Protecting Astronaut Health Beyond Earth: Space Radiation, Simulated microgravity and Emerging Countermeasures with Cerium Oxide Nanozymes and P7C3

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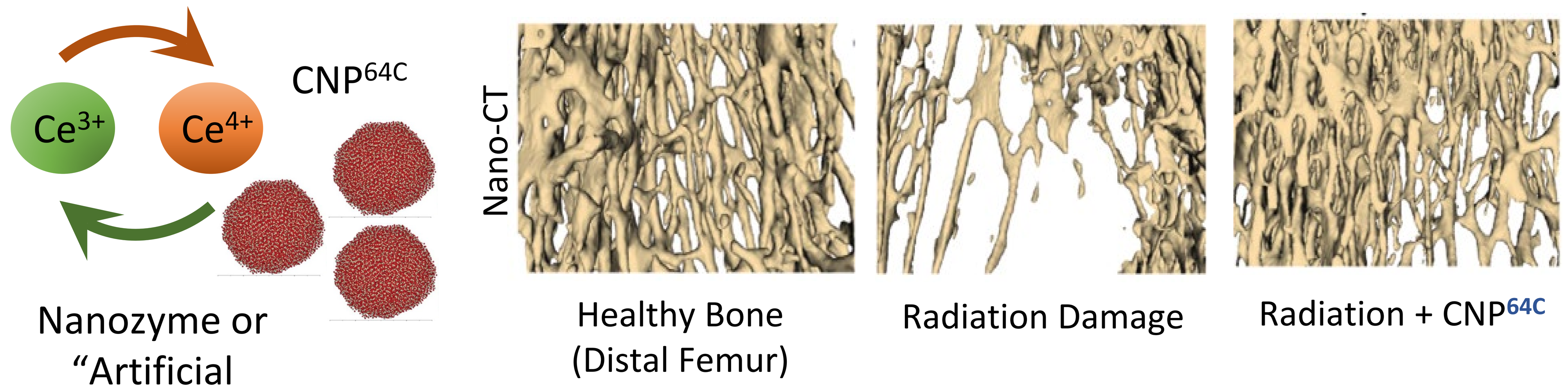
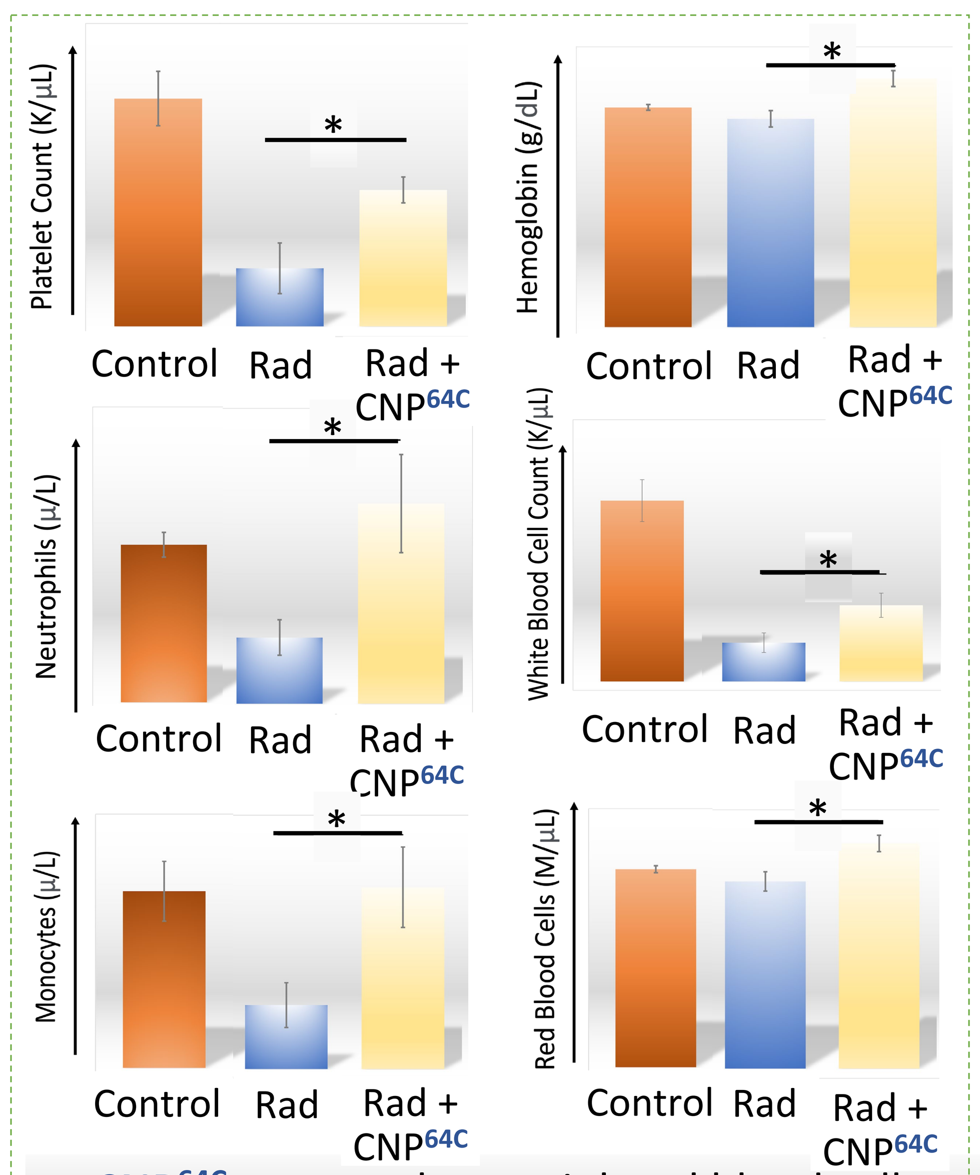
INTRODUCTION

