Concepts of cancer immunotherapy
History

• Paul Ehrlich first conceived the idea that tumor cells can be recognized as “foreign” and eliminated by the immune system.
• Subsequently, Lewis Thomas and Macfarlane Burnet formalized this concept by coining the term immune surveillance, which implies that a normal function of the immune system is to constantly “scan” the body for emerging malignant cells and destroy them.
• This idea has been supported by many observations
  – the presence of lymphocytic infiltrates around tumors and reactive changes in lymph nodes draining sites of cancer
  – experimental results, mostly with transplanted tumors;
  – the increased incidence of some cancers in immunodeficient people and mice;
  – the direct demonstration of tumor-specific T cells and antibodies in patients;
  – most recently and most directly, the response of advanced cancers to therapeutic agents that act by stimulating latent host T-cell responses
Cancer *immunoediting*

- The fact that cancers occur in immunocompetent individuals indicates that immune surveillance is *imperfect*.
- It follows that the tumors that do grow out must be composed of cells that are either invisible to the host immune system or that release factors that actively suppress host immunity.
- The term cancer immunoediting has been used to describe the ability of the immune system to shape and mold the immunogenic properties of tumor cells in a fashion that ultimately leads to the darwinian selection of subclones that are best able to avoid immune elimination.
Tumor Antigens

- Product of mutated genes
- Consequence of enhanced or aberrant expression
- Product of oncogenic viruses
- Oncofetal antigens
- Altered cell surface glycolipids and glycoproteins
- Differentiation antigens
Tumor antigens recognized by CD8+ T cells.

<table>
<thead>
<tr>
<th>Normal host cell displaying multiple MHC-associated self antigens</th>
<th>No T cell response</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal self proteins</td>
<td>MHC Class I</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No T cell response</td>
<td></td>
</tr>
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<td></td>
<td>T cell</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor cells expressing different types of tumor antigens</th>
<th>CD8+ CTL</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product of oncogene or mutated tumor suppressor gene</td>
<td></td>
<td>Oncogene products: mutated RAS, BCR/ABL fusion proteins</td>
</tr>
<tr>
<td>Mutated self protein</td>
<td></td>
<td>Tumor suppressor gene products: mutated p53 protein</td>
</tr>
<tr>
<td>Overexpressed or aberrantly expressed self protein</td>
<td></td>
<td>Various mutant proteins in carcinogen, or radiation, induced animal tumors; various mutated proteins in melanomas</td>
</tr>
<tr>
<td>Oncogenic virus</td>
<td></td>
<td>Overexpressed: tyrosinase, gp100, MART in melanomas</td>
</tr>
<tr>
<td>Virus antigen-specific CD8+ CTL</td>
<td></td>
<td>Aberrantly expressed: cancer-testis antigens (MAGE, BAGE)</td>
</tr>
<tr>
<td>Virus antigen-specific CD8+ CTL</td>
<td></td>
<td>Human papilloma virus E6, E7 proteins in cervical carcinoma; EBNA proteins in EBV-induced lymphoma</td>
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</tbody>
</table>

Tumor antigens recognized by CD8+ T cells.
Product of mutated genes

• Cancer mutated genes encode variant proteins that have never been seen by the immune system and are thus recognized as non-self
• these acquired mutations are likely to be “passengers,” mutations that are neutral in terms of cancer cell fitness and thus unrelated to the transformed phenotype. However, by chance, some of these passenger mutations may fall in the coding sequences of genes and give rise to protein variants that serve as tumor antigens.
• The products of altered proto-oncogenes, tumor suppressor genes, and “passenger” genes are translated in the cytoplasm of tumor cells, and like any cytoplasmic protein, they may enter the class I MHC antigen-processing pathway and be recognized by CD8+ T cells.
• In addition, these proteins may enter the class II antigen-processing pathway in antigen-presenting cells that have phagocytosed dead tumor cells, and thus be recognized by CD4+ T cells also.
• In animals, immunization with mutated RAS or p53 proteins induces CTLs and rejection responses against tumors expressing these mutated proteins. However, the tumor-specific neoantigens that are recognized by CTLs in patients with cancer are for the most part currently unknown.
Overexpressed and aberrantly expressed proteins

