Harnessing the Immune System with Novel Biotherapies

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Disclosure Statements

Robert Scheinman, PhD
I have no relevant financial relationships with commercial interests pertaining to the content presented in this program.

Cindy O’Bryant, PharmD
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Introduction to the Immune System

Your favorite topic

The Good...
- Tumor Surveillance
- Fight Infection
- Trauma Healing
- Immunity Protects us From Dangers Without and Within.

The Bad...
- Type 2 Diabetes
- Cancer
- Atherosclerosis
- Acute Respiratory Distress Syndrome
- Inflammation underlies and potentiates MANY diseases.

The Ugly...
- Type 1 Diabetes
- Systemic Lupus Erythematosus
- Rheumatoid Arthritis
- Multiple Sclerosis
- Self as Enemy: The Immune System at its Worst.
The 2 Parts of the Immune System

**Innate Immune System**
- Ancient
- Recognizes conserved pathogen molecules
- Includes macrophages (MΦ), dendritic cells (DC), and neutrophils

**Adaptive Immune System**
- More recently evolved
- Recognizes antigens
- Includes T cells and B cells

Antigens are Recognized by T cells

- T cell receptor (TCR)
- MHC + antigen
- Inflammatory mediators (e.g., TNFα)
- Reactive compounds
- Complement

T Cells Must Be Controlled

- In animal experiments where T cells are allowed to remain active – the animal dies.

- T cells are regulated at many levels:
  - After activation, T cells begin to express an inhibitory receptor: Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4).
  - Some T cells become regulatory "U.N. Peacekeepers" (Tregs).
  - Some T cells signal macrophages to change from soldiers (M1) to healers (M2).
  - Some T cells initiate a self-destruct program called "apoptosis" or "programmed cell death".

Regulating T Cell Activity

- CTLA4

Macrophages Explore their Environment

- Sentinel cells (tissue macrophages) test the environment continuously.
- Pathogen recognition turns the MΦ into a Soldier.
- Phagocytosis of pathogen
- Secretion of signaling molecules
- Secretion of reactive compounds
- Secretion of complement proteins

The Macrophage Provides "Context" to the T Cell as well as Antigen

- Signal 1: antigen
- Signal 2: co-stimulation
- This tells the T cell that the antigen is dangerous
Regulating T Cell Activity

Signal to change phenotype

T cell

M1

M2

Decreased antigen

differentiation

Immunosuppression

T cell

T cell

T cell

Macrophages as Healers

Immunosuppression

M2

Phagocytosis of Debris
(clean up duty)

Secretion of VEGF
(Promote Angiogenesis)

Secretion of Growth Factors
(Promote Proliferation of Epithelial Cells)

Summary so far

- The innate immune system recognizes pathogens through evolutionarily conserved molecules.
  - Example: macrophages

- The adaptive immune system responds to peptides (antigens) presented by activated MΦ.
  - Example: T cells

- There exist key regulatory points which keep the immune response in check.
  - Examples: CTLA4 and M2 MΦ

Soldiers versus Healers

THERAPEUTIC APPLICATIONS OF MODULATING MΦ PHENOTYPE

Changing Soldiers to Healers

Hypothesis: if M2 MΦ are immunosuppressive, perhaps they can decrease the damage caused by autoimmune disease.

Robert Scheinman, Uday Kompella:
Department of Pharmaceutical Sciences, Skaggs School of Pharmacy

Goal: Design a system to deliver a therapeutic which will block M1 and promote M2. Apply this therapeutic to a mouse model of Rheumatoid Arthritis

Design of the Therapeutic

- Knock down a key protein that enforces the M1 state and blocks the M2 state using an inhibitory RNA.
  - STAT1

- Encapsulate this RNA in nanometer sized polymer spheres.
  - PLGA, FDA approved for human use

- Place a peptide on the surface of these spheres that targets them to arthritic tissue.
  - Contains Arg-Gly-Asp peptide; homes to new blood vessels.
Scanning Electron Micrograph of Nanospheres

Addition of peptide to nanospheres targets arthritic tissue

Efficacy of the Therapeutic

Changing Healers to Soldiers

Hypothesis: Block of macrophage differentiation into M2 will slow the progression of lung cancer.

Robert Scheinman, Rafael Nemenoff:
Department of Pharmaceutical Sciences, Skaggs School of Pharmacy and Division of Renal Diseases and Hypertension and Pulmonary Sciences, School of Medicine.

Goal: Create a mouse in which all white blood cells are missing a gene that is required for immunosuppressive functions of macrophages. Give this mouse lung cancer. Follow tumor growth and metastasis.

How the Mouse was Made

- Lethally irradiate recipient mice (bone marrow dies).
  - Wild type mouse
- Rescue with I.V. injection of bone marrow cells from donor.
  - Mice with disrupted cPLA₂ gene.
- Wait for new bone marrow to regenerate the blood cell populations.
  - Lung cells are wild type. Macrophages are missing cPLA₂.

Disruption of cPLA₂ in macrophages decreases metastasis in a lung cancer model
Conclusions

• Macrophages can play an important role in modulating the immune response.