Radioprotective (Prophylactic) Activity

1. **Cerium oxide nanoparticles (CNPs)^{64C}** engineered with an increased trivalent fraction (Ce^{3+}) are radioprotective as shown below and when investigated in a hypofractionated (3 x 8 Gy) rat partial body irradiation (PBI) model after 7 and 14 days.



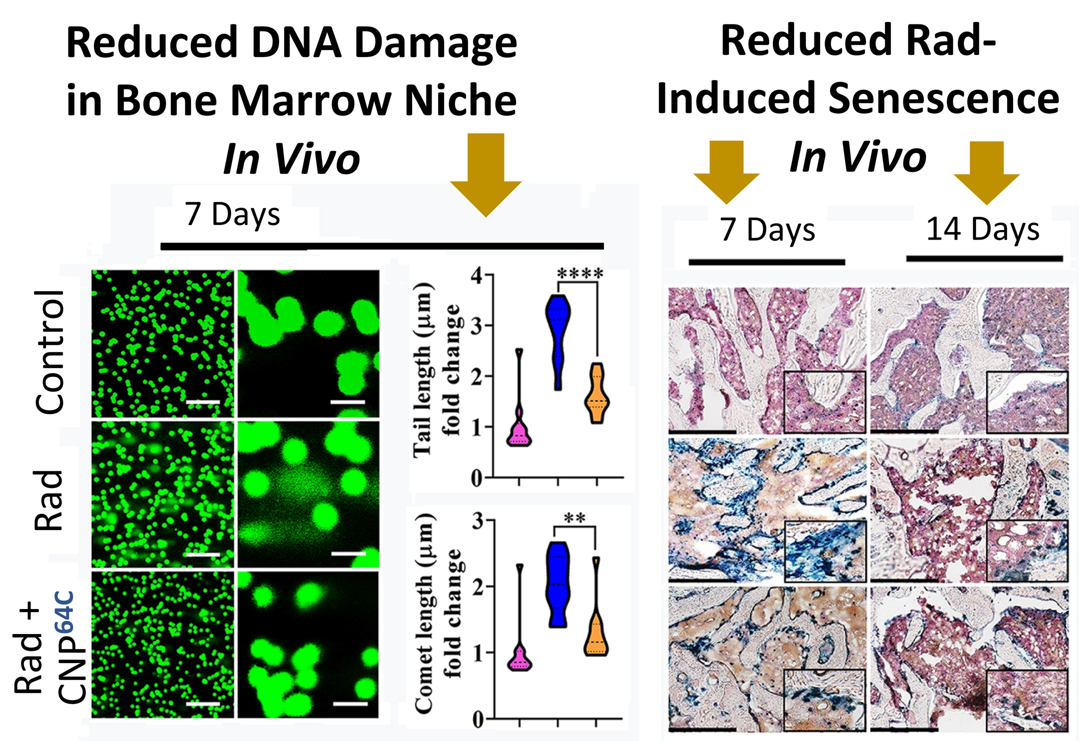
Protection of Peripheral Blood Cells



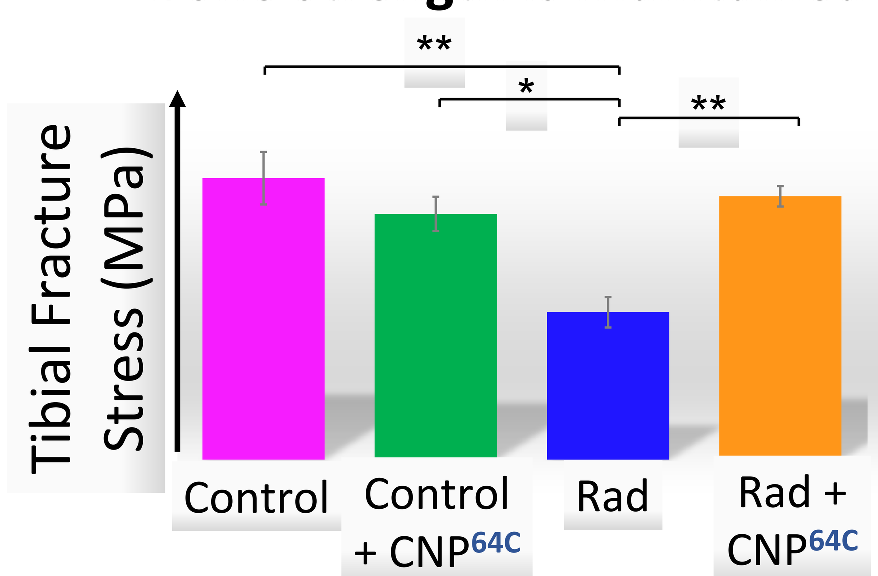
CNP^{64C} protects key peripheral blood cells against radiation damage

Reduced DNA Damage in Bone Marrow Niche ***In Vivo***

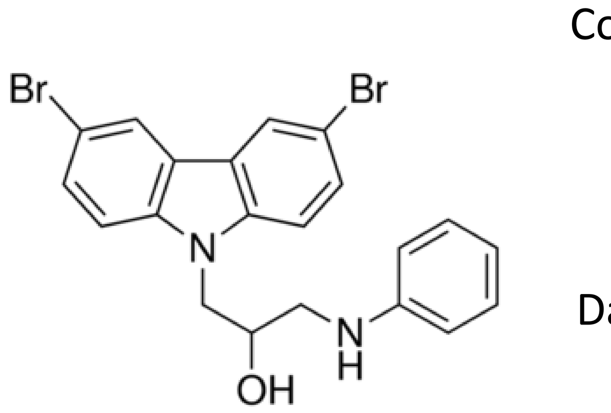
Reduced Rad-Induced Senescence ***In Vivo***



