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Comment on 'Tumour antigen expression in hepatocellular carcinoma in a low-endemic western area'

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Sir,

We read with great interest the study by Sideras *et al* (2015) that combines tissue microarrays (TMA) and immunohistochemistry to investigate the expression pattern of 15 antigens belonging to different categories, including cancer testis antigens (CTAs) and oncofetal proteins in primary hepatocellular carcinoma (HCC). Because current therapies for HCC are far from ideal (Ilan, 2014) and immunotherapy has been proposed as a potential therapeutic option, the authors aimed at identifying a panel of relevant tumour antigens with broad expression in a Western European population of HCC patients and specific expression in the tumour tissue (Sideras *et al*, 2015). Cancer testis antigens represent a family of >200 proteins selectively expressed in malignant cells, but not in their natural counterpart except for human germ cells (Simpson *et al*, 2005; Gjerstorff *et al*, 2015; Grizzi *et al*, 2015). Among the different types of tumour antigens, CTAs identified highly promising therapeutic targets (Gjerstorff *et al*, 2015). In contrast to previous studies (Xu *et al*, 2012; Liang *et al*, 2013; Xia *et al*, 2013; Wang *et al*, 2015), Sideras *et al* (2015) found a low (<10% of patients) prevalence of expression of MAGE-A3/4, NY-ESO-1, MAGE-A1 and MAGE-A10. Moreover, a low (<10% of patients) prevalence of expression of the foetal specific glycoprotein alpha-fetoprotein (AFP) was found. Although its serum level falls rapidly after birth and its synthesis in adult life is repressed, >70% of HCC-affected patients have usually a high serum concentration of AFP. Today, AFP and ultrasonography are the main tests for HCC surveillance in clinical practice, and in the interim, using ultrasonography and AFP in combination may be the best strategy to optimise early HCC detection (Mehta and Singal, 2015). Sideras *et al* (2015) stated that the observed prevalence of expression of CTAs and oncofetal antigens was generally lower because previous studies have been conducted in East Asia where hepatitis B virus infection is the prevalent cause of HCC and the majority of HCC patients have liver cirrhosis. Furthermore, previous investigators used RT-PCR measuring mRNA expression, whereas they evaluated protein expression by immunohistochemistry. Here, we would like to discuss additional points underlying these discrepancies and that impact on the CTAs as immunotherapeutic targets. In an effort to accelerate translation of new developments in basic immunology into cancer patients, representatives from eight immunotherapy organisations representing Europe, Japan, China and North America convened an 'Immunotherapy Summit' at the 24th Annual Meeting of the International Society for Biological Therapy of Cancer (now called Society for Immunotherapy of Cancer, SITC). One of the concepts raised by SITC and defined as critical was the need to identify hurdles that impede effective translation of cancer immunotherapy (Fox *et al*, 2011). The critical hurdles highlighted have been grouped into nine general themes. Among these have been identified the 'complexity of cancer', its 'heterogeneity' and 'immune escape' (Fox *et al*, 2011). Hepatocellular carcinoma originates and progresses throughout a dynamic process involving different 'driven alterations' that ultimately lead to the malignant transformation of hepatocytes. Malignant transformation may occur regardless of the aetiological agent through a pathway of increased liver cell turnover, induced by chronic liver injury and regeneration in a context of inflammation, immune response and oxidative DNA damage (Li and Wang, 2015). Hepatocellular carcinoma is a heterogeneous disease in 'space' and in 'time'. The term 'heterogeneity' defines the presence of cell clones, within a tumoral mass, with different genetic aberrations that mediate divergent biology defining the natural history of that particular tumour, that is, one clone does not represent the entirety of the tumour cell population. This variability is what ultimately determines the evolutionary progression of neoplastic disease and its response to therapy (Luo *et al*, 2009). Singular cells respond differently to the same stimulus, with some not responding at all (Floor *et al*, 2012; Almendro *et al*, 2013). These considerations, in conjunction with the complexity of 'tumour-host' interactions caused by temporal changes in tumour phenotypes and an array of immune

mediators expressed in the tumour microenvironment, might explain the limited reliability and applicability of current therapeutic strategies. Sideras *et al* (2015) did not report fundamental hallmarks of cancer, including 'cancer complexity', 'tumour heterogeneity' and 'field cancerization', that is, the presence of abnormal tissue surrounding primary cancerous lesions. These observations lead us to reflect on the appropriateness of TMAs to state the CTAs and oncofetal proteins as potential therapeutic targets. It is known that diagnostic accuracy of a histological assay may be affected if the 'target antigen' is uniquely present in a fraction of a tumour (Sottoriva *et al*, 2015). Tissue microarray consists of small fractions of tissue inserted into a recipient paraffin block such that a tissue section on a single glass slide can contain numerous patient samples in a spatially structured pattern. Although the study of whole-tissue sections for the evaluation of large tumour cohorts is tedious and costly, the genome-wide network of intra-tumour heterogeneity across multiple spatial and temporal scales, and patient-specific patterns of cancer evolution limits the appropriateness of investigating a small fraction of tissue, and is prone to controversial results and consequences for treatment design (Chiriva-Internati *et al*, 2004). In addition, Sideras *et al* (2015) applied a scoring system, called 'H-score' obtained by multiplying the intensity score (range: 0–3) with the level of % of positive cells, where $1 \leq 5$, $2 = 5-25$, $3 = 25-75$ and $4 \geq 75$ %. However, this approach generates equivalent 'mathematical products', (i.e., condition 1: intensity = 1 multiplied with the level of % of positive cells $2 = 5-25$ is the same product obtained multiplying intensity = 2 with the level of % of positive cells $1 \leq 5$ %; condition 2: intensity = 1 multiplied with the level of % of positive cells $3 = 25-75$ is the same product obtained multiplying intensity = 3 with the level of % of positive cells $1 < 5$ %; condition 3: intensity = 1 multiplied with the level of % of positive cells $4 \geq 75$ is the same product obtained multiplying intensity = 2 with the level of % of positive cells $2 = 5-25$ %; condition 4: intensity = 2 multiplied with the level of % of positive cells $3 = 25-75$ is the same product obtained multiplying intensity = 3 with the level of % of positive cells $2 = 5-25$ %), although their biological significance is completely different. In other words, these overlapping 'scores' subtend different impacts on the capacity of CTAs to elicit the immune response and the heterogeneous behaviour of HCC. In conclusion, to advance our knowledge in a currently widely debated field of investigation such as that of immunotherapy and HCC, a clearer distinction must be made between the exploration of CTA expression pattern and their real application in human clinical trials. Because the analysis of CTA expression is useful in identifying patients who are most likely to benefit from immune intervention strategies, we need to adopt a more adequate experimental approach and a change in our 'mind' from a 'qualitative' or 'semi-quantitative' to a more advanced 'quantitative' thinking.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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