Citation: IBMS BoneKEy **9,** Article number: 40 (2012) | doi:10.1038/bonekey.2012.40

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MEETING REPORT

11th International Conference on Cancer-Induced Bone Disease

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IBMS BoneKEy **9**, Article number: 40 (2012) | doi:10.1038/bonekey.2012.40; published online 7 March 2012

Cancer-Induced Bone Disease: Meeting Report from the 11th Annual Meeting on Cancer-Induced Bone Disease, Chicago, IL, USA, 30 November–3 December 2011.

The 11th Annual Meeting on Cancer-Induced Bone Disease took place at The Westin, Chicago, IL, USA, in November 2011. This meeting, jointly organised by the International Bone and Mineral Society, the Cancer and Bone Society (a program of IBMS) and the Bone and Cancer Foundation (a program of the Paget Foundation), continues to meet its objective of facilitating collaborations and knowledge transfer between clinicians and scientists working in the fields of cancer and bone biology. The meeting was attended by the worlds leading experts, sharing their insights into breast and prostate bone metastasis, as well as the bone disease multiple myeloma. For all of these disease states, there have been substantial advances in the understanding of mechanisms involved in tumour cell trafficking, colonisation and growth in bone in addition to identification of new therapeutic targets and clinical applications of bone-targeted therapy. Furthermore, this meeting was host to the first Gregory R Mundy Fellowship for Cancer-Induced Bone Disease. This $40 000 fellowship established to support the research of an outstanding early-career scientist/clinician was awarded to Penelope Ottewell (University of Sheffield, UK) to investigate genes responsible for breast cancer homing and colonisation of bone.

Meeting Highlights

Imaging technologies. The meeting commenced with a session on imaging technologies. Patricia Keeley (University of Wisconsin, USA) described the use of state-of-the-art non-linear optical imaging techniques (fluorescence-lifetime imaging microscopy and second harmonic generation) for visualising tumour and cells at the tumour–stromal boundary in live, mammary tumours. Using these methods, Dr Keely's research team have made ground-breaking discoveries into the role of stroma alignment in metastasis: During tumour progression, the structure and alignment of collagen fibres is altered in such a manner that perpendicular rearrangement of the collagen fibres is coincidental with areas of local invasion. Furthermore, in human samples, presence of perpendicularly aligned collagen was shown to be a prognostic indicator of poor patient survival. Following on, Gabri van der Pluijm (University of Leiden, Netherlands) gave an overview of recent developments in imaging of bone metastasis. Professor van der Pluijm described a number of imaging techniques that have been implemented in pre-clinical bone metastasis models for sensitive real-time cancer cell tracking, bone homing (functional studies) and drug response, including the following: optical imaging of fluorescence and bioluminescence, multiphoton microscopy, μ-computed tomography, positron emission tomography, magnetic resonance imaging and single-photon emission computed tomography. This talk highlighted the current limitations of real-time *in vivo* imaging. Although sensitivity and specificity of imaging technology continue to advance at a phenomenal rate, currently, no ideal imaging modality exists that combines excellent special resolution, cancer cell detection sensitivity and quantification; therefore, it is fundamental that the choice of equipment and imaging strategy should be specific for the objectives of the study.

A prime example of developing accurate visualisation methods for real-time *in vivo* imaging was discussed by Vasilis Ntziachristos (Helmholtz Zentrum Munchen and Technische Universitat, Germany). This talk described multi-spectral opto-acoustic tomography coupled with photo-absorbing molecules and nanoparticles for visualising cellular and subcellular processes through entire small animals. Using this technique, Dr Zentrum demonstrated real-time detection of cellular function and biochemical changes *in vivo* through intact tissues at high sensitivity and molecular specificity. In addition, multi-spectral opto-acoustic tomography with targeted fluorescent probes may have huge potential within the clinical setting; it was hypothesised that real-time visualisation of tumour cells during surgery could prospectively increase the efficiency and specificity of tumour excision.

Cancer stem cells, micro RNAs and metastasis. The increasingly popular hypothesis that cancers, such as breast and prostate, are formed from a small number of tumour-initiating cells termed 'cancer stem cells' was a hot topic for discussion at this year's meeting. It remains to be established whether cancer stem cells originate from the normal stem cell population or

from a de-differentiated cell type. However, evidence suggests that tumour progenitor cells share self-renewal properties and many characteristics of normal stem cells, including specific cell surface markers, drug efflux pumps and the expression of genes involved in developmental pathways. Similarly to normal stem cells, cancer stem cells are programmed to survive a host of insults, and probably exist in a protective niche, in a semi-quiescent state. These properties render cancer stem cells resistant to treatment, and therefore, it is likely that these cells are responsible for maintaining residual disease. Using gene expression analysis of cancer stem cells isolated from primary prostate tumours, Norman Maitland (University of York, UK) has identified specific genes implemented in cancer stem cell survival. Furthermore, reduced expression of these genes abrogated tumour initiation *in vivo*. Although these are early data, this information should prove useful for the development of novel therapeutics. In a separate study, Margaret Read (Infinity Pharmaceuticals, Inc., USA.) explored the efficacy of targeting the Hedgehog pathway in prostate cancer stem cells. The small molecule (IPI-926) antagonises the Hedgehog pathway by inhibiting Smoothened. In pre-clinical mouse models in which established prostate tumours had been partially removed, administration of IPI-926 significantly reduced tumour regrowth, thus delaying time to tumour relapse. This small molecule is currently being evaluated in clinical trials.

