Published in final edited form as:
Expert Rev Proteomics. 2014 April ; 11(2): 135–136. doi:10.1586/14789450.2014.897614.

Proteomic cancer biomarkers from discovery to approval: it's worth the effort

Danni Li and
Department of Laboratory Medicine and Pathology, University of Minnesota, Twin Cities, 420 Delaware Street SE, Minneapolis, MN 55455, USA

Daniel W Chan
Department of Pathology, The Johns Hopkins University, 1550 Orleans St, Baltimore, MD 21287, USA

Abstract

The current landscape of cancer biomarkers is changing rapidly, with new and exciting developments. With the advances of proteomic technologies, many potential cancer biomarkers have been discovered. However, the number of new cancer biomarkers cleared or approved by the US FDA is rather limited. Although technological advances are important, clearly defining intended use, good study design and appropriate patient specimens are critical for the success of FDA approval. While obtaining FDA clearance/approval for newly developed and clinically useful cancer biomarkers has been slow, the reward for patient care could be enormous.

Keywords

biomarker; cancer; IVDMIA; OVA1; proteomics

Biomarkers are important in the fight against cancer. Historically, most of the US FDA-approved/cleared cancer biomarkers were measured in serum and used clinically for the monitoring of disease progression and responses to therapy (e.g., CA125). The exception was prostate-specific antigen (PSA). It was approved for the detection of prostate cancer. Today, cancer biomarkers can be measured in other body fluids such as urine and tissue. They exist in a variety of different molecular and cellular forms: proteins, DNA, circulating tumor cells. Their clinical utilities have been expanded to the prediction and prognosis of cancer. Currently, there are over 20 FDA-approved/cleared protein biomarkers for a variety of cancers. However, there are many unmet clinical needs, for example, in lung cancer, biomarkers are needed for the differentiation of lung nodules detected via CT scans; in breast cancer, biomarkers are needed for predicting patients' responsiveness to taxane

Author for correspondence: Tel.: +1 612 626 0299 Fax: +1 612 625 1121 dannili@umn.edu.

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

chemotherapy and endocrine therapy and in prostate cancer, biomarkers are needed for identifying aggressive prostate cancer that requires treatment.

Proteomic biomarkers are often referred to those biomarkers discovered using technologies capable of analyzing many proteins simultaneously, such as protein microarray and mass spectrometry (MS). Although aberrant protein expression in cancer had been known for decades, discovery of proteomic cancer biomarkers only began in the last 15 years with the advent of proteomic technologies. Although thousands of new potential cancer biomarkers have been reported in the literature, very few have been granted FDA clearance or approval. OVA1 is the first and the only FDA-cleared *in vitro* diagnostic multivariate index assay of proteomic biomarkers. It tests the levels of five proteins: CA125, prealbumin, apolipoprotein A1, β_2-microglobulin and transferrin. With the exception of CA125, the other four proteins in this panel were discovered using SELDI-TOF-MS [1].

Cancer biomarkers could be discovered by other proteomic technologies. Risk of ovarian malignancy algorithm (ROMA) and prostate health index (phi) are two examples. Both were FDA-cleared/approved recently. ROMA includes a panel of two proteins, CA125 and human epididymis protein 4. Human epididymis protein 4 was initially discovered by Hellström *et al*. as an overexpressed mRNA in ovarian cancer by cDNA microarray analysis [2]. Beckman Coulter (Pasadena, CA, USA) developed phi, which includes a panel of three tests: total PSA, free PSA and pro-2PSA. Isoforms of PSA were discovered throughout the years from 1979 to 1997 using traditional protein purification and characterization techniques (e.g., liquid chromatography) [3,4].

One approach that these cancer biomarkers have in common is the use of multiple biomarkers to improve clinical performance. Both OVA1 and ROMA improve the performance of CA125 in predicting ovarian malignancy in patients with pelvic mass, and phi improves the performance of total PSA and free PSA in detecting prostate cancer and avoiding unnecessary biopsies. However, one should be aware of the potential pitfall of developing *in vitro* diagnostic multivariate index assays. The ability of multivariate models to capture complex patterns in high-dimensional data could be confounded with non-disease-related artifacts existed in the patient samples [5]. Therefore, great care should be taken while designing clinical studies.

