Harnessing the Immune System to Prevent Cancer: Basic Immunologic Mechanisms

(the language of immunology)

Barbara K. Dunn
NCI/Division of Cancer Prevention
October 23, 2017
Harnessing the Immune System to Prevent Cancer: Basic Immunologic Mechanisms

Definition of IMMUNE SYSTEM

-the bodily system that protects the body from foreign substances, cells, and tissues

-by producing the immune response which includes the…

(1) thymus, spleen, lymph nodes, special deposits of lymphoid tissue (as in the gastrointestinal tract and bone marrow),
(2) macrophages, lymphocytes including the B cells and T cells, and
(3) antibodies and cytokines
Basic immunologic mechanisms that are relevant to cancer prevention *(terms to remember)*

- Components of the immune system: cells & antibodies, cytokines
- Host's defense system: **Tolerance** - distinguish **Self** from **Non-self**/immunosuppression
- **Adaptive** versus **Innate** immunity
- **Antigen** = any substance which provokes an adaptive immune response *(epitope)*
- **Humoral** versus **Cellular** immunity
- **CD4**/helper versus **CD8**/cytotoxic T cells
- **CD4**: Type 1 versus Type 2 response
Harnessing the Immune System to Prevent Cancer: Basic Immunologic Mechanisms and Therapeutic Approaches that are Relevant to Cancer Prevention

I. Overview of these immunologic mechanisms: Context

II. Structure/physical components of the immune system

III. How immunologic mechanisms are used in medical interventions to treat and prevent cancer

1. Antibodies as drugs

2. Vaccines: general principles
   
   I. Vaccines to prevent cancers caused by infectious agents
   
   II. Vaccines to prevent non-infection associated cancer (directed toward tumor associated antigens)

3. Immune checkpoint inhibitors
I. Overview of these immunologic mechanisms: Context
   - Carcinogenesis
   - Microenvironment: Immune system & carcinogenesis

II. Structure/physical components of the immune system

III. How immunologic mechanisms are used in medical interventions to treat and prevent cancer
   1. Antibodies as drugs
   2. Vaccines: general principles
      I. Vaccines to prevent cancers caused by infectious agents
      II. Vaccines to prevent non-infection associated cancer (directed toward tumor associated antigens)
   3. Immune checkpoint inhibitors
What is Carcinogenesis?
Premalignant Progression to Cancer

- Normal
- Initiated
- Precancer/Premalignancy
- Cancer

**Breast**
- Atypical Hyperplasia
- CIN I
- 5 - 20 yrs

**Cervix**
- 14 - 18 yrs
- 9 - 13 yrs
- DCIS
- 6 - 10 yrs

**Colon**
- Adenoma
- CIN III/CIS
- 10 - 20 yrs
- 5 - 15 yrs

**Prostate**
- PIN
- Latent Carc.
- 3 - 15 yrs

Genetic changes cumulative
What is Carcinogenesis?
Premalignant Progression to Cancer

Cancer is a "genetic disease"

Genetic changes cumulative
What is Carcinogenesis?
Premalignant Progression to Cancer

Cancer is a “genetic disease”
-not so simple!

Microenvironment (includes the immune system)
Epigenetic influences, etc.

See Mukherjee New Yorker article – “seed versus soil”
Start with an intact immune system

As carcinogenesis progresses, the immune system gets suppressed = **immunoediting**:

“Good” immune cells go away & “bad” cells emerge & dominate.

Lollini, Nature Reviews Cancer 6 March 2006
As carcinogenesis progresses, the immune system gets suppressed, a process known as immunoediting. "Good" immune cells go away, and "bad" cells emerge.

