Summary of SGLT2 inhibitor effects on bone

Model	SGLT2 inhibitor	Effects on bone
STZ and high-fat diet induced type 2 diabetic male mouse model[1]	Dapa or Cana or Empa 10mg/kg/day; for 10 weeks	Cana improved diabetic bone parameters; Cana promoted osteogenesis of MC-3T3 cells via AMPK/RUNX2 pathway
DBA/2J male mice treated with STZ[2]	diabetes with Cana 50ppm or without Cana; non-diabetes with Cana 62.5ppm or without Cana; for 10 weeks	Cana didn't improve diabetic bone parameters; Cana aggravated bone parameters of control mice
healthy human volunteers[3]	Cana (300 mg/d) or placebo; for 5 days	Cana increased serum phosphorus, plasma FGF23 and parathyroid hormone, decreased 1,25-dihydroxyvitamin D level
sglt2 knock-out Sweet Pee mice at 15- and 25-week-old[4]	/	no alteration in FGF23, PTH, and $1,25(OH)_2D_3$, trabecular or cortical bone parameters but reduced cortical bone mineral density and femur length at 25 weeks
patients with the syndrome of inappropriate antidiuresis (hyponatremia)[5]	randomized treatment with SGLT-2 inhibitors or placebo for 4 days	normalized hyponatremia by Empa lead to no change in bone resorption marker CTX but improved bone formation marker PINP
nondiabetic, female rats[6]	Dapa (1.4 mg/kg p.o.) or Cana (4.2 mg/kg p.o.) for 4 weeks	no effect on bone turnover markers, osteocalcin and CTX-I; no effect on bone mass; Cana increased bone mineral density; both injured the micro-architecture of cancellous bone and lowered the energy for fracture load;
old UM-HET3 mice at 7-month-olds[7]	control or Cana-containing diet (180 ppm) for 15 months	compromised bone morphology and mineral composition of bones

(Blue denotes the positive effect, red for negative)

1. Song, P.*, et al.* Canagliflozin promotes osteoblastic MC3T3-E1 differentiation via AMPK/RUNX2 and improves bone microarchitecture in type 2 diabetic mice. *Front Endocrinol (Lausanne)*, 2022, **13**, 1081039.
2. Thrailkill, K.M.*, et al.* SGLT2 inhibitor therapy improves blood glucose but does not prevent diabetic bone disease in diabetic DBA/2J male mice. *Bone*, 2016, **82**, 101-107.
3. Blau, J.E.*, et al.* Canagliflozin triggers the FGF23/1,25-dihydroxyvitamin D/PTH axis in healthy volunteers in a randomized crossover study. *JCI Insight*, 2018, **3**.
4. Gerber, C.*, et al.* Long-Term Effects of Sglt2 Deletion on Bone and Mineral Metabolism in Mice. *JBMR Plus*, 2021, **5**, e10526.
5. Potasso, L., Refardt, J., Meier, C. & Christ-Crain, M. Effect of hyponatremia normalization on osteoblast function in patients with SIAD. *Eur J Endocrinol*, 2021, **186**, 1-8.
6. Londzin, P.*, et al.* Unfavorable effects of sodium-glucose cotransporter 2 (SGLT2) inhibitors on the skeletal system of nondiabetic rats. *Biomed Pharmacother*, 2022, **155**, 113679.
7. Yildirim, G.*, et al.* Long-term effects of canagliflozin treatment on the skeleton of aged UM-HET3 mice. *Geroscience*, 2023, **45**, 1933-1951.

