Looking Deeper into the Science of Immuno-Oncology

Utilizing the body’s own immune system to fight cancer
At the back of this document, there are resources and images about I-O.

Slides have been color-coded based on educational topic to help gain an understanding of Immuno-Oncology (I-O).
# Topics covered (by subject)

## INTRODUCTION TO I-O THERAPY
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  - CTLA-4
  - B7-H3
  - PD-1

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  - Mediators of T-cell activation
- Adverse effects (AEs)
- Clinical implications of immune-associated AEs
What’s immuno-oncology (I-O)

Improved survival remains a challenge in some advanced cancers. 5-year survival remains poor for many patients with metastatic solid tumors.¹ There is an ongoing need for new treatments and therapeutic modalities for patients with advanced cancers.²

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>5-year Survival (%)</th>
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</thead>
<tbody>
<tr>
<td>Lung</td>
<td>3.9</td>
</tr>
<tr>
<td>Colorectal</td>
<td>12.5</td>
</tr>
<tr>
<td>Kidney and renal pelvis</td>
<td>12.3</td>
</tr>
<tr>
<td>Melanoma</td>
<td>16</td>
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</tbody>
</table>

I-O therapies are being investigated in an attempt to utilize the body's own immune system to fight diseases.³⁵

There are over 900 oncology clinical trials of immunotherapy in various phases of development.⁶

References:
History of immunotherapy

**I-O has progressed considerably since 1986** with approvals for the use of various I-O therapies, including vaccines, cytokines, tumor-directed monoclonal antibodies, and immune checkpoint inhibitors.¹,²

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**Timeline of Immunotherapy**

- **1796**: First use of immunotherapy to control disease³
- **1863**: First demonstration that bacterial products had benefits for inoperable cancers
- **1890**: Discovery of dendritic cell⁵
- **1909**: Proposal that immune system suppresses tumor formation, later known as “immune surveillance”⁴
- **1913**: First human testing of biological therapy¹
- **1973**: Technology to generate monoclonal antibodies developed⁶
- **1975**: First connection between inflammation and cancer
- **1978**: Approval of I-O therapies for various tumors
- **1986**: First connection between inflammation and cancer
- **Enthusiasm phase (1978-1985)¹**
- **Skepticism phase (1985-1997)¹**
- **Renaissance phase (1997-present)¹**
- **1991**: Skepticism phase (1985-1997)¹
- **1998**: Renaissance phase (1997-present)¹
- **2004**: Renaissance phase (1997-present)¹
- **2006**: Renaissance phase (1997-present)¹
- **2010**: Renaissance phase (1997-present)¹
- **2011**: Renaissance phase (1997-present)¹

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3. Murphy JF. Oncology. 2010;4:67-80
Hallmarks of cancer

As normal cells *progressively evolve to a neoplastic state*, they can acquire a succession of *hallmark capabilities*¹:

1. Resisting cell death
2. Inducing angiogenesis
3. Enabling replicative immortality
4. Deregulating cellular energetics
5. Avoiding immune destruction
6. Evading growth suppressors
7. Sustaining proliferative signaling
8. Activating invasion and metastasis

For **Immuno-Oncology therapies (I-O therapies)** to work, they generally incorporate an understanding of the *mechanisms of tumor escape*.²,³

I-O therapies seek to modulate the immune system to *promote antitumor activity*, and counteract this hallmark.⁴

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¹ Hanahan D, Weinberg RA. *Cell.* 2011;144(5) 646-674.
The immune system and cancer: immunoediting

The process by which the immune system recognizes, destroys, and sculpts tumors is known as **immunoediting**. There are 3 phases in immunoediting:

- **ELIMINATION** (cancer immunosurveillance) - Cancer cells are detected by the immune system and/or eliminated. Tumor cells not destroyed may enter the equilibrium phase.
- **EQUILIBRIUM** (cancer dormancy) – Some cancer cells persist, but the immune system prevents tumor outgrowth.
- **ESCAPE** (cancer progression) – Resistant variant cancer cells acquire the ability to evade immune detection or elimination. This results in clinically apparent disease.

The goal of I-O therapy is to restore the ability of the immune system to eliminate cancer cells by either activating the immune system directly or by inhibiting mechanisms of suppression by tumors.

Some tumors may escape the immune system by interfering with various mechanisms of immune system activation and suppression.