**Prevention intervention**

**CANCER GROWTH**
- Precancer
- Cancer
- Tumor Growth

**IMMUNE RESPONSE**
- Immunosurveillance
- Immunooediting
- Immunosuppression

**Elimination**
- Equilibrium
- Escape

**Prevention vaccines**
- Treatment vaccines

Adapted from Zitvogel, Nature Reviews Immunology 6 October 2006  Figure 1
Harnessing the Immune System to Prevent Cancer: Basic Immunologic Mechanisms and Therapeutic Approaches that are Relevant to Cancer Prevention

I. Overview of these immunologic mechanisms: Context

II. Structure/physical components of the immune system
   - Cells, antibodies (proteins), cytokines, chemokines, etc.
   - How is the immune system organized? Its hierarchy of mechanisms?

III. How immunologic mechanisms are used in medical interventions to treat and prevent cancer

1. Antibodies as drugs
2. Vaccines: general principles
   I. Vaccines to prevent cancers caused by infectious agents
   II. Vaccines to prevent non-infection associated cancer (directed toward tumor associated antigens)
3. Immune checkpoint inhibitors
Basic Immunological Mechanisms

II. Structure/physical components of the immune system

1. What are the physical components of the immune system?
   - Cells, antibodies (proteins), cytokines, chemokines, etc.

2. How is the immune system organized? Its hierarchy of mechanisms?
   a. Innate versus Adaptive Immunity – 2 compartments
   b. Focus on Adaptive Immunity – 2 cell types: B cells and T cells
      (1) B cells = humoral immunity (antibodies)
      (2) T cells = cellular immunity (cells do the work)
         (a) Cytolytic T cells/CTLs (CD8)
         (b) T helper cells (CD4)
      1- Type 1 response
      2- Type 2 response
Physical components of the immune system: cells, Abs, cytokines

Hematopoiesis
Physical components of the immune system:

Hematopoiesis

Antibodies
Physical components of the immune system:

Hematopoiesis

Humeral immunity

Cellular immunity
Physical components of the immune system:

Hematopoiesis
II. Structure/physical components of the immune system

1. What are the physical components of the immune system?
   - Cells, antibodies (proteins), cytokines, chemokines, etc.

2. How is the immune system organized? Its hierarchy of mechanisms?
   a. Innate versus Adaptive Immunity – 2 compartments
   b. Focus on Adaptive Immunity – 2 cell types:
      B cells and T cells
      (1) B cells = humoral immunity (antibodies)
      (2) T cells = cellular immunity (cells do the work)
         (a) Cytolytic T cells/CTLs (CD8)
         (b) T helper cells (CD4)
         1- Type 1 response
         2- Type 2 response
II. Structure/physical components of the immune system

1. What are the physical components of the immune system?
   - Cells, antibodies (proteins), cytokines, chemokines, etc.

2. How is the immune system organized? Its hierarchy of mechanisms?
   a. Innate versus Adaptive Immunity – 2 compartments
   b. Focus on Adaptive Immunity – 2 cell types:
      B cells and T cells
      (1) B cells = humoral immunity (antibodies)
      (2) T cells = cellular immunity (cells do the work)
         (a) Cytolytic T cells/CTLs (CD8)
         (b) T helper cells (CD4)
         1- Type 1 response
         2- Type 2 response
## Basic Immunological Mechanisms: Innate versus Adaptive Immunity

### 2 Compartments of Immunity

<table>
<thead>
<tr>
<th>Innate</th>
<th>versus</th>
<th>Adaptive</th>
</tr>
</thead>
<tbody>
<tr>
<td>No specific molecule/antigen needed to induce innate response</td>
<td></td>
<td>Specific molecule/antigen needed to induce adaptive response</td>
</tr>
<tr>
<td>Nonspecific immune response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quick response to generalized “inducer” (0-4 hours)</td>
<td></td>
<td>Response takes time/slow (&gt;96 hours)</td>
</tr>
<tr>
<td>Short-lived response</td>
<td></td>
<td>Lasts long time (lifelong)</td>
</tr>
<tr>
<td>Macrophages, dendritic cells, natural killer cells, neutrophils</td>
<td></td>
<td>T cells, B cells, dendritic cells</td>
</tr>
</tbody>
</table>
Innate immunity:

