

## Stromal Responses among Carcinomas—Response

Robert B. West, Matt van de Rijn, and Julia L. Chen

We thank the authors for their interest in our study on the clinical relevance of stromal signatures (1). We have been delighted to see how the field of stromal signatures, as defined by gene expression profiling, in cancer has grown since our description of clinical variation in stromal signatures in our 2005 publication (2). Others, subsequently, have identified slight variations on this desmoid type fibromatosis (DTF) signature, and the differences seem attributable to the platforms used by each laboratory (3, 4). Triulzi and colleagues raise the possibility that the different correlation with outcome seen for the DTF signature in breast versus ovarian carcinoma may be due to stage, as in general, breast may be lower stage than ovarian, when discovered. Data from one of our prior studies do not seem to support that. We have previously looked at the correlation of the DTF signatures in breast cancer with stage. In our study in 2008 (5), looking at 561 breast cancer cases by gene expression profiling and 745 cases by immunohistochemistry, we found no statistically significant difference between the presence of the DTF signature and the stage of the breast cancer. However, we agree that existing outcome predictors (or traditional clinicopathologic features) can have opposite effects with regard to stromal signatures. For example, in our 2009 CCR article (6), we demonstrated that the colony-stimulating factor 1 (CSF1) macrophage signature that we described had a correlation with features known to predict poor outcome (high grade, ER/PR negativity, p53 mutation status). However, when we restricted the analysis to estrogen receptor (ER)-negative cancers, there was a trend for the CSF1 signature to correlate with improved survival. These

findings are consistent with the growing large body of genomic evidence to suggest that there are many reproducible subtypes of cancer within an organ system and that any one feature, like ER status or stromal signature, may correlate with good outcome if all cases are studied together, but may also correlate with bad outcome if only a specific subtypes is examined. For example, ER positivity that is generally associated with good outcome has a HR greater than 1 when looking at cases with patient survival over 10 years (7). Although the findings of tumor subtype differences in stromal signatures are interesting and clinically relevant, we think that the underlying biology of these signatures is ultimately more significant and even more so as we have now shown that the DTF signature is present in many different types of cancer. Ultimately, we think that these signatures are important for their potential impact on cancer in terms of identifying new therapeutic targets and understanding cancer etiology. The latter point is clearly important as we have shown in our 2009 study of ductal carcinoma *in situ* (8) that the DTF signature is present in preinvasive stages of cancer, suggesting that stromal signatures arise well before the neoplasia invades into the stromal. This finding raises the possibility that the DTF stromal signature plays a role in carcinogenesis. Others with model systems have demonstrated that altering stroma gene expression can induce neoplasia. The presence of the DTF signature at early (preinvasive) and late stages of cancer (at least in breast, possibility others) suggests that there is a fundamental role of the stroma in cancer biology. We think we can all agree that stromal signatures are clinically relevant and are promising areas of research to identify cancer treatment targets and targets for prevention strategies.

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**doi:** 10.1158/1078-0432.CCR-13-3238

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## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Received November 27, 2013; accepted December 18, 2013; published online March 3, 2014.

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*Clin Cancer Res* 2014;20:1397.

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