Dynamic contrast-enhanced magnetic resonance imaging quantification of leukemia-induced changes in bone marrow vascular function

Ana L. Gomes,[1] John Gribben,[2] Bernard Siow,[3#] Diana Passaro[1,4#] and Dominique Bonnet[1#]

[1]Haematopoietic Stem Cell Laboratory, The Francis Crick Institute; [2]Department of Haemato-Oncology, Barts Cancer Institute, Queen Mary University of London and [3]In Vivo Imaging, The Francis Crick Institute, London, UK

[#]BS, DP and DB contributed equally as co-senior authors.

Correspondence:

DOMINIQUE BONNET - dominique.bonnet@crick.ac.uk

DIANA PASSARO - diana.passaro@inserm.fr

BERNARD SIOW - bernard.siow@crick.ac.uk

doi:10.3324/haematol.2020.277269

Supplementary Figures and legends

Figure S1. BM Vascular changes in aging and leukemia cell line models, measured by DCE-MRI. **(A)** Age, in weeks, of non-injected young mice (young NI), non-injected old mice (old NI), and mice injected with human CD34 positive cells derived from cord blood (CB). (**B**) Bone marrow DCE-MRI time intensity curves of non-injected young mice (young NI, grey), non-injected old mice (old NI, black), and mice injected with human CD34 positive cells derived from cord blood (CB, red), showing absence of vascular changes between non-injected and CB injected mice. **(C)** Disease burden quantified by percentage of human CD33 positive cells in the BM of mice injected with either HL60, ML1 or U937 cell lines. Each dot represents one mouse. White columns represent average of group and error bars represent standard deviation of the mean. (**D**) Effect of aging on DCE-MRI bone marrow parameters CE and WoR in a population of control mice. Each dot represents one mouse. (**E**) Quantification of DCE-MRI parameters CE, WIR, WoR, and iWoR for the BM of non-injected mice (NI) and HL60 mice, by age group with young being <16 weeks of age and old being >19 weeks of age. **(F)** Representative z stacks of BM vasculature in the calvarium of or mice engrafted with ML1, HL60 or U937 cells, as depicted. Scale bars represent 100 μm. Green dotted areas represent leukemia engrafted vasculature showing reduced perfusion and irregular vessels, white dotted areas represent non engrafted vasculature with normal vasculature. BM: Bone Marrow; AML: Acute Myeloid Leukemia; DCE-MRI: Dynamic Contrast Enhanced Magnetic Resonance Imaging; CE: Contrast Enhancement; WiR: wash-in Rate; WoR: Wash-out Rate; iWoR: initial Wash-out Rate; *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns: not significant.

