B Cells vs. T Cells: Which arm of the immune system is likely to be more relevant for anti-viral or anti-tumor responses?

- recognition of extracellular versus intracellular pathogens
  - B cells produce antibodies which bind to circulating pathogens or toxins, leading to 'neutralization' of pathogenic activity
  - T cells, in contrast, directly bind to abnormal cells (i.e., infected or neoplastic), leading to target cell destruction
The Central Players of the T Cell Response

- CD8\(^+\) cytotoxic T lymphocytes (CTLs)
- CD4\(^+\) T\(_{1}\) (induces the generation of CTLs)
- CD4\(^+\) T\(_{2}\) (promotes antibody production)

Role of the Antigen Presenting Cell in the Activation of Naïve T Cells

Dendritic cells are essential for the induction of the naïve T cell response, and do so through regulation of three major events known as the 3-signal model:

1. Recognition of MHC-peptide complex (& conjugate formation)
   i. antigen processing
   ii. antigen presentation
   iii. co-receptors (CD4 or CD8)
   iv. adhesion (LFA-1/ICAM-1; CD2/LFA-3)

2. positive co-stimulation (CD28/CD80 or CD28/CD86)

3. cytokine production (e.g., Interleukin-2; IL-2)

Surface Interactions Important for T Cell Activation
**Generation of T Cell Immunity: an Indispensable Role of the Antigen-Presenting Cell**

Signal 1: T Cell Recognition of MHC-Peptide Complexes

Antigen specificity is governed by the TCR, which recognizes an antigenic peptide in the context of self-MHC, a concept known as MHC restriction. MHC restriction is absolutely essential to ensure and instruct immune reactivity against ‘alterations of self’.

- MHC class I = heavy/light pair
- MHC class II = similar size pair

**Markers of Self: Major Histocompatibility Complex**
Summary: The Generation of MHC-Peptide Complexes for T Cell Receptor Recognition

1. MHC class I and class II molecules deliver peptides to the cell surface from two distinct intracellular compartments.
2. Peptides presented by MHC class I molecules are generated within the cytosolic compartment (aka, endogenous pathway).
3. Peptides presented by MHC class II molecules are generated in acidified endocytic vesicles (aka, exogenous pathway).
4. Cross-presentation allows exogenous proteins to be presented on both MHC class I and II molecules (i.e., via dendritic cells, which are highly effective).
5. CD8^+ T cells recognize MHC class I-peptide complexes.
6. CD4^+ T cells recognize MHC class II-peptide complexes.

Steps of CTL-Mediated Target Cytolysis

1. Conjugate formation:
   - CTL-target cell interaction
   - CTL-granule exocytosis
2. CTL-target cell conjugation:
   - CTL-granule exocytosis
3. CTL-mediated target cell lysis:
   - CTL granule exocytosis
Tumor Development and Progression

- Intrinsic mechanisms
  - genetic and epigenetic alterations within normal organs or tissues

Vogelstein et al. Science 2013;339:1546-1558

Tumor Development and Progression

- Extrinsic mechanisms: 'host-tumor interaction'
  - positive and negative consequences on tumor outcome


Table 1. Tumor Development Data

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Effect on Hours</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal epithelial cells</td>
<td>resistance to apoptosis</td>
<td>Scalzo et al., 1997</td>
</tr>
<tr>
<td>Adenocarcinoma cells</td>
<td>proliferation, invasion</td>
<td>Edge et al., 2000</td>
</tr>
<tr>
<td>Melanoma cells</td>
<td>invasion, metastasis</td>
<td>Schade et al., 2003</td>
</tr>
<tr>
<td>Fibroblasts</td>
<td>proangiogenic, matrix remodeling</td>
<td>Eisenberg et al., 2001</td>
</tr>
</tbody>
</table>

Egeblad et al. Dev Cell 18:884, 2010

Breast

DeNardo et al. Cancer Disc 1:54, 2011
Approaches for the Treatment of Human Cancer

- Surgery - to debulk; effective if cancer has not spread
- Radiation - local/regional tumor spread
- Chemotherapy - systemic spread, but approaches are generally toxic to normal cells/tissues (limits its therapeutic potential)

Immunotherapy: A Fourth Modality?

- Immunotherapy principles:
  - improve patient's immune response against their own cancer
  - 'vaccines'
  - 'adoptive cell transfer'
- rationale and goals:
  - a highly potent immune reaction
  - target cancer cells with high specificity
  - diminish toxicity toward normal cells

Metastatic Disease is a Major Challenge in Cancer Treatment

- Most cancer patient deaths are due to metastatic disease or disease resistant to conventional treatments
- Metastasis typically is not accessible to surgery because it can give rise to many lesions at multiple locations, some of which can be small and undetectable
Manipulation of T Cell Responses for Therapeutic Purposes in Cancer

Based on basic biology to clinical practice...

1. **Signal 1**: dendritic cell vaccines expressing relevant MHC/peptide complex (e.g. 'Provenge' in prostate cancer)
2. **Signal 2**: 'immune checkpoint inhibitors' to prevent negative costimulation (anti-CTLA-4 or anti-PD-1 mAbs)
3. **Signal 3**: IL-2 administration
4. Adoptive T cell transfer of ex vivo-expanded tumor-infiltrating lymphocytes

Benefits of Clinically Engaging the Antitumor T Cell Response Against Cancer

Before and after pictures of a patient with advanced melanoma who underwent treatment with tumor-infiltrating lymphocytes. Within 2 weeks of treatment, the large tumor had disappeared. Source: Cancer.gov

- **Cancer vaccines** (most appealing)
  - similar in concept to classical vaccination
  - immunize against tumor ('foreign') proteins that are selectively or uniquely expressed
  - two recent examples of vaccines:
    - HPV vaccine (Gardasil)
    - Prostate cancer vaccine ('Provenge')