veillance and treatment were performed at each site) [6]. In fact, Lee’s survival signature [5], developed in Chinese patients whose outcome is assumedly driven by “early” recurrence, had no obvious association with survival in patient series collected from the US, Europe, and Japan, in which “late” recurrence was the major driver of outcome, although the signature was clearly reproduced in all of these series [2].

There is no doubt tumor-derived molecular information is important in terms of therapeutic target discovery, and it is ideal to confirm that it is associated with patient outcome, i.e., “early” recurrence, at least in the particular patient series in the study to rationalize targeting the gene or pathway. However, the unstable association could be a significant limitation to utilize the tumor-derived molecular information as a prognostic marker, which should stably work across diverse patient populations across the world.

References


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Genome-based predictors for HCC outcomes: A matter of tumor and/or stroma

To the Editor:

We appreciate the response by Yujin Hoshida [1] regarding our interpretation [2] of his failure to identify tumor-associated survival genes when using the informative gene panel approach described in his recent study [3]. Hoshida argues that the informative gene panel contains many genes reported to be silenced in human tumors and thus insists that the lack of tumor-derived survival genes in his recent study is not due to the methodology used. Hoshida concludes that the reason they are unable to identify tumor-derived survival associated genes is due to the type of recurrence they are studying. A majority of cases in their cohorts have a late-recurrence, rather than early-recurrence commonly found with cases from most Asian cohorts. It is commonly believed that late-recurrence is largely contributed by the development of additional new tumor lesions due to high carcinogenic activities in an at-risk liver while early-recurrence is mainly attributed to metastatic disease. His conclusion implies that no measurable molecular change in the original HCC can be used to predict the development of a new HCC, i.e., de novo HCC, rather the ability to develop new HCC is only dictated by the liver microenvironment. This is an interesting idea but should be interpreted cautiously. We believe such a conclusion is premature based on the current body of evidence. Numerous tumor suppressor genes and oncogenes have been identified to be responsible for the development of HCC. For example, p53, APC, beta-catenin and Myc, along with the transcripts of their downstream targets, are frequently disregulat-ed in HCC. The transcripts associated with these molecular signaling pathways should be readily detectable in tumor cells. It is conceivable that some of these transcripts could be predictive of the carcinogenic activity common to HCC. While the informative gene panel may contain many tumor suppressor genes, many other important genes apparently are not included. Because of the availability of the whole-genome DASL platform, such an uncertainty can now be formally addressed. The mechanism for HCC recurrence is currently unclear. Both early- and late-recurrences can be independently attributed to meta-
static and de novo HCC. Our preliminary experiments suggest that a tumor-derived gene signature could be found to be predictive for HCC late-recurrence (Budhu et al., unpublished data). This is analogous to the recent findings that both tumor and non-tumor-derived gene signatures can predict HCC early-recurrence in multiple cohorts [4–9]. Thus, the jury is still out and further studies are needed.

References


To the Editor:

In his recent article, DS Chen indicated that the hepatitis B vaccine was an innovation from France [1]. When listing the challenges that need to be overcome to extend hepatitis B mass vaccination he could have cited France again. The percentage of one-year-olds immunized with three doses of Hepatitis B in France was 29% in 2006 (vs. 86% in Germany, a comparable country), lower than most of the very poor countries in the world [2].

Recently, a paper by a French team published in a major journal concluded that “Engerix B vaccine appears to increase the risk of CNS inflammatory demyelination in childhood” [3]. A pre-publication release campaign worsened the message in the newspapers.

This research was conducted with public funding from several major national bodies. Evaluation could have helped avoiding: (a) subgroup analyses without a priori definition on the basis of known mechanisms or in response to previous findings; (b) absence of declaration of the number of analyses performed; (c) lack of adjustment for multiple testing with tests for heterogeneity [4]. These pitfalls are easy to remember: Sleight showed, in a subgroup analysis of patients from the ISIS-2 trial, that aspirin therapy was significantly beneficial for all patients except those born under the astrological signs of Gemini or Libra [5]!

Guidelines were generated to improve quality of epidemiological studies (eg STrengthening the Reporting of OBServational studies in Epidemiology’ (STROBE) [6]. Funding agencies, reviewers and journals editors must have actively endorsed these guidelines.

References