Bone Strength is Maintained

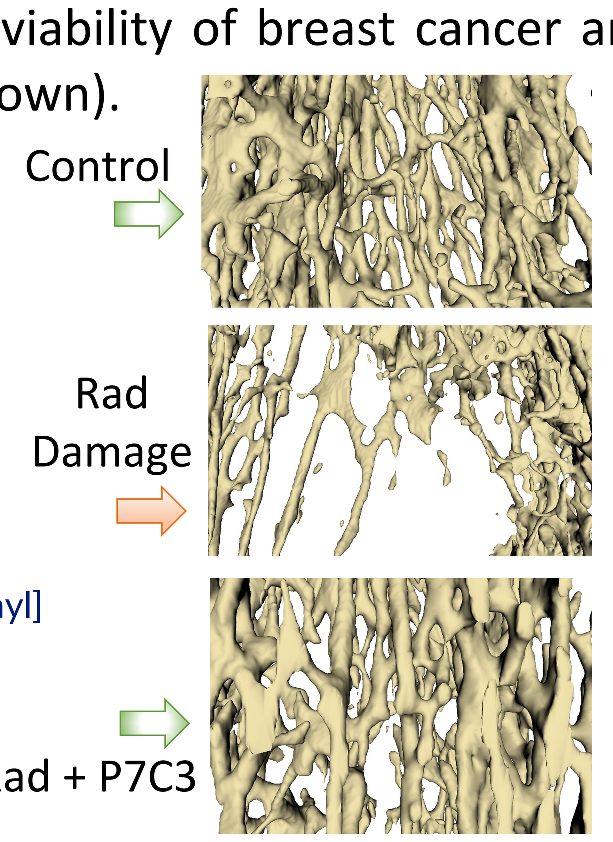


2. **Pool 3 Compound 7 (P7C3)** is radioprotective as shown below and when investigated in a hypofractionated rat PBI model (data below). At the same protective dose, P7C3 reduced the viability of breast cancer and osteosarcoma cells *in vitro* and is antibacterial (data not shown).

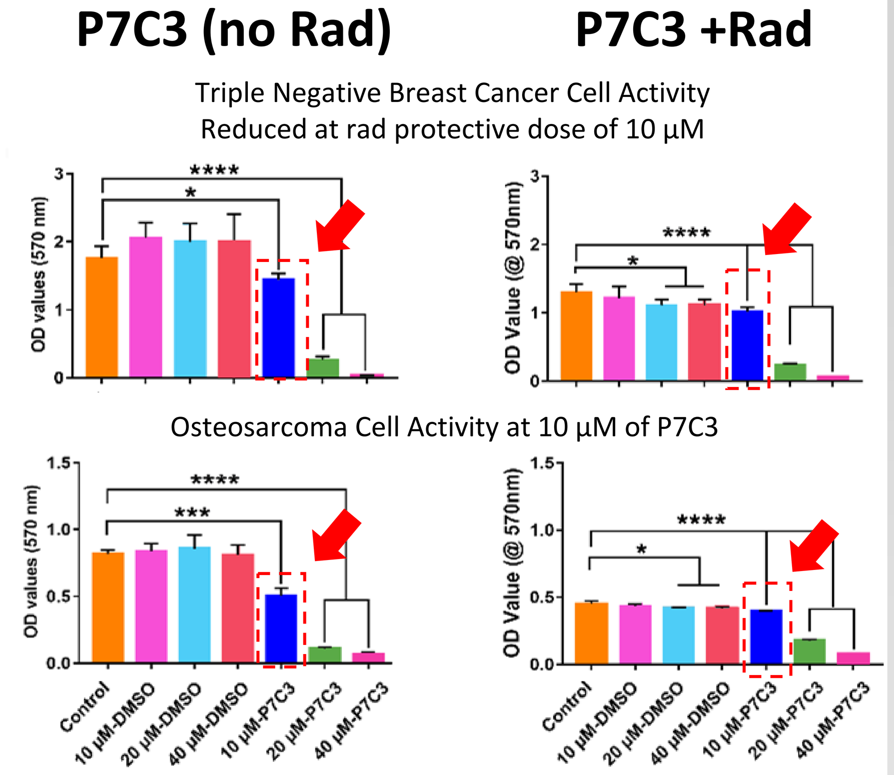


3,6-dibromo-α-[(phenylamino)methyl]-9H-carbazole-9-ethanol

$C_{21}H_{18}Br_2N_2O$



P7C3 (no Rad) **P7C3 +Rad**



STUDY AIM

Q: With no currently approved therapies, can cerium oxide nanoparticles (CNPs), P7C3, or their combination (64c-73) serve as effective countermeasures against radiation and microgravity-induced damage relevant to deep-space exploration?

