Immunotherapy has been under evaluation for more than a century, but only recently has it entered a renaissance phase with approval of multiple agents for the treatment of cancer. Now, immunotherapy stands poised to join with traditional modalities, including surgery, chemotherapy, radiation, and hormone therapy, as a pillar of cancer treatment. Importantly, immunotherapy is not a single entity but represents several types of treatments, such as cytokines, checkpoint inhibitors, monoclonal antibodies, and therapeutic cancer vaccines. Different immunotherapies have different mechanistic approaches, but each aims to boost or restore the ability of the immune system to fight cancer.

This monograph provides urology healthcare professionals with an overview of how the immune system works, the role the immune system plays in cancer, and describes how various immunotherapies are designed to target cancer cells. This information is highly relevant to understanding immunotherapy and may improve outcomes of patients with certain cancers.

Key Objectives

After reading this monograph, urology healthcare professionals will further understand:

- The evidence supporting the immune system's role in cancer
- Characteristics of an immune response
- Mechanisms of immunotherapy
- Treatment considerations of cancer immunotherapy
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## Summary

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Everyday Functions of the Immune System
The principal role of the immune system is to prevent and eradicate infections. The immune system does this by using 2 different defense mechanisms: initial defenses that are non-specific and specialized defenses that mount a targeted response.\(^1\) Non-specific defenses include epithelial barriers, such as the skin, that prevent entry of microbes as well as contain specialized cells and natural antibiotics that block entry of microbes. In addition, the non-specific immune system can quickly recognize foreign pathogens that breach epithelial barriers and mount a generalized attack.\(^1\) For those microbes that are capable of resisting initial defenses, the immune system utilizes specialized defenses that generate a targeted response. These specialized defenses recognize and respond to pathogens and use specific cells to target and eliminate those pathogens.\(^1\) Vaccination provides a prime example of how our immune system recognizes foreign pathogens to which it has been previously exposed and mounts a specific attack to eradicate them.\(^1\)

It is important to note that the immune system also recognizes cancer cells as foreign and uses immune defenses to attack cancer cells.\(^1\) The evidence for this will be elaborated on in the next section, “The Immune System’s Role in Cancer.”

Native Immune Response
The immune system is complex and relies on many interrelated components to target foreign antigens to effectively prevent and eradicate infections.\(^1\) A simple representation of the cell-mediated immune response upon exposure to an antigen (eg, foreign substance that generates an immune response, such as proteins on the surface of a microbe or other cell) is illustrated in Figure 1.\(^1\) Antigen presenting cells (APCs) are specialized cells that recognize foreign antigens and present antigen fragments to T cells, immune cells capable of recognizing and attacking microbially-infected or other cells containing specific antigen.\(^1\) APCs are generally located in the peripheral tissues, such as the digestive and respiratory tracts.\(^1\) The interaction between APCs and T cells activates the T cells, which replicate and specialize to mount an attack on cells expressing the specific antigen. This specialization includes proliferation of target cells that attack cells expressing antigen, the activation of additional immune cells and mediators to enhance the immune response, and the development of memory T cells that can rapidly respond upon re-exposure to the same antigen.\(^1\)

APCs interact with T cells to elicit a specific and enduring immune response. This immune response is thought to be critical to controlling cancer.
Hallmarks of Cancer Pathogenesis
Over 10 years ago, the development of cancer was characterized in a landmark paper by Hanahan and Weinberg published in Cell as having 6 hallmark traits that are common across most, if not all, cancers. In 2011, this classic paper was updated to include the immune system because several lines of evidence had been published implicating a critical role of the immune system in cancer pathogenesis such that tumors have the ability to specifically evade the immune system, allowing cancers to grow and spread. The updated hallmark traits common to cancers are listed in Table 1.

