SUPPORTING INFORMATION

Table 1S.

Gen	Forward (5´→3´)	Reverse (5´→3´)
Il6	GTATGAACAACGATGATGCACTTG	ATGGTACTCCAGAAGACCAGAGGA
Il4	GGTCTCAACCCCCAGCTAGT	GCCGATGATCTCACTCAAGTGAT
Ccl2	GGGCCTGCTGTTCACAGTT	CCAGCCTACTCATTGGGAT
Il1β	CTCCACCTCAATGGACAGAA	GCCGTCTTTCATTACACAGG
Tgfβ	TACAGCAAGGTCCTTGCCCT	GCAGCACGGTGACGCC
Il13	CCTGGCTCTTGCTTGCCTT	GGTCTTGTGTGATGTTGCTCA
Gapdh	TGGCAAAGTGGAGATTGTTGCC	AAGATGGTGATGGGCTTCCCG
PPARγ2	GCGATTCCTTCACTGATACACTG	GAGTGGGAGTGGTCTTCCATTAC
ADIPOQ	CATGACCAGGAAACCACGACTC	CCGATGTCTCCCTTAGGACCA
CEBPA	CCTTGTGCCTTGGAAATGCAAAC	CTGCTCCCCTCCTTCTCTCA
HPRT	ATGGGAGGCCATCACATTGT	ATGTAATCCAGCAGGTCAGCAA

Figure S1. MSCs differentiation.

Human mesenchymal stem cells (MSC) were cultured in α- MEM containing, 15% FCS, 2 mM UltraGlutamine, 1 ng/ml bFGF and antibiotics. Cells were maintained at 37 °C and 5% CO_2 in a humidified atmosphere. Adipogenic differentiation was performed as previously described (Santiago-Mora et al., 2011). Treatment with the compound started in parallel with the differentiation process. To confirm adipogenesis, after 21 days cells

were fixed in 3.7% formaldehyde for 10 min, washed and stained for 20 min with an oil red O solution. To quantify the mRNA expression of adipocytes markers, total RNA was extracted using the High Pure RNA Isolation kit (Roche Diagnostics, IN, USA) at day 14 of differentiation and analysed using the real-time PCR method.

