Immunotherapy: The Newest Treatment Route

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......or the Oldest

William Coley 1891
Changing View of the Holy Grail of Immuno-Oncology

Pre-2011

"I don't want to talk to you no more, ...you empty headed animal food trough wiper"

Monty Python and the Holy Grail

Post-2011

Image courtesy of Gajewski
Outline

• Immunology 101

• What makes cancer immunotherapy special?

• What are some of the current approaches?

• What are the existing challenges and emerging approaches?
Different kind of immune cells that mediate protection

Immune cells that detect danger
# Types of Immune Cells

<table>
<thead>
<tr>
<th></th>
<th>Adaptive immunity (Cell mediated)</th>
<th>Adaptive Immunity (Non-cell mediated)</th>
<th>Innate Immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Components</td>
<td>T cells</td>
<td>Antibodies</td>
<td>NK, NKT, macrophages</td>
</tr>
<tr>
<td>Target</td>
<td>Inside the target cell</td>
<td>Cell surface</td>
<td>Not antigen-specific</td>
</tr>
<tr>
<td>Kinetics</td>
<td>Lag time</td>
<td>Lag time</td>
<td>Immediate</td>
</tr>
<tr>
<td>Memory</td>
<td>Yes</td>
<td>Yes</td>
<td>No (? some exceptions)</td>
</tr>
<tr>
<td>Anti-tumor Mechanism</td>
<td>Kill tumor cells</td>
<td>Engage innate immunity</td>
<td>Kill/ eat tumor cells</td>
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**Antibodies**

- **B cells**
- **NK**
- **CD8\(^+\)** \(\text{CTL}\)
- **CD4\(^+\)** \(\text{CTL}\)
- **NKT**

**Non-cell mediated immunity**

- **Peptide**
- **MHC II**
- **CD1d**
- **Lipid**

**MHC**

- **MHC I**
- **MHC II**

**Dendritic Cells**
T-cell Activation and Function is Controlled by Multiple Signals

1. Co-stimulation via CD28 ligation transduces T cell activating signals

2. CTLA-4 ligation on activated T cells down-regulates T cell responses

3. T cell function in tissue is subject to feedback inhibition

Take Home Message: When the immune system is activated – it also activates the brakes!!
How can the immune system see tumors

• Tumors contain mutations in the DNA that can lead to abnormal proteins.....which can be seen by the immune system.

• They may also express proteins they are not supposed to express.
Cancer Immunity Cycle and Immune Set Point

Take Home Message:
Regulation of Tumor Immunity is Complex
### Some Properties of Tumors That Create Therapeutic Challenges

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<th>Challenge</th>
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<td>Obstacle to cure...need for ongoing Rx.</td>
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<td>Genetic/epigenetic complexity</td>
<td>Many and often undruggable targets</td>
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### Some Properties Of Tumors That Create Therapeutic Challenges and Opportunities for Immune-Targeting

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<td>Long-lived immunologic memory</td>
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<td>Genetic complexity</td>
<td>Many and often undruggable targets</td>
<td>Ability to target “undruggable” and drug resistant cells.</td>
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<td>Tumor Heterogeneity</td>
<td>Resistance / Relapse</td>
<td>Diverse repertoire of immune cells</td>
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<td>Shared properties with normal tissue</td>
<td>Toxic effects of therapy on normal cells</td>
<td>Specificity</td>
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Diversity of Approaches for Anticancer Immunotherapy

Take Home Message:

There are several emerging options for immune therapy of cancer.

Galuzzi et al, Oncotarget 2014
Immunologic Diversity in Cancer—One Size does not fit all

Barriers:
- Inadequate immune activation
- Inhibitory checkpoints

Vaccines
Adoptive T cell therapy

Start the Engine
Press on Gas Pedal
Then take foot off the brake

Engine Already On
Take foot off the brake

Blockade of Immune Checkpoints
Immune Checkpoint Blockade

• Principle of taking the brakes off T cells.

• Expected to work only if immune cells pre-existing but just suppressed.

