Innate Immunity and Inflammation

Willem Overwijk, Ph.D.
MD Anderson Cancer Center
Center for Cancer Immunology Research
Houston, TX
Innate Immunity and Inflammation

- Definitions
- Cells and Molecules
- Innate Immunity and Inflammation in Cancer
- Bad Inflammation
- Good Inflammation
- Therapeutic Implications
Innate Immunity and Inflammation

- Definitions
- Cells and Molecules
- Innate Immunity and Inflammation in Cancer
- Bad Inflammation
- Good Inflammation
- Therapeutic Implications
• **Innate Immunity:** Immunity that is naturally present and is not due to prior sensitization to an antigen; generally nonspecific. It is in contrast to acquired/adaptive immunity.

Adapted from *Merriam-Webster Medical Dictionary*
• **Innate Immunity:** Immunity that is naturally present and is not due to prior sensitization to an antigen; generally nonspecific. It is in contrast to acquired/adaptive immunity.

• **Inflammation:** a local response to tissue injury
  - Rubor (redness)
  - Calor (heat)
  - Dolor (pain)
  - Tumor (swelling)

Adapted from *Merriam-Webster Medical Dictionary*
“Innate Immunity” and “Inflammation” are vague terms

• Specific cell types and molecules orchestrate specific types of inflammation
“Innate Immunity” and “Inflammation” are vague terms

- Specific cell types and molecules orchestrate specific types of inflammation
- Innate Immunity $A \neq$ Innate Immunity $B$
- Inflammation $A \neq$ Inflammation $B$
CD4⁺ T cell

Zhou et al., *Immunity*, 2009
CD4+ T cell: Th1 or Th2?

Zhou et al., *Immunity*, 2009
CD4+ T cell: Th1 or Th2?

Zhou et al., *Immunity*, 2009
CD4\(^+\) T cell: Th1 or Th2 or Th17 or Th9 or Treg or Tfh or ?

Zhou et al., *Immunity*, 2009
Today, the term “CD4+ T cell” can mean many things

Zhou et al., *Immunity, 2009*
“Innate Immunity” and “Inflammation” can mean many things

• Specific cell types and molecules orchestrate specific types of inflammation

• Innate Immunity A ≠ Innate Immunity B

• Inflammation A ≠ Inflammation B

• Some immune responses promote cancer, others suppress it
Innate Immunity and Inflammation

Functions:

• Rapid response to tissue damage
• Limit spread of infection
• Initiate adaptive immune response (T, B)
• Initiate tissue repair
Innate Immunity and Inflammation: A Paper Cut

Janeway, Immunobiology, 7th Ed.
Innate Immunity and Inflammation: A Paper Cut

**Adherence to epithelium**
- Normal flora
- Local chemical factors
- Phagocytes (especially in lung)

**Local infection, penetration of epithelium**
- Wound healing induced
- Antimicrobial proteins and peptides, phagocytes, and complement destroy invading microorganisms
- Activation of γδ T cells?

**Protection against infection**

Innate Immunity and Inflammation: A Paper Cut

**Adherence to epithelium**
- Normal flora
- Local chemical factors
- Phagocytes (especially in lung)

**Local infection, penetration of epithelium**
- Wound healing induced
- Antimicrobial proteins and peptides, phagocytes, and complement destroy invading microorganisms
- Activation of γδ T cells?

**Local infection of tissues**
- Complement, cytokines, chemokines, Phagocytes, NK cells
- Activation of macrophages
- Dendritic cells migrate to lymph nodes to initiate adaptive immunity
- Blood clotting helps limit spread of infection

Innate Immunity and Inflammation: A Paper Cut

**Adherence to epithelium**
- Tissue macrophage
- Tissue dendritic cell

**Local infection, penetration of epithelium**
- Blood vessel

**Local infection of tissues**

**Adaptive immunity**

**Protection against infection**

- Normal flora
- Local chemical factors
- Phagocytes (especially in lung)

- Wound healing induced
- Antimicrobial proteins and peptides, phagocytes, and complement destroy
- Invading microorganisms
- Activation of γδ T cells?