The Immune System in Cancer: Clinical Evidence
A significant and growing body of scientific evidence substantiates the role of the immune system in battling cancer. Evidence has demonstrated that patients with compromised or suppressed immune function have an increased risk of cancer compared to individuals with intact immune systems. In particular, it has been shown that patients who have undergone organ transplantation and are chronically immunosuppressed to prevent transplant rejection have an increased incidence of several cancers (Figure 2). In patients who have undergone kidney transplantation, this increased cancer risk ranges

Table 1. Hallmarks of Cancer Cells

<table>
<thead>
<tr>
<th>Hallmark</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Grow in the absence of growth signals</td>
</tr>
<tr>
<td>2.</td>
<td>Evade the normal signals that stop growth</td>
</tr>
<tr>
<td>3.</td>
<td>Evade the normal death signals that prevent proliferation of damaged cells</td>
</tr>
<tr>
<td>4.</td>
<td>Escape from an intrinsic signal that limits cell replication to a finite number</td>
</tr>
<tr>
<td>5.</td>
<td>Induce the formation of new blood vessels to feed themselves</td>
</tr>
<tr>
<td>6.</td>
<td>Acquire the ability to invade other tissues and spread throughout the body</td>
</tr>
<tr>
<td>7.</td>
<td>Change cellular metabolism to support proliferation of cancer cells</td>
</tr>
<tr>
<td>8.</td>
<td>Evade the immune system to avoid destruction</td>
</tr>
</tbody>
</table>

Figure 2. Increased Incidence of Cancer in Immunocompromised Individuals
from 2-fold for common tumors, like colon, prostate, and breast, to greater than 20-fold for non-melanoma skin cancer and non-Hodgkin’s lymphoma compared to the general population with intact immune systems.\(^4\)^5 A similar trend toward an increased cancer risk has been seen with patients who have undergone liver or heart transplants.\(^6\)^7 In addition, cancer rates are increased in human immunodeficiency virus (HIV)-infected individuals, and an estimated 40% of all patients with acquired immune deficiency syndrome (AIDS) develop cancer during their lifetime.\(^8\) In several observational studies, the risk of malignancies in patients with AIDS increased as certain immune cell counts declined.\(^9\)^10

Additionally, intratumoral T cells, which are key mediators of cellular immunity, have been associated with increased overall survival (OS) in different cancers.\(^11\)-\(^13\) Figure 3 depicts a Kaplan-Meier curve from a study of patients with bladder cancer and showed that higher numbers of T cells within the tumor (>8) of patients with muscle-invasive cancer had better OS than did similar-staged patients with fewer intratumoral T cells (\(P<0.001\)).\(^11\) Taken together, these data support the importance of the involvement of the immune system in cancer.

**Key Learnings**
- The immune system is recognized as having a critical role in controlling cancer. Studies have demonstrated that diminished immune system function was associated with an increased risk of cancer. Additionally, an association has been established between tumor-infiltrating T cells and increases in OS in various cancers.

**Cancer and the Immune System: A Dynamic Relationship**

The regulation of tumor growth represents a dynamic state, in which the immune system can either block tumor growth, development, and survival (ie, immune protection) or may promote development of tumors (ie, immune evasion).\(^14\) This process can be conceptualized by a seesaw that balances immune...
Adapted from Dunn GP, et al.14

A) Elimination: Immune System Eradicates Cancer Cells

B) Equilibrium: Immune System Controls Cancer Cells

C) Escape: Cancer Cells Evade Immune System

Figure 4. The 3 E’s: Elimination, Equilibrium, Escape14

Elimination refers to the stage in which cancer cells are identified and effectively eliminated by the immune system. In this stage, the balance is shifted in favor of immune protection (Figure 4A).14 This is a natural process that is generally thought to operate for early tumors (in clinic, probably undetected tumors).14,15

The equilibrium phase is entered in the event that the immune system is not able to completely eliminate all cancer cells but can control or prevent further outgrowth.14 As a result, the tumor cells persist but are ultimately prevented from spreading by the actions of the immune system. In the equilibrium stage, the conceptual seesaw is balanced (Figure 4B). This stage is thought to be the longest of the 3 stages and may persist for many years.

The escape phase is characterized by the inability of the immune system to eliminate and control the outgrowth of cancer cells.14 This stage may occur as a result of immune system exhaustion or when cancer cells acquire phenotypic alterations, thereby allowing them to evade or avoid the immune system.14 In the escape stage, the conceptual seesaw tips in favor of immune evasion, leading to progressive disease (Figure 4C).

