# REGIONAL CENTRE FOR BIOTECHNOLOGY

## Seminar series

# GENE AND CELL BASED THERAPIES FOR METASTATIC CANCER

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**3:00 PM**
**Seminar Room**

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## Abstract

Majority of the solid tumors metastasize to the skeleton during advanced stages and cause significant morbidity and mortality. Bone disseminated cancer is highly painful and accompanied by susceptibility to fracture, spinal cord compression and anemia. Once the cancer colonizes in the skeleton it is incurable. Bone metastatic cancers grow within the skeleton by generating osteolytic lesions which results in release of growth factors from the bone calcified matrix and required for the growth of the cancer cells. Osteolysis also provides space for the growing tumor. Normal bone remodeling is carried out by the balanced activity of osteoblasts and osteoclasts. Osteoblasts originate from the bone marrow mesenchymal stem cells whereas the osteoclasts originate from the hematopoietic precursors. During normal wear and tear the osteoblasts secrete RANKL which upon binding to RANK on the pre-osteoclasts transforms them into multinucleated active osteoclasts. These osteoclasts resorb the damaged bone. Osteoblasts then secrete osteoprotegerin, a decoy receptor for RANKL which stops further osteoclast activation by blocking RANKL-RANK binding. Osteoblasts now lay new bone at the damaged site leading to repair. During skeletal metastasis the cancer cells stimulate the osteoblasts to produce more RANKL while inhibit osteoprotegerin which results in enhance maturation and activity of the osteoclasts and net bone loss. Bisphosphonates are commonly used to treat osteolysis which limits the osteoclast access to bone surface but this often cause osteonecrosis. Systemic delivery of osteoprotegerin is considered of very high therapeutic value for sequestering RANKL. But delivery of osteoprotegerin as protein therapy is not cost-effective and has short half-life. In our study a recombinant adeno-associated virus (rAAV) was used to deliver osteoprotegerin in a preclinical model of osteolytic bone metastasis. Results indicated significant prevention of bone loss which also resulted in reduced tumor growth by limiting space. Systemic osteoprotegerin gene therapy affected bone remodeling even in the areas of the skeleton, where there was no metastasis. To avoid this we used bone marrow derived mesenchymal stem cells (BM-MSC) to deliver osteoprotegerin. During tumorigenesis BM-MSC home to the tumor sites and become an important component of the tumor stroma. This tumor-homing property of BM-MSC is now being used to deliver therapeutic molecules directly to the tumor. BM-MSC expressing OPG were able to prohibit tumor growth within the skeleton by preventing osteolysis.