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PRECISION THERAPEUTICS for CANCER MEDICINE

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Time to Dig Deeper Than Genes?

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Curing the Precision Deficit Disorder in Cancer Medicine: Time to Dig Deeper Than Genes?

Precision medicine is emerging as a foundational strategy for cancer treatment. Unlike more conventional, cookbook approaches to therapy, precision medicine relies on customized interventions tailored to the individual patient and the specific tumor. By using advanced sequencing technologies that can determine the presence of mutations in cancer driver genes within a specific tumor—the so-called "driver" mutations—and by applying this information to selecting targeted drugs shown to be effective for specific mutations, cancer specialists are able to match tumors with therapies to which they are most likely to respond. Based on the premise that one drug does not fit all tumor types and targets, the precision-focused paradigm is trying to use objective data, in consideration of the tumor's DNA sequence, to make informed decisions about therapeutic options.

Precision Medicine is Under Attack

Despite the many documented successes of precision medicine and the inevitability of its pivotal role in the future of cancer treatment, many within the medical profession have begun to question the wisdom and value of this strategy. Whether the approach is based on the identification of mutations that can be targeted with a new generation of drugs or uses drugs that activate the immune system to bolster the body's defenses against cancer cells, precision medicine is under attack.

In fact, a recent article by Drs. Ian Tannock and John Hickman in the *New England Journal of Medicine*, one of the world's leading journals for clinical medicine in which seminal advances are frequently published, portrays targeted cancer therapy as an overall failure.[1] The takedown of precision medicine in the press has been compounded by other reports in cancer journals as well as the lay press, where caution against the toxicity associated with immunotherapy has been highlighted as a deterrent to its deployment.

Far from signaling the demise of precision medicine, these extreme views reflect a lack of understanding of cancer as a complex disease. Equally problematic, they are being given greater voice by the media, where an otherwise relevant public conversation about precision cancer medicine is caught up in a seesaw of conflicting reports that juxtapose claims of astonishing successes with those of irremediable failures. In this age of "facts" and "alternative facts," where do the so-called facts lie with respect to precision cancer medicine?

The Complexity of Cancer

The rub is this: Cancer is not black and white. Nor should our responses to precision medicine be black or white because this is not how this extraordinarily complex disease works. So, while we should not hail every new precision-based cancer therapy that shows some success in the clinic as a silver bullet that will cure all cancers, we should also recognize that immunotherapy and mutation-targeted treatments effectively save or prolong the lives of 20% or more of patients who were once thought to have incurable, rapidly progressive disease. These advances have already produced significant decreases in cancer mortality, affecting tens of thousands of individuals and their families.

Rather than discounting the imperfections of a work in progress as the violation of a promise, as many are doing, we should instead view them as a sign that what we already have achieved, while remarkable, may still need to be complemented by new methodologies and approaches before precision medicine can realize its full potential.

In particular, and perhaps counterintuitively, there is a growing realization that the next step in precision medicine is to address the actual lack of precision that may well represent the paradoxic Achilles heel of current precision-based strategies for cancer. In other words, the concept is spot on, but the devil is in the details—the precise details, to be exact, and these still need to be worked out. Indeed, although the concepts of precision and personalized medicine are bandied about in the press as if they are fully matured disciplines, current treatments directed at mutations or the immune system are not nearly as exact as we would like them to be.

Beyond some statistical associations, there is still little mechanistic understanding of exactly how mutations in the genes targeted by FDA-approved drugs or immune checkpoints targeted by immunotherapy may drive clinical response, or lack thereof, in actual patients. And we have even less insight into why some patients with identical driver mutations for a specific cancer type who are treated with the same drug relapse while others do not.

Lack of precision means that drugs may be deployed, as they frequently are in patients, against molecular targets that may not be the optimal on-off switches responsible for locking cells into the aberrant states that we call cancer. And equally problematic, the mutations that have emerged to direct our treatment strategies may be insufficiently precise biomarkers for predicting exactly which patients will or will not likely benefit from mutation-targeted therapy. Put simply, more precision is needed.

The Emerging Role of Cancer Systems Biology

One of the most promising new and complementary approaches now embraced by leading cancer centers—including those at Harvard, Columbia, Mount Sinai, Memorial Sloan Kettering, and MD Anderson—is based on the rapidly evolving discipline of cancer systems biology. It is predicated on the need to understand, at the deepest and most mechanistic level, the complex biological machinery that makes the cancer cell tick so that its most critical and unsuspected vulnerabilities can be identified and targeted.