I-O therapy regimens

I-O therapies have the potential to be used as *monotherapy* or *part of combination regimens*.\(^1\)

- I-O therapies are designed for various specific targets in the antitumor immune response; because of this, it is thought that combinations of complimentary I-O therapies may have the potential to enhance antitumor effects.\(^{1,2}\) There is also a potential for enhanced antitumor activity in combining I-O therapies with other cancer treatment modalities.\(^{1,2}\)

**Potential applicability of I-O for different tumors**

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Infiltrating immune cells reported</th>
<th>Evidence of tumor-associated immunosuppression reported</th>
<th>Tumor-immune interactions known to correlate with clinical prognosis</th>
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</thead>
<tbody>
<tr>
<td>Bladder</td>
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<td>16,19</td>
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<td>Colorectal</td>
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<td>22</td>
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<td>Lung</td>
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<td>Pancreatic</td>
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<tr>
<td>Prostate</td>
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<td></td>
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<tr>
<td>Renal cell carcinoma</td>
<td>3,11,14</td>
<td>2,14</td>
<td>3,11,14</td>
</tr>
</tbody>
</table>

Introduction to the immune system

In order to protect an individual, the immune system:

1. detects the presence of an infection or malignant cells,\(^1\)
2. carries out effector functions to contain or to eliminate the affected cells,\(^1\)
3. performs self-regulation to minimize collateral damage to healthy cells in the body,\(^1\) and
4. generates immunological memory so that subsequent exposures to the same antigen are dealt with efficiently.\(^1\)

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Components of the immune system

**Tumor-associated antigens**
- are abnormal cell substances/proteins (tumor antigens) which can be recognized and responded to by the immune system

**Antigen-presenting cells**
- take up antigens from infected or malignant cells and processes them into shorter peptide segments
- present antigen to T cells to mobilize an immune response

**T cells**
- have T-cell receptors, which can recognize tumor-associated antigens
- play a major role in killing infected or malignant cells when activated
- help perpetuate ongoing immune responses

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Components of the immune system

**B cells**
- display B-cell receptors, which can bind free floating antigens in the blood or lymph
- once activated, B cells differentiate to become plasma cells which can secrete large quantities of antibodies against a specific antigen

**Antibodies**
- are secreted by activated B cells, called plasma cells
- tag antigen-containing cells for attack by other parts of the immune system, or neutralize their targets directly by blocking important mechanisms

**NK cells**
- can recognize infected or malignant cells innately without contact with an antigen-presenting cell or antibody (this allows NK cells to launch rapid responses against stressed cells)
- can also attack based on recognition of antibodies on a cell surface

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T-cell activation: tumor-associated antigens

Tumor-associated antigens can trigger a tumor-specific immune cell response:

1. **Tumors** express a multitude of proteins, known as tumor-associated antigens\(^1,2,3,4\)

2. **Antigen presenting cell (APC)** captures tumor-associated antigens\(^2\)

3. **Activated APC** can interact with T cells\(^4\)

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**T-cell activation: cytotoxic T cells**

1. **Activated APC** presents the **tumor-associated antigen** to the T cell along with a **co-stimulatory signal**.

2. **Inactive T cell** is activated by **Antigen** recognition and the **co-stimulatory signal**.

3. **Activated T cell** proliferates and activates **Tumor cell**.

4. **Activated APC** presents the tumor-associated antigen to the T cell along with a co-stimulatory signal.

5. **Cytotoxic T cell** induces **apoptosis** in **tumor cell**.

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Immune system pathways

• Under normal conditions, there are a number of immune activation and inhibition pathways that modulate the immune response and protect healthy tissues from collateral damage during an immune response.\(^1,7\)
• Tumor evasion of the immune system may be associated with an imbalance in immune activation and inhibition.\(^1-5\)

Tumors may down-regulate co-stimulatory pathways.\(^2-3\)
Co-stimulatory receptors include:

• CD28
• CD40
• OX40
• CD137

Tumors may up-regulate immune checkpoints (inhibitory signaling pathways).\(^2,3,5,6\)
Checkpoint pathway molecules include:

• LAG-3
• CTLA-4
• B7-H3
• PD-1
**Known molecules involved in activation**

**CD28** binding to its ligand CD80 or CD86 **enhances T-cell activation** via co-stimulation.¹³

**CD40** signaling **promotes APC activation** and enhances the antitumor immune response.¹²

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¹ Pardoll DM. *Nat Rev Cancer*. 2012;11:252-264  
Known molecules involved in activation

**OX40** (aka CD134) promotes antitumor immune responses by **promoting T-cell proliferation and survival**.¹,²

**CD137** (aka 4-1BB) promotes the **activation and proliferation of T cells**.¹,³

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Known molecules involved in inhibition

LAG-3 (aka CD223) is an immune “checkpoint” molecule.¹

- It can inhibit T-cell activity and serve as a modulator of T-cell activation.¹,²

CTLA-4 is an immune “checkpoint” receptor that plays a key role in modulating T-cell function.¹,³

- Interaction of CTLA-4 on T cells with its ligand CD80 (aka B7-1) and CD86 on APCs leads to T-cell inhibition.¹,³
Known molecules involved in inhibition

**B7-H3** (a member of the B7 family) is thought to be an immune “checkpoint” pathway.¹
- It may inhibit the T-cell response beyond CD80/CD86 T-cell response.²
- Precise mechanism is under investigation.

