The Era of Immunotherapeutics: Overcoming the challenges to fulfill the potential

SUMMARY

Immunotherapeutics are changing the paradigm in cancer treatment by stimulating the patient’s immune system. However, unique challenges still prevent widespread adoption of these agents and must be overcome if we are to realize their full potential.

Although a great amount of information is known and more understanding is gained every day, technologies that will help unravel these complexities and support the development of safe and effective therapies are still needed.
Immunotherapeutics are changing the paradigm in cancer treatment and hold great promise for use in other disease areas as well. These agents bring about their therapeutic effects by stimulating the patient’s immune system. The quest to identify and develop new immunotherapeutics has become one of the most active areas in cancer research, bringing the exciting possibility of robust and long-lasting treatment response in patients with fewer side effects than traditional chemotherapies.

However, unique challenges still prevent widespread adoption of these agents and must be overcome if we are to realize their full potential. Solving these issues requires us to better understand the complex pathways involved in disease progression and immune response along with the intricate interactions between the two. Although we already know a great amount and are learning more every day, we need tools that will help us unravel these complexities and support the development of safe and effective therapies.

While the main focus of immunotherapeutics so far has been in oncology, they could be used in autoimmune, infectious, and neurodegenerative diseases as well. The underlying biology differs across diseases, but the ways to modulate the immune system are similar, so technologies developed for the cancer area will likely be applicable to other areas. (1) Once we learn how to reliably and safely apply these treatments, the benefit to risk profiles will be more suitable for increasing application in other diseases.

Unique challenges associated with immunotherapeutics

Target and candidate selection

Discovery and development of immunotherapeutics differs from that of traditional small molecule drugs. While novel small molecule candidates can be discovered using high-throughput screens without prior knowledge of the molecule’s target, immunotherapies require a great deal of knowledge, as they are specifically designed based on the target, its role in the disease pathway, and the interactions between the immune system and the disease. Immune-therapeutic agents are also very diverse, including antibodies, cells, cytokines, viruses, and other biologics.

As our knowledge of the immune system and disease pathways increases, so does the number of potential immunotherapeutic targets. We are still learning how cancer cells avoid detection and attack by our immune systems. These evasion pathways offer many attractive targets for designing therapeutics. However, disease and immune pathways are already complex individually. Considering each in the context of the others compounds the challenge of fully understanding all of the important interactions. To succeed, we must be able to see exactly how each piece of information fits into the overall picture.

Models and biomarkers

A lack of suitable assays and models complicates mechanism of action studies for potential immunotherapeutic candidates. Our inability to accurately predict toxicity and treatment outcomes hinders development of these therapies. Furthermore, due to disease and patient heterogeneity, not all people will profit from a particular immunotherapeutic, so biomarkers that can identify those patients most likely to benefit must be developed.
Adverse events
Unwanted irAEs pose a serious challenge to the immunotherapeutics field. Exaggeration of on-target interactions can lead to infections, malignancies, cytokine release syndrome (CRS), tumor lysis syndrome, and autoimmunity. Intrinsic properties of an immunotherapeutic such as immunogenicity can cause production of anti-drug neutralizing antibodies or lead to hypersensitivity reactions. Plus, unanticipated interactions with healthy cells can lead to toxicities and other off-target effects.

Systematic characterization of irAEs in recent years has made it possible to include mitigation strategies in clinical treatment algorithms. However, complete risk management requires that we understand the complex interactions among the disease, the immune system, the target, and the immunotherapeutic candidate. Reliable prediction of irAEs is critical to managing them quickly and effectively without patient harm, but there is still a lack of tools to predict their likelihood and severity.

Development
Immunotherapeutics such as the anti-CTLA4 antibody ipilimumab initially followed the traditional approach to oncology chemotherapy drug development, but it became clear in the process that a new development paradigm was needed. Conventional endpoints were not suitable for assessing the efficacy of immunotherapeutics, so new immune-related response criteria were defined with endpoints more appropriate for these agents. In addition, strategies for mitigating irAEs were included in the treatment protocols.

Manufacturing and logistics
Autologous cellular therapies are associated with several special logistical issues related to production and administration. Harvesting a patient's cells usually takes place in one facility, while the subsequent ex vivo cell treatments occur in another. Maintaining chain of identity across various sites and ensuring quality control throughout the entire process are difficult challenges that cannot be compromised.

Combining multiple therapies
Although immunotherapeutics are demonstrating much success, many cancer patients do not respond to treatment with just a single agent. Combining multiple therapies into a treatment regimen can potentially increase the number of patients who will benefit by decreasing toxicity profiles, overcoming resistance issues, and improving the level and duration of response.

Many trials are underway assessing various combinations of immunotherapeutics or immunotherapeutics combined with radiation or chemotherapy. Optimizing these complex treatment regimens poses a significant challenge. It is difficult to predict how combining multiple therapies will affect treatment responses and toxicity issues. Determining the optimal dose for each therapy, how often to administer the therapies, the treatment sequence, and treatment durations are other issues that complicate optimization of multi-therapy combinations.

