











## 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.<sup>7</sup>

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.

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<sup>7</sup> See e.g. de Lartigue, "New Paradigms Emerge for Translating Immunotherapy Into Broad Clinical Use," *OncoLive*



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.<sup>8</sup> In fact, these studies show that patients exhibiting what researchers refer to as a high Immunoscore™ 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®

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®, 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.

Immune status can play an important role in not only determining clinical outcomes but also the development of effective immunotherapeutic treatments.

<sup>8</sup> Bernhard Mlecnik et al., "Histopathologic-Based Prognostic Factors of Colorectal Cancers Are Associated With the State of the Local Immune Reaction," *Journal of Clinical Oncology*, Vol. 29, no. 6. (January 18, 2011)

<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)

<sup>10</sup> Jérôme Galon et al., "Towards the Introduction of the 'Immunoscore' in the Classification of Malignant Tumours," *The Journal of Pathology*, Vol. 232 no. 2. (December 10, 2013)



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.

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**DEFINIENS**<sup>®</sup>  
*the tissue phenomics company*

### Corporate Headquarters

Definiens AG  
Bernhard-Wicki-Straße 5  
80636 Munich  
Germany  
Email: [info@definiens.com](mailto:info@definiens.com)  
Tel. +49-89-231180-0  
Fax. +49-89-231180-90

### Americas Headquarters

Definiens Inc.  
125 Cambridge Park Drive, Suite 300  
Cambridge, MA 02140  
USA  
Email: [info@definiens.com](mailto:info@definiens.com)  
Tel. +1-617-949-4000  
Fax. +1-617-949-4001

