

between erbB3 and IRS-1 in MCF-7, T47-D and BT-474 cells with HRGβ1 treatment enhancing this recruitment and promoting IRS-1 phosphorylation at tyrosine (Y) 612, a specific PI3-K binding site. In addition, siRNA knockdown of IRS-1 greatly impaired HRGβ1 signalling via PI3-K/AKT in these cells. This novel interaction may have clinical relevance as immunohistochemical analysis of ER-positive BC patient samples revealed IRS-1 Y612 expression positively correlated with total erbB3, p-AKT and Ki67 expression. Importantly, we found that association of IRS-1 by erbB3 impaired IRS-1 recruitment by IGF-1R in both MCF-7 and T47D cells, whilst blockade of IGF-1R enhanced erbB3/IRS-1 interaction and sensitised both cell lines to HRGβ1. Consequently, knockdown of IRS-1 reduced HRGβ1 action and enhanced the effects of IGF-1R inhibition in these cells. In conclusion, these and previous findings suggest that IRS-1 can be recruited to IGF-1R, EGFR and erbB3 in ER-positive BC cells and this may provide an adaptive resistance mechanism when these receptors are targeted individually. Consequently co-targeting of IGF-1R and erbB receptors/IRS-1 may prove to be a more effective strategy for the treatment of ER-positive BC.

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#### O-37 SOX11 AND PSMD3 EXPRESSION IN HER2 POSITIVE BREAST CANCER

Y. Pang<sup>a</sup>, G.R. Ball<sup>b</sup>, E.A. Rakha<sup>a</sup>, D.G. Powe<sup>a</sup>, C. Caldas<sup>c</sup>, I.O. Ellis<sup>a</sup>, A.R. Green<sup>a</sup>. <sup>a</sup>Division of Pathology, Nottingham University Hospitals, University of Nottingham, Nottingham, UK. <sup>b</sup>School of Biomedical and Natural Sciences, Nottingham Trent University, UK. <sup>c</sup>Cancer Research UK, Cambridge Research Institute, Cambridge, UK

Human Epidermal Receptor 2 (HER2)+ have attracted attention as a poor prognostic class of breast cancer. However, HER2+ tumours appear to encompass biologically and clinically heterogeneous tumours.

In order to refine HER2+ breast cancer, we analysed over 48,000 gene transcripts in 132 invasive breast carcinomas using Artificial Neural Network analysis and identified high expression of two novel genes (SOX11, PSMD3) significantly associated HER2+ positivity. Using a large invasive breast carcinoma cohort ( $n = 1,298$ ), prepared as tissue microarrays, we assessed these targets using immunohistochemistry and investigated associations with clinicopathological variables, patients' outcome and ability to refine HER2+ classification.

PSMD3 nuclear expression was observed in 219/942 (23%) of tumours and was significantly correlated to HER2 positivity ( $p = 0.004$ ), tubule formation ( $p = 0.047$ ) and NPI ( $p = 0.007$ ). PSMD3 expression conferred a strong trend towards a longer breast cancer specific survival in the whole series ( $p = 0.065$ ). SOX11 nuclei staining was observed in 96/869 (3.8%) tumours and was significantly associated with ER ( $p = 0.006$ ) and PSMD3 nuclear ( $p < 0.001$ ) positivity and ck14 negativity ( $p = 0.018$ ) but not HER2. SOX11 expression did not predict patient clinical outcome in either the whole series or HER2+ tumours only.

This study confirms the biological and clinical heterogeneity of HER2+ tumours and the difficulties in translating global gene

expression data into routine practice using immunohistochemistry. We have identified two novel genes associated with HER2+ tumours and further studies analysing the role of PSMD3 expression in this important subtype is warranted.

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#### O-38 DYSREGULATED CANCER-SPECIFIC MiRNAs IN THE CIRCULATION OF BREAST CANCER PATIENTS

N.A. Healy, H.M. Heneghan, A.J. Lowery, N. Miller, M.J. Kerin. Department of Surgery, National University of Ireland, Galway, Ireland

**Introduction:** Recent seminal findings from our institution indicate that systemic miR-195 and *Let-7a* levels have potential as non-invasive breast cancer biomarkers. We aimed to validate these findings in an expanded cohort and to identify further miRNAs which augment the sensitivity and specificity of circulating miRNAs as diagnostic and prognostic markers for breast cancer.

**Methods:** The expression levels of nine miRNAs were evaluated in an expanded cohort of 265 breast cancer patients, 80 non-breast malignancies (colon, renal, prostate and melanoma) and 63 age-matched disease-free controls using RQ-PCR. Eleven additional miRNAs were evaluated as potential miRNA endogenous controls. Advanced QBase plus software and SPSS were used for biostatistical analysis of the data and correlation with clinicopathological variables.

**Results:** This study confirmed significantly deranged expression levels of systemic miR-195 and *Let-7a* and two additional miRNAs in breast cancer patients compared to disease-free controls. Elevated miR-195 was identified to be breast cancer-specific, with a sensitivity of 88% and a specificity of 91%. A combination of three circulating miRNAs, including miR-195 and *Let-7a*, increased the discriminatory power of this test for breast cancer to 94%. Of the eleven candidate miRNAs selected for normalisation, two were identified to be stably expressed in a subset of the original cohort and thus are ideal endogenous controls for blood based miRNA studies.

**Conclusion:** This study highlights the presence and dysregulation of cancer-specific miRNAs in the circulation of breast cancer patients and illustrates the potential for this systemic miRNA signature to aid in the diagnosis and prognostication of this disease.

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#### O-39 HER2 POSITIVE EARLY BREAST CANCERS: WHAT PROPORTION ARE RECEIVING ADJUVANT TRASTUZUMAB THERAPY? A MULTICENTRE AUDIT

S. Marla<sup>a</sup>, J. Cardale<sup>b</sup>, D.J. Dodwell<sup>b</sup>, A.I. Skene<sup>c</sup>, O. Gojis<sup>e</sup>, P. Abram<sup>d</sup>, C. Palmieri<sup>e</sup>, S.J. Cleator<sup>f</sup>, A. Bowman<sup>g</sup>, J.C. Doughty<sup>a</sup>. <sup>a</sup>Western Infirmary, Glasgow and University of Glasgow, UK. <sup>b</sup>St. James's Institute of Oncology, Leeds, UK. <sup>c</sup>Royal Bournemouth Hospital, Bournemouth, UK. <sup>d</sup>Northern Ireland Cancer Centre, Belfast, UK. <sup>e</sup>Department of Oncology, Cancer Research UK Laboratories,