Perspectives

Clinical Cancer Research

The Obama Administration's Cancer Moonshot: A Call for Proteomics

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Abstract

The Cancer Moonshot Program has been launched and represents a potentially paradigm-shifting initiative with the goal to implement a focused national effort to double the rate of progress against cancer. The placement of precision medicine, immunotherapy, genomics, and combination therapies was placed at the central nexus of this initiative. Although we are extremely enthusiastic about the goals of the program, it is time we meet this revolutionary project with equally bold and cutting-edge ideas: it is time we move firmly into the post-genome era and provide the necessary resources to propel and seize on innovative recent gains in the field of proteomics required for it to stand on equal footing in this narrative as a combined, synergistic engine for molecular profiling. After all, although the genome is the information archive, it is the proteins that actually do the work of the cell and represent the structural cellular machinery. It is the proteins that comprise most of the biomarkers that are measured to detect cancers, constitute the antigens that drive immune response and inter- and intracellular communications, and it is the proteins that are the drug targets for nearly every targeted therapy that is being evaluated in cancer trials today. We believe that a combined systems biology view of the tumor microenvironment that orients cancer studies back to the functional proteome, phosphoproteome, and biochemistry of the cell will be essential to deliver on the promise of the Cancer Moonshot Program. *Clin Cancer Res; 22(18); 4556–8. ©2016 AACR.*

In his State-of-the-Union Address (SOTU) on January 12, 2016, President Barack Obama called for a "moonshot" to cure cancer, "for the loved ones we've all lost, for the family we can still save, let's make America the country that cures cancer once and for all." President Obama tasked Vice President Joe Biden, who recently lost his son Beau who died of recurrent glioblastoma, with leading the moonshot charge. Vice President Biden indicated in a statement released during President Obama's 2016 SOTU that the "Cancer Moonshot" will be enabled through increasing resources and by breaking down silos to bring all cancer fighters together to work together, share information, and end cancer as we know it. In addition to this admirable deliverable, Vice President Biden established a firm goal of the Cancer Moonshot initiative, which is to double the rate of progress and to make a decade worth of advancements in the next five years. He specifically pointed out key areas that he views as revolutionary, and by doing so, it would seem to indicate these disciplines will likely enjoy the increased resources needed to significantly advance the Cancer Moonshot, specifically immunotherapy, genomics, and combination therapies. We laud the Obama Administration's call to action through this Cancer Moonshot as we view the state of biomedical research is in an innovation renaissance. It is well recognized that the science of genomics has accelerated at a pace that far outstrips Moore's law, the foundation of which was a prediction by Gordon E. Moore in 1965 that the doubling of the number of components in an integrated circuit every year would continue for a decade (1). He later revised this prediction in 1975, reducing it to a doubling time of every two years. We suspect this metric is driving the goal of advancing a decade's worth of cancer research in five years. Genomics has indeed outstripped Moore's law, and this is largely due to major advances in analytical techniques and instrumentation that have enabled deep digital next-generation sequencing, along with the bioinformatic and computational approaches that enable data analyses. The genomics revolution has benefited by a massive investment from the U.S. Federal Government, totaling $14.5 billion dollars from 1988 to 2012 (The Impact of Genomics on the US Economy, June 2013, prepared by Battelle Technology Partnership for United Medical Research), which is estimated to have generated a ~$1 trillion impact on U.S. economic growth.

The promise of genomics was the expectation that the output of genomics research would lead to our improved understanding of cancer (and other diseases) and that this better understanding would translate into our ability to predict those at risk, detect cancers earlier, and better manage the course of patient treatment, ultimately leading to improved patient outcome. Unfortunately, many are quick to point out that despite the use of genomic analysis to (re)characterize tumors under the auspices of a number of large projects, such as The Cancer Genome Atlas (TCGA) project, the promise of genomics has fallen short in a number of aspects with regards to precision medicine. Certainly, the measurement of important genomic and targetable drivers of cancer, such as ABL, HER2, ALK, EGFR, BRAF, etc., has changed the landscape of precision medicine and patient outcomes and

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provides strong rationale for the continuing use of genomic analysis and profiling of cancers. However, at the same time, it is also becoming very clear that a genomics only approach to patient selection and stratification is deficient in both identifying the full complement of responding patients (2, 3), as well as limiting the accrual efficiencies due to very low frequencies of many targetable genomic derangements across a given patient population (2, 4). Of course, in some instances as well, there are patients who have genomic profiling performed without any druggable targets identified or who have undruggable genomic targets emerge (e.g. RAS), which point to potentially added value by including proteomics-based molecular profiling. Moreover, genomic research has taught us that "cancer" is far more complicated than we appreciated before our ability to "routinely" (and cheaply) sequence the human genome. This complexity is contributed by vast levels of molecular and cellular (tumor microenvironment) heterogeneity, heterogeneity that next-generation sequencing of the human genome alone does not capture. It is for this reason that the genotype-to-phenotype relationship seldom directly correlates. This is further evidenced by the well-known challenge in delineating so-called cancer driver mutations from passengers, which, along with the infrequency of actionable genomic alterations in any individual patient's tumor, is a further reason why a precision medicine engine underpinned by genomics alone cannot provide the fullest deliverable to the cancer patient. Indeed, delineating driver from passenger mutations is further complicated when one considers the spatial and temporal context of cancer, where it is more likely that there exist early (e.g., those that support initiation), middle (e.g., those that support transformation/progression), and advanced (e.g., those that drive metastasis, resistance, and recurrence) stage driver mutations, whose carcinogenic window is determined by the molecular context.