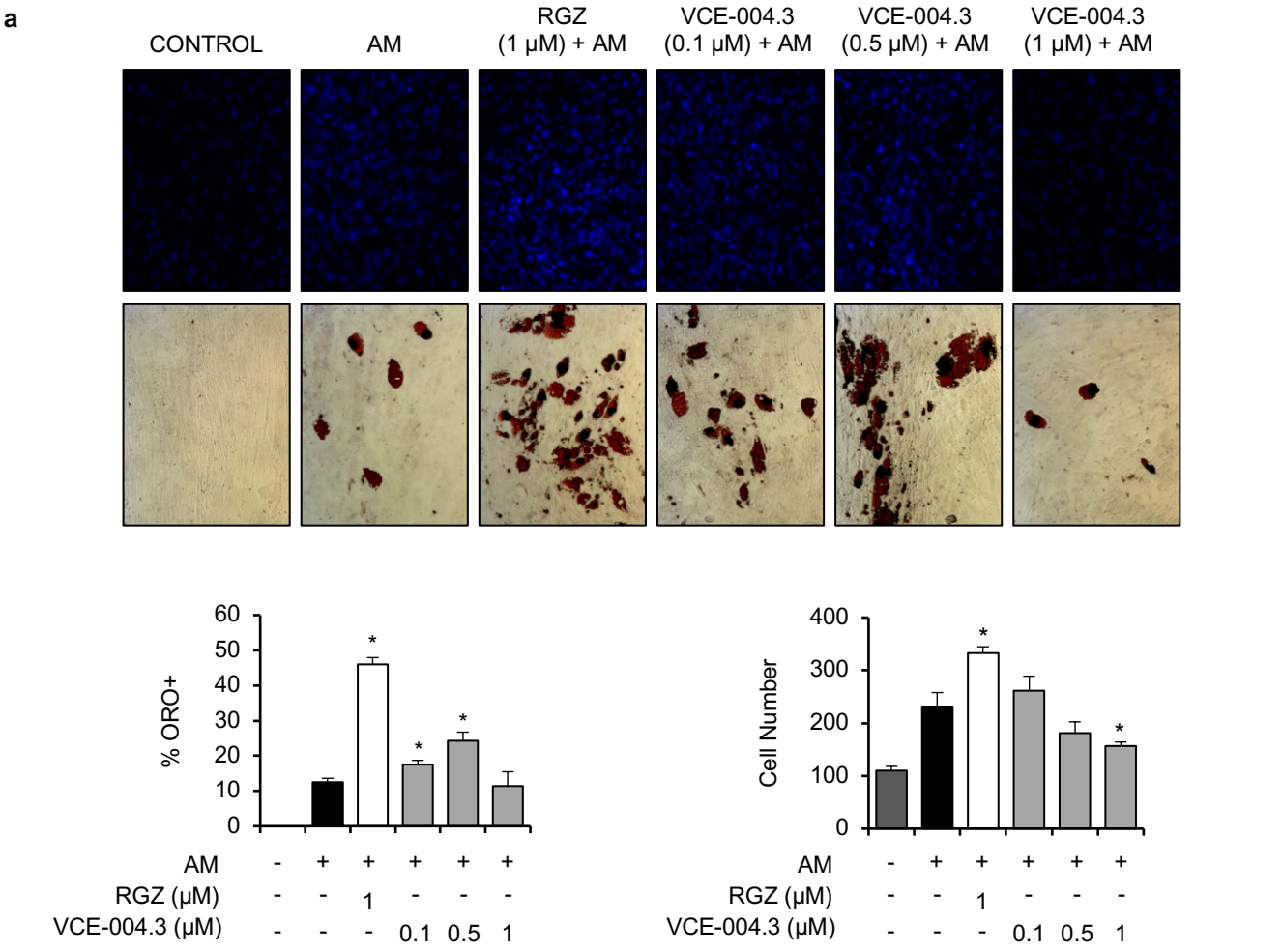
