Targeting Neuron-Sarcoma Interactions via Anti-CGRP Therapies

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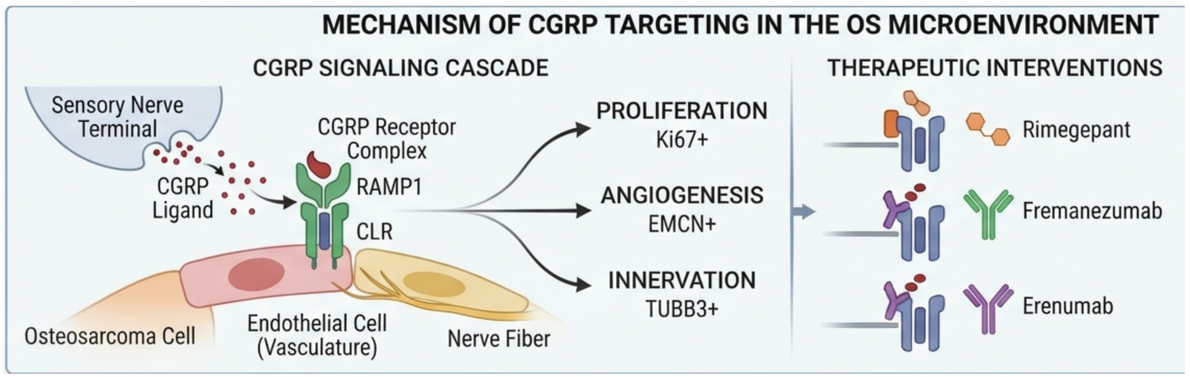
Graphical Abstract



Introduction:

Military exposures including ionizing radiation, chemical agents, and trauma may increase sarcoma risk in U.S. veterans. Annually, about 50,000 new cancer cases in Veterans are reported. Osteosarcoma (OS), the most common primary bone malignancy, affects younger individuals and those with prior radiation exposure, with <20% 5-year survival in metastatic disease. OS imposes significant clinical and socioeconomic burdens, impacting military readiness. OS-derived nerve growth factor (NGF) activates TrkA signaling, driving neuropathic pain, while our studies reveal abnormal expansion of TrkA$^+$ sensory nerves and implicate CGRP signaling as a critical, yet unexplored, neuro-tumor interaction (PNAS, 2025). Notably, CGRP-targeting drugs are FDA-approved for migraine pain. Here, we test these agents for off-label therapeutic targeting of OS using an established murine model.

Materials and Methods:

To model human OS, 1×10^6 143B cells were injected subperiosteally into the proximal tibia of 10-week-old Nod/Scid mice (n=8/group). Mice received CGRP-targeting FDA-approved drugs: rimegepant (CGRP receptor inhibitor), fremanezumab (anti-CGRP ligand), or erenumab (anti-CGRP receptor), with appropriate vehicle or antibody controls. Tumor growth was measured over 4 weeks. Immunohistochemistry for TUBB3 (innervation), Ki67 (proliferation), and EMCN (vasculature) was performed, along with von Frey testing for behavioral pain assessment. Data are presented as mean ± SD; significance was determined using an unpaired Student's t-test ($p<0.05$).

Results:

Treatment with rimegepant, fremanezumab, or erenumab resulted in significant reductions in tumor growth (~45%; $p<0.01$ vs control). Reduced tumor burden was associated with decreased Ki67$^+$ proliferative index (~60% reduction). Treated tumors also showed a marked decline in TUBB3$^+$ nerve fiber density (~69% reduction). Tumor-associated vasculature was reduced by ~60%, with a significant impairment in vasculogenesis (~30.7% reduction) based on EMCN staining. Importantly and in addition, CGRP inhibition significantly alleviated pain, evidenced by a 40% reduction in paw-withdrawal frequency in von Frey testing.

Conclusion:

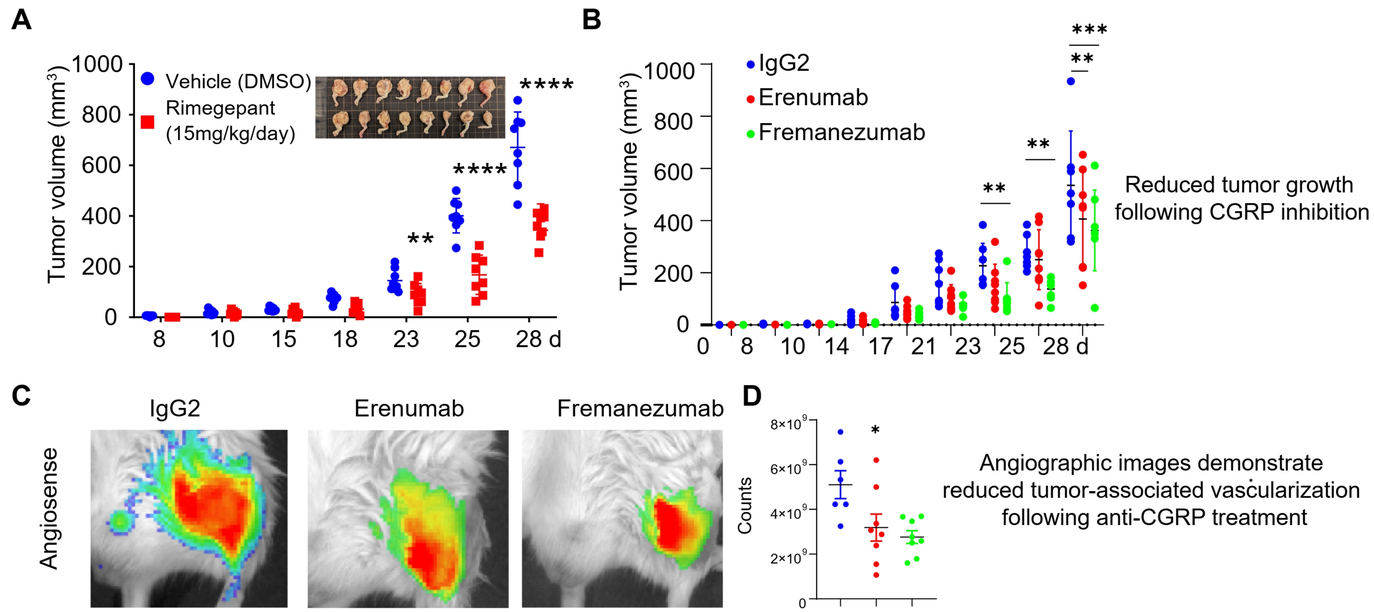
Overall, these findings demonstrate that systemic CGRP pathway inhibition using multiple FDA-approved agents reduces sarcoma-associated pain and suppresses disease progression by limiting tumor proliferation, innervation, and angiogenesis, highlighting CGRP signaling as a promising therapeutic target in osteosarcoma.

Learning Objectives:

(1) To define the role of CGRP-mediated neuro-tumor crosstalk in neoplastic bone

(2) To determine the impact of CGRP inhibition on tumor progression and pain

(3) To evaluate therapeutic potential CGRP-mediated neuroregulation to improve outcomes for Service Members, Veterans, and beneficiaries



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2. Lee, Seungyong, et al. Nat Commun. 12.1 (2021).
3. Qin, Qizhi, et al. Bone Res 10.1 (2022): 43.

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