Key Learnings
- There is a dynamic relationship between the immune system and tumor cells. Normally, the immune system is capable of eliminating tumor cells. However, tumor cells use multiple evasion techniques to avoid the immune system.

Characteristics of an Effective Immune Response
The ability of the immune system to protect against foreign antigens has made it an attractive target of clinical research.1,16 There are several key characteristics or features of an effective immune response that result in the ability of the body to protect against foreign antigens. These key characteristics include specificity, trafficking, adaptability, and durability (memory).1,16,17 These characteristics allow the immune system to effectively target a specific antigen, broaden the immune response to additional antigens, and confer an optimized and long-lasting response.1
An important characteristic of an effective immune response is specificity, which ensures that distinct antigens elicit a specific immune response.\textsuperscript{1} Our immune response to the flu virus following annual vaccination is a good example of specificity.\textsuperscript{18} The flu virus mutates surface antigens each year (eg, antigenic drift) because of selective pressure from the immune system.\textsuperscript{18} As shown in Figure 5, following vaccination, the immune system is able to selectively identify surface antigens of the annual strain and mount a specific attack.\textsuperscript{1,18} Without vaccination toward the new strain the following year, the immune system may not recognize its distinct antigens and respond with a specific attack.\textsuperscript{1,18} Thus, new vaccination is required each year to protect against annual flu strains.\textsuperscript{18}

Another characteristic of an effective immune response is trafficking, which refers to the ability of activated immune cells to migrate to particular antigens throughout the body.\textsuperscript{1,17,19} This involves activated T cells, which are mobilized to areas containing antigen.\textsuperscript{19} Naive T cells normally circulate in the lymphatic system.\textsuperscript{1,19} Following exposure to antigen presented by APCs, T cells become activated and migrate to the target antigen in organs throughout the body.\textsuperscript{19}

Adaptability (broadening of the immune response) is another important characteristic, which allows the immune system to respond to additional antigens on a pathogen or tumor through a process called antigen spreading.\textsuperscript{1,20} An example of this process is when a tumor-specific T cell kills (lyses) a tumor and additional tumor fragments (antigens) are taken up by APCs, thereby activating an immune response to additional antigens.\textsuperscript{21} Illustrated in Figure 6, a T cell that specifically targets an antigen on a prostate tumor cell kills the cell, which releases other
antigens to APCs. Once released, this may allow other tumor-associated antigens to activate additional T cells specific for those antigens. This process allows the immune system to broaden and adapt to subsequent mutations.\textsuperscript{21}

Another key characteristic of an effective immune response is durability or memory, the ability of T cells to recognize antigens over time, mount an expedited and optimized immune response upon re-exposure to antigens and confer a long-lasting response. Once the immune system has been exposed to an antigen, upon re-exposure, it is able to more rapidly and effectively mount an immune response against that specific antigen for many years.\textsuperscript{1} An example of this characteristic is shown in Figure 7, where 100\% of patients immunized against smallpox maintain a T-cell immune response to smallpox 20-30 years after vaccination, ~90\% of patients maintain a T-cell immune response after 31-50 years, and >50\% of patients maintain a T-cell immune response after 51-75 years of receiving the single immunization.\textsuperscript{22}

Key Learnings

- APCs are the initiators of T-cell driven immune responses. An effective immune response includes the key characteristics or features of specificity, trafficking, adaptability, and durability (memory).

![Figure 6. Adaptability\textsuperscript{21}](image_url)

**Figure 6.** Adaptability\textsuperscript{21}

![Figure 7. Durability (immune memory)\textsuperscript{22}](image_url)

**Figure 7.** Durability (immune memory)\textsuperscript{22}

Volunteers With CD4\(^+\) T-Cell Memory After One Smallpox Vaccination

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-30 years</td>
<td>100%</td>
</tr>
<tr>
<td>31-50 years</td>
<td>90%</td>
</tr>
<tr>
<td>51-75 years</td>
<td>&gt;50%</td>
</tr>
</tbody>
</table>

**Activated T-cell target and kill tumor cell**

**APC takes up additional released antigens**

**Activated APC presents antigen to naive T cell**

PSMA, prostate-specific membrane antigen; PSCA, prostate stem cell antigen; PAP, prostatic acid phosphatase; MUC-1, mucin-1.