In addition to their role in tumour initiation, cancer stem cells have also been implicated in metastasis. Huiping Liu (University of Chicago, USA) has isolated tumour-initiating cells from primary breast tumours and lung metastasis; Luc2-enhanced green fluorescent protein labelling of these cells has enabled tracking of cancer stem cells through the entire metastatic process *in vivo*. Using optical reporters expressed along with miRNA precursors or inhibitors, the effects of introduced miRNA candidates are being evaluated by selective imaging of transduced tumour cells. Dr Liu's team is currently using this model to identify miRNAs that regulate breast cancer stem cells and metastatic cancer stem cells. Further insights into the role of miRNA's in metastases were given by Xijie Yu (West China Hospital, China) and Martine Croset (Universite de Lyon, France) who, in independent studies, found significantly decreased expression of miR-335 in bone metastatic cells in addition to decreased expression of miR-29a and miR-30 in bone metastatic cells from lung and breast cancer, respectively. These studies all imply that targeting miRNAs may represent novel targets for bone metastasis therapies.

For tumour cells to metastasise, they must first grow at the primary site, extravasate into the blood stream, survive in the blood stream, home to and lodge in a metastatic site, and proliferate to form a secondary tumour. For tumour cells to go through this process, they must phenotypically adapt. A topic of considerable interest was the plasticity of tumour cells and their ability to undergo epithelial–mesenchymal transition and mesenchymal–epithelial transition during cancer progression and metastasis. Using *in vivo* model systems, Erik Thompson (University of Melbourne, Australia) demonstrated different steps in metastasis being facilitated by opposite ends of the epithelial–mesenchymal plasticity spectrum; mesenchymal features favoured local dissemination of cells from the primary tumour, whereas successful colonisation of the metastatic site appeared to require a cohesive epithelial state. In agreement with this, Nyam-Osor Chimge (University of Sothern California, USA) showed that inducing the epithelial–mesenchymal transition by downregulating Runx2 activity increased the invasive phenotype of MCF7 cells.

Clinical discussions on bone-targeted therapies. The clinical discussions centred on the merits of using traditional bisphosphonates compared with the RANKL inhibitor denosumab for controlling cancer-induced bone disease. This meeting saw compelling arguments for adjuvant use of both of these targeted agents. Matthew Smith (Massachusetts General Hospital Cancer Center, USA) showed convincing evidence for increased efficacy of denosumab compared with zoledronic acid in breast and prostate cancer patients. In patients with early stage disease, treatment with denosumab increased bone metastasis-free survival and time to first bone metastasis, compared with zoledronic acid. Furthermore, denosumab treatment increased time to first skeletal-related event in patients with cancer-induced bone disease. Interestingly, no differences in overall survival were observed between the two agents and adverse side effects were comparable. However, these data may not be as clear-cut as they first appear. Robert Coleman (University of Sheffield, UK) showed benefits of zoledronic acid in a subset of breast cancer patients. The AZURE and Zo-FAST studies in which zoledronic acid was added to endocrine therapy both showed improved disease-free survival and improved overall survival for post-menopausal patients, these patients also had significantly decreased extra-skeletal metastasis. Similarly, in the ABCSG 12 trial, which evaluated the effects of zoledronic acid in pre-menopausal women with breast cancer receiving ovarian suppression therapy, a survival advantage was observed in patients whose ovarian function was fully inhibited, strongly suggesting that the benefits of zoledronic acid are dependent on low levels of reproductive hormones.

A highlight of this meeting was an introduction into the promising new bone metastasis drug cabozantinib. Cabozantinib is a new small molecule kinase, MET-VEGFR2, inhibitor that appears to be hugely beneficial to patients with castrate-resistant prostate cancer bone metastasis. In a small study containing 62 patients, administration of cabozantinib resulted in reduction or complete remission of bone metastases in 85% of patients. This drug is now in phase II clinical trials, and to date has shown unprecedented effects against prostate cancer-induced bone disease; the outcome of further clinical trials is awaited with great anticipation. Furthermore, Exelixis have stated that they are keen for researchers to utilise this drug in the laboratory setting and urge interested scientists to contact them with regards to setting up collaborations.

Conflict of interest

The author declares no conflict of interest.