An Introduction To Immunotherapy
And The Promise Of Tissue Phenomics®

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The Potential of Immunotherapy

In recent years, immunotherapy has been hailed as one of the most promising advancements for the treatment of cancer, and with good reason. Labeled “Top Scientific Breakthrough” by Science magazine in 2013, immunotherapy is generating considerable excitement among researchers and physicians alike. The promise of immunotherapy lies in its potential to not only treat a wide-range of cancer types but also produce more durable results than chemotherapy or radiation, with more manageable side effects. It is not surprising then that some analysts predict that within the next ten years, immunotherapy will constitute 60% of all cancer treatments.

The latest FDA approvals, coupled with the growing number of treatments in different phases of the clinical trial process, serve to underscore immunotherapy’s long-term potential. And yet, despite these considerable advancements, significant challenges remain regarding the translation of novel treatments into therapies suitable for widespread clinical adoption.

Undoubtedly, the future success of immunotherapy depends on a more precise understanding of the interaction between cancer and the immune system at the cellular level. This requires the ability to accurately profile immune cells in the tumor micro-environment and quantitate cell types and morphological features in the context of cancer tissue. This level of analysis, however, goes beyond what the human eye can accomplish alone.

Definiens’ Tissue Phenomics® approach uses advanced automated image analysis and data mining to analyze, extract, and fully quantify the high volumes of data that reside in tissue samples. This level of automation applies the power of big data to tissue analysis, allowing researchers to derive unparalleled insights regarding cellular interaction, complex tissue signatures, and tissue-based biomarkers; all of which are critical to improving patient outcomes and fulfilling the promise of immunotherapy.

“Immunotherapy marks an entirely different way of treating cancer – by targeting the immune system, not the tumor itself. Oncologists, a grounded in reality bunch, say a corner has been turned and we won’t be going back.”

– Jennifer Couzin-Frankel, Science Magazine, Breakthrough of the Year 2013

2 Ibid.
Towards An Understanding Of Immunotherapy

While traditional methods of cancer treatment, from radiation to chemotherapy, focus primarily on the tumor itself, at its most basic level, immunotherapy makes use of the body’s own internal defense system to combat cancer cell growth and metastasis. Developing effective treatments requires an acute understanding of the entire tumor microenvironment, and the ways in which cancer cells change and grow in relation to surrounding cellular tissue. In taking the immune system and immunosuppression as its central area of focus, immunotherapy involves a diverse number of strategies to boost the immune system’s ability to not only recognize and fight cancer in the short-term but to decrease the possibility of tumor recurrence as well.

The idea of using the immune system to combat cancer progression seems simple enough. However, while the immune system typically detects and responds to abnormal cell growth, there are a number of ways in which cancer cells pose a unique problem for immune responsiveness. Cancer often impairs the body’s T cells from functioning properly by actively evading immune surveillance and destruction. This process, described by Dr. Robert Schreiber as “immune editing,” involves the loss of “mutated antigens that allow tumors to be recognized by the immune system.”

In other instances, cancer may work to suppress the immune system altogether. According to Dr. Theresa Whiteside, some cancers “induce reductions in the quantities of circulating T cells, which likely influences clinical outcomes.” In response, immunotherapies are specifically designed to stimulate the immune system’s ability to detect cancer cells as foreign agents and induce lasting antitumor responses.

Current Approaches To Immunotherapy

The origins of cancer immunotherapy date back to the 19th century, when Dr. William Coley observed that the presence of bacterial infections could be used to trigger immune responses in cancer patients. From Coley’s initial experiments to present-day clinical trials, technological innovation has empowered researchers to derive insights previously unimaginable at the cellular and molecular levels. FDA approval of sipuleucel-T, an immunotherapeutic vaccine for the treatment of advanced stage prostate cancer in 2010, and the subsequent approval of ipilimumab, a checkpoint inhibitor of CTLA-4 for the treatment of metastatic melanoma in 2011, represent just two of the most significant advances in the development and translation of immunotherapies for clinical use in the past decade.

Currently, cancer immunotherapies can be classified in one of two ways. Active treatments, such as immunotherapy vaccines, are designed to induce tumor cell recognition. Passive treatments, on the other hand, bypass immune response, “by directly administering components of the immune system (such as antibodies and T cells) to the patient.”

Developing effective treatments requires an acute understanding of the entire tumor microenvironment.

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5 Ibid.
Four common approaches to immunotherapy include:

- **Immune Modulators** – The primary function of immune modulators is to combat the immunosuppressive aspects of cancer by significantly increasing the system’s overall number of active immune cells, which triggers the immune system to respond to the presence of cancer cells. As opposed to other types of cancer immunotherapy, immune modulators work to boost the patient’s entire immune system and not simply the immune cells active within the tumor microenvironment.

- **Tumor-targeted monoclonal antibodies** – Monoclonal antibodies are designed to target specific antigens found on cancer cells. The effectiveness of this type of treatment depends on prior identification of the correct antigens for the antibodies to bind themselves to. One mode of action of these antibodies is to block growth signals of tumor cells, or induce apoptosis. But in addition, once attached to the tumor cell, the body’s immune system is recruited and can also trigger tumor cell paralysis.

- **Checkpoint inhibitors** – Currently one of the most talked about forms of immunotherapy, checkpoint inhibitors mitigate the ways in which cancer cells silence the body’s T cells by taking advantage of the immune system’s natural checkpoints designed to maintain proper equilibrium and prevent autoimmunity. Checkpoint inhibitors release the breaks on the body’s immune system and induce T cells to actively combat tumor growth.