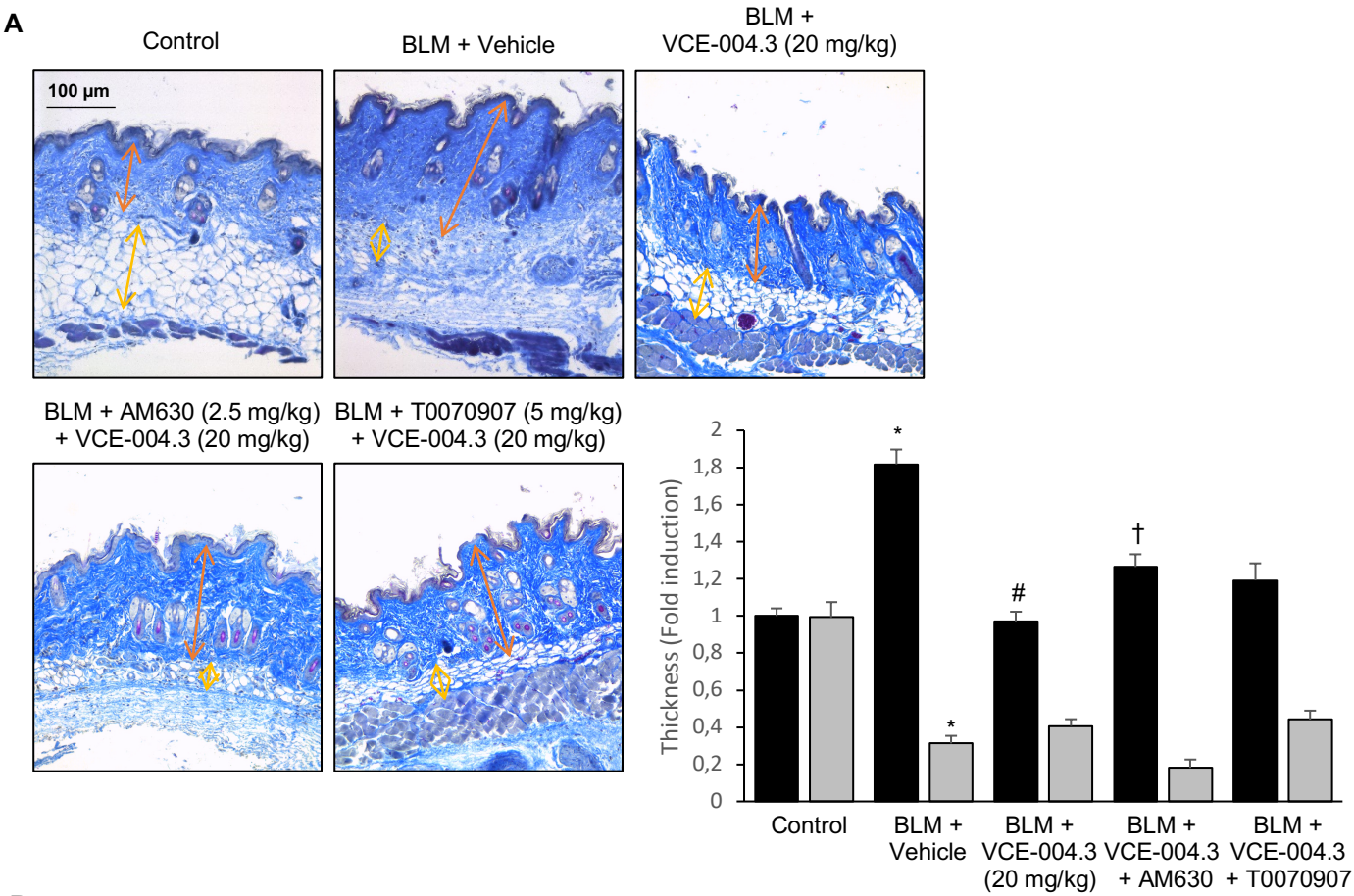