CELLS OF THE INNATE IMMUNE SYSTEM

- Neutrophil
- Dendritic
- Macrophage
- Natural Killer

Epithelial barriers
- Phagocytes
- Dendritic cells
- Plasma proteins
- NK cells

Antigen Presenting Cell (Adaptive immunity)

http://missinglink.ucsf.edu/lm/immunology_module/prologue/objectives/obj02.html
-Toll-like receptors (TLRs) = proteins of the **innate immune system** (on macrophages, dendritic cells)
-TLRs respond to **danger signals** (microbes/pathogen-associated molecular patterns (PAMPS))

-Innate Immune Response (Immune cells, Cytokines)
II. Structure/physical components of the immune system

1. What are the physical components of the immune system?
   - Cells, antibodies (proteins), cytokines, chemokines, etc.

2. How is the immune system organized? Its hierarchy of mechanisms?
   a. Innate versus Adaptive Immunity – 2 compartments
   b. Focus on Adaptive Immunity – 2 cell types: B cells and T cells
      (1) B cells = humoral immunity (antibodies)
      (2) T cells = cellular immunity (cells do the work)
         (a) Cytolytic T cells/CTLs (CD8)
         (b) T helper cells (CD4)
         1- Type 1 response
         2- Type 2 response
Adaptive Immunity

- **Humoral** versus **Cellular** immunity

B cells

- antibodies

T cells

- T-cell receptors

The *cell* does the work
Physical components of the immune system:

Hematopoiesis

Antibodies

Humoral immunity

Cellular immunity
B cells = humoral immunity (antibodies do the work)

This part targets specific antigens

Humoral immunity in cancer: important in fighting viruses that cause cancer, e.g. HPV vaccines
T cells = cellular immunity
(cells do the work)
T cells = cellular immunity
(cells do the work)

CD = cluster of differentiation
T cells = cellular immunity (cells do the work)

In cancer:
We want TH1 cells - to kill cancer cells
We do not want Treg & TH2 cells
T cells = cellular immunity (cells do the work)

In cancer:
- We want TH1 cells - to kill cancer cells
- We do not want Treg & TH2 cells

In normal cells:
- We want Treg cells - to protect these normal cells
T cells = cellular immunity (cells do the work)

In cancer:
We want TH1 cells - to kill cancer cells
We do not want Treg & TH2 cells

In normal cells:
We want Treg cells - to protect these normal cells

Distinguish **Self from Non-self:**
save the self!

Immune Tolerance
• Host’s defense system: distinguish Self from Non-self

WHAT DOES THE IMMUNE SYSTEM SEE IN CANCER?

Tolerance signals

Self Antigen

Non-self/Foreign, Unwanted Antigen

Attack signals
T regulatory cells (Tregs):

Suppress the immune response

Prevents autoimmune responses 😊

But also prevents anti-cancer responses 😞
Adaptive Immunity: Cellular Immunity (T cells)

Antigen Presentation & T Cell Activation

Specific part of T cell activation

Infection
(virus)
Cancer

Bad Antigen

Processed Bad Antigen (epitope)

APC/
antigen presenting cell

MHC/HLA

Signal 1

T cell

IFN-γ
IL-17

MHC = Major Histocompatibility Antigen
TCR = T cell receptor
HLA = Human Leukocyte Antigen
Adaptive Immunity: Cellular Immunity (T cells)

Antigen Presentation & T Cell Activation

**Generalized part of T cell activation**

- Infection (virus)
- Cancer

Bad Antigen

- Processed Bad Antigen (epitope)

APC/antigen presenting cell

- MHC = Major Histocompatibility Antigen
- TCR = T cell receptor
- HLA = Human Leukocyte Antigen

**Signal 1**

- MHC/HLA
- TCR

**Signal 2**

- CD28
- B7
- (CD80,86)

Co-stimulatory molecule

- IFN-γ
- IL-17

T cell activation
Adaptive Immunity: Cellular Immunity

Antigen Presentation & T Cell Activation

Antagonizing T cell activation

Infection (virus)
Cancer
Bad Antigen

APC/
antigen presenting cell

Processed Bad Antigen (epitope)

