Clarion Healthcare's Highlights from the

Termeer Center Roundtable Panel Discussion

Inside the Immunotherapy Revolution

*On March 1, 2016, Clarion attended a roundtable event hosted by **Keith Flaherty**, **Daniel Haber**, and **Henri Termeer** of the Termeer Center for Targeted Therapies at MGH. The panel included distinguished immunotherapy experts, **Arlene Sharpe** (Harvard Medical School), **Glenn Dranoff** (Novartis Institutes for Biomedical Research), **Elizabeth Jaffee** (Johns Hopkins) and **David Kaufman** (Merck Research Labs), and was moderated by **Nir Hacohen** (MGH). 50+ renowned academic experts, biopharma execs, and other industry professionals came together to discuss how to overcome key challenges in immuno-oncology*

The field of immuno-oncology has exploded with a profusion of new agents, clinical trials, scientific data, collaborations, and licensing deals. However, the panel agreed that we will struggle to move beyond the early successes of immune checkpoint inhibitors in melanoma and a few other cancer types if we do not address three fundamental challenges: 1) we do not understand enough about the immunobiology of the tumor microenvironment, 2) we cannot yet predict which combinations of immunotherapies will be best for which patients, and 3) we have not coordinated and standardized our efforts sufficiently to fill the gaps in our understanding.

3 Fundamental Challenges Limiting the Immunotherapy Revolution

Limited understanding of the tumor microenvironment

The traditional approach to immunotherapy has been T cell-centric, and elements of the tumor microenvironment (TME) beyond T cells remain in early stages of exploration. Furthermore, tumor immunobiology is dynamic and changes during treatment and as the tumor evolves, and tumor heterogeneity further obscures our understanding. Current biopsy practices may suffice for initial cancer diagnosis and molecular testing for certain mutations, but are rarely adequate for generating a robust picture of the immune dynamics of the TME. Furthermore, we have not adequately leveraged the knowledge and learnings from immunology more broadly to our understanding of cancer immunobiology—e.g., we need to further evaluate commonalities between cancer and immunodeficiencies.

Limited ability to identify the right combinations for the right patients

As a result of our limited understanding of the TME, the field is still wrestling with understanding how response to immunotherapy varies by regimen and across tumor types. An emerging hypothesis is that a "T cell-inflamed" microenvironment—in which T cells have been activated and have infiltrated the tumors—may define response to immunotherapy. Tumors that are T cell-inflamed respond robustly to checkpoint inhibitors, even as monotherapy, while T cell non-inflamed tumors respond poorly. The key question is how can we convert poorly responsive tumors into immunotherapy-sensitive tumors?

The expectation is that the right combination will vary depending on the mechanism(s) behind the non-inflamed status: insufficient neoantigens, myeloid-derived suppressor cells, T cell anergy/exhaustion, etc. Limited understanding of the TME and of different mechanisms of immune escape and resistance to therapies restricts our ability to identify the right combination treatments for a particular tumor or patient type. Inadequate knowledge of predictive biomarkers and lack of standardized precision medicine tools further compound the challenge.

Need for improved industry-academia partnerships and coordination

Panelists agreed that current R&D efforts among different companies and between industry and academia tend to be siloed and lack standardization, leading to duplication of effort and ultimately impeding development of optimal immunotherapy regimens. As each study is conducted differently and utilizes different markers, lack of transparency in efforts prevents the community from being able to draw on learnings across studies. Greater coordination, collaboration, and standardization would greatly accelerate the closing of our gaps in understanding, and would inform smarter, earlier, and more efficient investments in immunotherapy clinical development.

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Emerging Solutions: How to Overcome the Challenges of Immunotherapy

Importantly, the panelists and audience did not dwell on challenges, but went on to articulate potential solutions in three interrelated categories, all demanding collaborative effort: enabling science, enabling clinical trials, and enabling technologies.

Enabling Science

"Tumor Immunity Atlas": Collaborate to build a multi-modality data-sharing platform. The scientific gap is too vast; we must work together to bridge it. The approach:

- Integrate data from clinical trials, patient tissue analyses, and preclinical studies—to form a predictive model
- Include as many patients/patient samples as possible, across academic and industry-sponsored trials
- Collect and synthesize data on a spectrum of immune cells and markers at DNA, RNA, and protein levels
- Capture spatial and temporal dimensions addressing tumor heterogeneity and mechanisms of immune escape
- Integrate with clinical findings, e.g., effect of prior therapies to inform sequencing decisions

Patient samples from collaborative trials will feed into building the Atlas, and the Atlas will generate/ validate hypotheses for new clinical trials

Studies with new preclinical models & new diagnostics would feed into the Atlas, which will help identify potential biomarkers for new diagnostics and refinements for new models

Enabling Clinical Trials

Foster greater collaboration across trial sponsors and trial sites to improve the standardization, speed, and efficiency with which trials are done. Examples of recommendations:

- Develop new approaches to facilitate collaborative, cross-company combination therapy trials
- Standardize and augment collection of tissue and data and analyses of safety/toxicology
- Institute process efficiencies, e.g. standardized or centralized IRBs, master protocols
- Expand sharing of patient samples and data with academic researchers

Collaborations in combination trials will support collaborations for novel diagnostics, and vice versa

Enabling Technologies

Collaboratively invest in the development of improved technology platforms, including:

- **New biomarker diagnostics:** Companies should consider collaborations such as the Blueprint Initiative, a cross-industry collaboration to study analytical similarity across PD-L1 companion diagnostics, or at minimum to share best practices, and to continue to collaborate with tumor immuno-biologists
- **New preclinical models:** Refine and broaden use of humanized, conditional mouse models for preclinical testing of combinations

A Proposal for Moving Forward

The panel envisioned sweeping changes in how the field works together to study tumor immunobiology and to develop novel immunotherapy combinations and novel diagnostics, but recognized that such changes must start small. One specific proposal was to start the Atlas with a pilot initiative focused on just three tumor types across the spectrum of tumor immunogenicity, e.g. melanoma (highly immunogenic), bladder cancer (moderately immunogenic) and pancreatic cancer (poorly immunogenic). For patients with those tumor types—with their consent and the agreement of the trial sponsors—participating centers would conduct a panel of standardized assessments on immune markers. The centers would curate the data in a way that links to clinical parameters, including treatment outcomes. The pilot effort would begin with a "coalition of the willing", but its success would inspire broader participation and would be the foundation for a more comprehensive atlas. The insights emerging from even this initial project may be invaluable for moving the immunotherapy revolution forward.