• Pushing macrophages towards an M2-like (healer) phenotype shows promise as a target for Rheumatoid Arthritis therapies.

• Pushing macrophages towards an M1-like (soldier) phenotype show promise as a target for Cancer therapies.

Immunotherapy in Rheumatoid Arthritis (RA) and Cancer

• Advances in molecular biology have led to a variety of new treatment approaches

• Biologic approaches include agents that
  - Interfere with cytokine function
  - Inhibit signals required for T-cell activation
  - Deplete B cells
  - Alter signaling through receptor binding
  - Mediate antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC)

Rheumatoid Arthritis

• RA is an autoimmune disease triggered by a faulty immune system

• At least 1.3 million U.S. adults have RA
  – 75% are women

• Extra-articular involvement
  – Eye, heart, lung, nervous system

Pathophysiology of RA

Treatment of RA

• Mainstay of therapy
  – Disease modifying anti-rheumatic drugs (DMARDS)
    • Role in treatment of early disease

• Biologics
  – Role in the treatment of moderate to severe disease
    • Failed ≥ 1 DMARD
    • Shown to decrease signs/symptoms and bone erosion
    • More costly than DMARDS
  – No large head to head trials comparing biologics
Biologic Agents in Treatment of RA

- Place in treatment
  - Moderate to severe RA
  - Per 2012 American College of Rheumatology guidelines may use in early RA if high disease activity or lack of response to DMARD therapy
  - Decision which to use requires evaluation of patient characteristics and stage of disease
  - Generally used in combination with a DMARD
    - Not used in combination with another biologic

TNF-α Blockers

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage</th>
<th>Time to effect: 2-4 weeks</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>Dosing 40 mg SQ every other week May increase to 40 mg SQ every week if not taking methotrexate (MTX)</td>
<td>~$1,300 per injection</td>
<td>Serious infection, Tuberculosis, Cancer, Viral reactivation, Lupus-like syndrome, Exacerbation or new onset demyelinating disease, Hypersensitivity reactions, Interaction with live vaccines</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>400 mg SQ at 0, 2 and 4 weeks or 200 mg SQ every 2 weeks or 100 mg SQ every 4 weeks</td>
<td>~$2,000 per injection</td>
<td>Improvement in swelling and tenderness of joints, Improvement in pain</td>
</tr>
<tr>
<td>Golimumab</td>
<td>50 mg SQ monthly in combination with MTX</td>
<td>~$2,000 per injection</td>
<td>Improvement in swelling and tenderness of joints, Improvement in pain</td>
</tr>
<tr>
<td>Infliximab</td>
<td>3-5 mg/kg IV at 0, 2, 6 weeks then every 8 weeks in combination with MTX</td>
<td>~$900 per 100 mg</td>
<td>Interaction with live vaccines</td>
</tr>
<tr>
<td>Etanercept</td>
<td>50 mg SQ weekly</td>
<td>~$725 per 30 mg</td>
<td></td>
</tr>
</tbody>
</table>

Immunotherapy in Cancer

- Historical
  - Interleukins
  - Interferon
  - Bacille Calmette-Guérin (BCG)
  - Thalidomide

- Modern
  - Monoclonal antibodies
  - Cancer Vaccines
  - Lymphokine-activated killer cell therapy
  - Tumor-infiltrating lymphocytes

Cancer

- Cancer is the general name for a group of more than 100 diseases that start because abnormal cells grow out of control
- Estimated cancer prevalence in the US in 2009 ~ 12.5 million people
  - Half of all men and one-third of all women in the US will develop cancer during their lifetime
- The National Institutes of Health estimated the 2008 overall annual costs of cancer to be $201.5 billion

Ipilimumab

- Fully human monoclonal antibody against CTLA-4
Ipilimumab

- **Indication**
  - Treatment of unresectable or metastatic melanoma

- **Dosing**
  - Ipilimumab 3 mg/kg IV every 3 weeks for a total of four doses

- **Cost**
  - $120,000 ($30,000 per dose)

- **Risk Evaluation and Mitigation Strategy (REMS) program**

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**Phase III Trial: Ipilimumab and gp100**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>OS months</th>
<th>OS 1 year</th>
<th>OS 2 year</th>
<th>Response Rate</th>
<th>Disease Control Rate</th>
<th>2-year Response Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>10.1</td>
<td>43.6%</td>
<td>21.6%</td>
<td>36%</td>
<td>26.5%</td>
<td>60%</td>
</tr>
<tr>
<td>Ipilimumab + GP100</td>
<td>10.0</td>
<td>45.6%</td>
<td>23.5%</td>
<td>19%</td>
<td>20.1%</td>
<td>17.4%</td>
</tr>
<tr>
<td>GP100</td>
<td>6.4</td>
<td>25.3%</td>
<td>13.7%</td>
<td>HR, 0.64</td>
<td>HR, 0.81</td>
<td>0%</td>
</tr>
</tbody>
</table>

HR = hazard ratio

Primary endpoint: Overall Survival (OS)

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**Phase III: Ipilimumab +/- Dacarbazine**