MHC = Major Histocompatibility Antigen
TCR = T cell receptor
HLA = Human Leukocyte Antigen

MHC = Bad Antigen

B7 or PD-L1

B7 or PD-L1

TCR

CD28

CD80,86

T cell

T cell inactivation = immune suppression
Adaptive Immunity: Cellular Immunity

Antigen Presentation & T Cell Activation

Antagonizing T cell activation

Infection (virus)
Cancer

Bad Antigen

Processed Bad Antigen (epitope)

APC/antigen presenting cell

B7 or PD-L1

MHC/HLA

CD28

TCR

CTLA-4 or PD-1

Bad Antigen

Process Bad Antigen (epitope)

B7 or PD-L1

MHC/HLA

CD28

TCR

CTLA-4 or PD-1

Adaptive Immunity: Cellular Immunity

Antigen Presentation & T Cell Activation

Antagonizing T cell activation

Infection (virus)
Cancer

Bad Antigen

Processed Bad Antigen (epitope)

APC/antigen presenting cell

B7 or PD-L1

MHC/HLA

CD28

TCR

CTLA-4 or PD-1

T cell

T cell inactivation
= immune suppression
Suppression of T-Cell Activation: Antigen Presenting Cell’s (APC’s) (Dendritic Cell) B7 binds T cell’s CTLA-4 receptor

T-cell activation in the lymph node requires both immunologic signal 1 and immunologic signal 2

Tumor cell devised a way to evade the immune system and escape destruction

Suppression of T-Cell Activation: Tumor cell’s PD-L1 binds T cell’s PD-1 receptor

Acts like APC

By expressing PD-L1---which suppresses T cell activation by binding PD-1 on the T cell
Adaptive Immunity: Cellular Immunity

- **CD4**/helper **versus** **CD8**/cytotoxic T cells

- **MHC** = Major Histocompatibility Antigen
- **TCR** = T cell receptor
- **HLA** = Human Leukocyte Antigen

**Infection**

- APC (antigen presenting cell)
  - Processed Bad Antigen
  - CD28
  - Co-stimulatory molecule

**Cancer**

- **CD4** T cell
  - MHC class II - restricted
- **CD8** T cell
  - MHC class I - restricted
- CD8 / cytotoxic T cell / CTLS (cytotoxic T lymphocytes)
Adaptive Immunity: Cellular Immunity
Antigen Presentation & T Cell Activation:
What are the APCs?

- Dendritic cells
- Macrophages
- Certain B-cells
- Certain activated epithelial cells
- Fibroblasts (skin)
- Thymic epithelial cells
- Thyroid epithelial cells
- Glial cells (brain)
- Beta cells (pancreas)
- Vascular endothelial cells

- Professional APCs
- Non-Professional APCs

- CD4+/helper vs CD8+/cytotoxic T cells
Adaptive Immunity: Cellular Immunity

Antigen Presentation & T Cell Activation:

What are the APCs?

- Fibroblasts (skin)
- Thymic epithelial cells
- Thyroid epithelial cells
- Glial cells (brain)
- Beta cells (pancreas)
- Vascular endothelial cells
- Dendritic cells
- Macrophages
- Certain B-cells
- Certain activated epithelial cells

**Professional APCs**

**Non-Professional APCs**

- CD4+/helper vs CD8+/cytotoxic T cells

![Diagram](image)
■ Adaptive Immunity: Cellular Immunity
■ **CD4**/helper **versus** **CD8**/cytotoxic T cells

- **CD4**/Helper T cell
  - MHC class II – restricted
  - Immature CD4⁺ T cell
  - TCR
  - Mature helper T cell (Th1 or Th2)

- **CD8**/cytotoxic T cell
  - MHC class I - restricted
  - Immature CD8⁺ T cell
  - TCR
  - Mature cytotoxic T cell (Tc)
  - Antigen Presenting Cell
  - Antigen
- **Adaptive Immunity: Cellular Immunity**
  - **CD4/helper** versus **CD8/cytotoxic T cells**
  - **Th1** versus **Th2** CD4 T helper cells