- Complement, cytokines, chemokines, Phagocytes, NK cells
- Activation of macrophages
- Dendritic cells migrate to lymph nodes to initiate adaptive immunity
- Blood clotting helps limit spread of infection

- Infection cleared by specific antibody, T-cell dependent macrophage activation and cytotoxic T cells

Innate Immunity and Inflammation

- Definitions
- Cells and Molecules
- Innate Immunity and Inflammation in Cancer
- Bad Inflammation
- Good Inflammation
- Therapeutic Implications
Innate Immune Molecules: Cyclooxygenase-2 (COX-2)

Recognize
• inflammation

Cause
• inflammation
Innate Immune Molecules: Complement System

Recognize
• pathogens
• antibodies
• lectins

Cause
• pathogen clearance
• chemotaxis
• inflammation

Janeway, Immunobiology, 7th Ed.
Innate Immune Molecules: type I IFN(-α, β)

• Induced by infection/danger
• Antiviral/Antiproliferative
• Increase innate and adaptive immunity

• Cause inflammation
Innate Immune Cells

Bone marrow
- pluripotent hematopoietic stem cell
- common lymphoid progenitor
- common myeloid progenitor
- granulocyte/macrophage progenitor
- megakaryocyte/erythrocyte progenitor
- megalakocyte
- erythroblast

Blood
- Granulocytes (or polymorphonuclear leukocytes)
  - neutrophil
  - eosinophil
  - basophil
  - unknown precursor of mast cell
- monocyte
- platelets
- erythrocyte

Lymph nodes
- immature dendritic cell
- mature dendritic cell

Tissues
- immature dendritic cell
- mast cell
- macrophage

Effector cells
- plasma cell
- activated T cell
- activated NK cell

Janeway, Immunobiology, 7th Ed.
Innate Immune Cells

Janeway, Immunobiology, 7th Ed.
Innate Immune Cells: granulocytes

<table>
<thead>
<tr>
<th>Cell</th>
<th>Activated function</th>
<th>Cell</th>
<th>Activated function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil</td>
<td>Phagocytosis and activation of bactericidal mechanisms</td>
<td>Mast cell</td>
<td>Release of granules containing histamine and active agents</td>
</tr>
<tr>
<td>Eosinophil</td>
<td>Killing of antibody-coated parasites</td>
<td>Basophil</td>
<td>(Unknown) Antigen Presentation</td>
</tr>
</tbody>
</table>

Recognize
• pathogens
• antibodies

Cause
• pathogen clearance
• inflammation

Janeway, Immunobiology, 7th Ed.
### Innate Immune Cells: phagocytes

<table>
<thead>
<tr>
<th>Cell</th>
<th>Activated function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monocyte</td>
<td>Blood precursor of tissue Macrophages and Dendritic Cells</td>
</tr>
<tr>
<td>Macrophage</td>
<td>Phagocytosis and activation of bactericidal mechanisms</td>
</tr>
<tr>
<td>Dendritic cell</td>
<td>Antigen uptake in peripheral sites</td>
</tr>
</tbody>
</table>

**Recognize**
- pathogens
- antibodies

**Cause**
- pathogen clearance
- adaptive immunity
- inflammation

Janeway, Immunobiology, 7th Ed.
Innate Immune Cells: NK, NKT and γδ T cells

Recognize
• pathogens
• stressed cells
• “altered self”

Cause
• pathogen clearance
• stressed/abnormal cell clearance
• inflammation
Danger signals start inflammation

**PATHOGENS**

- Flagellin
- LPS
- Peptidoglycans
- Glycolipids
- Zymosan
- Protein
- ssRNA
- Envelope
- T. Gondi
- Bacteria

**DAMAGE**

- Necrosis
- HMGB1
- IL-18
- IL-1α
- Heparan sulphate
- Uric Acid
- Hyaluronan
- Extracellular matrix
- Injury
- Tumour cells
- ATP
- DNA
- Normal tissue
- Injury

**PRRs**

- (TLRs, NLRs, RLRs)

**Adaptive immune response**

**Innate immune response**

Rubartelli & Lotze, *Trends in Immunology* 2007
Danger signals start inflammation

PATHOGENS

- Flagellin
- LPS
- Peptidoglycans
- Glycolipids
- Zymosan
- Profilin
- T. Gondii

Virus
- ssRNA
- Envelope

DAMAGE

- Necrosis
- Tumour cells
- HMGB1
- IL-18
- IL-1α
- Heparan sulphate
- Uric Acid
- Hyaluronan

- Extracellular matrix
- Injury
- Normal tissue
- Injury

PRRs
- (TLRs, NLRs, RLRs)

