Has the funding of this project led to the receipt of other funds? If so, what is the total amount?

The findings and results derived from this project will be used to apply for federal funding. No other grants related with this research were obtained during the course of the award.

Abstract (electronic and hard copy)

Background. Bone metastases (BM’s) to he spine are a common source of pain (acute and chronic) in cancer patients. The secondary effects of BM’s include severe pain, bone fractures, hypercalcemia, and neurological deficits that significantly reduce quality of life for patients. Bone cancer-induced pain is presumed to be caused by osteoclast-mediated acidosis. As a consequence of this process, microfractures occur in regions of metastatic cancerous bone that can no longer handle the typical axial load, causing deformation of the spine and impingement of nerves. As the disease progresses, pain severity increases and becomes more difficult to treat, causing further decrease in the quality of life of patients. The molecular mechanism(s) behind this progressive increase in pain are unknown. SRC is a non-receptor tyrosine kinase associated with cancer cell growth and bone pathology. There is evidence to support that SRC-mediated interactions between cancer cells and osteoclasts participate in the process of cancer-induced pain. The activity of SRC has been studied in the context of cancer metastasis to other skeletal bones; however, the activity of SRC in spinal metastasis has not been evaluated. Our main goal was to develop a reliable animal model to study pain derived from metastatic cancer. We evaluated the effect of a SRC inhibitor on bone degeneration and pain response in a model of metastatic breast cancer to the spine. In doing so, behavioral evaluation was conducted in a group of 30 athymic rats: 10 tumor-implanted (human mammary adenocarcinoma, L5 vertebral body); 10 sham (surgery performed, no tumor implanted), and 10 control rats (nontumor or surgery). Our methodology included the use of a mechanical nociceptive test (modified Randal-Sellitto) and videotaped locomotion gait analysis in rats harboring breast cancer in the VB L5. Tumor growth was monitored by bioluminescent imaging (BLI) and CT. We hypothesized that orthotopic implanted rats will demonstrate increased nociceptive response, and SRC kinase inhibition will decrease pain sensibility, as measured by mechanical nociceptive testing. Our results showed that rats bearing breast cancer tumors (TIR) had increased tumor burden and increased pain relative to controls or sham. TIR demonstrated pain response at lower pressures than control or sham animals, indicating that tumor-bearing rats required less stimulation to elicit pain than control or sham rats. Locomotion parameters were negatively affected; there was a decrease of the stride length, velocity and duration with extended stance and decreased hind limb flexion in TIR group; which most likely indicated epidural spinal cord compression. Tumor growth was evidenced by bioluminescent signal, radiance was increased at D45 and CT scanning confirmed osteolytic lesions, showed as complete ablation of the ventral and posterior elements of the VB. Histology using H&E stain, reveal the presence of breast cancer in the VB’s. Complete invasion of the bony trabeculae was noted in regions consistent with BLI-positive signal for 90% of the RBC3 implanted-animals. We conclude a successful use of an orthotopic model of breast cancer into the spine to evaluate mechanical pain using the modified Randal-Sellitto pressure meter. We were able to evaluate the nociceptive response in rats with tumors that showed a decrease in the gait locomotion parameters, and increased tumor burden and osteolytic activity and increased nociceptive response. Our intraspinal metastatic tumor model animals showed locomotor and sensory signs that are in accordance with some of the clinical manifestations in humans. These signs included a locomotor deficit and an increase in noxious sensation. Our model offers a reliable method to evaluate alternative approaches to treat pain in patients with metastatic spine disease.