What these efforts have in common is the use of industrial-strength computational horsepower, combined with comprehensive molecular profiling of cancer tissue, to build actionable models of cancer cell behavior and to interrogate them so that the foundational drivers—that is, the precise checkpoints—of malignant misbehavior can be pinpointed.

The objective is to make sense of the complexity of enormous amounts of data, including mutational and gene expression patterns, using underlying, computable models of cancer cell behavior. Using such approaches—which until only recently were relegated to the purely academic and theoretical sphere—to elucidate the mechanistic underpinnings of cancer may be just what is needed now in cancer medicine.

Integrating Different Approaches

Fortunately, many alternative avenues are under investigation, some more likely than others to be successful. Machine learning analysis of “big data,” for instance, represents a fashionable trend underway at multiple cancer centers. However, unless deeply informed by the biology of cancer, it is unlikely that these efforts will produce the definitive advances we are looking for, beyond identification of some low-hanging fruits. This is because the potential number of possible mutational patterns that may trigger cancer is astronomical—larger, in fact, than the number of atoms in the universe. As a result, most of these patterns will be unique or will occur in such a small number of cancer patients that they simply cannot be discovered or studied in isolation; and, even if such signatures *were* identified, testing their therapeutic actionabilty in clinical trials would be extremely difficult if not impossible, because of the challenges in identifying enough patients with those specific mutations to achieve statistical power.

Clearly, there is a need to untangle the causes of and provide solutions for the “precision deficit disorder” that still afflicts the two most successful strategies for cancer therapy. We will need to know—in advance, before a targeted therapy is prescribed—exactly which patients and which tumors will respond to a specific drug, for how long, and what to do if and when relapse occurs.

To make real progress, we need to complement current data-driven methodologies that are focused primarily on genetic mutations with mechanism-based models that will help us exploit the computer-like logic of the cancer cell. This will help us understand which mutational patterns may be functionally identical, and therefore support the same therapeutic approach, even though specific mutations may occur in completely different genes. This requires a convergence of brute-force, big-data crunching approaches with methodologies that leverage our understanding of the cancer cell’s overarching (ie, genome-wide) regulatory logic that is responsible for initiating and sustaining the tumor state.

Among the many promising models that have recently been introduced, some have revealed an intriguing recurrent architecture of the cancer cell across virtually all tumors. This discovery, which we have called “oncotecture,” has led to the identification of novel cancer targets representing bottlenecks or “tumor checkpoints” that, unlike mutational patterns, are conserved in vast subsets of cancer patients. What distinguishes this precision-focused approach from others is that it can be applied universally, to almost every individual who presents with a cancer, independent of the tumor’s specific mutations or immunologic status. This offers the hope of making precision-based cancer medicine both more precise and available to virtually every cancer patient.

In addition to elucidating a new stratum of actionable targets against which cancer drugs can be deployed, these discoveries suggest that developing a better understanding of the role of proteins is an important prerequisite for making precision medicine more precise. It is this level of cancer decoding that is likely to push the frontiers forward.

While genetics has been the foundational science for the initial development of precision medicine, the evolution of cancer research has dramatically expanded our universe from gene mutations to the ultimate effects they have on the activity of proteins—which, for want of a better analogy, are the foot soldiers governing critical cell functions at the front lines of cancer regulation. Methods that focus on the systematic detection of aberrantly activated proteins, representing the master regulators of a cancer cell, are now showing surprising success. As a result, they are being incorporated into the design of even more precise and predictive clinical trials.

Advances in quantitative sciences are revolutionizing our approaches to precision cancer medicine. By relying on mechanistic models of cancer cell regulation—using technologies that dig even deeper than genes, into the regulatory machinery of the cancer cell—they are opening up new avenues that have the potential to introduce a higher level of precision into current clinical paradigms of cancer care. A consensus is developing that such complementary approaches, merged with the existing framework of precision-focused cancer medicine, are poised to benefit even more patients with greater predictability, safety, and lasting results.

Reference

1. Tannock IF, Hickman JA. Limits to precision cancer medicine. *N Engl J Med.* 2017;376:96-97.

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