AIM: Evaluate the protective potential of CNPs, P7C3, and/or their combination (64c-73) in mitigating space-relevant hazards such as space radiation and simulated microgravity.

MATERIALS AND METHODS

#1 In vivo Analyses (n=6/Group): Products given 24 post-IR (8 Gy/Fraction)

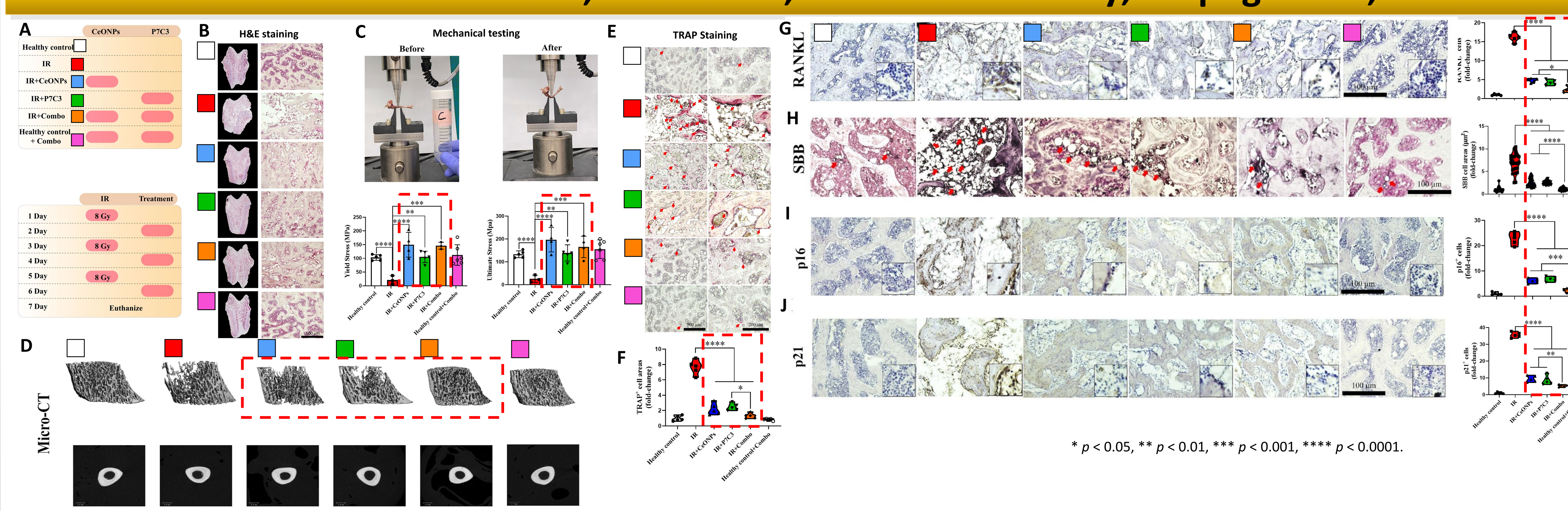
Animal model: IR-induced bone loss model in SAS Sprague Dawley rats; delayed treatment initiated 24 hours post-irradiation.
Bone microarchitecture: H&E staining and MicroCT imaging.
Bone mechanical properties:3-point bending test.
Osteoclast activity: TRAP staining, RANKL IHC.
Cellular senescence: IHC for p16 and p21.

#2 In vivo Analyses (n=4/Group):

Animal model: Hind limb suspension (HLS)-induced bone loss model in SAS Sprague Dawley rats;
Bone microarchitecture: H&E staining and MicroCT imaging.
Osteoclast activity: TRAP staining.
Adipogenesis: SBB staining.

Statistical analyses carried out using GraphPad Prism (v 8.0, U.S.) and groups compared using the nonparametric Mann-Whitney test. *p* values < 0.05 were considered significant.

In vivo results#1: Bone Structure, Mechanics, Osteoclast Activity, Adipogenesis, Senescence



* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.