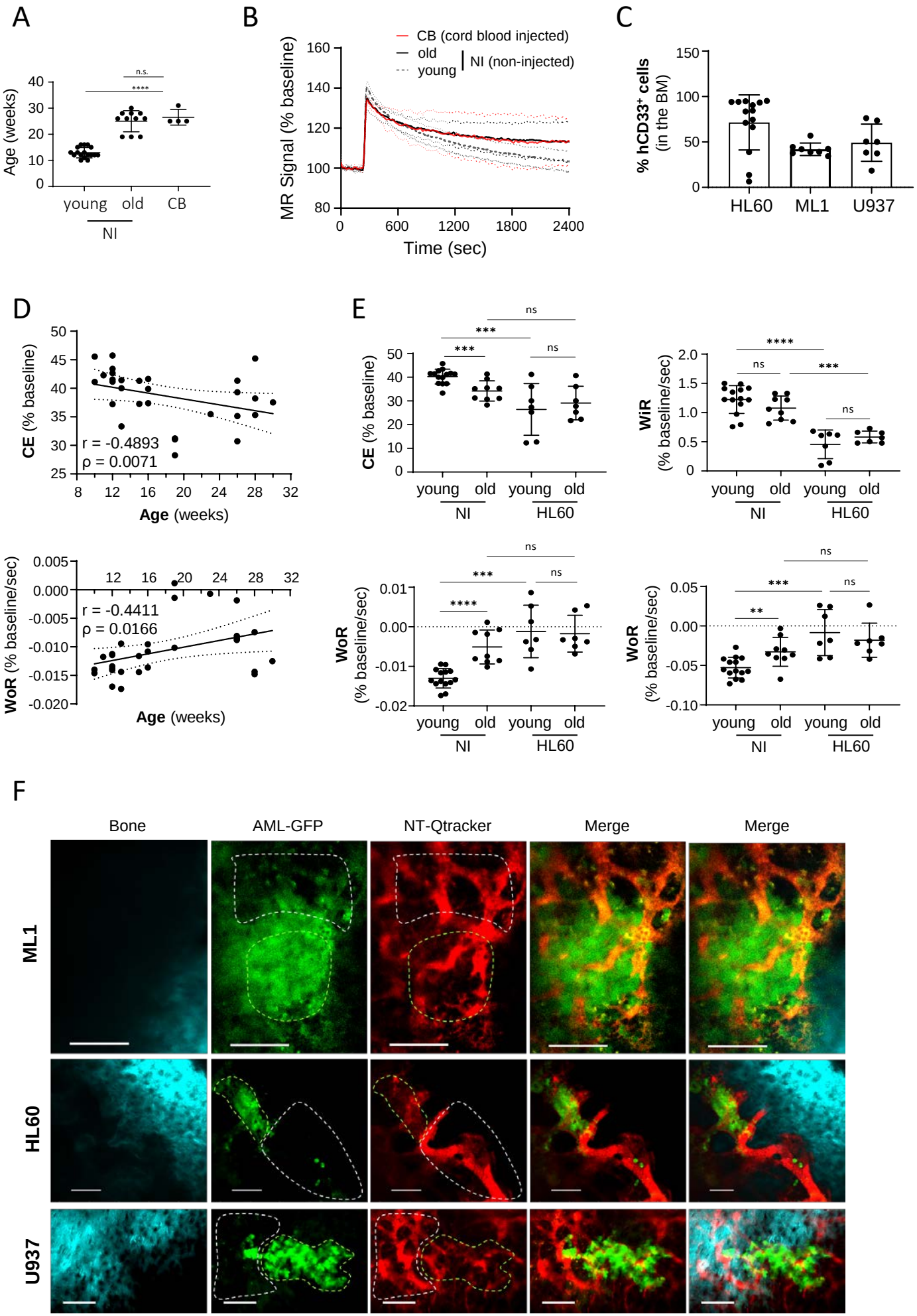
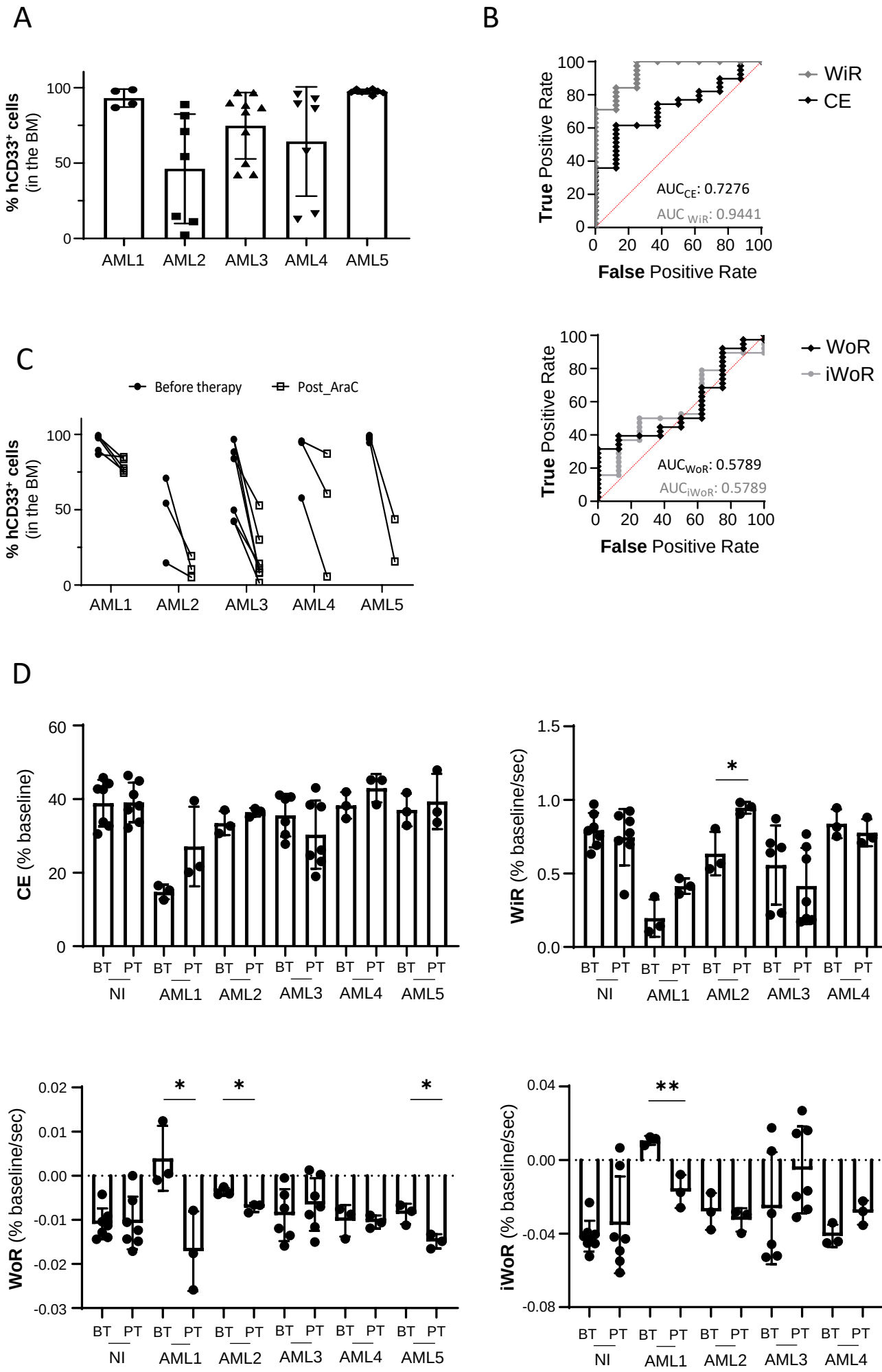

