Cell

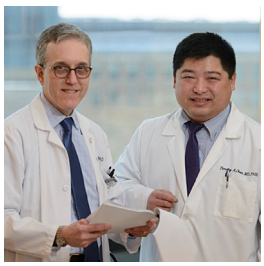
Immunotherapy: The Path to Win the War on Cancer?

On Breakthroughs and Evolution

Suzanne L. Topalian
Johns Hopkins Kimmel Cancer Center

Drugs targeting immune checkpoint molecules such as CTLA-4, PD-1, and PD-L1 are being heralded as a breakthrough in oncology. However, "breakthrough" is a misnomer belying several decades of basic immunology advances and clinical trial and error leading up to this point. It was only after basic science uncovered the protean pathways restraining antitumor immunity that we could begin to unravel how to subvert them. The broad activity spectrum of PD-1 pathway blockers against multiple cancer types has validated this as a "common denominator" treatment approach and dispels the perception that "immunogenic" cancers are anomalies. We are now challenged to understand immune resistance mechanisms utilized by "non-responsive" tumor types (e.g., prostate cancer) as well as the 50% or more of individuals with "responsive" tumor types who do not benefit from these drugs. Identifying collateral pathways for co-targeting in combination treatment regimens requires an intellectual leap to consider unexpected intersections between the immune system and genetics, epigenetics, and metabolism. For instance, tumor mutational density, a surrogate indicator of neoantigens available for immune recognition, correlates with the responsiveness of melanoma to anti-CTLA-4, and lung cancer to anti-PD-1. In the final analysis, teamwork with cross-fertilization of ideas across different scientific disciplines has driven the evolution to today's "breakthroughs" and will meet tomorrow's challenges.

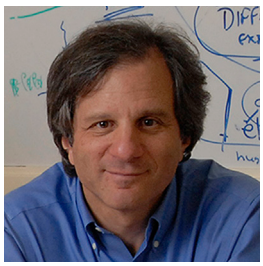
Central Dogma for Immunotherapy



Jedd D. Wolchok and Timothy A. Chan
Memorial Sloan Kettering Cancer Center

In biology classes, we learned about the central dogma of molecular biology—DNA makes RNA and RNA makes protein. We've also learned about factors that regulate this central process, such as the influence of epigenetics, micro-RNAs, and mechanisms regulating post-transcriptional and translational control. Despite the fine intricacies, the central dogma of molecular biology remains intact—inherently elegant and graspable. A unifying concept for cancer immunology, on the other hand, has remained elusive until recently. We now have discovered the existence of molecular mechanisms of immune surveillance (thanks to Bob Schreiber) and that the number and quality of immune cells within the tumor microenvironment has significant prognostic impact in a variety of cancers. The quantity and quality of so-called "passenger" mutations in the tumor are also very important in determining the likelihood of success of immunologic checkpoint blockade with CTLA-4 or PD-1 pathway blocking antibodies. A putative dogma therefore is that mutations drive baseline immune reactivity and baseline immune reactivity is what determines the potential for benefit of immune potentiating therapies. As in molecular biology, there are likely to be modifiers, such as inhibitory cells populations, hostile microenvironments, and loss of antigen presenting capacity. Yet, a unifying concept will likely allow the field to further refine its approaches and specifically address the immunologic needs of individual patients.

Not Just Another Hallmark



Ira Mellman
Genentech

After an incubation period of nearly 100 years, cancer immunotherapy has emerged as a transformative approach to treat a wide variety of cancers. Although still early days, immunotherapy provides a degree of sustained clinical benefit rarely observed with more traditional cancer treatments. The excitement is, therefore, being largely driven by clinical results rather than by "breakthroughs" in the laboratory. There are nevertheless two daunting challenges. First, the field has progressed so rapidly in the clinic that our understanding of the underlying basic science and mechanisms of action are remarkably thin. Second, the tools we have to assess mechanism and correlates of treatment response (or lack thereof) remain rudimentary. Meeting these challenges is critical, since only a minority of patients as yet exhibit maximal benefit from immunotherapy. Importantly, clinical responses to agents such as anti-PD-L1/PD-1 are often clear and dramatic, thereby creating the opportunity to discover biomarkers and use them to understand inevitable patient to patient variations. Exploiting these correlates of clinical response will provide insights into basic cancer biology and inform immunotherapy combinations that can be expected to result in higher response rates and disease cures. Our task will be to backfill the science behind an exciting and validated therapeutic approach, ensuring that the field can look forward to a very exciting next decade both in the lab and in the clinic.