**CD4 / Helper T cell**
- MHC class II – restricted

**Mature helper T cell** (Th1 or Th2)

**CD8 / cytotoxic T cell / CTLS (cytotoxic T lymphocytes)**
- MHC class I - restricted

**Mature cytotoxic T Cell** (Tc)
**T\(_H\)**CD4 cell subtypes

T helper/T\(_H\) cells are functionally of 2 types:

- **TH1/Type 1 versus TH2/Type2**

**Immune Response**

We want Type 1/TH1 response to fight cancer
Adaptive Immunity: Cellular Immunity

- **CD4**/helper versus **CD8**/cytotoxic T cells

- **CD4** T cell
  - **CD8** T cell
  - **CTLS** (cytotoxic T lymphocytes)
  - **MHC** class I - restricted

- **CD4**/Helper T cell
  - **MHC** class II - restricted

- **APC**/antigen-presenting cell

**MHC** = Major Histocompatibility Antigen
**TCR** = T cell receptor
**HLA** = Human Leukocyte Antigen

**Bad Antigens**
- Infection
- Cancer
Harnessing the Immune System to Prevent Cancer: Basic Immunologic Mechanisms and Therapeutic Approaches that are Relevant to Cancer Prevention

I. Overview of these immunologic mechanisms: Context

II. Structure/physical components of the immune system

III. How immunologic mechanisms are used in medical interventions to treat and prevent cancer

1. Antibodies as drugs

2. Vaccines: general principles
   I. Vaccines to prevent cancers caused by infectious agents
   II. Vaccines to prevent non-infection associated cancer (directed toward tumor associated antigens)

3. Immune checkpoint inhibitors
Harnessing the Immune System to Prevent Cancer: Basic Immunologic Mechanisms and Therapeutic Approaches that are Relevant to Cancer Prevention

I. Overview of these immunologic mechanisms

II. Structure/physical components of the immune system

III. How immunologic mechanisms are used in medical interventions to treat and prevent cancer

1. Antibodies as drugs --- "passive immunity"

2. Vaccines: general principles – "active immunity"
   I. Vaccines to prevent cancers caused by infectious agents
   II. Vaccines to prevent non-infection associated cancer (directed toward tumor associated antigens)

3. Immune checkpoint inhibitors
Harnessing the Immune System to Prevent Cancer: Basic Immunologic Mechanisms and Therapeutic Approaches that are Relevant to Cancer Prevention

I. Overview of these immunologic mechanisms

II. Structure/physical components of the immune system

III. How immunologic mechanisms are used in medical interventions to treat and prevent cancer

1. Antibodies as drugs --- “passive immunity”

Examples:
- Herceptin (trastuzumab) – binds Her2 receptor on breast cancer cells
- Rituxan (rituximab) – binds CD20 on B cells in non-Hodgkin’s lymphoma, chronic lymphocytic leukemia

2. Vaccines: general principles – “active immunity”

   i. Vaccines to prevent cancers caused by infectious agents
   ii. Vaccines to prevent non-infection associated cancer (directed toward tumor associated antigens)

3. Immune checkpoint inhibitors

--------used as drugs “off-the-shelf”
Harnessing the Immune System to Prevent Cancer: Basic Immunologic Mechanisms and Therapeutic Approaches that are Relevant to Cancer Prevention

Elicits a specific response from the body’s own immune system.
Vaccines - “active immunity”
Adaptive Immune System

**KEY COMPONENTS OF VACCINES**

**the specific component:**

the Antigen

- Peptide-long vs short
- Pentamer of a protein

**the nonspecific component:**

the Adjuvant

- Adjuvants = agents added to vaccine formulations that enhance the immunogenicity of antigens *in vivo*

**Epitope** (antigenic determinant) = the part of an antigen that is recognized by the immune system (antibodies, B cells, T cells)