Adaptive immune response

Innate immune response

Rubartelli & Lotze, Trends in Immunology 2007
Receptors sense Danger: Pathogens

Kawai & Akira, Nat. Immunol. 2010
Receptors sense Danger: Damage

Kawai & Akira, Nat. Immunol. 2010
Innate Immunity and Inflammation

- Definitions
- Cells and Molecules
- Innate Immunity and Inflammation in Cancer
- Bad Inflammation
- Good Inflammation
- Therapeutic Implications
Innate Immunity and Inflammation in Cancer

- Outcomes vary:
  - Promote cancer (Bad inflammation)
  - Suppress cancer (Good inflammation)
Innate Immunity and Inflammation

- Definitions
- Cells and Molecules
- Innate Immunity and Inflammation in Cancer
- Bad Inflammation
- Good Inflammation
- Therapeutic Implications
Bad Inflammation Causes Cancer

**DANGER**

*cellular damage caused by*
- pathogens
- physical damage
- chemicals
- UV
- etc
DANGER → IMMUNE RESPONSE → INFLAMMATION
DANGER

IMMUNE RESPONSE

INFLAMMATION
IMMUNE RESPONSE

INFLAMMATION

COLLATERAL DAMAGE

DANGER
IMMUNE RESPONSE

INFLAMMATION

COLLATERAL DAMAGE
Immune Response

Collateral Damage

Danger

Inflammation
IMMUNE RESPONSE

CHRONIC DANGER

COLLATERAL DAMAGE

INFLAMMATION
CHRONIC IMMUNE RESPONSE INFLAMMATION

CHRONIC COLLATERAL DAMAGE

CHRONIC DANGER
IMMUNE RESPONSE

COLLATERAL DAMAGE

CHRONIC

DANGER

CANCER

CHRONIC IMMUNE RESPONSE INFLAMMATION
cancer: a “never-healing wound”
Inflammation can Promote Cancer: collaboration with K-ras mutation

no smoking

4 cigarettes per day

K-ras mutation & normal myeloid cells

Takahashi et al., Cancer Cell 2010
Inflammation can Promote Cancer: collaboration with K-ras mutation

no smoking

4 cigarettes per day

K-ras mutation & normal myeloid cells

K-ras mutation + IKK^-/- myeloid cells

Takahashi et al., Cancer Cell 2010
Inflammation can Promote Cancer: collaboration with K-ras mutation

Takahashi et al., Cancer Cell 2010

no smoking

4 cigarettes per day

K-ras mutation & normal myeloid cells

K-ras mutation & IKK−/− myeloid cells

↓ NF-κB
↓ pSTAT3
↓ IL-6
↓ neutrophils
↓ angiogenesis
Inflammation can Promote Cancer: collaboration with HPV E6/E7 oncogene

De Visser et al., Cancer Cell 2005
Andreu et al., Cancer Cell 2010
Inflammation can Cause Mutation

Able to repair DNA

days post acute gut inflammation

Inflammation can Cause Mutation

Able to repair DNA

Inflammation can Cause Mutation

Inflammation can Cause Mutation


deoxyguanosine

8-hydroxydeoxyguanosine

Deoxyribose

Tumor initiation

ROS, RNI

Cytokines

Mutations

Epigenetic mechanisms
Tumors can induce bad inflammation

Apoptotic Death of CD8$^+$ T Lymphocytes After Immunization: Induction of a Suppressive Population of Mac-1$^+$/Gr-1$^+$ Cells$^1$


Tumors can induce bad inflammation

Bronte et al., J. Immunol. 1999
Tumors can induce bad inflammation

Normal immune system + T cell treatment

Tumors induce bad inflammation ➔ Blocks treatment

Marigo et al., *Immunity* 2010
Tumors can induce bad inflammation

Normal immune system + T cell treatment

Cebpb-deficient immune system + T cell treatment

Tumors induce bad inflammation → Blocks treatment

Tumors cannot induce bad inflammation → Treatment works

Marigo et al., *Immunity* 2010
Tumors can induce bad inflammation

Ugel et al., *Curr. Opin. Pharmacol.* 2010
Tumors can induce bad inflammation
Oncogenic STAT3

Yu et al., Nat. Rev. Cancer 2009
Tumors can induce bad inflammation
Oncogenic STAT3

Yu et al., Nat. Rev. Cancer 2009
Mutations can Drive Bad Inflammation

Mutated BRAF → tumor cells produce bad, immunosuppressive cytokines

Sumimoto et al., *J. Exp. Med.*. 2006
Mutations can Drive Bad Inflammation

Mutated BRAF \rightarrow \text{tumor cells produce bad, immunosuppressive cytokines}

\[ \text{block production of good cytokines in DCs} \]