Adapted from Gulley JL.\textsuperscript{21}
The Renaissance of Immunotherapy

For more than a century, advancements in cancer immunotherapy have spread across several phases. In 1890, Coley developed the first cancer vaccine (based on bacterial toxins), which was shown to have benefit in patients with inoperable cancer. Driven by findings from Coley and others, researchers developed tumor-specific monoclonal antibodies in 1978. Interests soared in cancer immunotherapy, and the 

Enthusiasm Phase was born. However, the clinical benefit or promise of cancer immunotherapy did not reach initial expectations, thus ushering in the 

Skepticism Phase in 1985. Subsequently, in 1997 there was a resurgence of interest in cancer immunotherapy as a viable treatment option. This 

Renaissance Phase was initiated with a number of therapeutic advances in cancer immunotherapy that has resulted in important drug approvals.

Immunotherapy Approaches

The National Cancer Institute defines immunotherapy as “treatment to boost or restore the ability of the immune system to fight cancer, infections, and other diseases.” Immunotherapy encompasses several different treatment approaches: cytokines, tumor antigen–targeted monoclonal antibodies, immunological checkpoint inhibitors, and therapeutic cancer vaccines. Each of these treatment types has a distinct mechanism of action; however, they all are designed to boost or restore immune function in some manner.

Cytokines

Cytokines, such as interleukin-2 (IL-2) and interferon-α (IFN-α), are proteins naturally secreted by immune system cells, such as T cells, to mediate inflammatory and immune reactions in the body. Cytokine immunotherapy stimulates a broad-based immune response as opposed to generating a targeted response to a specific antigen. As an example, IL-2 has numerous effects on the immune system and acts as a general T-cell growth factor. It does this by binding to receptors on the surface of T cells. This binding stimulates the proliferation of T cells, continued cytokine production, and activation of multiple types of immune cells. It is interesting to note that IL-2 therapy has been shown to lead to a complete response in ~4%-6% of patients with renal cell carcinoma and melanoma; this response can potentially be durable. This suggests that for this subset of patients, IL-2 therapy is able to successfully manipulate the endogenous antitumor immune response.

Monoclonal Antibodies

Monoclonal antibodies are designed to bind to specific substances in the body, such as tumor cells. Tumor-specific monoclonal antibodies can elicit a direct or indirect immune response that leads to cell death. There are a variety of monoclonal antibodies and these work via different mechanisms of action to cause cell death. Some of these mechanisms include blocking signaling pathways needed for tumor cell growth, triggering an immune-mediated cytotoxic response (eg, antigen-dependent cellular cytotoxicity), or blocking angiogenesis. Tumor-specific monoclonal antibodies have become part of the therapeutic repertoire in treating leukemia, breast, colorectal, and head and neck cancers after improving OS and progression-free survival in randomized, Phase 3 clinical trials. Response rates of 8%-10% are observed when these are used as a single agent in advanced stage, heavily pretreated, and recurrent disease. These rates increase to 30% when combined with traditional chemotherapy and/or radiotherapy.

Checkpoint Inhibitors

The immune system depends on multiple checkpoints or “immunological brakes” to avoid overactivation of the immune system on healthy cells. Tumor cells often take advantage of these checkpoints to escape detection by the immune system. CTLA-4 and PD-1 are checkpoints that have been studied as targets for cancer therapy. CTLA-4 has been shown to be aberrantly upregulated and present on the surface of T cells in certain cancers, dampening T-cell activation in response to tumor cells. PD-1 is another immunologic checkpoint that has been found to be upregulated in certain tumors; it inhibits T-cell function contributing to the tumor’s ability to evade the immune system. Inhibiting a checkpoint (ie, “releasing the brakes”) on the immune system may enhance the antitumor T-cell response. This class of therapy has shown efficacy in cancer and clinical trials are ongoing.