- Viral-like Protein/VLP
- Pentamer of a protein
- Viral vector

- Cell-based vaccines

Adjuvants = agents added to vaccine formulations that enhance the immunogenicity of antigens *in vivo*
Harnessing the Immune System to Prevent Cancer: Basic Immunologic Mechanisms and Therapeutic Approaches that are Relevant to Cancer Prevention

I. Overview of these immunologic mechanisms

II. Structure/physical components of the immune system

III. How immunologic mechanisms are used in medical interventions to treat and prevent cancer

1. Antibodies as drugs

2. Vaccines: general principles

   I. Vaccines to prevent cancers caused by infectious agents

   II. Vaccines to prevent non-infection associated cancer (directed toward tumor associated antigens)

3. Immune checkpoint inhibitors

   ■ Host’s defense system: **Tolerance** - distinguish **Self** from **Non-self**/ immunosuppression
Remember T regulatory cells (Tregs)?

Suppress the immune response

Prevents autoimmune responses

But also prevents anti-cancer responses

Components of the immune system: cells & cytokines

- Distinguish Self from Non-self: save the self!
Adaptive Immunity: Cellular Immunity
Antigen Presentation & T Cell
Activation/Inactivation

Infection
Cancer
Bad Antigen

APC/antigen presenting cell

MHC = Major Histocompatibility Antigen
TCR = T cell receptor
HLA = Human Leukocyte Antigen

Just like Treg cells, “immune checkpoints” suppress the immune system

Remember CTLA-4?
Remember PD-1 and PD-L1?

T cell inactivation
→ immune suppression
Suppression of T-Cell Activation: Antigen Presenting Cell’s (APC’s) (Dendritic Cell) B7 binds T cell’s CTLA-4 receptor

Suppression of T-Cell Activation: Tumor cell’s PD-L1 binds T cell’s PD-1 receptor

We want to block these: CTLA-4 and PD-L1/PD-1
With immune checkpoint inhibitors
As carcinogenesis progresses, the immune system gets suppressed = immunoediting.

“Good” immune cells go away & “bad” cells emerge.

PD-1/PD-L1, CTLA-4 kick in during immunoediting and immunosuppressive phases (these are “immune checkpoints”).
## IMMUNE CHECKPOINT INHIBITORS

Drugs that **suppress the suppressor molecules** ---

use these in cancer

<table>
<thead>
<tr>
<th>Immune Checkpoint Receptor, Cellular location</th>
<th>Immune Checkpoint Receptor Engages this Molecule</th>
<th>Drug that Inhibits this Immune Checkpoint</th>
<th>FDA Approval, Clinical development</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CTLA-4</strong> - on activated T cells</td>
<td>CD80/ B7.1 CD86/B7.2 on APC</td>
<td><strong>Anti-CTLA-4:</strong> Ipilimumab (Yervoy)</td>
<td>Yes: advanced melanoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tremelimumab</td>
<td>In phase II devt: mesothelioma,others</td>
</tr>
<tr>
<td><strong>PD-1</strong> - on activated T cells</td>
<td><strong>PD-L1</strong> - on tumor cells, T cells, epithelial cells, endothelial cells PD-L2</td>
<td><strong>Anti-PD-1:</strong> Pembrolizumab (Keytruda)</td>
<td>Yes, FDA approval</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nivolumab (Opdivo)</td>
<td>Yes, FDA approval: melanoma, NSCLC</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Anti-PD-L1:</strong> Atezolizumab (Tecentriq)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Avelumab (Bavencio)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Durvalumab (Imfinzi)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Anti-PD-L1, L2:</strong> AMP-224</td>
<td></td>
</tr>
</tbody>
</table>

---

Disis 2014 SemOnc 41 Supp5; Chen, Mellman 2013 Immunity; Sharma, Allison 2015 Science
Immune checkpoint inhibitors

Ipilimumab = Anti-CTLA4

Inhibit the immunosuppressive effect of these molecules in cancer --> T cells are re-activated

