Cancer Immunotherapy: 
Harnessing the immune system to treat cancer

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Disclosure
- I serve on a scientific advisory board for Luminary Therapeutics
- I hold patents in cell therapy reagents

What is cancer immunotherapy?
- Stimulating a patient’s own immune system to attack cancer
  - Immune Checkpoint Blockade
- Giving a patient synthetic (man-made) components to specifically target cancer
  - Chimeric Antigen Receptor (CAR) T cell therapy
Why immunotherapy?

- Immune cells have evolved over millions of years to specifically recognize and kill abnormal and/or infected cells

Immunology 101:
The Immune System Maintains Balance/Equilibrium/Homeostasis

- The immune system is activated when the body experiences injury, infection, or disease.
- The end result of immune system activation (and subsequent deactivation) is a return to a healthy state.
  - The wound is healed.
  - The infection is resolved.
  - The disease is eradicated.

The Immune System Works via Cells and Secreted Molecules (Proteins)

- Cells
  - White blood cells (leukocytes)
White Blood Cells are Immune Cells

Blood Sample

Plasma
Antibodies (Secreted Proteins)

Immune Cells (White Blood Cells)

Red Blood Cells

**Many Immune Cell Types**

<table>
<thead>
<tr>
<th>Cell Types</th>
<th>Function</th>
<th>Recognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytes (WBCs)</td>
<td>Rapid, No Memory</td>
<td>Very Specific</td>
</tr>
<tr>
<td>Neutrophils</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrophages</td>
<td></td>
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<tr>
<td>DC</td>
<td></td>
<td></td>
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<tr>
<td>NK</td>
<td></td>
<td></td>
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<tr>
<td>B cell</td>
<td></td>
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<tr>
<td>T cell</td>
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</table>

**Immune System Continuum**

- **Innate**
- **Adaptive**
Expression of Receptors Involved in Immune Activation

**Innate**
- General
- All cells express same pathogen-recognition receptors

**Adaptive**
- Diverse
- Very Specific
- Each cell expresses a unique receptor

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**Time Course of an Innate Immune Response**

![Innate Immune Response Diagram]

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**Time Course of a Primary Adaptive Immune Response**

![Adaptive Immune Response Diagram]
Time Course of a Secondary Adaptive Immune Response

The Immune System Works via Cells and Secreted Molecules (Proteins)

- Cells
  - White blood cells (leukocytes)
- Molecules
  - Cell-cell communication
  - Locally and at a Distance
  - Target pathogens and kill infected cells

Antibody

- Antibodies are proteins
- Produced by B cells
- Fight infection
- Bind specifically to Antigens
Antigen

- Any molecule that stimulates an immune response
- Typically a protein expressed by a pathogen
- But can be anything
- Antibodies Bind Antigens

How Antibodies Work

- Antibodies are specific
- Antibodies are secreted by adaptive immune cells
- Antibodies can be drugs

Mark cells for destruction by immune cells

Monoclonal Antibodies are Essentially Chemically Defined (Identical) Molecules
The Immune System Maintains Balance/Equilibrium/Homeostasis

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  - The disease is eradicated = immune surveillance

Cytotoxic T lymphocytes (T cells)

- Major immune cell type that mediates tumor cell killing
- Specific recognition
- Release cytotoxic molecules into cell
- Spare neighboring cells

The HPV vaccine is effective for cervical cancer so why don’t we have vaccines for other cancers?

- HPV is virus (foreign pathogen)
- HPV infection causes cervical cancer
- Vaccine is to HPV (not cervical cancer)
Why don’t we have vaccines for other cancers?

- Most cancers are not caused by foreign pathogens (viruses)
- Most cancers arise from spontaneous/random mutations in DNA in normal self tissues
- There is no way to predict what “proteins” to vaccinate against to prevent cancer in any individual
- Vaccines tend to only work if administered in a preventative setting

What is the evidence that the immune system plays a role in cancer control?

- Tumors that contain more T cells (TILs) favor a better prognosis
- Increase risk for cancer as we age, and immune system becomes less functional as we age
- Patients with HIV infection with low T cell numbers are at much greater risk for developing some cancers

T cells proliferate in response to infection

- Millions of T cells in the body!
- Each T cell expresses a unique T cell receptor
- Only those T cells that are specific to the particular infection will proliferate
T cells must be tightly controlled or they will cause autoimmunity and pathology

- Most T cells that are reactive to self proteins die during development
- T cells in the body should express receptors that are "tolerant" to self proteins but not to foreign proteins
- Organ transplant – need a “Match”, e.g., similar immune proteins between transplant and recipient or T cells will see another individual’s immune proteins as foreign and attack the transplant

How are tumors detected by the immune system?