A
Age (weeks)
n.s.
****
young
old
CB
NI
B
CB (cord blood injected)
old
young
NI (non-injected)
MR Signal (% baseline)
Time (sec)
C
% hCD33+ cells
(in the BM)
HL60
ML1
U937
D
CE (% baseline)
r = -0.4893
ρ = 0.0071
Age (weeks)
WoR (% baseline/sec)
r = -0.4411
ρ = 0.0166
Age (weeks)
E
CE (% baseline)
WiR
(% baseline/sec)
WoR
(% baseline/sec)
WoR
(% baseline/sec)
young
old
NI
HL60
ns
F
Bone
AML-GFP
NT-Qtracker
Merge
Merge
ML1
HL60
U937

Figure S2. BM Vascular changes in PDX, before and after Ara-C treatment measured by DCE-MRI. (A) Disease burden quantified by percentage of human CD33 positive cells in the bone marrow of mice injected with AML samples 1-5 (AML1-AML5). Each dot represents one mouse. White columns represent average of group and error bars represent standard deviation of the mean. (**B**) Receiver operating characteristic analysis of the diagnostic capabilities of the BM DCE-MRI parameters to distinguish malignant from non-malignant BM using the data from the AML patient samples. **(C)** Disease burden quantified by percentage of human CD33 positive cells in the bone marrow of mice injected with AML samples 1-5 (AML1-AML5), before (BT) and post (PT) AraC therapy. **(D)** Quantification of BM DCE-MRI parameters CE, WIR, WoR, and iWoR for mice from C. DCE-MRI: Dynamic Contrast Enhanced Magnetic Resonance Imaging; CE: Contrast Enhancement; WiR: wash-in Rate; WoR: Wash-out Rate; iWoR: initial Wash-out Rate; *p<0.05; ***p<0.001; ****p<0.0001; ns: not significant.


A
% hCD33+ cells (in the BM)
100
50
0
AML1
AML2
AML3
AML4
AML5
B
True Positive Rate
False Positive Rate
WiR
CE
AUC_CE: 0.7276
AUC_WiR: 0.9441
WoR
iWoR
AUC_WoR: 0.5789
AUC_iWoR: 0.5789
C
Before therapy
Post_AraC
D
CE (% baseline)
WiR (% baseline/sec)
WoR (% baseline/sec)
iWoR (% baseline/sec)
BT
PT
NI
AML1
AML2
AML3
AML4
AML5