Promotes Leukemogenesis and Confers Drug Resistance in AML. Blood (2019) 133:2305–19. doi: 10.1182/blood-2018-12-889725

116. Schmid RS, Graff RD, Schaller MD, Chen S, Schachner M, Hemperly JJ, et al. NCAM Stimulates the Ras-MAPK Pathway and CREB Phosphorylation in Neuronal Cells. J Neurobiol (1999) 38:542–58. doi: 10.1002/(SICI)1097-4695(199903)38:4<542::AID-NEU2>3.0.CO;2-I

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.

Publisher’s Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2021 Grenier, Testut, Fauriat, Mancini and Aurand-Lions. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.