• Clinical efficacy of PD1/PD-L1 targeted antibodies in several human tumors.
  • Hodgkins, lung, melanoma, renal, head/neck, bladder, subsets of colon cancer, subset of breast cancer, non-Hodgkin lymphoma....

• Durable responses observed.

• Combination therapies with higher responses (but also toxicities)
Clinical Activity of Checkpoint Blockade in Hodgkin Lymphoma

Ansell et al. NEJM 2015
Clinical Activity of Checkpoint Blockade in Richter Syndrome after Ibrutinib

Baseline to Best Response, Richters Patients

- PD
- SD
- RT
- PR
- CR

% Change

- Prior Ibrutinib
- No Prior Ibrutinib

Patient Number

RS1 RS2 RS3 RS4 RS5 RS6 RS7 RS8 RS9 RS10
Signals regulating T cell activation as Targets of Cancer Therapies

I Mellman et al. Nature 480, 480-489 (2011) doi:10.1038/nature10673
Unmet Needs for Immune checkpoint therapies:

• Better understanding of who will respond to therapy?

• Better understanding of how these drugs work or why some tumors do not respond while others do?

• Who might be at greater risk of autoimmunity or other toxicity?

• How to design and test rational combination therapies?
Current and Emerging Immune Therapies

Adaptive immunity

T cell immunity

Cytokines

T cell therapies

Cancer vaccines

T cell checkpoint modulators

‘Connecting’ bi-specific antibodies

Innate immunity

B cell immunity

NK cell therapies

Checkpoint modulators

Dual-specific antibodies

Small molecules

Oncolytic viruses

Adjuvants

 Clinically validated modalities through approved therapies
 Modalities under investigation
Adoptive T cell therapy

June et al SciTM 2015
Chimeric Antigen Receptor (CAR)-T cells

- Combine binding properties of antibodies and tumor kill properties of T cells.
- Can target drug-resistant/high risk clones of tumor cells.
- Immunologic memory - may yield durable responses.
CAR-T cells

• Impressive clinical responses in some leukemias, relapsed lymphoma.

• Key toxicities:
  • Cytokine-release syndrome
  • Neurotoxicity

• Anticipated approval for pediatric ALL and lymphoma.
Other Emerging Approaches

• Other Cell Therapies

• Emerging Vaccine Platforms
Estimate Of Mutation Load In Human Cancer

Schumacher, and Schreiber Science 2015;348:69-74
Mutation-Derived Antigens As Targets in Tumor Immunity

Advantages:

- Tumor Specific
- High potency T cells
Strategies to target the patient-specific mutations

A. Induce tumor cell destruction
   - Provide checkpoint blockade

B. Identify potential neoantigens
   - Create synthetic vaccine (RNA, DNA, peptide)
   - Provide in combination with adjuvant and checkpoint blockade

C. Identify potential neoantigens
   - Induce or expand neoantigen specific T cells
   - Provide in combination checkpoint blockade

Schumacher, and Schreiber Science 2015;348:69-74
Targeting the Messenger Cells Enhance To Tumor Immunity

Two Broad Approaches:

• Isolate cells from patients – make vaccine – then inject vaccine. (example- Provenge for Prostate Cancer)

• Inject antibodies or nanoparticles into patients.

Ex vivo DCs

Targeting DCs in vivo

Palucka et al. Immunity 2010

Dhodapkar et al. Science TM 2015
Why do we need immune therapies for WM?

• Recent Advances in Therapies...(e.g. Rituxan, Ibrutinib, ....)

but

• most do not completely eliminate tumor cells.
• Tumors can evolve and acquire additional mutations.
• Not curative.
• Require ongoing therapy...with associated cost and toxicity
Some Questions

• Can we harness immunity against mutations found in WM tumors cells?

• Will engaging innate immunity against these tumors be of benefit?

• Can we develop robust models to test these approaches and facilitate translation to the clinic?
Conclusions

• Immune-based therapies are rapidly transforming therapeutic approach to several human cancers.

• Integration of basic biology into next generation therapies and detailed evaluation of patients is essential to understand mechanisms underlying response and resistance.

• There is an unmet need to develop/test new approaches to harness immune system against WM cells.
Thank you— to IWMF for your support

And to our patients for their inspiration