• Tumor antigens may also be normal cellular proteins that are abnormally expressed in tumor cells.
• Examples: tyrosinase, expressed only in normal melanocytes and melanomas
  — tyrosinase is normally produced in such small amounts and in so few normal cells that it is not recognized by the immune system and fails to induce tolerance.
• Cancer-testis antigens, are encoded by genes that are silent in all adult tissues except germ cells in the testis.
  — sperm do not express MHC class I antigens, so these proteins are not immunogenic normally.
  — Melanoma antigen gene (MAGE) family. Although originally described in melanomas, MAGE antigens are expressed by a variety of tumor types.
Products of oncoviruses

- Oncoviruses produce proteins that are recognized as foreign by the immune system.
- Examples in humans include human papilloma virus (HPV) and Epstein-Barr virus (EBV).
  - Abundant evidence that CTLs recognize antigens of these viruses and that a competent immune system plays a role in surveillance against virus-induced tumors
  - The concept of immune surveillance against tumors is best established for DNA virus-induced tumors.
Oncofetal proteins

- Oncofetal antigens are proteins that are expressed at high levels on cancer cells and in normal developing (fetal) tissues.
- Amounts of these proteins are increased in tissues and in the circulation in various inflammatory conditions, and they are even found in small quantities in normal tissues.
- There is no evidence that oncofetal antigens are important inducers or targets of antitumor immunity.
- Oncofetal proteins are sufficiently specific that they can serve as markers that aid in tumor diagnosis and clinical management.
- The two most thoroughly characterized oncofetal antigens are carcinoembryonic antigen (CEA) and α-fetoprotein (AFP). These are used extensively as tumor markers in clinics.
Cell surface glycolipids and glycoproteins

- Most tumors express higher than normal levels and/or abnormal forms of surface glycoproteins and glycolipids
- These altered molecules include:
  - gangliosides
  - blood group antigens
  - mucins.
- Mucins are high-molecular-weight glycoproteins containing numerous carbohydrate side chains on a core polypeptide. Tumors often have dysregulated expression of the enzymes that synthesize these carbohydrate side chains, which leads to the appearance of tumor-specific epitopes on the carbohydrate side chains or on the abnormally exposed polypeptide core.
- Several mucins have been the focus of diagnostic and therapeutic studies, including CA-125 and CA-19-9, expressed on ovarian carcinomas, and MUC-1, expressed on both ovarian and breast carcinomas.
- MUC-1 is an integral membrane protein that is normally expressed only on the apical surface of breast ductal epithelium. In ductal carcinomas of the breast, however, the molecule is expressed in an unpolarized fashion and contains new, tumor-specific carbohydrate and peptide epitopes that induce both antibody and T-cell responses in cancer patients and are therefore considered candidates for tumor vaccines in patients with breast cancer and possibly ovarian cancer as well.
Cell-type specific differentiation antigens

• Tumors express molecules that are normally present on the cells of origin, called differentiation antigens because they are specific for particular lineages or differentiation stages of various cell types.

• Differentiation antigens are typically normal self-antigens, and therefore they do not induce immune responses in tumor-bearing hosts.
  – Their importance is as potential targets for immunotherapy and for identifying the tissue of origin of tumors.
An example: CD20

• CD20 is a transmembrane protein that is expressed on the surface of all normal mature B cells
• Antibodies against CD20 have broad cytocidal activity against mature B-cell lymphomas and leukemias and are widely used in the treatment of these tumors.
• These antibodies are believed to induce cell killing through several mechanisms, including opsonization and phagocytosis of tumor cells, antibody-dependent cell-mediated cytotoxicity and complement fixation.
• Anti-CD20 antibodies also kill normal B cells, but because hematopoietic stem cells are spared, normal B cells reemerge following treatment.
Mechanism of action of anti-CD20 antibodies
Mechanism of action of anti-CD20 antibodies

Figure 1. Mechanisms of Action of Anti-CD20 Antibodies.

