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Opportunities for Proteomics in The Community Oncology Setting

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Cancer medicine has increasingly moved away from one-size-fits-all treatment pathways, plans and protocols, to personalizing treatment based on molecular profiling of the disease guided by cancer genomics and more recently advancements in proteomics. This newsletter describes and discusses how the application of proteomics platforms is taking us beyond even large gene assays to facilitate providers' decision-making on treatment options for patients diagnosed with many different types of cancer.

Fred Ashbury (FA): What is the state of the science of proteomics and how might it inform us in cancer therapeutic decision making?

Chip Petricoin (CP): I might preface that question with a point about why we in the oncology space care about proteins, to begin with, and then describe the state-of-the-art technology-wise. During my 15 years of experience on the regulatory side (being at the FDA), I came to realize why proteins are pretty important. Most of today's targeted therapies, used in many diseases, have a mechanism of action that is actually against the protein, not the gene itself. In section 12 of a drug's package insert, it tells us a lot about what the pharmaceutical company and the FDA think is the real mechanism of action is of that drug. Many of the package inserts of many of the targeted FDA approved therapies describe a proteomics-based mechanism of action. These drugs worked on modulating protein activity, protein expression, bind to target proteins, and sometimes even the therapeutic itself is a protein like Trastuzumab.

Furthermore, many biomarkers that we use to measure cancer burden, CA19-9, PSA, CA-125 for example,

are protein biomarkers. So, proteomics at a very fundamental level is extremely important. Most of the time proteins are the drug target itself from a functional standpoint and many times, are how we measure the amount of the disease in a patient. So, I became very interested in proteomics early for these reasons.

If we agree the protein is important, protein biomarkers are important, the drug targets are important, then how do we understand the proteome as well? Compared to the number of genes involved in driving cancer, you may have hundreds of thousands, perhaps even millions of different protein and protein isoforms in any given patient's tumor, tumor cell, or in the blood. So, we have to develop different types of proteomics technologies to questions about the protein content to understand the landscape of the proteome in a given patient.

Genomic-guided medicine has condensed around very specific and relatively few genomic alterations – specific genes known to be involved in tumorigenesis, and then a very few specific type of sequencing and/or PCR based platforms. The proteomics space, however, is populated by many different types of platforms and a much larger molecular space. Physicians are very familiar with and actually use immunohistochemistry to measure HER2 for defining who should get trastuzumab, for example, or measuring ER or PD-L1 protein expression, again all proteins, and of course there's a well-worn and institutionalized CLIA/CAP accredited immunohistochemistry (IHC)-based approach to look at that expression in human tissue.

Then there's newer generation technologies, new types of protein arrays that allow us to look at a much larger set of specific proteins than can be measured by IHC- to be able to give us more of a panel-based representation of the levels and even activation state of important drug targets say akin to what an oncologist may be thinking about when ordering a next generation sequencing (NGS) test, where it's a panel-based exome test from different companies. These new protein array technologies likewise looking at specific "actionable targets," but in completely novel ways. It's not just whether the protein is there, but is it activated, is it in use? Since the proteins are the drug targets, it makes sense to ask these questions. If it's a drug that can turn the protein on or off, shouldn't we know if it's on or off to begin with?

These new types of protein arrays, and uniquely the reverse phase protein array- can now provide key missing information to the oncologist concerning a direct measurement of the of the activation architecture of the drug target in the tumor- now for the first time and that cannot be provided by genomics assays. Because of that, we've had to develop new technologies that can utilize very small amounts of material yet can give us very important panel-based content. I think that's a very exciting aspect for us as scientists and oncologists.

Joyce O'Shaughnessy (JS): I am very, very interested in proteomics. To me it's the real wiring diagram of these cancer cells in their microenvironment. It's what's keeping the engine running. We know genes are the blueprints, but what's the engine? Without knowing that, we can't get meaningful and durable benefit for patients.

So, what drew me to the field is we still have so many deadly breast cancers about which we don't understand the biology. On the other hand, when we do have an important driver, we can make incredible progress for patients. Cures due to estrogen receptor and HER2 are examples here. So, this is something

we need to know, because having this information means you can make huge progress in treating cancer and thereby improve patient outcomes.