Sumimoto et al., *J. Exp. Med.*, 2006
Conclusion: Inflammation and Cancer

• Inflammation can Cause Cancer
• Inflammation can Cause Mutation
• Mutation can Cause Inflammation
• Mutation can Cause Cancer
• Cancer can Cause Inflammation
Inflammation and Cancer: A Vicious Cycle

- MUTATION
- CANCER
- INFLAMMATION
Classic Hallmarks of Cancer

Mantovani et al., *Nature* 2009
Hanahan & Weinberg, *Cell* 2000
Inflammation is (now) a Classic Hallmark of Cancer

Mantovani et al., Nature 2009
Hanahan & Weinberg, Cell 2000
Inflammation is (now) a Classic Hallmark of Cancer

Mantovani et al., Nature 2009
Hanahan & Weinberg, Cell 2000
Innate Immunity and Inflammation

- Definitions
- Cells and Molecules
- Innate Immunity and Inflammation in Cancer
- Bad Inflammation
- Good Inflammation
- Therapeutic Implications
**Good vs. Bad Inflammation in Cancer**

Immunity, Inflammation, and Cancer

Sergei I. Grivennikov,¹ Florian R. Greten,² and Michael Karin¹,*

Cell 140, 883–899, March 19, 2010

---

Cancer and Inflammation: Promise for Biologic Therapy

Sandra Demaria,* Eli Pikarsky,† Michael Karin,‡ Lisa M. Coussens,§ Yen-Ching Chen,∥
Emad M. El-Omar,¶ Giorgio Trinchieri,# Steven M. Dubinett,** Jenny T. Mao, †† Eva Szabo,‡‡
Arthur Krieg, §§ George J. Weiner,∥∥ Bernard A. Fox,¶¶ George Coukos,## Ena Wang,***
Robert T. Abraham,† † † Michele Carbone,‡‡‡ and Michael T. Lotze §§§

J Immunother • Volume 33, Number 4, May 2010
IFN-γ Suppresses Human Tumor Development

Multiple cutaneous squamous cell carcinomas in a patient with interferon γ receptor 2 (IFNγR2) deficiency

Toyoda et al., J. Med. Genetics 2010
At 17 years of age, the patient developed multifocal Squamous Cell Carcinomas on the face and both hands. Despite local tumour excision, multiple lesions occurred and the patient died at 20 years of age of disseminated SCC. Inherited disorders of IFN-γ–mediated immunity may predispose patients to SCC.

Toyoda et al., J. Med. Genetics 2010
Human Immune System can Suppress Existing Tumors for Years

1982: patient with primary, resected melanoma
1997: declared disease-free and “cured”
1998: died of brain hemorrhage, donated kidneys
2000: - kidney recipient 1 died of metastatic donor melanoma
       - kidney recipient 2 taken off immunosuppression; start IFN-α
       - kidney recipient 2 rejects kidney and melanoma

MacKie et al., *NEJM* 2003
Human Immune System can Suppress Existing Tumors for Years

1982: patient with primary, resected melanoma
1997: declared disease-free and “cured”
1998: died of brain hemorrhage, donated kidneys
2000: - kidney recipient 1 died of metastatic donor melanoma
   - kidney recipient 2 taken off immunosuppression; start IFN-α
   - kidney recipient 2 rejects kidney and melanoma

MacKie et al., NEJM 2003
Post-transplant Immunosuppression Increases Cancer Incidence

Type I IFNs Suppress Growth of Transplanted Tumors

Type I IFNs Suppress Development of Carcinogen-Induced Tumors

IFN-α treatment enhances anti-cancer vaccination

IFN-α treatment enhances anti-cancer vaccination

CpG Causes Tumor Inflammation and Intratumoral T cell Accumulation

Intratumoral PBS  Intratumoral CpG  Intravenous CpG

Lou et al., unpublished results
CpG Causes Tumor Inflammation and Intratumoral T cell Accumulation

Lou et al., unpublished results

Tumor size (mm²)

Days after Vaccination

i.t PBS
i.t CpG
vaccine + i.t PBS
vaccine + i.t CpG

P<0.01

0 5 10 15

0 150 300 450
Adapted from Grivennikov et al. Cell 2010

- Tumor-induced Inflammation
- Chronic Inflammation Autoimmunity Infection
- Dietary & Environment-induced Inflammation
- Therapy-induced Inflammation