On the road to developing clinical diagnostics, it is important to define the clinical intended use. ‘Intended use’ is the key for the successful development of any clinical diagnostics, including proteomic cancer biomarkers. Examples of the intended use include cancer screening, diagnosis or prognosis. The intended use of a diagnostic test will determine the target population of the test, and therefore, inclusion and exclusion criteria of the study subjects; and the clinical intervention as a result of the diagnostic test, and therefore, the desired clinical performance. These are the key components that one should keep in mind for the development of cancer biomarkers from discovery to approval.

Cancers are heterogeneous. Cancer biology is complex. Clinical situations are complicated. Cancer biomarkers are the keys to guide clinical decision-making. Promising technologies, such as high-resolution and accurate mass spectrometers, as well as novel approaches in

using these instruments (e.g., SWATH™ and multiple reaction monitoring) could speed up discovery and validation of new biomarkers. However, on the road from discovery to approval, clearly defined intended use, good study design and appropriate patient specimens are critical for the success FDA approval. Even after FDA clearance/approval, diagnostic companies still face challenges of the clinical adoption of their new biomarkers. Many of these companies, therefore, take a different approach. They launch their biomarkers by providing testing in clinical laboratory improvement amendments certified laboratories as laboratory developed tests (LDTs) instead of conducting clinical trials and obtaining FDA clearance/approval. While this approach is certainly legal, the major concern is the variability in both analytical and clinical performances of these diagnostic tests. Caution should be exercised in the acceptance of these tests: some LDTs have undergone extensive validations while others have limited data available. Recently, there have been a couple of proteomic-based MS tests approved by FDA for the first time (e.g., BioMérieux VITEK® MS for identification of microorganisms cultured from human specimens and Bruker MALDI Biotyper CA System for identification of Gram-negative bacterial colonies cultured from human specimens). Obtaining FDA approval of these microbiology-related tests may have a significant impetus to future FDA approval for MS-based LDTs.

The best approach for the development of cancer biomarkers is the model using public and private partnership. This was exemplified by the recent success of FDA-cleared/approved cancer biomarkers such as OVA1, ROMA and phi. While there is an urgent need for more and better cancer biomarkers, obtaining FDA clearance/approval for newly developed, clinically useful cancer biomarkers has been slow. However, the reward for patient care could be enormous. We strongly believe that it is worth the efforts in conducting discovery research and in obtaining FDA clearance/approval of new proteomic cancer biomarkers.

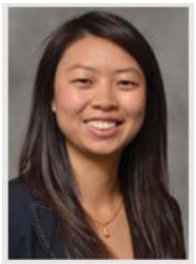
Acknowledgments

Financial & competing interests disclosure DW Chan has grant support from the National Cancer Institute (NCI) Early Detection and Research Network Reference Lab (BRL) and Clinical Proteomics Tumor Analysis Consortium (CPTAC). DW Chan is also one of the co-inventors of OVA1, which was licensed to Vermillion, Inc.

No writing assistance was utilized in the production of this manuscript.

Biography

Danni Li



Daniel W Chan

References

1. Zhang Z, Bast RC Jr, Yu Y, et al. Three biomarkers identified from serum proteomic analysis for the detection of early stage ovarian cancer. Cancer Res. 2004; 64(16):5882–90. [PubMed: 15313933]
2. Hellström I, Raycraft J, Hayden-Ledbetter M, et al. The HE4 (WFDC2) protein is a biomarker for ovarian carcinoma. Cancer Res. 2003; 63(13):3695–700. [PubMed: 12839961]
3. Mikolajczyk SD, Grauer LS, Millar LS, et al. A precursor form of PSA (pPSA) is a component of the free PSA in prostate cancer serum. Urology. 1997; 50(5):710–14. [PubMed: 9372880]
4. Wang M, Valenzuela L, Murphy G, Chu T. Purification of a human prostate specific antigen. Invest Urol. 1979; 17(2):159–63. [PubMed: 89106]
5. Zhang Z. An in vitro diagnostic multivariate index assay (IVDMIA) for ovarian cancer: harvesting the power of multiple biomarkers. Rev Obstet Gynecol. 2012; 5(1):35. [PubMed: 22582125]