In terms of the reverse-based protein array, this need to know predated the availability of NGS. I have examples of metastatic patients where we did a reverse based protein array on the tumor to reveal activated proteins with further downstream activation and the application of this information has led to very positive treatment outcomes.

In another example, post NGS availability, we found co-mutations of unknown significance at the time, so we got reverse base protein array, and it revealed activations again that led to positive treatment outcomes. It was these examples that got my interest because I wouldn't have picked those treatments without the reverse-based protein array.

FA: What are some of the challenges community oncologists might face to apply proteomics assay at the point of treatment decision-making?

JS: This is a real challenge for practices these days. Getting your NGS results and knowing what to do with your NGS results whether it be tissue, blood, or both can be challenging. A lot of times you get things that are more inferential. You don't know what the driver is, you don't know even how to interpret variant allele frequency. These are difficult issues. Sometimes I find that proteomics findings provide additional information about the cancer, whether it can be applied now or in the future.

For example, if you have triple negative breast cancer, you don't have a lot of targets. The patient's primary may be refractory. Your next step should be to order NGS to see if any potential targets exist. I would argue that the physician should order a reverse-based protein array to provide additional and potentially useful information. In my experience, the results from the proteomics assay can sometimes identify targets that align with the NGS results, increasing my confidence that these are potentially actionable, driving alterations that should be targeted therapeutically. Proteomics is a technological asset, and it's still evolving, but this is where we are headed.

FA: What resources might be needed for Community oncologists to be able to participate in proteomics science and clinical decision making?

CP: The interesting thing I'm observing sitting in on molecular tumor boards, is looking at a systems-level and patient-specific view of the biology of the tumor to determine if you can help with treatment selection. The proteomic and phosphoprotein data is tremendously synergistic with NGS profiling. The functional phosphoprotein data can be used to adjudicate some of the genomic findings to facilitate prioritization or identify actionable targets missed by genomic analysis.

For some cancer patients, depending on where they are in their course of disease, you may only have a few more shots at successful treatment. If there's nothing actionable coming back from an NGS profile, many times the proteomic/phosphoprotein data can fill in the gap and not only help prioritize, but actually find, a potential actionable target to go after. The field is going towards a multi-omic view of the tumor. For that reason, the molecular profiling field could be viewed as becoming more frightening for an oncologist because that means more data to try to understand and manage. So, we need to come up with decision support tools to help take this data and integrate it on an algorithmic basis that doesn't facilitates the doctor and patient care discussion. That means, not an artificial intelligence (AI) computer telling you what to do, but perhaps maybe just giving you a rationalized and prioritized list of things to consider. We're working on ways to give oncologists almost a ranked option, with the rankings based upon levels of evidence, or being related to actual outcome prediction based on clinical trial results. From there, you would take that system, and integrate that with the patient's comprehensive clinical data, including

treatment history.

The application of AI gives the doctor some considerations to focus on and if integrated in real time, it allows providers to be more efficient with their time and not have to read the 35 papers to figure out should I gives a number 1 versus a number 2.

With respect to proteomics results, for the first time we're able to do that technically, in a CLIA setting, and deliver a panel assay result back to the oncologist in around two weeks. That solves a huge pressure point because doctors can't wait four to six weeks for the data. We have to be able to deliver robust and believable data back as quickly as possible.

FA: What advice would you give to your peers in Community practice, who must come to grips with the plethora of clinical data, including "omics" data, to help them in practice?

JC: I think most community doctors, who are generalists, need to have very clear algorithms. So, I really think any of these assays must be based in science and have to produce actionable findings.

I think the onus is on the diagnostic companies and laboratories that are developing new "omics" to say, "here is the priority". Some doctors even ignore a lot of NGS results because they're not getting that much out of NGS in terms of actions they can take to help their patients. In such situations, they ask themselves, "why would I order it"? As such, it is up to the scientific community to grow the list of options that physicians can consider making it worthwhile.

Personally, I find it useful to make biologically based recommendations to my patients. **I really try to be biologically based, at least as much as I can.**

CP: **Diagnostics companies must apply technology and generate results that can be visualized in a clear and concise manner in actionable ways that immediately highlight the therapeutic opportunities** - specific clinical trials matched to their patient specific tumor/state, specific molecularly guided on and off-label therapies etc., so that the results show themselves self-evidently and thus communicate clearly to the treating oncologist what actions they can consider to optimize treatment for their patients.

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