Figure S1. Effect of VCE-004.3 on MSC differentiation into adipocytes. (A) MSC underwent adipocytic differentiation in the presence of VCE-004.3 or RGZ as positive control. Representative images showing OilRed O staining (upper panel) and cell number (bottom left) and Oilred positive cells (bottom right) were counted. (B) Gene expression of PPAR-γ2, ADIPOQ and CEBPA in MSCs differentiated for 14 days. Data represent the percentage of increase over AM considered as the 100% of adipogenic induction (n=5) $^{*}p<0.05$ versus AM.


A
Control
BLM + Vehicle
BLM +
VCE-004.3 (20 mg/kg)
100 µm
BLM + AM630 (2.5 mg/kg)
+ VCE-004.3 (20 mg/kg)
BLM + T0070907 (5 mg/kg)
+ VCE-004.3 (20 mg/kg)
Thickness (Fold induction)
2
1,8
1,6
1,4
1,2
1
0,8
0,6
0,4
0,2
0
*
*
#
†
Control
BLM +
Vehicle
BLM +
VCE-004.3
(20 mg/kg)
BLM +
VCE-004.3
+ AM630
BLM +
VCE-004.3
+ T0070907

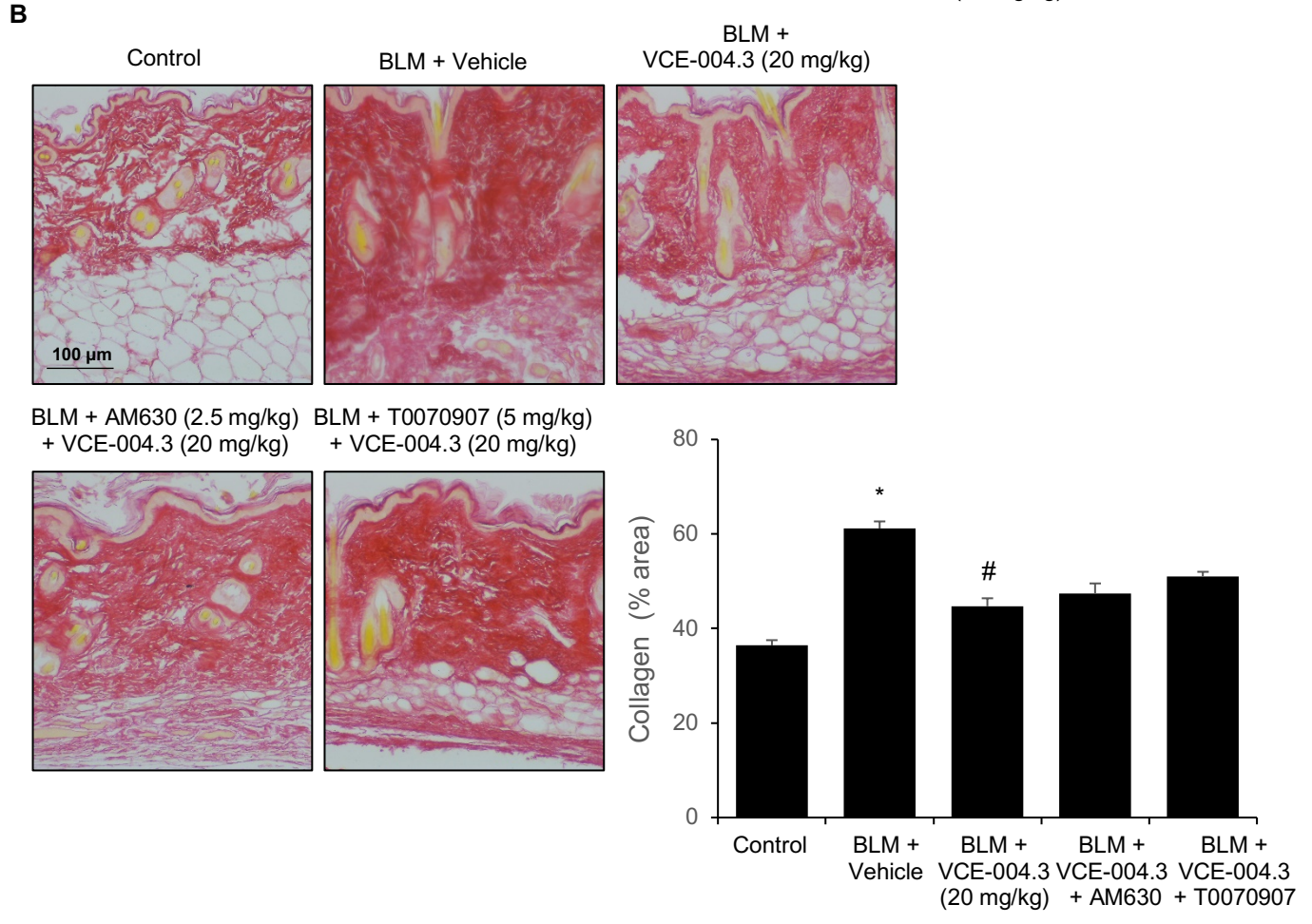

B
Control
BLM + Vehicle
BLM +
VCE-004.3 (20 mg/kg)
100 µm
BLM + AM630 (2.5 mg/kg)
+ VCE-004.3 (20 mg/kg)
BLM + T0070907 (5 mg/kg)
+ VCE-004.3 (20 mg/kg)
Collagen (% area)
80
60
40
20
0
*
#
Control
BLM +
Vehicle
BLM +
VCE-004.3
(20 mg/kg)
BLM +
VCE-004.3
+ AM630
BLM +
VCE-004.3
+ T0070907

Figure S2. Pretreatment with the CB_2 antagonist AM630 but not the PPARγ antagonist T007907 partially abrogated the effect of VCE-004.3 on BLM-induced chronic model of SSc. Mice were injected with BLM for six weeks and treated with the compound in the presence of either AM630 or T0070907 during the last three weeks of BLM challenge. **A.** Representative images of Masson's trichrome staining of skin sections and their respective measurement of dermal and subcutaneous adipose layer thickness. **B.** Representative images of picrosirius red dye in mice skin and their quantification. Values are represented as mean ± SEM (n=9 animals per group). $^{*}p<0.05$ versus control; $^{\#}p<0.05$ versus BLM-treated mice; $^{\dagger}p<0.05$ versus BLM + VCE-004.3.

REFERENCES

Santiago-Mora R, Casado-Diaz A, De Castro M D & Quesada-Gomez J M. (2011). Oleuropein enhances osteoblastogenesis and inhibits adipogenesis: the effect on differentiation in stem cells derived from bone marrow. *Osteoporos Int,* **22,** 675-84.