Anti-CD20 antibodies bind to the CD20 molecule on the surface of the malignant B cell in non-Hodgkin’s lymphoma (NHL), leading to cell death. Three mechanisms of action of anti-CD20 antibodies have been proposed. In complement-dependent cytotoxicity, the first component of complement (C1) binds to the Fc portion of the anti-CD20 molecule, resulting in the activation of the complement cascade and cell lysis through the formation of membrane attack complexes (MAC). In antibody-dependent cell-mediated cytotoxicity (ADCC), effector cells, such as natural killer cells or macrophages, bind to the Fc portion of the anti-CD20 molecule through Fcγ receptors; the effector cells then release effector molecules such as perforin, which cause cell lysis. In direct cytotoxicity, the anti-CD20 antibody induces internal signaling within the tumor cell, causing antiproliferative effects or cell death, which may involve apoptosis or other cell-death pathways. In the top inset, anti-CD20 antibodies bind to an extracellular portion of the CD20 molecule. Most anti-CD20 antibodies, including rituximab, tositumomab, and obinutuzumab, bind to the larger of two extracellular loops within the CD20 molecule; this loop includes the alanine-N-proline (ANP) residues at positions 170 to 172. Ofatumumab binds to two sites on the CD20 molecule: the smaller extracellular loop and positions 159 to 166 on the larger loop. This unique binding pattern of ofatumumab, which results in increased proximity of the antibody to the cell membrane, may account for the greater potency of the drug in inducing complement-mediated lysis. In the lower inset, the structure of chimeric and human antibodies is shown.
Other approaches

• Monoclonal antibodies may also be covalently coupled to drugs, toxins, or radiochemicals
  – the antibody serves as guided missile that delivers a therapeutic warhead to cancers expressing particular surface antigens

• Anti-CD30 antibodies:
  – CD30 is a member of the TNF receptor family of transmembrane proteins that is expressed by particular T cell lymphomas and most Hodgkin lymphomas.
  – Antibodies against CD30 linked to a cytotoxic drug have recently produced remarkable responses in patients with CD30-positive lymphomas that have failed conventional therapies.

• Bispecific antibodies engineered to have two different antigen recognition surfaces, one that binds tumor antigens and a second that binds to the CD3 signaling molecule on T cells, have produced some promising results in clinical trials.
Antitumor Effector Mechanisms

- Humoral immunity: negligible
- Cellular immunity: main mechanism
Cytotoxic T-lymphocytes

- The antitumor effect of cytotoxic T cells reacting against tumor antigens is well established in experimentally induced tumors.
- In humans, CD8+ CTLs have a clear protective role against virus-associated neoplasms (e.g., EBV- and HPV-induced tumors)
- Several studies have shown that the number of tumor-infiltrating CD8+ T cells and the presence of a “gene signature” associated with CD8+ CTLs correlates with a better prognosis in a variety of cancers, not only those caused by oncogenic viruses.
Natural Killer cells

• NK cells are lymphocytes that are capable of destroying tumor cells without prior sensitization and thus may provide the first line of defense against tumor cells.
• After activation with IL-2 and IL-15, NK cells can lyse a wide range of human tumors, including many that seem to be nonimmunogenic for T cells.
• While the importance of NK cells in host response against spontaneous tumors is still not well established, cytokines that activate NK cells are being used for immunotherapy.
Macrophages

- Activated macrophages exhibit cytotoxicity against tumor cells in vitro.
- T cells, NK cells, and macrophages may collaborate in antitumor reactivity, because interferon-γ, a cytokine secreted by T cells and NK cells, is a potent activator of macrophages.
- Activated macrophages may kill tumors by mechanisms similar to those used to kill microbes (e.g., production of reactive oxygen species)
Immune surveillance against cancer

• Increased frequency of cancers in the setting of immunodeficiency.
  – Persons with congenital immunodeficiencies develop cancers at about 200 times the rate in immunocompetent individuals.
  – Immunosuppressed transplant recipients and persons with AIDS also have an increased incidence of malignancies.
  – Particularly illustrative is the rare X-linked recessive immunodeficiency disorder termed XLP (X-linked lymphoproliferative syndrome), caused by mutations in the gene encoding an adapter protein, SAP, which participates in NK and T-cell signaling pathways. In affected boys, EBV infection does not take the usual self-limited form of infectious mononucleosis but instead evolves into a chronic or sometimes fatal form of infectious mononucleosis or, even worse, a lymphoma comprised of EBV-infected B cells.