Therapeutic Cancer Vaccines

Therapeutic cancer vaccines are designed to stimulate the patient’s own immune system against tumor antigens.
triggering the immune system, therapeutic vaccines can initiate a durable antitumor response that can attack tumor cells and lead to improved survival.\textsuperscript{46,47} It is important to recognize, however, that therapeutic cancer vaccines differ from traditional preventative vaccines, such as those for various infectious diseases. Notably, the primary goal of a therapeutic cancer vaccine is NOT to prevent disease but to generate an active immune response against an existing cancer.\textsuperscript{48}

Some therapeutic cancer vaccines have contained a recombinant protein comprised of a tumor antigen and an immune cell activator. Once injected or infused, APCs process the antigen and then express antigenic fragments on their surface for presentation to the patient's T cells. These activated APCs are able to interact with naive T cells in the initiation of a T-cell driven immune response, as described earlier.\textsuperscript{1}

**Table 2. Features of Immunotherapy\textsuperscript{50}**

<table>
<thead>
<tr>
<th>Active</th>
<th>Passive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engages immune system</td>
<td>Enhances pre-existing immune response</td>
</tr>
<tr>
<td>Durable</td>
<td>Short-lived</td>
</tr>
<tr>
<td>Some examples:</td>
<td>Some examples:</td>
</tr>
<tr>
<td>• Therapeutic cancer vaccines</td>
<td>• mAbs</td>
</tr>
<tr>
<td></td>
<td>• Cytokines</td>
</tr>
</tbody>
</table>

mAbs, monoclonal antibodies. Active immunotherapies are personalized. Checkpoint inhibitors may share characteristics of both passive and active therapies. Immunotherapies may be tumor-antigen specific or non–tumor-antigen specific.

Passive immunotherapy is based on the use of an agent (eg, monoclonal antibody, cytokine) or cell type, which is administered to the patient to initiate an antitumor effect. In general, passive therapies do not generate immunologic memory and consequently may require chronic administration to elicit an effect. In contrast, active immunotherapy stimulates the host immune system, with the goal of having the patient's cells mount an immune response against the tumor. Because of how the immune response is generated, active immunotherapy can result in immunologic memory and a durable effect after treatment has stopped.\textsuperscript{50}

Immunotherapy can be further classified as non-specific and specific. Cytokines and non-specific adjuvants are examples that produce a wide range of antitumor effects. In contrast, most monoclonal antibodies used in immunotherapy produce a specific immune response to a target antigen. Similarly, active immunotherapy would also be classified as generating a specific tumor antigen response.\textsuperscript{50}

**Key Learnings**

- Immunotherapy is defined as a treatment designed to boost or restore the ability of the immune system to fight cancer, infections, and other diseases. Effective types of immunotherapy include monoclonal antibodies, checkpoint inhibitors, and cytokines. Each treatment works via different mechanisms and has varying levels of target specificity, but does not have the ability to generate durable responses through immune memory cells. Therapeutic cancer vaccines mimic key features of a patient's natural immune response and can create a durable response.

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**Immunotherapy: Present and Future**

Today, immunotherapy is an established treatment modality in oncology spanning numerous solid tumors and hematologic malignancies. The US Food and Drug Administration (FDA) has approved at least 12 monoclonal antibodies for use in cancer treatment, starting in the late 1990s.\textsuperscript{49} Besides these agents, the FDA has approved several cytokines, an immune checkpoint targeting agent, and a cancer vaccine. The future of immunotherapy looks very promising as numerous cancer immunotherapies are currently in advanced stages of clinical development.

**Features of Immunotherapy**

Depending on how they engage the patient's immune system, immunotherapies can be classified in a number of ways, including whether they act in a passive or active manner, and/or whether they specifically target tumor antigens (Table 2).\textsuperscript{50}

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“Cancer treatment vaccines are designed to treat cancers that have already developed. They are intended to delay or stop cancer cell growth; to cause tumor shrinkage; to prevent cancer from coming back; or to eliminate cancer cells that have not been killed by other forms of treatment.”\textsuperscript{48}

- National Cancer Institute, 2011
Dynamics of Immunotherapy
Immunotherapy may have the potential to continuously refine its effect on mutating cancer cells through the dynamic interplay between cancer and the immune system. As the immune system targets and lyses ever-mutating cancer cells, additional tumor antigens are able to be taken up by APCs, potentially activating a broader immune response (eg, adaptability; see Figure 6). This dynamic process between the immune system and cancer may contribute to the different kinetics of response that immunotherapy has compared with traditional cancer therapy (ie, chemotherapy).