Pembrolizumab = Anti-PD-1

Durvalumab = Anti-PD-L1
the problem with immune checkpoint inhibitors...autoimmune responses

**Toxicity of these agents:**

Central acting anti-CTLA-4 toxicity

Distal acting anti-PD-1, PD-L1

i.e.,

Lower incidence of immune AEs with PD-1/PD-L1 inhibitors vs CTLA-4 inhibitors (ipilimumab)

Most frequent toxicities:
mild fatigue, rash, pruritic, diarrhea, colitis

These drugs also inhibit the good part of immune suppression, i.e. the part that protects normal cells -> autoimmunity

Too toxic for cancer prevention!
IMMUNE CHECKPOINT INHIBITORS

The latest hot item!!!!!!

But...

Toxicity precludes use (at present) in prevention......
Sum up the good and the bad of

**IMMUNOSUPPRESSION**

Suppressive/inhibitory / tolerogenic components of the immune system:

- T regulatory cells (Tregs)
- Myeloid derived suppressor cells
- CTLA-4 (cytotoxic T-lymphocyte associated protein 4/CD152) - on the T cell
- PD-1 (programmed cell death protein 1) - on the T cell, cell surface receptor in Ig superfamily
- PD-L1, L2 (programmed death ligand/B7.1,2 receptor) – on macrophages, DCs, tumors
- Certain cytokines: IL-10, IL-4

---

*Tolerance → prevents autoimmune responses* but
*Cancer → inhibits immune response to fight cancer*

Chen, Mellman Immunity 2013
Harnessing the Immune System to Prevent Cancer: Basic Immunologic Mechanisms and Therapeutic Approaches that are Relevant to Cancer prevention

I. Overview of these immunologic mechanisms

II. Structure/physical components of the immune system

III. How immunologic mechanisms are used in medical interventions to treat and prevent cancer

1. Antibodies as drugs --- “passive immunity”

2. Vaccines: general principles – “active immunity”
   I. Vaccines to prevent cancers caused by infectious agents
   II. Vaccines to prevent non-infection associated cancer (directed toward tumor associated antigens)

3. Immune checkpoint inhibitors
Harnessing the Immune System to Prevent Cancer: Basic Immunologic Mechanisms and Therapeutic Approaches that are Relevant to Cancer prevention

I. Overview of these immunologic mechanisms

II. Structure/physical components of the immune system

III. How immunologic mechanisms are used in medical interventions to treat and prevent cancer

1. Antibodies as drugs --- “passive immunity”

2. Vaccines: general principles – “active immunity”

   I. Vaccines to prevent cancers caused by infectious agents
   II. Vaccines to prevent non-infection associated cancer (directed toward tumor associated antigens)

3. Immune checkpoint inhibitors

   Why are vaccines promising in cancer prevention (vs treatment)?
   Why are vaccines (vs drugs) promising in cancer prevention?
Why are vaccines more promising in cancer prevention (vs treatment)?

Evaluate vaccines in the states of:

“minimal residual disease”
and Cancer Prevention

WHY?

Vaccination early in disease process:

→ **Intact** immune system
  - *(active immunity)*
→ Permissive microenvironment
→ Pre-cancers are **smaller lesions**
→ **Immune mechanisms** in early lesions involve
  - \(CD4^+ T_H\), \(IFN_\gamma\), Antibodies & Cytotoxic T-Lymphocytes (CTL) that fight cancer
Why are vaccines (vs drugs) promising in cancer prevention?

Vaccines may be better than other interventions/agents for Cancer Prevention (clinical advantages)

- Better **compliance**
- **Long-term** anti-cancer **protection** (immune memory)
- **Less expensive**
- **Spare** debilitating **surgeries**
- **Adverse events** expected to be less frequent
  - Local inflammation
  - Transient flu-like symptoms
HARNESSING THE IMMUNE SYSTEM TO PREVENT CANCER

DCP CANCER Immunoprevention
Acknowledgements:

Asad Umar
Margaret Wojtowicz
Vik Sahasrasbuddhe

dunnb@mail.nih.gov