• Most cancers occur in persons who do not suffer from any overt immunodeficiency. It is evident, then, that tumor cells must develop mechanisms to escape or evade the immune system in immunocompetent hosts.
The 3 “E”s: Elimination

A) Elimination: Immune System Eradicates Cancer Cells

Normal cells/tissue

Immune Protection

Immune Evasion
The 3 “E”s: Equilibrium

B) Equilibrium: Immune System Controls Cancer Cells

Abnormal cells/tissue outgrowth controlled
C) Escape: Cancer Cells Evade Immune System

Abnormal cells/tissue continue to replicate
Evasion of the immune response

- **Failure to produce tumor antigen**
  - Antigen-loss variant of tumor cell
  - Lack of T cell recognition of tumor

- **Mutations in MHC genes or genes needed for antigen processing**
  - Class I MHC-deficient tumor cell
  - Lack of T cell recognition of tumor

- **Production of immunosuppressive proteins or expression of inhibitory cell surface proteins**
  - Inhibitory ligand, Inhibitory receptor
  - Immunosuppressive cytokines
  - Inhibition of T cell activation
Mechanisms of evasion of the immune response

• Selective outgrowth of antigen-negative variants.
  – During tumor progression, strongly immunogenic subclones may be eliminated, an example of immunoediting that has already been discussed.

• Loss or reduced expression of MHC molecules.
  – Tumor cells may fail to express normal levels of HLA class I molecules, thereby escaping attack by cytotoxic T cells. Such cells, however, may trigger NK cells if the tumor cells express ligands for NK cell activating receptors.
Mechanisms of evasion of the immune response

• Secretion of immunosuppressive factors by cancer cells.
  – Tumors may secrete products that inhibit the host immune response.
    • TGF-β is secreted in large quantities by many tumors and is a potent immunosuppressant.
    • Other tumors secrete galectins, sugar-rich lectin-like factors that skew T-cell responses so as to favor immunosuppression.
    • Many other soluble factors produced by tumors are also suspected of inhibiting the host immune response, including interleukin-10, prostaglandin E2, certain metabolites derived from tryptophan, and VEGF, which can inhibit the diapedesis of T cells from the vasculature into the tumor bed.

• Induction of regulatory T cells (Tregs).
  – Some studies suggest that tumors produce factors that favor the development of immunosuppressive regulatory T cells, which could also contribute to “immunoevasion.”
Mechanisms of evasion of the immune response

• Activation of immunoregulatory pathways.
  – tumor cells actively inhibit tumor immunity by engaging normal pathways of immune regulation that serve as “checkpoints” in immune responses.

• Tumor cells may downregulate the expression of costimulatory factors on antigen-presenting cells, such as dendritic cells
  as a result, the antigen-presenting cells fail to engage the stimulatory receptor CD28 and instead activate the inhibitory receptor CTLA-4 on effector T cells.

• This not only prevents sensitization but also may induce long-lived unresponsiveness in tumor-specific T cells.

• Tumor cells also may upregulate the expression of PD-L1 and PD-L2, cell surface proteins that activate the programmed death-1 (PD-1) receptor on effector T cells.

• PD-1, like CTLA-4, may inhibit T cell activation.
Forms of Cancer Immunotherapy

• Non-Specific: Generalized, Non-Antigen-Specific Immune Activation

• Specific: Antigen-specific Response Induced in the Mouse or Patient or Passively Transferred in from Donor Source
Forms of Cancer Immunotherapy

**Active**: Induced Directly in the Tumor-Bearing Animal or in the Patient

- Can be Specific or Non Specific

**Passive or Adoptive**: Immunologically Active Material Transferred into Mouse or Patient as a Passive Recipient

- Can be Specific (Antibodies, T-Cells, Antigen-presenting cells – Dendritic Cell Vaccines)
- Or Non-Specific (Non-specifically-activated T-Cells; Cytokines)
Active Non-Specific Immunotherapy

