Most investigators using human tumor cell lines have not initiated the tumor cell lines, but rather obtained them from colleagues or repositories. Although the latter source would seem to offer some security regarding the authenticity of the cell lines, investigators bear the burden of assuring that the cell lines selected are appropriate to the research and maintained in a way that preserves their identity.

In this issue of the Journal, Boonstra et al. (1) report a survey of available esophageal adenocarcinoma (EAC) tumor cell lines. They show that three very widely used cell lines are, in fact, derived from other tumor types and concluded that the use of these cell lines “threatens the development of treatment strategies for esophageal adenocarcinoma.” Certainly, it is important for this information to be available to the research community and, to the extent that EAC
cell lines may reflect important aspects of biology unique to therapeutic targeting of that tumor type, their conclusion is valid.

Misidentification, cross-contamination, and confusion regarding tumor cell lines is not a new problem. Beginning in the 1970s, evidence of widespread contamination by HeLa cells was recognized by Nelson-Rees et al. (2) based on cytogenetic analyses. This finding led to the development of some early recommendations for quality control of cell lines, which also included analysis of isoenzyme expression patterns (3). Although state-of-the-art at the time, these methods were time consuming and required a high level of expertise. The identification of HeLa marker chromosomes or derivatives by G-banding in highly aneuploid metaphases with many chromosomal rearrangements is no easy task. The advent of spectral karyotyping has added objectivity and resolution to the process and supported identification of instances of contamination in tumor cell lines with extremely abnormal karyotypes (4). The development of molecular biological techniques, such as DNA fingerprinting, has provided for a quantum increase in resolution. Masters et al. (5) have advocated the use of short tandem repeat (STR) fingerprinting, a straightforward standardized method that has gained wide acceptance. Forensic applications of this technology have generated a large commercial market for DNA fingerprinting. This, in turn, has led to the marketing of affordably priced kits for STR fingerprinting. Moreover, large publicly accessible databases with STR fingerprint results provide a useful reference against which investigators can compare data. Boonstra et al. have made a substantial contribution with STR characterization of the available EAC tumor cell lines.

The authors opine that because of the misidentification of SEG-1, the sole tumor cell line used in studies supporting the rationale for clinical testing of sorafenib, this trial should be reconsidered. To the extent that the acid induction of the mitogen-activated protein kinase pathways and the corresponding high sensitivity of SEG-1 to sorafenib are unique to this cell line or to large cell lung cancer, this misidentification may be important. However, given the knowledge that cancer is a heterogeneous disease, one might question the rationale for any therapeutic maneuver that is based on studies conducted in a single cell line. In fact, alterations in mitogen-activated protein kinase pathways are common in many tumor types, and it would not be surprising if studies conducted using the bona fide EAC cell lines might provide a preclinical rationale for a sorafenib trial. Likewise, telomerase expression is viewed as a rather general feature of tumor cells, particularly of tumor stem cells. A rationale for clinical evaluation of a telomerase inhibitor in EAC could be advanced in the absence of studies in EAC tumor cell lines. A positive prospective use of the 10 authenticated EAC tumor cell lines might be to systematically evaluate them for therapeutic targets unique to this disease.

In other research studies, tissue of origin may not be important. For example, during the early development of in vitro drug screening models, National Cancer Institute investigators selected “KB” cells for use in screening. Although tumor of origin was not important in this application, which included bioassay-directed isolation of natural products, identification of the derivation from HeLa and publication of the situation when recognized was believed to be important (6). The 10 cell lines authenticated by the authors may be adequate for many types of studies of EAC. For some other tumor types, complexity at the molecular level has been identified that enables a molecular taxonomy (7) defining clinically significant subtypes. In breast cancer, the multiple subtypes and known heterogeneity would argue for use of large numbers of cell lines. In assembling a panel of breast cancer cell lines for large-scale analysis of gene expression, Neve et al. (8) collected and analyzed 51 tumor cell lines. Genomic profiling data generated by GlaxoSmithKline on more than 300 tumor cell lines of various tumor types is publicly available via the National Cancer Institute CaBig Web site at https://cabig.nci.nih.gov/cabig_GSKdata/?searchterm=GSK. Certainly, the burden of individually banking and characterizing this many cell lines is beyond the capability of most investigators. Nonetheless, adherence to rigorous cell banking and characterization using modern protocols (9) could avoid many problems in the future.

Boonstra et al. (1) are to be commended for putting forth a substantial effort to evaluate the validity of the EAC cell line resources available using state-of-the-art methods suitable for linking archival patient material to derived cell lines. The finding that 10 of 13 cell lines could be proven to be derived as reported substantially exceeds what one might expect from the prevailing notion cited by the authors that “up to one third of all cell lines have an origin other than that supposed.” Although one might conclude that the most important result of their work is the potential to “de-bunk” research done using misidentified cell lines, the most enduring result will likely be the definition of 10 EAC tumor cell lines of proven authenticity for use in studies addressing this disease.

References

Notes
The content of this editorial reflects the views of the author, not necessarily the policy of the US Government.

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