- Mutations in DNA can create a novel (non-self) protein
- Mutated protein (neoantigen) can be recognized as foreign by T cells

Cancers differ greatly in mutational burden

<table>
<thead>
<tr>
<th>Mutation Prevalence</th>
<th>Formation of neoantigens</th>
</tr>
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<tbody>
<tr>
<td>Frequently</td>
<td></td>
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<tr>
<td>Regularly</td>
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<tr>
<td>Rarely</td>
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Activated T cells express an inhibitory protein PD-1 that binds PD-L1 expressed on tumor cells

- PD-1 binding to PD-L1 shuts down T cells
- "Immune Checkpoint"

Drugs that interfere with PD-1:PD-L1 are now FDA approved cancer immunotherapies

- Blocking PD-1:PD-L1 releases the brakes on T cells
- Drugs that block PD:PD-L1 are antibodies
Tumor cells often highly express PD-L1

Which cancer types respond to PD-1/PD-L1 blockade?

- In general, those cancers with a lot of mutations
- Greater # mutations = Greater immunogenicity (more foreign)

Which cancer types respond to PD-1/PD-L1 blockade?

<table>
<thead>
<tr>
<th>Neoantigen-positive</th>
<th>Neoantigen-negative</th>
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Burrack et al., Cell Reports, 2019
2018 Nobel Prize in Physiology & Medicine:

• Decades of basic immunology research using mouse models led to the discovery of a new way to treat cancer

Immune checkpoints inhibitors have benefit in only a subset of cancer patients

- Response rates are high (45-60%) in melanoma or subset of tumors with many of mutations!
- Response rates are more typically ~15-30% (but can be dismally low in some cancer types)
- Why?
Heterogeneity (diversity) in T cell infiltrate in pancreatic cancer

Few T cells “Cold”  Many T cells “Hot”

Activation of self-reactive T cells leading to “off-tumor” toxicity

Tumor-specific T cell  Auto-reactive (self-specific) T cell

Antibody to PD-1

PD-1+  PD-1+

Attack Tumor  Attack Normal cells

Immune-related adverse events (irAE) can correlate with clinical efficacy
What are the current challenges?

- Immune checkpoint inhibition + drug X, Y, Z
  - Critical to model the human disease faithfully
  - Directly test for safety in cancer patients that have not responded to standard of care in Phase 1 trials
- Identify patients more likely to respond
  - High mutational burden
  - High PD-L1
- Identify mechanisms of resistance
- Identify new immune checkpoints
  - CD200, Tigit, Tim-3, NKG2A, Lag3...
- Identify when to stop treatment
  - Expensive
  - Durable control yet not cancer elimination

Preclinical research in Minnesota: novel combinations to enhance immunotherapy

How can the immune system be manipulated to target tumors that don’t have many mutations?
Genetically engineered T cell therapies

- Chimeric antigen receptor (CAR) T cells
  - Synthetic receptor expressed in a patient's own T cells
  - CAR binds an extracellular protein expressed on cancer cells

- T cell receptor (TCR) T cells
  - T cells are modified to express a tumor-specific TCR
  - TCRs can recognize intracellular proteins

What is a Chimeric Antigen Receptor (CAR)?

CARs are further modified to enhance T cell activation
CAR T cells are infused into a cancer patient: Living therapy

Patients are enrolled who have not responded to many other aggressive treatments (chemotherapy, radiation, bone marrow transplantation)

Adapted from Robert Mazjner & Crystal Mackall, Nature Medicine, 2019

CAR-T cell therapy is FDA approved for B cell malignancies

- CAR T cells are specific to a molecule express on malignant B cells, CD19
- CD19 is also expressed on normal B cells
- CD19 CAR T cells proliferate robustly, kill tumor and also kill normal B cells in patients

CD19 CART cell therapy has toxicity

- Cytokine Release Syndrome
- Neurological Toxicity
- Toxicity can be fatal if not managed
- Toxicity can be a sign that the therapy is working
- Currently no way to predict who will respond and how
- Toxicity is highly unpredictable among individuals
CD19 CART cell therapy outcomes

- Apheresis
- Large B cell Lymphomas
- Manufacturing Failure
- T cells
- Primary Resistance
- Complete Response
- Relapse
- Antigen
- Antigen
- Relapse
- Sustained Response

Immune Editing and Tumor escape

- Antigen-loss variants - relapsed malignant B cells no longer express CD19

Loss of T cell function: Exhaustion
Can CAR T cells work in other types of malignancies?

- Identifying a protein that is unique to cancer and is also reproducibly expressed among cancers is challenging

T cell receptor engineering (alternative approach to target mutations that are expressed inside the cell)

Gene Editing T cells for Cancer Therapy

Final thoughts:

- Cancer is not a single disease
- Immunotherapy is changing the standard of care
- Challenging to separate efficacy from toxicity
- Toxicities are hard to predict (not like chemotherapy)
- Field is moving so fast, technologies are unprecedented, how can good quality science keep up?
- Funding basic research is critical
- Interdisciplinary Team Science (U of MI)
- Since most drugs fail in clinic, we need better preclinical models
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Advancing Knowledge, Enhancing Care

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