Induced in the Patient or Mouse: Non-Antigen-specific

Bacterial Extracts: Non-Specific Immune Adjuvants
- BCG: Bacillus Calmette-Guerin (Attenuated Bovine Tuberculosis Bacterium)
- Membrane Extracts of BCG
- C Parvum: Corynebacterium parvum (related to diphtheria bacillus)

Bacterial Endotoxins: Muramyl Dipeptide

Chemical Adjuvants:
- Levamisole
- Poly IC (Poly-inosinic-Poly-cytidylic acid)

Cytokines: (Can be actively induced or passively transferred)
- Interferons
- Interleukin 2 (IL2)
- Tumor Necrosis Factor (TNF)
Tumor Necrosis Factor (TNHa) in Immunotherapy of Cancer (Passive or Active)
Adoptive Immunotherapy of Cancers
(Passive: Donor to Recipient)

Non-Specific:
• Lymphokine-activated Killer Cells (LAK Cells)\n• Cytokines (TNF alpha; IL2; Interferon)

Specific: Molecular Transfer
• Monoclonal Antibodies (antibodies are specific)

Specific: Cellular Transfer (antigen-specific)
• Tumor-Infiltrating Lymphocytes (TIL Cells)
• Engineered Antigen-Presenting Cells (Dendritic Cells)
LAK Cells in Mice & Humans

1. Isolate lymphocytes from blood.
2. Lymphocytes are cultured with IL-2 for 3 days.
3. Intravenous infusion of LAK cells and IL-2.
4. LAK cells infiltrate the tumor.
5. IL-2 activates LAK cells.

Healthy mouse

Mice with tumor

Spleen

Solafite lymphocytes

Captured with IL-2 for 3 days

LAK cells

IL-2

LAK Cells

Lung tumor

Blood return

MACHINE isolates lymphocytes from blood.

LAK cells, IL-2}

Lymphocytes cultured with IL-2 for 3 days.
Schematic overview of the high-affinity interleukin-2 receptor complex, including the receptor chains, downstream signaling components and target genes.
Cytokines – IL-2 Targets

• This is a basic overview of the mechanism of
Adoptive Immunotherapy

• Immunotherapy
  – IL–2, alone, can be used as a cancer treatment by activation of cells which are cytotoxic for the tumor

• Some success has been obtained with renal cell carcinoma and metastatic melanoma.
  – Rosenberg study
Adoptive Immunotherapy using TILs

- Technique involves isolating tumor-infiltrating lymphocytes (TIL’s)
  - Primarily activated cytotoxic T-lymphocytes
  - Lymphocytes with antitumor reactivity found within the tumor
- Expanding their number artificially in cell culture by means of human recombinant interleukin-2.
- The TILs are then put back into the bloodstream, along with IL-2, where they can bind to and destroy the tumor cells.
This figure shows adoptive immunotherapy isolation techniques.
The Immune Model

- LAK or TIL cells
  - cell death

- Effector T Cells
  - synthesis
  - IL-2
  - +ve
  - degradation
  - external source

- Tumour Cells
  - cell death
  - population growth
The Immune Pathway

1. IL-2 binds IL-2 Receptor
2. Effector Cell with bound IL-2
3. Effector Cell Activated
4. Tumor Eating Site Activated
5. Locates Tumor
6. Attack Mode!

Think Michaelis-Menton
The Model

Change in Effector cells over time
Change in Tumor cells
Change in IL-2

Antigenicity and size of tumor
Death rate
IL-2 Stimulation
Effector Cell Injection
Logistic growth rate of Tumor
Killing rate by Effector cells
IL-2 Injection

\[
\frac{dx}{d\tau} = cy - \mu_2x + \frac{p_1xz}{g_1 + z} + s_1
\]

\[
\frac{dy}{d\tau} = r_2y(1 - by) - \frac{axy}{g_2 + y}
\]

\[
\frac{dz}{d\tau} = \frac{p_2xy}{g_3 + y} - \mu_3z + s_2
\]
Implications of Model

• No Treatment Case
  – (1) For very low $c$, tumor reaches a stable steady state.

