Friday, 26 March 2010 08:30–09:15

EUROPA DONNA TEACHING LECTURE

Breast unit implementation − A national response

422 Invited

Breast unit implementation − A national response

N. O'Higgins[1]. [1]*Medical University of Bahrain, Bahrain*

Many breast cancers, formerly fatal, are now curable because of (i) quality of diagnosis, combining increasing accuracy with minimizing error, (ii) advances in therapy, (iii) improved clinical audit and accountability and comparing outcomes with the international norms, (iv) better training of cancer specialists, (v) collaborative effort in research and (vi) appreciation that when specialists, working together as a team, care for a large number of patients, expertise is maintained, skills are enhanced and innovation and research are developed.

The only realistic way to deliver this type of care is in a small number of specialized breast cancer centres. Patients treated in these settings have better survival and quality of life compared with those treated elsewhere. The public is quick to appreciate the value of multidisciplinary and multiprofessional care. When such care is absent, the potential for errors in diagnosis and treatment increases. Mismanagement is nowadays frequently brought to public attention. Publication in the media of suboptimal care provides a further powerful stimulus for improvement.

Medical evidence, public pressure and support by health authorities and the body politic place the need for breast centres on the political agenda. To set them up properly with highly-trained staff, top-quality equipment and a system of audit often requires a more sustained campaign. Governments are always assailed by a myriad of demands, each clamouring for priority. Medical personnel, although always supporting the need, find it difficult to be in tune with an arrangement that may result in removal of services from the hospitals in which they operate. Politicians often see withdrawal of cancer facilities from their local hospital as a threat to the community. Local communities often perceive that centralization or regionalisation of breast cancer care will reduce the quality of personal, individual attention and cause inconvenience and economic loss because of the loss of time and the expense of travelling to the specialist centre.

The implementation of a national programme for breast cancer care requires collaboration of many groupings in a society:-medical profession, nursing profession, training bodies, universities, politicians, health authorities, hospital managers, advocacy groups, cancer societies, patients, the general public and the audio-visual and print media.

Representatives of each of these groups must operate with evidence, effort, education, explanation and enthusiasm. In addition, they must be patient, persuasive and persistent. When these combinations are in place, a high-quality national breast cancer service, both for screening and symptomatic women, can be established.

Friday, 26 March 2010 11:00–12:30

KEYNOTE SYMPOSIUM

Understanding progression of breast cancer and its clinical implications

423 Invited

Models to study breast cancer invasion and metastases: lessons from normal

M. Bissell[1]. [1]*Lawrence Berkeley National Laboratory, Division of Life Sciences, Berkeley, USA*

Our work in the last three decades has underscored the plasticity of both the differentiated state and tumors. I will discuss how we use the normal mammary gland to understand breast cancer. I will describe a number of recent and unpublished works shedding light on the importance of the microenvironment, context and the tissue architecture on gene expression and tissue behavior.

These will include description of a novel forward genetic screen which takes advantage of the 3-dimensional assays of malignant and 'reverted' human breast cells we have developed over the years. The screen has allowed identification of a number of previously undescribed genes that could provide new targets in the EGFR and PI3K pathways. Upon screening for resistance to reverting agents acting on the EGFR pathway, we identified FAM83A, a previously uncharacterized protein, as conferring resistance to EGFR-inhibitors that could otherwise revert the malignant cells in 3D matrices. I will describe in vivo and culture studies that provide evidence that this novel family of previously uncharacterized proteins plays an important role in the EGFR/PI3K pathways, that it can cause malignant transformation, and that it can possibly explain some forms of resistance to EGFR therapies.

Other studies will highlight the importance of nuclear actin in growth regulation of epithelial cells by both growth factors and by extracellular matrix components. I will also describe an unexpected role for 14-3-3 sigma in malignant progressions. Finally, I will highlight how glucose transport and metabolism themselves constitute an axis of transformation with the ability to not only transform but also to modulate the classical oncogenic pathways such as EGFR, MAPK, PI3K and others.

425 Invited

Stem cells and cancer: treatment resistance, markers and novel therapeutic targets

R. Clarke[1]. [1]*Breast Biology Group, Paterson Institute for Cancer Research, University of Manchester, Manchester, UK*

There is emerging evidence that cancer stem cells (CSCs) are resistant to current therapies suggesting that CSC-specific treatments are needed. Due to their relative insensitivity to treatment, we and others have demonstrated that CSCs are enriched by radio, chemo and endocrine therapy. Increases in the proportion of CSCs after therapy is measured using cell surface markers and mammosphere colony assays of stem cell activity. DNA repair, survival and stem cell signalling pathways are strong emerging candidates for the underlying mechanisms of resistance. However, CSCs still respond to therapy-induced changes in microenvironmental signals. One candidate pathway known to regulate normal stem cells is Notch receptor signalling. We have evidence that activated Notch plays a key role in breast tumour initiation by CSCs and that therapies targeting Notch receptor are likely to be effective in preventing treatment resistance.

426 Invited

Resistance to anti-angiogenic therapy induced by hypoxia and notch signalling

A. Harris[1]. [1]*University of Oxford, Weatherall Institute of Molecular Medicine, Oxford, UK*

Hypoxia is a major driver to tumour angiogenesis, inducing vascular endothelial growth factor, VEGF, and many other growth factors. Bevacizumab has shown activity in early and late recurrent breast cancer, enhancing the effectiveness of chemotherapy in delaying disease progression but resistance is common. This may be either de novo with failure to respond at all to initial therapy or may be induced during treatment, and they are likely to have different mechanisms.

We have started a clinical trial of neoadjuvant Bevacizumab in a window study before neoadjuvant chemotherapy and this shows three patterns of response to Bevacizumab; a clear reduction in tumour vascularity, permeability and perfusion evenly across the tumour, a pattern of reduction of perfusion and permeability but increase in central necrosis and thirdly no response at all. We think these may mimic the major types of resistance. We have developed in vivo models for each type and show that upregulation of notch ligands, such as delta-like 4 in the tumour, can change the biology of the endothelial cells making them resistant to anti-VEGF therapy. This can be reversed with notch inhibitors and more recently we have shown that this is true with Ephrin B2 blockade. The study highlights the importance of understanding the vasculature in detail in a patient entering such studies.

We have also shown that after Avastin, although initially inhibiting tumour growth, tumours can carry on growing through treatment and they have marked changes in their biology. Amongst these changes is upregulation of the pH regulating protein, Carbonic Anhydrase 9, which we have previously shown is prognostic in of breast cancer and other tumour types. We inhibited Carbonic Anhydrase 9 expression in two tumour types and showed that in vivo the knockdown of Carbonic Anhydrase 9 was associated with much greater effect of Bevacizumab, a potentially turning a drug that had no effect at all on a tumour to one where the survival could be prolonged two-fold. This will support development of inhibitors against this target. We further investigated other mechanisms of adaptation to acid pH and found that bicarbonate transport is a key pathway and we are currently evaluating inhibitors developed for cardiac disease in this role.

In conclusion, resistance to anti-angiogenic therapy is complex, we need to profile patients for the mechanisms, and we can enhance the effectiveness through several different routes. It is likely, therefore, that anti-angiogenic therapy will increase in effectiveness as we target resistance