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EDITORIAL

Will Cancer Proteomics Suffer from Premature Death?

Daniel W. Chan

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At a recent quarterly review meeting of a major diagnostic company, one of the senior executives was questioning the Director of Research and Development. *Why haven't you discovered any new cancer biomarkers despite million of dollars spent? When are you going to give us some new cancer proteomic diagnostics? If not, we are going to stop funding your proteomics program very soon*. Similar questions were also asked at a government-funded program review meeting.

The question is "will cancer proteomics suffer from premature death?"

My view is that these people are shortsighted. Finding clinically useful cancer biomarkers is not easy. However, the potential impact on the clinical outcome of cancer patients could be fairly significant. Most people do not appreciate that the time frame for biomarker discovery, verification, validation, and translation into clinical practice is a long and difficult process.

Is the development of cancer proteomic diagnostics worthy of the investment?

First, let us look at the tremendous opportunities of cancer biomarkers in personalized medicine. Biomarkers can be used for the early detection of cancer, which could save life. Biomarkers can also be used in the assessment of cancer risk and in the monitoring of cancer development in a targeted high-risk population. They can be used in differential diagnosis and tumor staging to improve clinical accuracy and in the prognosis of clinical outcome. They can also be used to guide targeted therapy, which will improve the efficacy of treatment modality and generate less toxicity. Finally, they can be used to monitor responses of therapy and in the detection of cancer recurrence. This could improve patient survival.

Why haven't we taken advantage of these opportunities?

Currently, there are less than two dozen cancer proteomic biomarkers cleared or approved by the FDA in the United States for clinical use [1]. Furthermore, these biomarkers have significant limitations. Most of these biomarkers are for monitoring therapy. Few cancer biomarkers are for predicting therapy or prognosis. Only the prostate-specific antigen (PSA) is approved for the early detection of cancer. No biomarkers have been approved for cancer screening in a general population.

Why haven't we developed more cancer proteomic diagnostics to meet the clinical needs?

In the field of proteomics, discovery research in finding candidate biomarkers is relatively easy, as evident by the large number of biomarkers published in the scientific literature. However, the validation process in selecting biomarkers with consistent clinical significance in a general population is much more difficult. Few candidate biomarkers survive the validation step. Finally, the translation of these biomarkers into clinical diagnostics which could meet clinical and regulatory requirements is often time-consuming and costly.

There are significant obstacles in proteomics biomarker research. The first issue is the complexity of the plasma proteome with the extreme dynamic ranges of protein concentration in the order of 10^{10} and the constant changing of the proteomic profiles with varying conditions, such as significant biological variability among individuals within the same population and the specimen integrities in their collection, processing, storage, and stability. The two major technologies used in proteomics research have

D. W. Chan (✉)
Department of Pathology and Oncology,
Johns Hopkins Medical Institutions,
Baltimore, MD 21231, USA
e-mail: dchan@jhmi.edu

limitations. Mass spectrometry has limited sensitivity and requires extensive fractionation. Protein microarrays are a targeted approach in the detection of a limited number of proteins. We need standards or reference materials for comparison among different instruments or technologies as well as better study design to minimize systemic biases from non-disease-associated factors and standard operating procedures for proteomics studies. In the processing of proteomic data, we should minimize data processing error and over-fitting of high dimensional data (pattern recognition). In addition, there is no consensus among different groups for the requirements or performance characteristics for cancer diagnostics and no standard procedure exists for the development of cancer biomarkers into clinical diagnostics.

Why aren't we making more progress than expected in cancer proteomics?

Let's hear what these people had to say during a recent fund-raising reception for cancer research.

"I want to have testing for this new cancer biomarker that I read about on the internet," says a patient. "However, when I asked my doctor, the doctor had never even heard of it."

An oncologist says, "from my point of view, most of these cancer biomarkers are non-specific. When the test is 'positive', I don't know what to do with it! It often generates more unnecessary testing. What I really want are predictive biomarkers for directing therapies."

