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Biomarkers in Oncological Research

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Introduction

From time immemorial doctors have been using a panel of parameters to identify various diseases. Except the terminology used was not biomarkers- but diagnosis. Later, the parameters became -a set of biological indicators for pathological process which was subsequently redefined by NIH as "A biomarker is an objective measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention." A biomarker has to be reliable, measurable, specific, and predicative.

Scientists have studied the fundamental mechanisms of human diseases in vitro or in animal models. These are only substitutes for understanding human physiology and disease. Proving that a mechanism responsible for disease progression in a model system is also relevant to human diseases not to mention then translating it into a new therapeutic is a major bottleneck in biomedicine. In the end, only clinical interventions on humans will be a bridge models and human disease. In recent times interest in biomarkers has exploded, and thousands of articles are published each year that mention biomarkers.

Disciplines such as personalized medicine and drug discovery are evaluating gene expression profiling as a method for developing toxicity biomarker panels. Compounds having similar toxic modes of action are thought to induce specific changes in gene expression. Therefore, we hypothesized that the toxicity of unknown compounds can be predicted and managed during drug development by comparing their molecular fingerprints with those obtained with compounds of known toxicity. A major benefit gained by the development of limited content gene panels is the ability to switch from a relatively rudimentary hybridization microarray detection platform that surveys the entire genome to the more sensitive and faster technology of reverse-transcription real-time PCR arrays.

Genotoxicity with respect to DNA mutations and chromosomal damages are hallmarks of cancer. Various microarray screening studies have led to the understanding that eukaryotic cellular responses to genotoxic stress involve orchestrated activation and repression of genes in the pathways of DNA repair, cell survival, and cell death. Current and potential emerging applications of biomarkers in different fields such as oncology, cardiology, neurology, safety, and other applications. In our earlier studies we have identified potential biomarkers affecting treatment response in hematological malignancies [1], breast cancer [2,3], prognostic and diagnostic markers for lung cancer [4], cervical cancer [5], obesity associated breast cancer [6] and head and neck squamous cell carcinomas [7-9].

Some selected examples demonstrate the wide range of potential applications of biomarkers:

(i) A particular biomarker panel consisting of 14 genes (C1inh, C1s, Carhsp1, Chi3l1, Gat3, Gbp2, Hspb1, Icam1, Jak3, Kcne2, Lama5, Lgals3, Nppa, Timp1) can be used in diabetic retinopathy pharmacotherapeutic research and drug development [10].

(ii) Biomarkers indicative of oxidative stress - 15(S)-8-iso-prostaglandin F(2alpha) and 3-nitrotyrosinein, in urine samples have been assessed [11].

(iii) Alanine aminotransferase (ALT) is the principal reference standard biomarker to diagnose drug-induced liver injury (DILI) [12].

(iv) Increased cerebrospinal fluid concentration of the chemokine CXCL13 is correlated with active multiple sclerosis (MS) and can serve as a biomarker [13].

(v) Advanced ovarian cancer patients who achieve an excellent response to primary platinum-based chemotherapy with a cancer antigen 125 (CA-125) serum level less than 10 U/mL may be more amenable to the benefits of paclitaxel maintenance therapy [14].

(vi) High histone deacetylase 8 (HDAC8) expression is a prognostic marker associated with poor overall and event-free survival in neuroblastoma [15].

(vii) Regulation of ERBB2 by ER-PAX2 determines response to tamoxifen in breast cancer [16].

(viii) MicroRNAs have the potential to be used as clinical biomarkers for a wide range of diseases. MicroRNA signature can potentially predict colorectal cancer recurrence in stage II patients [17]. Similar studies have been reported for pancreatic, breast, lung, and liver cancer.

(ix) Circulating microRNAs from blood samples also provided reliable and highly differentiated diagnosis for multiple sclerosis and diabetes. Circulating microRNA-1 may be a novel, independent biomarker for diagnosis of acute myocardial infarction (AMI) [18].

(x) In tissues-such as adipose tissue, skeletal muscle and eye-in which a biomarker for senescence, p16(Ink4a), contributes to the acquisition of age-related pathologies, life-long removal of p16(Ink4a)-expressing cells delayed onset of these phenotypes. It indicates that cellular senescence is causally implicated in generating age-related phenotypes and that removal of senescent cells can prevent or delay tissue dysfunction and extend healthspan [19].

(xi) BRCA1 or BRCA2 and CCNE1 aberrations are biomarkers for breast cancer and ovarian cancer survival [20].

(xii) MicroRNAs 103 and 107 regulate insulin sensitivity. Caveolin-1, a critical regulator of the insulin receptor, is a direct target gene

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of miR-103/107. MiR-103/107 could be biomarkers for insulin insensitivity [21].

Other types of biomarkers include predisposition biomarkers, screening biomarkers, diagnostic biomarkers, prognostic biomarkers, toxicity biomarkers, pharmacodynamic biomarkers, and others.

Methods to Detect

Among several methods, such as microarrays, Genotyping of specific genes such as oncogenes or tumor marker genes, apoptotic genes and looking for SNPs has led to the discovery of new biomarkers. I am not referring to SNP data bases, as they contain large data as is accessible on net – this article projects the contributions made by several authors more recently and may not be available in the Databases, but are nevertheless important contributions.

The use of RT2 Profiler PCR arrays could be used to pursue identification and validation of specific groups of biomarker genes that can be utilized as classifiers for genotoxic risk detection and management. The RT2 Profiler PCR Array System is a powerful tool that can be application-tailored for genomic biomarker discovery and validation.

Biomarkers feature in thousands of published articles each year, evidencing the high level of interest and research in this field. This report focuses on issues that must be addressed to utilize this growing knowledge about biomarkers and successfully commercialize them in therapeutic and diagnostic applications.

Biomarker discoveries cab be categorized into these sub themes

- Integrated biomarkers of various diseases
- Biomarkers for diseases prediction and Model biomarkers
- Biomarkers in clinical practice and Disease progression
- Biomarkers in newer areas like metabolomics and genomics
- Future trends in biomarkers for research and development

Biomarkers can be valuable tools in clinical diagnostics as well as in therapeutic discovery and development. They can be used to predict response to therapy or risk of side effects for personalized medicine applications. Additional types include predisposition, screening, diagnostic, prognostic, toxicity, pharmacodynamic, and other biomarkers.

Importantly, we question prognostic signatures as specific research tools, not as clinical guides: smoke does not drive fire, yet it is powerful indicator of when and where a fire is burning.

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