Kinetics of Response to Immunotherapy
Immunotherapy is associated with a delayed, but durable response that differs from the rapid, transient response of traditional chemotherapy. As an example, in metastatic castrate-resistant prostate cancer (mCRPC), chemotherapy can dramatically affect tumor growth rates during the active course of treatment. However, the tumor growth rate returns to its pretreatment value once chemotherapy is discontinued, reflecting the underlying tumor characteristics and the transient effect of traditional chemotherapy. In contrast, immunotherapy can induce immunologic memory and may change or boost the immune status of the patient, even after the course of immunotherapy has been completed. Because it may take several weeks or months to generate an effective immune response, immunotherapy may not necessarily cause a dramatic or immediate reduction in tumor burden or tumor-specific markers. However, it has been shown to ultimately prolong OS.

The differing immunotherapy response kinetics infer that biomarkers used to monitor the effects of traditional therapies may not always be appropriate. For example, prostate-specific antigen (PSA) is routinely used to monitor the effects of hormonal therapy in patients with prostate cancer. However, agents that slow tumor growth may not necessarily cause PSA reductions, and consequently changes in PSA levels may be difficult to interpret with immunotherapy. The Prostate Cancer Clinical Trials Working Group recommends expanding the focus from rising PSA levels to evaluating additional measures of disease progression (eg, bone lesions, substantive pain, soft tissue lesions) to make decisions about when to stop a given therapy in advanced prostate cancer.

Immunotherapy Treatment Considerations
Based on the noted difference in timing and duration of response compared to traditional chemotherapy, it has been suggested that the relative efficacy of immunotherapy may be greater with a smaller tumor burden. This also suggests that improved treatment responses and outcomes may be expected at earlier stages of disease. In addition, evidence from clinical trials suggests that earlier use of immunotherapy in a patient with less compromised immunity has a better chance of effectively activating an immune response (Figure 8). For example, patients with metastatic cancer who received more rounds of chemotherapy or received a cycle of chemotherapy more recently were shown to mount a diminished magnitude of T-cell response following therapeutic vaccine.

Figure 8. Proposed Relationship Between Initiation of Immunotherapy and Outcomes

--- Expected clinical outcome if no treatment is provided
† Death
A Patient given a vaccine earlier
B Patient given a vaccine later

Adapted with permission from Gulley JL et al.
Another consideration is the use of immunotherapy with traditional agents, as combination therapy is now standard for the treatment of many types of cancer to improve clinical outcomes. Immunotherapy offers an additional mechanistic approach, thereby raising the potential for synergy when used in combination with chemotherapy, radiation, and/or hormone therapy. Indeed, several monoclonal antibodies that bind to specific targets on cancer cells when added to chemotherapy have been shown to improve survival compared with chemotherapy alone. It may also be possible to rationally combine 2 types of immunotherapy based on complementary mechanisms of action, although proof of this approach remains to be shown.

Key Learnings

- Immunotherapy demonstrates an initial lag in effect; but may be able to slow tumor growth over time and prolong OS. Based on delayed response kinetics, it is suggested that immunotherapy may be more effective in patients with lower tumor burden. Because immunotherapy has a different mechanistic approach than traditional agents, immunotherapy may act synergistically with other therapies.

SUMMARY

The immune system has a critical role in controlling cancer. Key features of an effective immune response include specificity (which ensures an antigen-targeted response), trafficking (which enables antigen targeting throughout the body), adaptability (which allows for a response against related antigens), and durability (which allows for an expedited and long-lasting response upon re-exposure to the antigen). Over time, cancer cells develop mechanisms to escape control by the immune system, leading to progression of disease. Immunotherapy is designed to boost or restore the ability of the immune system to fight cancer. It shows delayed response kinetics compared with traditional cancer treatment modalities, but has led to increased OS in certain cancers. Future use and clinical trials should take into consideration that immunotherapies may elicit a better immune system response if used while the patient is still immunocompetent. In addition, immunotherapy can offer the potential for durable clinical effects and synergy with subsequent therapies.

REFERENCES

REFERENCES (cont)
