Advancing Biomarker Science in the 21st Century

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“One of the primary objectives of scientific investigation in medicine is to inform patient care. The creative, imaginative, and intelligent study of advanced biomarkers, including genes, transcripts, proteins, and metabolic byproducts, may hold the key to redefining human disease and achieving optimal clinical outcomes. Given the global interest, overarching relevance, and inherent complexity, the most pertinent question becomes, “what is required of the scientific and medical communities to advance meaningfully the discipline of biomarker science in the 21st century?”

In this issue of the Circulation: Cardiovascular Interventions, Derer et al1 introduce vitronectin as an independent predictor of both early (30-day) and late (6-month) major adverse cardiovascular events after percutaneous coronary intervention (PCI) with or without stenting. Patients with a baseline serum vitronectin level of $49.7$ mg/mL (representing the upper quartile) experienced death, myocardial infarction, or urgent target-vessel revascularization at a 3-fold higher rate than patients in the 3 lower quartiles. Will vitronectin become a part of the armamentarium for procedural risk assessment? Will it one day assume the lofty status of troponin as a readily available and widely implemented measurement tool for clinicians?

Cardiac-specific troponin is considered the prototypical biomarker for several reasons. It is detectable in very low concentrations under normal conditions; it increases rapidly, predictably, and for a well-defined duration after myocyte necrosis; and it identifies patients at risk for subsequent cardiovascular events and those in whom antithrombotic pharmacotherapy and PCI offer the greatest benefit. Troponin assumed its rightful position in clinical practice and evidence-based guidelines not by chance, but through dedicated investigation in parallel with large-scale clinical trials. Assuming that PCI and stenting among the 63 hospitals participating in the Evaluation of Platelet IIb/IIIa Inhibition in Stenting Trial (EPISTENT) were performed using standardized techniques and that the original hypotheses were not fully tested, the reported contribution to the understanding of coronary artery disease, the anticipated yield from the biomarker investigation? What was the clinical subgroup for the current investigation was selected from the first 899 consecutively randomized patients who participated in an angiographic substudy. A simple random sample of 237 patients among whom baseline blood samples were collected served as the basis of the analysis. What was the anticipated yield from the biomarker investigation? What contribution to the understanding of coronary artery disease, PCI, or periprocedural pharmacotherapy to include abciximab was expected and subsequently validated?

A candidate-based approach to biomarker science, particularly in the context of a clinical trial, is traditional, as evidenced by a large number of publications within the medical literature detailing the potential merits of an isolated protein. Derer et al1 selected vitronectin, an abundant $75$ kDa glycoprotein encoded by the VTN gene, consisting of 459 amino acid residues and 3 domains (N-terminal somatomedin B domain, central domain, and C-terminal domain) as their candidate biomarker—a logical choice, given its well-characterized participation in coagulation, T-lymphocyte activation, apoptosis, and plaque matrix development and a reported association with the severity of coronary artery disease.1 Vitronectin is stored within platelets, expressed on their surface after activation, and participates in the formation of stable platelet aggregates. Globular vitronectin multimers assembled on fibrin strands attract plasma vitronectin, which, in turn, becomes anchored to the developing thrombus, potentially at increased rates with specific fibrinogen chain variants.4 In addition, plasma vitronectin, once incorporated within developing fibrin thrombi, attenuates fibrinolysis through mediation of a somatomedin B domain–directed plasminogen activator inhibitor–1–fibrin interaction. Vitronectin receptors ($\alpha_v\beta_3$) on vascular endothelial cells may also be involved directly with platelet binding by means of von Willebrand factor strings under high shear stress.5 Monoclonal antibodies, including abciximab and polyclonal antibodies, directed to the vitronectin receptor inhibit its functional activity.

An inability to show an incremental benefit from abciximab according to vitronectin levels, in the current study, may be a direct reflection of small sample size. A similar limitation may apply for the lack of predictive value surrounding the soluble vitronectin receptor. Although one may conclude that the original hypotheses were not fully tested, the reported...
findings should not deter further investigation, particularly on the subject of soluble receptors, their functionality in regulatory cellular events, and potential contributions to the pathogenesis of human disease and its characterization.6,7,8

Transmembrane receptors are ubiquitous in biological systems and transmit information from the outside to the inside of the cell. A traditional view of transmembrane protein and glycoprotein receptors questions their functional role in the soluble state; however, a contemporary perspective suggests otherwise. Soluble receptors can signal from recognition to effector domains through ligand-induced conformational change in the absence of transmembrane domains.6 In addition, cleavage or proteolytic processing of transmembrane receptors, referred to as ectodomain shedding, can produce soluble forms that bind or sequester 1 or more ligands, inhibiting their ability to signal normally and thus having a profound impact on overall cellular function. Last, soluble receptors can be expressed from alternately spliced mRNAs, exerting an effect in the absence a ligand-induced regulatory mechanism.7,8

Emerging Biomarker Science Platforms
Gene-expression profiles using RNA from peripheral blood collection for DNA microarray analysis has successfully characterized patients with antiphospholipid syndrome at risk for venous thrombosis and patients with early stage, non–small-cell lung cancer at risk for recurrence after surgical excision.9,10 A similar platform could be applied to patients undergoing PCI.

A metagene approach permits maximum yield through analysis of overlapping gene clusters and molecular signatures that define the dominant expression patterns within each cluster.11 Available software readily implement methods that provide an interface for gene-expression graphical models and biological constructs http://www.stat.duke.edu/~adobra/metagene.htm. The fundamental basis of this particular approach makes 3 assumptions: (1) the metagene represents a common pattern underlying a group of genes that show coexpression patterns; (2) enrichment of gene clusters and individual genes occur concomitantly; and (3) improved methods of covariate estimates can be achieved with a Bayesian statistical graphical model.

Although the metagene expression pattern or “signature” can itself be used for prognostication or gauging a preferred treatment approach, individual genes that are expressed can also serve as a “roadmap” for investigating biological pathways rather than protein biomarkers in isolation, with a focus on functionally related proteomics or metabolomic byproducts.

Finally, open-platform discovery proteomics with Meso Scale Discovery validation and advanced bioinformatics systems to search expression patterns of genes and proteins across related, or traditionally believed to be unrelated, diseases, species, and tissues represents an attainable component of the next frontier in our scientific journey.

Biomarkers and the emerging field of biomarker science offer the potential to advance our understanding of human disease, improve efficiency and lessen the cost of drug development, stimulate innovation, and personalize health care. The translation of promise to practice and, ultimately, acceptance of biomarker-based evidence as a component of drug development, regulatory recognition, and paradigms of patient care in the 21st century will only come to fruition through focused implementation of thoughtfully crafted and integrated programs. Until the existing barrier of minimalization is overcome and the scientific and clinical trial communities commit themselves to advancement beyond the initial discovery phase to dedicated validation studies, biomarker attrition will continue unabated.

Disclosures
None.

References


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