The evolving landscape of immunotherapeutics
Immunotherapeutics can be classified into two broad categories: passive and active. Passive immunotherapeutics include various immune components such as antibodies and T cells that are designed to directly target and kill tumors. Active immunotherapeutics, on the other hand, are designed to harness the power of the host immune system to kill the tumors for us. As we learn more about the interactions between cancer and the immune system, our ability to design more advanced therapies against more complex targets will continue to evolve.

The immune system can detect and suppress early tumor growth to prevent cancer, but despite this immunosurveillance, tumor cells still frequently evade detection and develop into cancer, becoming less immunogenic in the process. Widespread research is underway attempting to tweak the immune system so it will once again recognize these cancer cells as foreign and attack them.
Anticancer monoclonal antibodies (mAbs)
The introduction of anticancer mAbs revolutionized cancer treatment approaches, shifting the paradigm from use of general anticancer treatments to molecularly targeted agents designed to kill specific tumors. Anticancer mAbs locate and attach to tumor-specific antigen targets and then kill the tumor cells or prevent their proliferation via various mechanisms.(7) Some antibody isotypes bind to complement proteins and induce a cytolytic cascade that kills the tumor cells via complement-dependent cytotoxicity (CDC). Other mAbs bind to various immune effector cells, enabling the effectors to attack and lyse the antibody-coated tumor cells via antibody-dependent cellular cytotoxicity (ADCC). Yet another mechanism is for the anticancer mAbs to bind tumor-specific cellular receptors or circulating proteins, blocking the pathways essential for tumor cell growth.

Identifying optimal targets for designing anticancer mAbs is still difficult. A good target must be expressed at high levels exclusively on tumor cells to prevent off-target toxicity to healthy cells. Targeting a pathway critical to tumor growth requires comprehensive knowledge of both how the pathway operates in the context of the disease and how blocking it may affect other functions important to our health. While our knowledge of pathways and their interactions is large and still growing rapidly, actually understanding how all the pieces fit together into the big picture is no small feat.

One well-studied anticancer mAb target is human epidermal growth factor receptor 2 (HER2), which is overexpressed in around 20-30% of breast cancers and has been associated with aggressive disease and poor prognosis.(8) HER2 normally promotes cell growth and division, but increased amounts of the receptor on tumor cells activate other pathways, including MAPK, PI3K/AKT, and NF-κB. (8) The result is a constant signal for the tumor cells to proliferate. Trastuzumab (Herceptin) is a mAb designed to treat HER2-positive breast cancers, and it functions by binding HER2 and blocking its ability to send these signals.

In addition to the desired therapeutic activity, the on-target effects of various anticancer mAbs have also been associated with the incidence of irAEs, including increased risk of infections, development of progressive multifocal leukoencephalopathy (PML), and cytokine release syndrome (CRS).(2) Trastuzumab is no exception, and binding to its target downregulates neuregulin-1 (NRG-1), increasing the chance of developing serious heart problems.(9) It turns out that the same pathways involved with progression of these cancers are also critical for normal cardiac function. Thus, it is important to balance the therapeutic benefit of an agent against its ability to cause adverse events. To assess this effectively, we must fully understand the involved pathways in detail and their roles in both disease and healthy states.

The first anticancer mAbs were of murine origin, and patients recognized the agents as foreign, mounting immune responses against them, but we have since overcome this problem by using human, humanized, or chimeric antibodies instead.(7) One issue that still needs work is developing appropriate biomarkers to predict which patients will likely respond to treatment. Trastuzumab was developed using a biomarker-enrichment design strategy, in which only patients with HER2-positive tumors were enrolled in the trials, increasing the likelihood of a successful therapeutic effect.(10) This was possible due to an abundance of data showing the importance of HER2 in the disease and the strong antitumor response resulting from blocking it. However, these details are not always so clear for all candidates and targets, and including the wrong patients in trials can result in lack of efficacy or even patient harm.

Patients who do not respond to treatment with anticancer mAbs can rapidly develop resistance, which is a major problem facing the field.(11) Resistance is difficult to understand, because the multiple mechanisms by which mAbs can elicit antitumor effects translate into multiple mechanisms by which resistance can develop. In addition, using mAbs in combination with other therapies further complicates attempts to unravel resistance mechanisms. Existing murine

Resistance to Monoclonal therapy is difficult to understand, because the multiple mechanisms by which mAbs can elicit anti-tumor effects translate into multiple ways by which resistance can develop, which is a major challenge.
models are poorly suited for analyzing resistance to ADCC and CDC antitumor effects due to the differences between our immune systems and theirs, so we still have a lot to learn in this area.

Anticancer mAbs have been very successful therapeutic agents and are widely used against various types of cancer, usually in combination with another treatment. Although new types of immunotherapies are coming into focus, anticancer mAbs are still very useful. Efforts to identify and validate new targets and engineer antibodies with improved antitumor response will help keep the area active for some time.

