LETTER TO THE EDITOR

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Reply: A morpho-molecular prognostic model for hepatocellular carcinoma

S Srivastava[1] and M Salto-Tellez*[,1,2]

[1]Cancer Science Institute, National University of Singapore, Singapore and [2]Molecular Pathology Programme, Centre for Cancer Research and Cell Biology, Queen's University Belfast, Belfast, UK

Sir,

We thank Sahin and Kaseb (2012, this issue also) for the interest in our work, and their constructive criticism. They recognise the value of our morpho-molecular approach but express reservation in relation to (a) the detail of the clinical information available; and (b) the nature of CD44 as a stem cell biomarker.

The shortcomings of the clinical information available would be obvious to all readers that are in tune with the clinical dimension on hepatocellular carcinoma. Unfortunately, it was not within the scope of our group to complement our clinical information further. This was discussed with the reviewers of our manuscript during the review process. It was felt that, despite this, the results were robust enough to merit the interest of the reader.

Immunohistochemistry allows us to focus the analysis of protein expression in the cellular subtype of interest due to direct visualisation. Thus, the scoring of CD44 was focused to its expression in neoplastic and non-neoplastic hepatocytes. Having said that the considerations by Sahin and Kaseb (2012) on the nature of CD44 are very pertinent; they evoke an ongoing discussion on what represents a stem cell marker in general (Wright, 2012), what is the clinical value of liver cancer stem cell markers (Liu *et al*, 2011) and, indeed, the ambiguous role of CD44 as a cancer stem cell marker (Jaggupilli and Elkord, 2012). Sahin and Kaseb (2012) provide further argumentation to illustrate this dilemma, which we did not address in our manuscript as it was not its core focus, and we thank them for doing so.

In 1999, the director of the National Cancer Institute challenged 'the scientific community to harness the power of comprehensive molecular analysis technologies to make the classification of tumours vastly more informative.' This challenge aimed to change 'the basis of tumour classification from morphological to molecular characteristics' (NIH Guide, 2008). More than 10 years down the road, it would appear to us that a combined morpho-molecular approach (rather than a substitution of approaches) may be most relevant to establish a meaningful new taxonomy of diseases. These approaches will be clearly redefined by more complete clinical data and more robust biomarkers in the future, but it is likely that the principle will remain.

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*Correspondence: Professor M Salto-Tellez; E-mail: manuel_salto-tellez@nuhs.edu.sg