New Trends in Cancer Vaccines

Karolina Palucka and Jacques Banchereau
The Jackson Laboratory for Genomic Medicine

Clinical responses to checkpoint blockade are linked to the presence of T cell immunity to cancer-specific mutations. One way to increase the rate of clinical responses is to use vaccination to expand T cells specific for cancer mutations. Several phase III clinical trials testing different cancer vaccine candidates are currently ongoing. Exogenous vaccines utilize, for instance, dendritic cell-based and viral vectors-based approaches to boost the immune response in cancer patients. To be successful, these platforms will require applying high-throughput genomics to identify cancer-specific mutations and candidate peptide antigens in each patient in order to produce personalized vaccines. An alternative approach, endogenous vaccination, is based on exploiting the local release of antigens that happens upon standard cancer therapy (chemotherapy or radiotherapy) or oncolytic viral therapy. However, this strategy requires endogenous antigen presentation to be effective, in order to generate therapeutic T cell immunity. Dendritic cells are often skewed by tumors to generate pro-tumor immunity and thus reprogramming of their function in vivo is critical for the success of endogenous vaccination. Increasing the understanding of cancer genomics, the biology of antigen presentation and T cell biology will enable development of next-generation cancer vaccines which, combined with checkpoint blockade inhibitors, will pave the path to curative therapies for patients with cancer.

Personalized Immunotherapy

Steven A. Rosenberg
National Cancer Institute, NIH

Adoptive cell transfer (ACT) uses patient's lymphocytes to treat their autologous cancer. When tumor infiltrating lymphocytes are used for ACT, they can mediate complete, likely curative, regression in patients with metastatic melanoma. Lymphocytes genetically engineered to express anti-tumor receptors can treat patients with refractory lymphomas and leukemias. However, the majority of metastatic epithelial cancers are still resistant to immunotherapy. Recent approaches using deep exome sequencing along with high-throughput immunologic testing opened the door to treat these common types of cancer and to identify the rare somatic mutations that are immunogenic. ACT targeting these mutations is the ultimate ''personalized'' cancer treatment but is contrary to the mantra of many pharmaceutical companies who want ''drugs in a vial'' that can be mass produced and distributed. Although this approach has produced drugs that prolong the life of patients with solid metastatic cancers, curative treatments are rare and have had limited impact on overall death rates from cancer. A highly ''personalized'' immunotherapy for common cancers may require the development of a unique drug (autologous lymphocytes) for each patient. It will also need major changes and considerable flexibility on the part of industry. The effectiveness of treatment should trump simplicity of production and convenience of administration if progress is to be made in enabling patients with metastatic cancer to be cured and relish a normal lifespan.

The New Immune Engineers

K. Dane Wittrup
Koch Institute for Integrative Cancer Research, MIT

What vaccine best exploits the evolutionary weaknesses of a virus or a tumor's mutations? What is the intratumoral exposure history of intravenously injected antibodies? How does deregulated signaling tip the balance from healthy homeostasis to autoimmune disease? Can native T cell tropism overcome physical barriers to macromolecular drug delivery? How does our antibody repertoire respond to therapy or disease? How might innate and adaptive immunotherapies best be combined? How does lymphatic transport actively regulate adaptive immunity? Can injectable biomaterials program an effective anti-tumor immune response? A common thread through these varied and timely topics is the engagement of biological, chemical, and materials engineers at the forefront. At their disposal is an analytical toolkit honed to solve problems in the petrochemical and materials industries, which share the presence of complex reaction networks and convective and diffusive molecular transport. Powerful synthetic capabilities have also been crafted: binding proteins can be engineered with effectively arbitrary specificity and affinity, and multifunctional nanoparticles and gels have been designed to interact in highly specific fashions with cells and tissues. Fearless pursuit of knowledge and solutions across disciplinary boundaries characterizes this nascent discipline of immune engineering, synergizing with immunologists and clinicians to put immunotherapy into practice.