Cancer
Bottom Line: Inflammation can be Good or Bad: Pro or Anti-Tumor

| Table 1. Roles of Different Subtypes of Immune and Inflammatory Cells in Antitumor Immunity and Tumor-Promoting Inflammation |
|---|---|---|
| **Cell Types** | **Antitumor** | **Tumor-Promoting** |
| Macrophages, dendritic cells, myeloid-derived suppressor cells | Antigen presentation; production of cytokines (IL-12 and type I IFN) | Immunosuppression; production of cytokines, chemokines, proteases, growth factors, and angiogenic factors |
| Mast cells | | Production of cytokines |
| B cells | Production of tumor-specific antibodies? | Production of cytokines and antibodies; activation of mast cells; immunosuppression |
| CD8^+ T cells | Direct lysis of cancer cells; production of cytotoxic cytokines | Production of cytokines? |
| CD4^+ Th2 cells | | Education of macrophages; production of cytokines; B cell activation |
| CD4^+ Th1 cells | Help to cytotoxic T lymphocytes (CTLs) in tumor rejection; production of cytokines (IFNγ) | Production of cytokines |
| CD4^+ Th17 cells | Activation of CTLs | Production of cytokines |
| CD4^+ Treg cells | Suppression of inflammation (cytokines and other suppressive mechanisms) | Immunosuppression; production of cytokines |
| Natural killer cells | Direct cytotoxicity toward cancer cells; production of cytotoxic cytokines | |
| Natural killer T cells | Direct cytotoxicity toward cancer cells; production of cytotoxic cytokines | |
| Neutrophils | Direct cytotoxicity; regulation of CTL responses | Production of cytokines, proteases, and ROS |

Grivennikov et al. Cell 2010
In the Clinic: Cancer Therapies that Block Bad Inflammation
In the Clinic: Cancer Therapies that Block Bad Inflammation

• COX-2 inhibitor: Aspirin, Celecoxib (colorectal)
In the Clinic: Cancer Therapies that Block Bad Inflammation

• COX-2 inhibitor  Aspirin, Celecoxib (colorectal)
• VEGF blocker    Bevacizumab, Sorafenib (several)
In the Clinic: Cancer Therapies that Block Bad Inflammation

- COX-2 inhibitor: Aspirin, Celecoxib (colorectal)
- VEGF blocker: Bevacizumab, Sorafenib (several)
- IL-1β blocker: IL-1Ra (MM)
In the Clinic: Cancer Therapies that Block Bad Inflammation

- COX-2 inhibitor: Aspirin, Celecoxib (colorectal)
- VEGF blocker: Bevacizumab, Sorafenib (several)
- IL-1β blocker: IL-1Ra (MM)
- Cytokine Regulators: Lenalidomide (MDS, MM)
In the Clinic: Cancer Therapies that Block Bad Inflammation

- COX-2 inhibitor: Aspirin, Celecoxib (colorectal)
- VEGF blocker: Bevacizumab, Sorafenib (several)
- IL-1β blocker: IL-1Ra (MM)
- Cytokine Regulators: Lenalidomide (MDS, MM)
- Kill Helicobacter Pylori: Clarithrom./Amoxicillin (gastric)
In the Clinic: Cancer Therapies that Block Bad Inflammation

- COX-2 inhibitor: Aspirin, Celecoxib (colorectal)
- VEGF blocker: Bevacizumab, Sorafenib (several)
- IL-1β blocker: IL-1Ra (MM)
- Cytokine Regulators: Lenalidomide (MDS, MM)
- Kill Helicobacter Pylori: Clarithrom./Amoxicillin (gastric)
- Remove suppressors: Cycl/Fludar + T cells (melanoma)
In the Clinic: Cancer Therapies that Block Bad Inflammation

- COX-2 inhibitor: Aspirin, Celecoxib (colorectal)
- VEGF blocker: Bevacizumab, Sorafenib (several)
- IL-1β blocker: IL-1Ra (MM)
- Cytokine Regulators: Lenalidomide (MDS, MM)
- Kill Helicobacter Pylori: Clarithrom./Amoxicillin (gastric)
- Remove suppressors: Cycl/Fludar + T cells (melanoma)
- Cytotoxic Therapy?: Radiation/Chemother. (all cancers)
### In the Clinic: Cancer Therapies that Block Bad Inflammation

