Answering Reviewer:

1. Please fill in an English version of ARRIVE checklist.
Response:
Thank you for your reminder. We have created and uploaded the English version of the ARRIVE checklist.

2. Please fill in the STROBE checklist and add items necessary in STROBE.
Response:
the STROBE checklist is for Case-Control study, Observational study and Retrospective Cohort study. It's not applicable to our manuscript, which is of the Basic study.

3. Please discuss the limitations of the study.
Response:
Thanks, so much for your insight. We have incorporated your advice, below. "The specificity of Crif1 inhibitors and their effects on bone metabolism, such as increasing bone formation, decreasing bone resorption and adipogenesis, still need further in vitro and in vivo research, remained to be validated in clinical trials." Refer to pages 17-18 as highlighted in red.

4. Please provide the raw data files as appendixes or as supplementary online files.
Response:
Thank you for your advice. The raw data files have been uploaded as supplementary information.

5. Please calculate the test powers.
Response:
It's of 95% confidence. Look at pages 10-11. "The statistical significance of differences between two groups was assessed using two-tailed Student's t-tests. The statistical significance of differences among more than two groups was assessed using one-way ANOVAs with Sidak's multiple comparison tests."

6. In the introduction, please justify the study. (why it is important to the literature and what it adds?)
Response:
Thank you for asking. Here is our clarification.
"Current treatment of osteoporosis is based mainly on inhibiting bone resorption or stimulating bone generation to increase bone mass; however,

the side-effects of some drugs affect long-term administration and adherence. There is still a lack of effective prevention or treatment for irradiation-induced bone injury[5]."

"However, the molecular mechanisms of cell fate decisions in the differentiation of BM-MSCs and osteoclasts involved in irradiation-induced bone loss are still not fully understood.

Crif1 is a multifunctional protein that can interact with many proteins to induce cell cycle arrest, modulate oxidative stress and cell radiosensitivity, and regulate transcriptional activity through interactions with the DNA-binding domains of transcription factors[15-21]. It is also the constitutive protein of the large mitoribosomal subunit required for the synthesis and insertion of mitochondrial-encoded OxPhos polypeptides into the mitochondrial membrane[22]. Crif1 deficiency in macrophages impairs mitochondrial oxidative function and causes systemic insulin resistance and adipose tissue inflammation[23]. Our previous study showed that Crif1 promotes adipogenic differentiation of BM-MSCs after radiation by modulating the cAMP/PKA signaling pathway[24].

In this study, we investigated the role of Crif1 in osteoclastogenesis after radiation. Here, we show that *Crif1* deletion causes decreases in RANKL expression and the RANKL/OPG ratio and reduces osteoclastogenesis and adipogenesis after radiation. Through screening, we also identified five compounds that could effectively inhibit RANKL expression and adipogenesis. We demonstrate that Crif1 promotes osteoclastogenesis by inducing RANKL expression via the cAMP/PKA pathway."

"Our study suggests a role for Crif1 in modulating osteoclastogenesis and provides insights into potential therapeutic strategies targeting the balance between osteogenesis and adipogenesis for radiation-induced bone injury."

We have added the above statements in the introduction section in the revision.

7. Please correct and improve a few grammatical issues.
Response:
Thank you so much for your spot-on comments. Grammatical issues have been addressed through the entire manuscript (track changes were shown in the attached revision).

8. Please approach the conclusions with more caution.
Response:
Agreed. We have specified that this study's conclusion remains true only in the mouse model, which should be validated in clinical trials." Refer to pages 17-18 and page 4, as highlighted in red.