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Biomarkers and translational research

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ABSTRACT: Biomarkers have the potential to play important roles in diagnosis and in the identification of patient populations that could benefit from targeted therapy. They also serve as markers of drug efficacy and could be used to monitor treatment effectiveness, drug toxicity, and development of resistance. One example of a successful biomarker development is represented by the testing for Her-2/ERB2 over expression. Tissue sampling is crucial for the definition and validation of new biomarkers. In general, biomarker and its corresponding assay must be validated before phase III to be useful in reducing trial size.

Keywords: Biomarkers; Tissue sampling; Gefitinib development; Surrogate marker

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DEVELOPMENT OF BIOMARKERS: WHAT ARE THE SCIENTIFIC HURDLES?

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For next-generation therapies drug development by chance is moving toward cancer therapies that are molecularly targeted. Nevertheless, drug development still relies on the same basic strategies used for cytotoxic drugs. In the new era of cancer treatment, instead of applying the concept of maximum tolerated dose (MTD) as does cytotoxic drug therapy, we must think in terms of the optimal biologically active dose (OBAD) and, perhaps, the maximum tolerated economic cost. Only administration of molecularly targeted drugs at OBAD can demonstrate their optimum therapeutic efficacy.

Biomarkers could play important roles in disease diagnosis and in the identification of patient populations that could benefit from targeted therapy. They also serve as markers of drug efficacy and could be used to monitor treatment effectiveness, drug toxicity, and development of resistance. Moreover, some biomarkers appear to be surrogates for clinical benefit; as such, they have the potential to serve as endpoints in clinical trials. To use biomarkers to maximum advantage, several scientific hurdles must be surmounted. For example, a need exists to differentiate molecular and therapeutic targets, determine which targets to block to achieve tumour control, overcome resistance mechanisms, and identify patients who need treatment and are potential responders.

Many techniques – genomics, proteomics, interactomics, peptidomics, and degradomics – offer a spectrum of analytical possibilities. In the early days, procedures involved removing most proteins, e.g. albumin, prior to analysis. That approach, unfortunately, eliminates the opportunity to investigate interactomics involving the small peptides bound to large molecules. To identify potential biomarkers and study their roles in the disease pathway, it is necessary to look for small molecules in serum (peptidomics) as well as protein-degradation products (degradomics). Many peptides have excellent cancer signatures. Reverse-phase protein microarray provides a map of known cell-signalling proteins.[1]

Biomarker development should follow different pathways depending on the stage of drug development. For early stages of clinical development, biomarkers can identify or confirm molecular targets, help optimise dose schedules for the anticancer agent, and might correlate with clinical benefit. Identifying clinically relevant targets is challenging; in numerous examples, the intended target was found to be irrelevant. As not all molecular targets are legitimate therapeutic targets, however, biomarkers can provide a means of determining which target(s), when inhibited, correlate with tumour control. In the case of some anticancer agents (e.g. cetuximab, gefitinib, farnesyl transferase inhibitors, and inhibitors of vascular endothelial growth factor [VEGF]), it appears that the original molecular target is not the only therapeutic target.

In the later stages of clinical development, identified markers could be used to select the patients most likely to respond to the targeted agent. Any biomarker used as a basis for patient selection must demonstrate excellent sensitivity and specificity; otherwise, the risk of not treating patients who might benefit would be

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