A VP of new business development from a major diagnostic company says "I don't see any real winners (cancer biomarkers) to license. Even if I found one, the cost of developing cancer diagnostics, conducting a clinical study and obtaining FDA approval is just too time-consuming and costly."

A cancer researcher from a nearby well-known university says "my NIH grant only covers the discovery of biomarkers, not their validation or clinical studies. It is someone else's job to do the follow-up work. My academic promotion is dependent on publishing scientific articles in high-impact journals only."

A regulatory scientist from the Center for Devices and Radiological Health branch of the US FDA says "the submission document of the cancer biomarker test is terrible. This manufacturer obviously doesn't know what they are doing. The 'intended use' does not make any sense. The study population does not match the clinical intended use. There are insufficient data for the analytical and clinical validations. How can we approve such a poor submission for a cancer diagnostic test device?"

A manager of the Pathology Core Lab from a nearby teaching hospital says "I would love to offer this new cancer test, but the cost of the reagent kit/instrument and technical time is just too expensive for the amount of reimbursements."

Finally, a mid-level executive from an insurance company says "cancer biomarkers, in general, are not cost effective. Give me some evidence-based laboratory medicine before I can agree to any reimbursements."

What should we do?

First, we should define what biomarkers are needed clinically. Then, we could select those biomarkers that are promising for the development of cancer diagnostics. We need to create a team consisting of key players in the discovery, validation, development, approval, reimbursement, and use of cancer diagnostics. This would include researcher, clinician, diagnostics developer, and regulator from academia, government, and industry. We need to develop a consensus process and construct a roadmap for the development of in vitro cancer diagnostics. Technologies such as mass spectrometry and protein/lectin microarrays are useful technologies for proteomic biomarker discovery. For routine analysis of cancer diagnostics, an automated multiplex immunoassay platform might be more suitable. The key is to identify biomarkers with clinical potentials for the early detection and/or prognosis of cancer, followed by analytical and clinical validations of these biomarkers using well-characterized standard reference materials and targeted patient populations. The translation of cancer biomarkers will be facilitated via public–private partnerships and collaborative research networks, such as the National Cancer Institute Early Detection Research Network (NCI EDRN).

Finally, here is a recent "success story" of cancer proteomic diagnostics.

> On March 9, 2010, The Wall Street Journal reported a *Test to Help Determine If Ovarian Masses Are Cancer. Doctors and hospitals are getting a new test that many think will help fight ovarian cancer, one of the deadliest cancers, by helping them to more quickly distinguish cancerous from benign growths. The test, which is called OVA1 and will be available for general use Tuesday, was shown to correctly flag 92% of cancers, when used along with radiological imaging and a standard patient work-up, in a study of 27 hospitals, doctors' offices and clinics. Physicians using their usual detection methods but not OVA1 had previously found 72% of the cancers. 'It is an amazing move forward,' says Cara Tenenbaum, Vice President of Policy for the ovarian cancer national alliance, a nonprofit patient advocacy group.*

OVA1 is the first proteomics *in vitro diagnostic multivariate index assays* (IVDMIA) cleared by the US FDA for clinical use. It is based on two studies published in 2002 and 2004 [2, 3] from our laboratory and licensed to Vermillion Inc. A detailed story of the development of this cancer diagnostics can be found in an interesting article written by Eric Fung [4] "A recipe for proteomics diagnostic test development: The OVA1 test, from biomarker discovery to FDA clearance."

These are my final thoughts. Cancer will continue to be a major disease for many years to come. Early detection and prevention using cancer biomarkers will be the key to improving cancer survival. Cancer biomarkers will be even more important as more effective targeted therapies become available. Instead of cancer proteomics suffering from premature death, I believe that cancer biomarkers will be the driving force in the war against cancer. We should increase our efforts and funding in the area of research and development for cancer proteomic biomarkers. As I said earlier, the translation of cancer biomarkers into diagnostics will be facilitated with public–private partnership and a collaborative research network, such as the NIH/NCI EDRN program.

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