Immune checkpoint inhibitors (ICIs)
ICIs are a new class of immunotherapeutic that is changing the cancer treatment paradigm once again. Instead of targeting the tumor directly, ICIs target the patient’s immune system and restore the natural anti-tumor immune response. Since the approval of ipilimumab in 2011 for treating advanced melanoma, the interest in these agents has grown rapidly, intensifying efforts to identify novel immune checkpoint pathways and targets.

Selecting a target for an ICI requires a thorough understanding of how immune checkpoints work and how blocking them will affect the disease and our health. Immune checkpoints are co-inhibitory or co-stimulatory molecules that prevent attacks on healthy cells, but they can also keep our immune systems from attacking cancer cells. ICIs target these molecules and allow the immune system to remain activated.

The two best-characterized immune checkpoints are CTLA-4 and PD-1/PDL-1. CTLA-4 is a surface T-cell receptor that inhibits the co-stimulatory signal, thereby preventing subsequent activation of antitumor T-cell responses. The regulatory role of PD-1 comes after T-cell activation. Binding of PD-1 to PDL-1 (programmed death ligand 1) suppresses migration and proliferation of T-cells, restricting killing of cancer cells.

Blocking these immune checkpoints therapeutically activates the immune system and restores the antitumor immune response. To date, there are three approved immune checkpoint inhibitors, all of which are mAbs. Ipilimumab targets CTLA-4 and was
Knowledge on cancer and immune signaling pathways continues to grow rapidly. Expanding data

Unraveling the complexities of the interactions between disease and immune pathways will lead to the development of new predictive models.

While ICIs restore antitumor responses, the nonspecific stimulation of T cells they induce is associated with various unique irAEs, which usually involve problems with the skin, liver, and gastrointestinal or endocrine systems. Most patients receiving ICI treatment experience irAEs, which can range from mild to severe or occur at any time from soon after treatment up to many months later. These are often manageable with high-dose corticosteroids or other immune suppressants. However, about 10% of patients experience life-threatening irAEs that require hospitalization. We have no biomarkers to predict which patients will be affected or how severely, but improving our understanding of immune pathways and how an individual’s immune status affects response will certainly aid in their development.

Development of ICIs must take into account the differential response of tumors to this class of agents. In some patients, the tumor volume or number of lesions appears to increase initially upon treatment initiation. This appearance of disease progression is often caused by immune activation and infiltration of the tumor by inflammatory T cells. Furthermore, in some patients, the time for a complete response can be very long, up to 30 months for ipilimumab, for example.

As with other immunotherapeutics, ICIs are not effective in all patients, so we need to develop predictive biomarkers for efficacy and toxicity. Efforts to identify and validate such biomarkers are underway, but since these agents target the immune system instead of the tumor, the patient response is more complicated and involved a variety of parameters, including serum protein markers and immune cell phenotypes and functions. Determining the roles of these different parameters in efficacy and toxicity is difficult and requires that we understand a number of complex pathways in the context of each other.

Other types of immunotherapeutics

Many other types of immunotherapeutic agents and strategies are already in use or in various stages of development. Tools that can help us better understand the diseases and immune pathways involved will support their success in the clinic. Adoptive transfer of T cells expressing chimeric antigen receptors (CAR) has shown remarkable efficacy in clinical trials, bringing hope to certain patients with no further treatment options. (17) Co-stimulatory agonists targeting T cells are able to initiate several different signaling cascades and strengthen antitumor T cell receptor signaling. Efforts to create peptide-based vaccines to force the immune system to attack cancer cells have led to many failures, but better selection of targets and vaccine format may change that in the future. (19) Antibody-drug conjugates (ADCs) comprising a monoclonal antibody, a linker, and a payload can selectively deliver highly toxic payloads to specific disease sites. Oncolytic viruses that replicate in tumor cells release antigenic proteins that initiate a T cell response against the tumor cells. The tumor microenvironment (TME) also contains a number of potential targets involved in tumor growth and dissemination and is an area of great interest.

Looking to the future

Breakthroughs in the field of immunotherapeutics are changing the way we treat many cancers and bring the promise of durable, long-term survival to many patients. While our knowledge regarding various cancer pathways and immune signaling pathways has grown immensely and continues to grow, we must develop a comprehensive understanding of how disease pathways interact with immune pathways. Unraveling the complexities of these important interactions and combining this knowledge with new predictive models will help translate preclinical promise into clinical success for treating cancers and other diseases.
Works Cited
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JAPAN
Tel: + 81 3 5561 5034
Email: jpinfo@elsevier.com

KOREA AND TAIWAN
Tel: +82 2 6714 3000
Email: krinfo.corp@elsevier.com

EUROPE, MIDDLE EAST AND AFRICA
Tel: +31 20 485 3767
Email: nlinfo@elsevier.com

NORTH AMERICA, CENTRAL AMERICA AND CANADA
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SOUTH AMERICA
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