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Human specific models for studying ER + ve and ER-ve breast cancer bone metastasis

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Background: Bone metastasis is commonly modelled using xenograft transplantation in immunocompromised mice and are limited by the lack of a true metastatic pathway. It is also likely that there are species-specific differences involved in growing human cells in a murine environment. We have developed models where human breast cancer cells metastasise to human bone in mice.

Methods: Bone discs from femoral heads of patients undergoing hip replacement surgery were implanted subcutaneously into NOD/SCID mice. For metastasis studies PDX (BB3RC32, ER + PR + HER2-; BB2RC08, ER + PR-ER2-; BB6RC37, ER-PR-HER2- and BB6RC39, ER + PR + HER2+), MDA-MB-231-luc2 or T47D-luc2 cells were injected directly into human bone implants or into mammary fat pads and metastases detected by luciferase imaging. Bone discs were harvested weekly for 4 weeks, osteoblast viability measured by calcein uptake and bone integrity assessed by uCT. Osteoclasts/osteoblasts and blood vessels were identified following TRAP and CD31 staining.

Results: Following implantation of subchondral bone, MDA-MB-231 cells metastasised from mammary fat pads to the human bone discs in 70% of mice within 6–8 weeks and T47D cells in 60% of mice within 8–10 weeks. Following implantation of spongy bone, metastasis occurred in ~ 28% of animals 12–16 weeks after injection of either cell line. Interestingly, MDA-MB-231 cells specifically metastasised to the human bone implants whereas T47D cells BB3RC32, BB2RC08, and BB6RC37 metastasised to both human bone and mouse long bones. Analysis of bone implants in the absence of tumours showed re-vascularisation by both human and mouse endothelial cells. No change in bone volume was detected, however, osteocyte viability was reduced to 40% of control by day 7 ($p < 0.0001$) and then stabilised. Osteoblast activity was confirmed by active calcein uptake from day 21 and presence of osteoclasts on the bone surface increased with time.

Conclusions: In vivo implantation of human bone discs provides a species-specific metastatic site for breast cancer cells.