- **Adoptive T cell therapy** – Also known as adoptive cell transfer therapy, this approach works to enrich tumor infiltration lymphocytes by multiplying T cells removed directly from the patient’s tumor environment. Once the T cells are isolated, they are analyzed in order to determine which receptors are most specific to the tumor itself. These cells are then generated in greater numbers and administered to the patient in order to initiate a massive antitumor immune response.

These treatments represent just a fraction of the current advancements being made in the field of immunotherapy. However, as we’ll see in the following section, fulfilling immunotherapy’s full potential requires improvement in translational research, patient stratification, target validation and the development of predictive biomarkers.
The Immunotherapy Challenge

Though researchers now have a basic appreciation of the immune system, as well as how the immune system interacts with cancer, a complete understanding of tumor-immune cell interaction remains elusive.

One of the most significant challenges, however, lies in the area of translating basic research from the preclinical stage into safe and effective treatments for clinical practice. In part, this remains difficult because of the variance that exists between animal and human immune systems, which limits the translation of targets found in animal models into humans, and increases the inherent difficulty of determining optimal levels of dose selection and toxicity.7

At the clinical level, researchers continue to grapple with determining why certain patients respond to specific types of immunotherapies while others do not. In this regard, it is clear that the development of future treatments with the potential for widespread adoption depends on finding effective immune-based biomarkers that can help predict responses to treatment. Substantially improving patient stratification will also go a long way towards advancing the overall success of clinical trials and help lower the costs associated with drug development by shortening approval cycles.

But in each of these cases, there can be little doubt that better data, as well as technology to make use of that data, is needed to improve decisionmaking and enable successful outcomes at every phase of the clinical research process.

From Immune Status to Immunotherapy

In the face of these challenges, the limitations of traditional pathology could not be clearer. For instance, while globally accepted scoring systems, such as the TNM classification, exist for assessing and categorizing tumors, similar classifications for immune cells are lacking. The absence of universally accepted standards for immune cell classification results in high levels of subjectivity and decreases the consistency of reporting. It also engenders a lack of clarity with regards to what pathologists should be looking for when examining cancer patients.

Overcoming challenges in immunotherapy, however, involves not only knowing what to look for but also having the capacity to accurately assess relevant data. This begins with an analysis of the tumor microenvironment, comprised of a diverse set of host cells including immune cells and cancer cells that interact on the invasive margins of the tumor as well as in the tumor’s center. Gaining an accurate understanding of this interaction requires quantifying the number of immune cells present as well as an assessment of the density and spatial arrangement of immune cells in relation to cancer cells.

7 See e.g. de Lartigue, “New Paradigms Emerge for Translating Immunotherapy Into Broad Clinical Use,” OncLive
A complete analysis of the tumor microenvironment allows researchers to create a profile of a patient’s immune status, which is based on the number, type and location of tumor-infiltrating lymphocytes in tumors. Recent research in colorectal cancer demonstrates that the prognostic value of a patient’s immune status for determining long-term treatment success cannot be understated. In fact, these studies show that patients exhibiting what researchers refer to as a high Immunoscore<sup>TM</sup> exhibit greater resilience and lower rates of tumor recurrence than patients whose Immunoscore were lower.<sup>9</sup>

In addition to predicting the likelihood of tumor recurrence, immune status may also be a valuable indicator of responsiveness to treatment, providing greater insights for patient stratification and the identification of predictive markers than the traditional “gold-standard” TNM classification.<sup>10</sup> In this regard, immune status can play an important role in not only determining clinical outcomes but also in the development of effective immunotherapeutic treatments.

**Advancing Immunotherapy through Tissue Phenomics<sup>®</sup>**

Identification of immune status requires both standardized and automated solutions for tissue analysis. It is precisely at this juncture that Definiens’ Tissue Phenomics approach, which enables researchers to obtain more relevant and consistent readouts from high volumes of tissue data, has a critical role to play. To put this in more concrete terms, there can be an average of 75,000 T cells in a single tumor microenvironment alone. Tissue Phenomics provides the underlying approach that allows researchers to not only accurately quantify the number of tumor-infiltrating lymphocytes essential to immune status but to assess their location in relation to other cells in the tumor microenvironment; a vital component of developing tissue-based biomarkers for more effective clinical decision-making.

By making use of patented Cognition Network Technology<sup>®</sup>, Tissue Phenomics delivers a quantitative readout of the distances and embedded relationships between cells within the tumor microenvironment. Armed with these tools, researchers have the capacity to analyze each individual cell’s topography with respect to its surroundings, accurately detect structures of interest and place them in a hierarchical context. This type of analysis, which allows for the quantification and validation of whole slide tissue, can be done with consecutive sections and for any kind of immune cell.

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<sup>9</sup> Franck Pagès et al., “In Situ Cytotoxic and Memory T Cells Predict Outcome in Patients With Early-Stage Colorectal Cancer,” *Journal of Clinical Oncology*, Vol. 27, no. 35. (December 10, 2009)

Manual approaches to tissue analysis cannot offer the same level of insight into the number of active cells. Similarly, advanced imaging techniques, such as multiphoton microscopy or super resolution microscopy, are better suited for animal models used in the preclinical environment than they are for analyzing complex human tissue, while fluorescence-activated cell sorting (FACS) loses the important spatial context of the tissue sample. In contrast, Definiens’ automated image analysis solutions are designed to work with large cohorts of heterogeneous human tissue samples for the successful translation of results from preclinical animal models into clinical research and adoption.

Conclusion

To be sure, immunotherapy has given many in the research and medical communities a reason to be optimistic. Recent advancements in drug discovery and development underscore immunotherapy’s exciting potential for the future of cancer treatment. Against this backdrop, Definiens’ Tissue Phenomics can provide researchers with the technology necessary to improve translational research and patient stratification, as well as the capacity to identify predictive biomarkers and potential combination therapies; all of which are essential for the realization of immunotherapy’s full potential.