The ultimate determination of the relative tumorigenicity of a given mutation is based on the functional assessment as to whether a given mutation alters the activity of the gene product (protein) either alone or in the context of a molecular network. This requirement, then, suggests that the missing link between genotype to phenotype is the proteotype. It is within this genotype–proteotype–phenotype continuum that we posit that major advancements in our fundamental understanding of cancer lie, the output of which will provide a richer landscape for biomarker and therapeutic development. Indeed, most of the targeted therapies, either FDA approved or in experimental clinical trials, act on the proteome not the genome. Although the genome is the information archive, it is the proteins that do the work of the cell and it is the proteins that are, in actuality, the drug targets themselves. Moreover, derangements in protein signaling are the principal drivers of tumorigenesis, and these signaling pathways are controlled by and through proteins, protein posttranslational modifications (e.g., phosphorylation, glycosylation, ubiquitinylation etc.), and intra- and extracellular localization. Among the many reasons justifying the need for direct analysis of the proteome, perhaps the most relevant is the lack of association between RNA and protein expression. Furthermore, it is largely not currently possible to predict posttranslational modification occupancy and stoichiometry based solely on nucleotide sequence. Of course, although it appears self-evident, but is seemingly lost in the current narrative, recognition of tumors by the immune system is driven entirely by the proteome: antigens and neoantigens are peptides and the immune checkpoint system, MHC system, and immunoglobulins are all comprised of proteins.

Our ability to identify and quantify the proteomic landscape within the tumor tissue microenvironment is rapidly advancing. Advancements in technology and informatics now enable us to quantify in excess of 10,000 proteins in a single experiment, half of all human proteins annotated by the UniProt knowledge base (5). We now have CLIA/CAP–accredited proteomic assays today that can quantitatively measure the phosphorylation levels of most of the "actionable" drug targets, from small biopsies, often requiring less material than required for next-generation sequencing/genomic analysis. However, overall the field of proteomics is at a similar stage as was genomics in the mid-1990s, a limited number of laboratories with relatively low levels of federal funding aimed primarily at technology development and demonstration and only a few participating in real clinical research where data are used to make patient treatment decisions.

In the past, large-scale proteomics efforts [namely using mass spectrometry (MS)] have been limited to requiring large amounts of cellular sample input, indeed often requiring many thousands times greater than what could be routinely procured in the clinical setting (e.g., core needle biopsy), which could limit the understanding of which cells in the tumor sample were actually producing the protein. Efforts to simply grind up whole-tissue samples and analyze proteomic content would ostensibly generate signal, but it is impossible to discern whether that signal was actually generated from the tumor cells themselves or cells within the stroma compartment (6, 7). Fortunately, recent efforts to develop new multiplexed proteomic technologies, such as reverse phase protein array (8, 9), that can be efficiently coupled to upfront cellular enrichment techniques like laser capture microdissection (LCM) are now being used in a CAP/CLIA setting for real-time molecular profiling of tumor cell–specific profiling that provide increased accuracy for molecular profiling. Moreover, other much more well-known immunohistochemical analysis of protein biomarkers is being modified and adapted for multiplexed analysis as well (10). Finally, significant technological improvements to MS-based analysis have been made such that proteomic analysis of LCM-procured material has generated much more enriched data (11, 12) Genomic profiling at the DNA and RNA level has become possible with only a few cells or even a single cell. Similarly, to complement these genomic approaches, the proteomic field has begun developing similar abilities (13, 14).

We suggest that the cancer research community's rally to Vice President Biden's Cancer Moonshot project must include a petition for increased federal investment to establish robust standard operating procedures and quality assurance and quality control for collection and biobanking of human cancer specimens, to stimulate further development and standardization of instrumentation and methods for multiplexed protein identification and quantification, to fund increased bioinformatic development for conducting systems analyses and visualization of multiple "omics" data, and to increase funding and opportunities for education and training of the next generation of protein and proteomic scientists. This increased funding will ultimately stimulate increased application of proteomics for clinical translational applications at the bedside as an equal partner with genomics and increase the rate at which the promise of "ending cancer as we know it" is realized. Ending cancer, as we know it, will require the ability to "proteotype" cancer in the context of the tissue

microenvironment as efficiently as we can now genotype it; integrating these data together promises to truly revolutionize molecular cancer therapy. Recent clinical trial results wherein "multi-omic" analysis of tumor biology was used to prioritize therapy for patients with metastatic cancer revealed the type of promising results that should provide motivation for larger applications (15), and very recent publications have expanded on this through demonstration of clinical utility when a proteomic-based molecular profiling is used to assist in therapeutic decision making (16). With the appropriate federal investment, we predict that the field of proteomics can technologically advance along a similar trajectory as did genomics/next-generation sequencing over the past three decades. In addition to increasing the federal commitment to proteomics, the field will require expansion of transdisciplinary consortia comprised of "multi-omic" data analytics to integrate the molecular data into a pathway-centered systems biology view of the disease, technologists, applications scientists, and cancer physicians so that the advancements made remain focused on clinically relevant applications that will benefit patients and the clinicians that treat them. Careful data-driven applications of these "multi-omics" capabilities will help to assure that proteomics (and genomics) contributes to increasing the effective management of patients through precise and actionable molecular information gained through elucidating the genotype–proteotype–phenotype continuum.

Disclosure of Potential Conflicts of Interest

E.F. Petricoin is an employee of, has ownership interest (including patents) in, and is a consultant/advisory board member for Ceres Nanosciences, Perthera Inc., and Theranostics Health Inc. No potential conflicts of interest were disclosed by the other author.

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