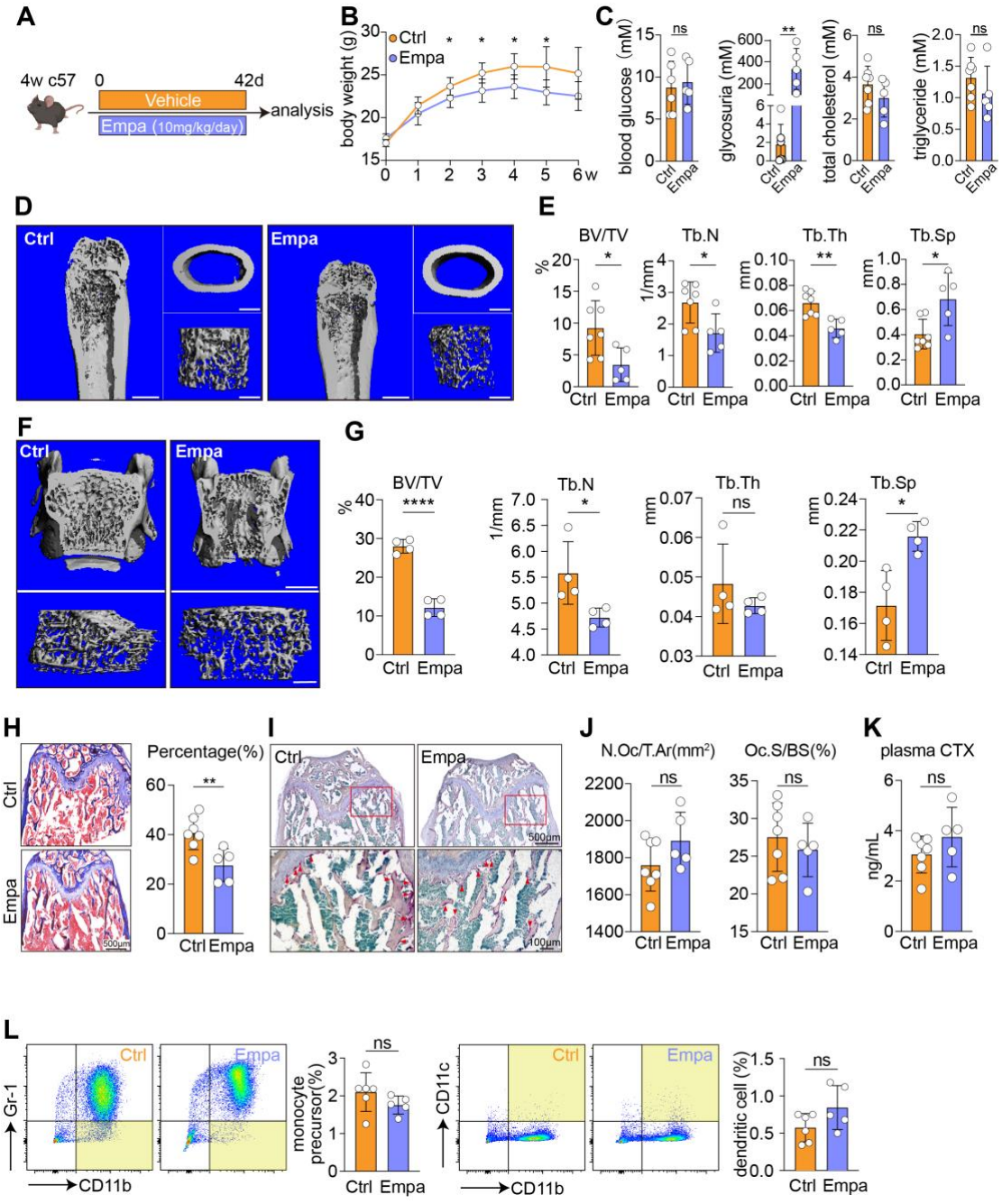

Figure1: Systemic administration of Empa inhibit bone development in mice

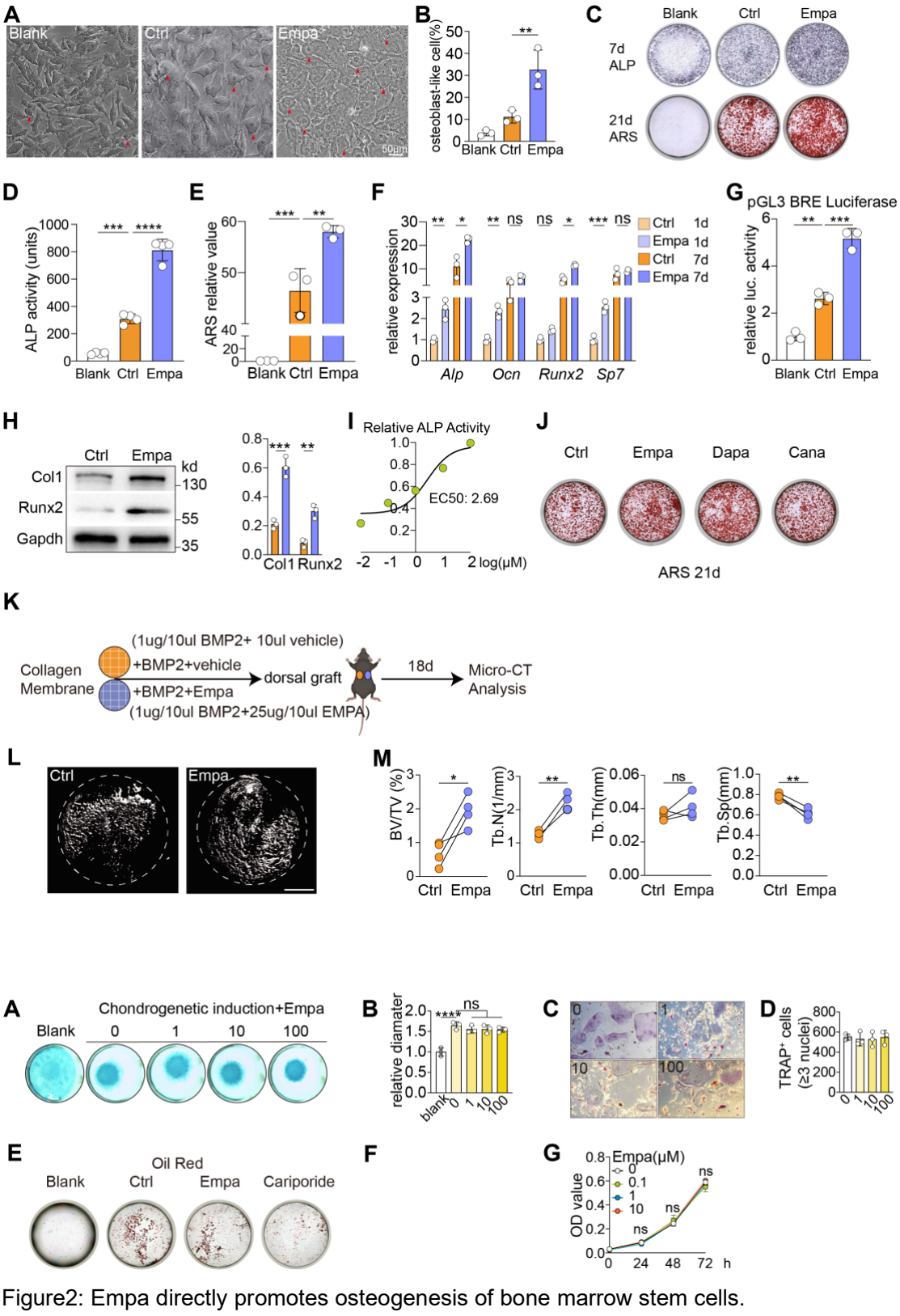

Figure2: Empa directly promotes osteogenesis of bone marrow stem cells.