Introduction
Although new drug technologies have brought enthusiasm to the field by reducing bone pain and the incidence of skeletal related events in patients with bone metastases, their positive effects on the median survival rate seem to be only marginal and treatment remains palliative in most cases. Overall, the development of effective therapeutic regimen has been impeded by the lack of adequate animal models that are able to recapitulate the biology of the disease in humans [1, 2]. The aim of this study was to establish and characterize a new reproducible mouse model which allows the mimicking of the human bone microenvironment as the intrinsic homing site of human osteotropic cancer cells.

Materials and Methods
Institutional review board approval was obtained before the initiation of this study. Melt electrospun polycaprolactone scaffolds coated with calcium phosphate were seeded with human primary osteoblasts and cultured in vitro under osteogenic conditions for 8 weeks. These constructs were then loaded with fibrin glue and rhBMP-7 and subcutaneously implanted into the flanks of 4-6 week old NOD/SCID mice. After 14 weeks of in vivo bone growth osteotropic prostate cancer cells (PC-3) were inoculated into the human tissue engineered bone construct (hTEBC) via the intracardiac route. Tumour growth and metastases were monitored via bioluminescent imaging using the Xenogen IVIS system for up to 4 weeks. After euthanasia histological and immunohistological analyses of the hTEBCs were performed.

Results
Histologic sections of the hTEBCs revealed appositional mature bone growth adjacent to the scaffold. Bone growth was restricted to the scaffold’s bore. In the center of the constructs we could detect mature and immature bone islets with hyaline cartilage indicating endochondral bone formation. Staining with nuclear mitotic apparatus protein 1 (NuMa) using human-specific antibodies revealed viable human osteocytes surrounded by extraxellular bone matrix. Bone marrow spaces were filled with mouse cells from the hematopoietic lineage. Intraosseous inoculation of cancer cells resulted in a tumour take rate higher than 80%. Micro-CT analyses revealed an osteolytic growth pattern of the cancer cells.

Discussion and Conclusions
These results show the successful integration of tissue engineering into models of human bone metastasis. The use of hTEBCs could be a highly attractive alternative to the use of human bone, since it allows a control of shape, size and porosity. The amount and viability of cells seeded onto the scaffold can be monitored before implantation into the host animal. Future work has to focus on the impact of the human bone marrow and hematopoietic system on the development of metastatic lesions in hTEBCs.

References