<table>
<thead>
<tr>
<th>Type</th>
<th>Example Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>COX-2 inhibitor</td>
<td>Aspirin, Celecoxib (colorectal)</td>
</tr>
<tr>
<td>VEGF blocker</td>
<td>Bevacizumab, Sorafenib (several)</td>
</tr>
<tr>
<td>IL-1β blocker</td>
<td>IL-1Ra (MM)</td>
</tr>
<tr>
<td>Cytokine Regulators</td>
<td>Lenalidomide (MDS, MM)</td>
</tr>
<tr>
<td>Kill Helicobacter Pylori</td>
<td>Clarithrom./Amoxicillin (gastric)</td>
</tr>
<tr>
<td>Remove suppressors</td>
<td>Cycl/Fludar + T cells (melanoma)</td>
</tr>
<tr>
<td>Cytotoxic Therapy?</td>
<td>Radiation/Chemother. (all cancers)</td>
</tr>
<tr>
<td>Targeted Therapy?</td>
<td>TKI inhibitors (many cancers)</td>
</tr>
</tbody>
</table>
In the Clinic: Cancer Therapies that Induce Good Inflammation
In the Clinic: Cancer Therapies that Induce Good Inflammation

- Bacteria  
  BCG (bladder)
In the Clinic: Cancer Therapies that Induce Good Inflammation

- Bacteria
- TLR agonists

- BCG (bladder)
- Imiquimod (basal cell carcinoma)
- CpG (B cell lymphoma)
In the Clinic: Cancer Therapies that Induce Good Inflammation

- Bacteria: BCG (bladder)
- TLR agonists: Imiquimod (basal cell carcinoma), CpG (B cell lymphoma)
- Cytokines: IL-2 (melanoma, renal), IFN-α (melanoma, renal, CML)
In the Clinic: Cancer Therapies that Induce Good Inflammation

- **Bacteria**: BCG (bladder)
- **TLR agonists**: Imiquimod (basal cell carcinoma)  
  CpG (B cell lymphoma)
- **Cytokines**: IL-2 (melanoma, renal)  
  IFN-α (melanoma, renal, CML)
- **Antibodies**: aCTLA4 mAb (melanoma)
In the Clinic: Cancer Therapies that Induce Good Inflammation

- Bacteria
  BCG (bladder)
- TLR agonists
  Imiquimod (basal cell carcinoma)
  CpG (B cell lymphoma)
- Cytokines
  IL-2 (melanoma, renal)
  IFN-α (melanoma, renal, CML)
- Antibodies
  aCTLA4 mAb (melanoma)
- Surgery
  Danger/inflammation? (cervical)
In the Clinic: Cancer Therapies that Induce Good Inflammation

• Bacteria  BCG  (bladder)
• TLR agonists  Imiquimod  (basal cell carcinoma)
  CpG  (B cell lymphoma)
• Cytokines  IL-2  (melanoma, renal)
  IFN-α  (melanoma, renal, CML)
• Antibodies  aCTLA4 mAb  (melanoma)
• Surgery  Danger/inflammation?  (cervical)
• Hem. Stem Cells  Stem Cell Transpl.  (leukemia, lymphoma)
In the Clinic: Cancer Therapies that Induce Good Inflammation

- Bacteria: BCG (bladder)
- TLR agonists: Imiquimod (basal cell carcinoma), CpG (B cell lymphoma)
- Cytokines: IL-2 (melanoma, renal), IFN-α (melanoma, renal, CML)
- Antibodies: aCTLA4 mAb (melanoma)
- Surgery: Danger/inflammation? (cervical)
- T cells: Adoptive T cell Transfer (melanoma)
In the Clinic: Cancer Therapies that Induce Good Inflammation

- Bacteria: BCG (bladder)
- TLR agonists: Imiquimod (basal cell carcinoma)  
  CpG (B cell lymphoma)
- Cytokines: IL-2 (melanoma, renal)  
  IFN-α (melanoma, renal, CML)
- Antibodies: aCTLA4 mAb (melanoma)
- Surgery: Danger/inflammation? (cervical)
- T cells: Adoptive T cell Transfer (melanoma)
- Vaccine: PAP-loaded DCs (prostate)
• Inflammation is a classic hallmark of cancer

• Innate Immunity & Inflammation can promote or suppress cancer

• Manipulating immunity can promote or suppress cancer

• Understanding of inflammatory cells & molecules in cancer is limited but growing, allowing therapeutic intervention