- **Previously untreated metastatic melanoma**
  - N=502
  - Randomized 1:1
  - Ipilimumab 10 mg/kg + dacarbazine 850 mg/m²
  - Placebo + dacarbazine 850 mg/m²

Primary endpoint: OS

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**Immune-Related Adverse Events (irAE)**

- Mediated by self-reactive T-cells
- Associated with tumor regression and prolonged time to relapse
- Timing is variable and can occur after cessation of drug
- Gastrointestinal, skin, hepatic, endocrine, ophthalmic, and neurologic toxicities are the most common irAEs observed
  - Grade III/IV irAEs occurred in 10% to 15% of the ipilimumab arms and 3% of gp100 arm
Patient Assessment & Management of irAEs

<table>
<thead>
<tr>
<th>Organ Toxicity</th>
<th>Signs/Symptoms</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal (enterocolitis)</td>
<td>Diarrhea, blood or mucus in stool, constipation, abdominal cramps, nausea/vomiting</td>
<td>Loperamide, oral steroids, IV corticosteroids</td>
</tr>
<tr>
<td>Skin (dermatitis)</td>
<td>Pruritus, rash, peeling</td>
<td>Antihistamines, topical steroids, IV corticosteroids</td>
</tr>
<tr>
<td>Hepatic (hepatitis)</td>
<td>Abnormal liver function tests, jaundice, jaundice of sclera</td>
<td>Oral corticosteroids, IV corticosteroids</td>
</tr>
<tr>
<td>Neurological (neuropathy)</td>
<td>Motor neuropathy, muscle weakness, sensory neuropathy</td>
<td>Consult neurology: treat symptoms accordingly, IV corticosteroids May consider IV immunoglobulin</td>
</tr>
<tr>
<td>Endocrine (hypophysitis)</td>
<td>Headache, weakness, visual defects, behavioral changes, electrolyte imbalance, endocrine imbalance</td>
<td>Replace hormones as necessary, high-dose oral corticosteroids</td>
</tr>
</tbody>
</table>

irAEs Time to Onset and Resolution

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Median Time to Onset (weeks)</th>
<th>Median Time to Resolution (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>3.6 - 4.4</td>
<td>6.1</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>6.6 - 6.9</td>
<td>2.3</td>
</tr>
<tr>
<td>Hepatic</td>
<td>6.7</td>
<td>4.0</td>
</tr>
<tr>
<td>Endocrine</td>
<td>9.2 - 10.1</td>
<td>20.1</td>
</tr>
</tbody>
</table>

Adapted from Lebbe C et al. Presented at Perspectives in Melanoma XII. New York City, NY; Oct 2008; Abs O-015.

Under Investigation in Cancer: Programmed Cell Death 1

- Blocking of programmed cell death 1 (PD-1) leads to stimulating T-cells and immune response

Phase 1: Nivolumab (BMS-936558)

- Fully human PD-1 antibody
- Phase 1 dose escalation trial
  - N=296
    - 104 advanced melanoma
    - 122 non-small cell lung cancer
    - 34 renal cell cancer
    - 17 castration-resistant prostate cancer
    - 19 Colorectal cancer
- Dosing
  - Given as IV infusion every 2 weeks of 8 week cycle
  - Escalating doses from 0.1-10 mg

- Adverse events
  - Fatigue, rash, diarrhea, pruritus, decreased appetite, and nausea
  - Potential irAEs
    - Pneumonitis, vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis
    - 3 deaths due to pneumonitis
- Management
  - Dose holding and symptomatic management
  - Steroids
  - Hormone replacement

Phase 1: Nivolumab (BMS-936558)

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Objective Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>28%</td>
</tr>
<tr>
<td>Non-small cell lung</td>
<td>18%</td>
</tr>
<tr>
<td>Renal cell</td>
<td>27%</td>
</tr>
</tbody>
</table>

- 20 responses lasted 1 year or more in patients with 1 year or more of follow-up

Objective Response: Complete or partial response
Phase 1b: Lambrolizumab (MK-3475)

• Humanized PD-1 antibody

• Phase 1b expansion trial in patients with advanced melanoma with or without previous ipilimumab (IPI) treatment
  — N= 294; 179 IPI-naive and 115 IPI-pretreated

• Dosing
  — 2 or 10 mg/kg administered IV every 2 or 3 weeks

Results

• Overall response rate > 35%
  • Across all doses and schedules and including both IPI-naive and IPI-pretreated patients
  • Median duration of response not been reached

• Adverse events
  • Most common
    — Fatigue (22%), rash (18%), and pruritus (14%
  • Incidence of severe AEs = 10%
  • Four drug-related cases of pneumonitis reported

Future Directions of Immunotherapy

• Other autoimmune disorders
• Other cancers
• Neurology
• Infectious disease
• Diabetes
• Allergy
• Hepatitis
• Renal disease

Conclusions

• The immune system is important as it protects you from infections and other diseases

• Manipulation of the immune system through drug therapy has been shown to improve disease symptoms and outcomes

• Alternatively caution should be taken when utilizing these agents due to increased immune related risks and adverse events