Figure 1. [A] A flow chart of the animal experiment. [B] Representative H&E-stained histology images of transverse sections through the femoral condyle. [C] The biomechanical properties of yield stress and ultimate stress at the tibial mid-point during 3-point bending analyses. [D] microCT anslysis. [E-F] TRAP activity assay and quantification. [G] Immunohistochemical analysis of RANKL and quantification. [H]SBB staining and quantification. [I-J]] Immunohistochemical analysis of p16 and p21 and quantification.

In vivo results#2: Bone Structure, Osteoclast Activity, Adipogenesis

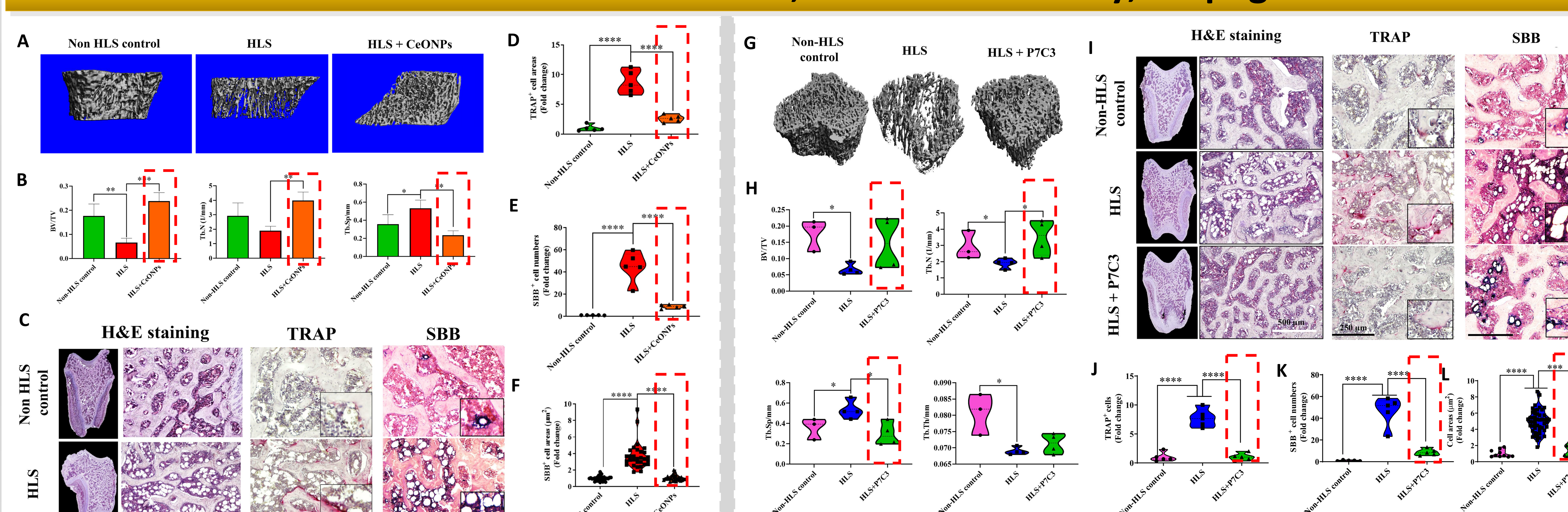


Figure 1. [A] Representative 3D microCT reconstructed images of distal femoral trabecular bone are shown. [B] microCT anslysis. [C] Representative H&E-, TRAP-, and Sudan Black B (SBB)-stained histology images of transverse sections through the femoral condyle. [D] TRAP activity assay and quantification. [E-F] SBB staining quantification. [G] Representative 3D microCT reconstructed images of distal femoral trabecular bone. [H] microCT anslysis. [I] Representative H&E-, TRAP-, and Sudan Black B (SBB)-stained histology images of transverse sections through the femoral condyle. [J] TRAP activity assay and quantification. [K-L] SBB staining quantification.

CONCLUSION

CeONPs and P7C3 hold substantial promise as novel countermeasures for protecting astronaut health beyond Earth