**PD-1** is an immune “checkpoint” receptor that inhibits the T-cell response and plays a key role in modulating T-cell function.¹

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Passive immunotherapies

Passive immunotherapies act on the tumor, in some cases using immune-based mechanisms to fight cancer, but they do not require the patient’s own immune system to initiate a response.¹⁻⁴

They include:

Tumor-directed monoclonal antibodies⁵⁻⁶
- Unconjugated
- Conjugated
- Single-armed

Cell therapies⁷⁻⁹
- Lymphokine-activated killer-cell therapy
- Tumor-infiltrating lymphocyte with IL-2
- Gene-modified lymphocytes

**Tumor-directed monoclonal antibodies**

**About**
Monoclonal antibodies (mAbs) can be produced with an affinity to a specific tumor-associated antigen (TAA). They are widely used in oncology therapy today.

**Potential adverse effects**
Toxic autoimmune responses may arise against non-malignant cells with the same antigens, or even against cells containing other self-antigens.

mAbs may:
- a) mark tumor cells for destruction,
- b) interfere with receptor signaling,
- c) promote receptor degradation, and/or
- d) deliver anti-cancer agents directly to tumor cells, minimizing exposure of normal tissues.

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Cell therapies

About
Autologous immune cells are removed from the cancer-bearing patient, then activated and expanded in culture away from the immunosuppressive tumor environment.¹⁻⁴

Potential adverse effects
Re-injected immune cells can target normal cells as well as tumor cells if they share the same target antigens.¹

Active immunotherapies act directly on the body’s own immune system to elicit an immune response to fight cancer.¹⁴

They include:

**Therapeutic cancer vaccines**⁵
- Dendritic-cell vaccines
- Tumor-cell vaccines
- Peptide/protein-based vaccines
- Recombinant vector vaccines

**Cytokines**⁶
- Interleukins
- Interferons
- Tumor necrosis factor-α
- Granulocyte-macrophage colony-stimulating factor
- Immunocytokines

**Mediators of T-Cell activation**⁷
- Immune checkpoints: CTLA-4, PD-1, PD-L1, LAG-3, B7-H3, B7-H4
- Co-stimulatory pathways: OX40, CD28, CD40, CD137

Therapeutic cancer vaccines

About
Therapeutic cancer vaccines may prime the immune system to attack existing cancer cells in the body by introducing immune cells to one or more tumor-associated antigens.¹

Potential adverse effects
Cancer vaccines may lead to the generation of T cells that attack self-antigens in normal healthy tissue.²

Cytokines

About
Cytokines are small proteins that modulate the proliferation, activation, and survival of lymphocytes. They are thought to boost the effector functions of these cells, thereby strengthening the antitumor response.

Potential adverse effects
Increased lymphocyte activity may be directed against normal tissues, leading to T-cell-, B-cell-, or NK cell-mediated autoimmunities.

Mediators of T-cell activation

About
Mediators of T-cell activation are monoclonal antibodies that have been engineered to either agonize or antagonize specific immune pathways thought to be manipulated by cancer cells to impede the antitumor response. In doing so, they may be able to strengthen the antitumor response.¹

Potential adverse effects
Interfering with immune checkpoints can cause a general disruption in immune homeostasis, leading to a greater number of self-reactive T cells that attack healthy tissues.²

I-O therapy-associated AEs

I-O therapy-associated adverse events (AEs) target certain organ systems:\(^1\):

- Skin\(^1\)\(^-\)\(^5\)
- Endocrine system\(^2\)\(^,\)\(^4\)\(^-\)\(^8\)
- Liver\(^2\)\(^,\)\(^5\)\(^,\)\(^9\)\(^,\)\(^10\)
- Gastrointestinal tract\(^2\)\(^,\)\(^5\)\(^,\)\(^7\)\(^,\)\(^11\)
- Nervous system\(^5\)\(^,\)\(^8\)\(^,\)\(^12\)\(^,\)\(^13\)
- Eyes\(^1\)\(^,\)\(^4\)\(^,\)\(^14\)\(^-\)\(^16\)
- Respiratory System\(^1\)\(^,\)\(^5\)\(^,\)\(^8\)\(^,\)\(^13\)\(^,\)\(^17\)
- Hematopoietic cells\(^7\)\(^,\)\(^10\)\(^,\)\(^18\)\(^,\)\(^19\)

Clinical implications of immune-associated AEs

Because most tumor-associated antigens are also expressed by some amount of normal cells in the body, the potential exists for toxicity against these healthy tissues.¹

- AEs can be serious and potentially fatal
- Remain vigilant throughout and after treatment
  - Educate and encourage patients to monitor for and report symptoms of immune-associated AEs

Not all AEs can be managed and some patients may have to discontinue treatment. To give patients the best chance of therapeutic success, follow management guidelines for immune-associated AEs.