  – (2) For intermediate $c$, tumor has large, long-period oscillations.

  – (3) For high $c$, tumor has small, low-period oscillations.
Reality of IL-2 Therapy

• High-dose IL-2 therapy alone has been shown to cause a variety of side effects.
  – Generally High Toxicity, e.g. Capillary Leak Syndrome

• Most of these are explainable by a runaway immune system.

• Question: IL-2 therapy does work in some cases; why does the model not predict this?
  – New models that incorporate “stop of treatment due to toxicity”
Overview: Adoptive T cell therapy

1. Isolation of TILs or tumor specific T-cells from blood
2. Expand and activate T-cells *ex vivo*
3. Infuse the "boosted" T-cells into the patient.

**Target therapy with Tumor specific T cells**
- Cancer: Melanoma
- Autologous tumor infiltrating lymphocytes (TILs); “Live drug”

**Advantages**
- High response rate (>50%),
- Long-term remission,
- Less toxic & gentler to the patient

**Limitation:**
- Extraction of TILs,
- Cell manufacturing

**Possible alternate**
- T cell Engineering (CAR-T cells)

Rosenberg SA & Dudley ME 2009 Current Opinion of Immunology
Adoptive T cell therapy: CAR-T cells

- **CAR-T cells (Chimeric antigen receptor-T cells)**
  - T cells transduced with tumor-specific CAR
  - CAR: Single fusion molecule with antigen specificity plus signaling domain
  - Three types of CAR: First/second/generations
    - Based on co-stimulatory receptors
  - Cancer: Solid tumor & hematological malignancies

**Advantages of CAR T cells**

- “Live drug”
- Tumor recognition independent of HLA (no HLA typing needed)
- Multiple anti-tumor immuno-modulators can be engineered
- Target variety of antigens (protein, carbohydrate, glycolipid)

Clinical significance of CAR-T cells

<table>
<thead>
<tr>
<th>Target</th>
<th>CAR</th>
<th>Cancer</th>
<th>Objective response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD19</td>
<td>CAR:CD28-CD3ζ</td>
<td>Lymphoma and CLL</td>
<td>N=7: 1CR, 5 PR &amp; 1SD</td>
</tr>
<tr>
<td></td>
<td>CAR:CD137-CD3ζ</td>
<td>ALL</td>
<td>2CR</td>
</tr>
<tr>
<td></td>
<td>CAR:CD28-CD3ζ</td>
<td>ALL</td>
<td>5CR</td>
</tr>
<tr>
<td>CD20</td>
<td>CAR:CD137-CD28-CD3ζ</td>
<td>NHL</td>
<td>N=3: 1PR, 2NED</td>
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<tr>
<td>CEA</td>
<td>CAR-CD3ζ (1st gen)</td>
<td>Colorectal &amp; breast</td>
<td>N=7: minor responses in two patients</td>
</tr>
<tr>
<td>GD2</td>
<td>CAR-CD3ζ (1st gen)</td>
<td>Neuroblastoma</td>
<td>N=19: 3CR</td>
</tr>
<tr>
<td>ERBB2</td>
<td>CAR:CD28-CD137-CD3ζ</td>
<td>Colorectal cancer</td>
<td>N=1, patient died</td>
</tr>
</tbody>
</table>

Kershaw et. al. 2013 Nature Reviews cancer
Challenges of CAR-T cells

- **Toxicities**
  - **On target/off tumor toxicities**
    - Metastatic colon cancer patient died after 5 days of infusion of ERBB2+CAR-T cells
      - Low levels of ERBB2 express on lung epithelium (lung tox)
    - Renal cell carcinoma: 5/11 patients developed liver toxicity
  - **Cytokine syndrome**
    - Elevated levels of pro-inflammatory cytokines
      - Treatable by anti-IL-6mAb and steroids
Some Examples of Active, Specific Immunotherapy (Tumor Vaccines): Induced in the Patient

Unmodified Killed or Attenuated Tumor Cells
Unmodified Tumor Antigens
Altered Tumor Cells or Tumor Antigens
• Lipidized Tumor Antigens
• Chemically Derivatized Tumor Antigens
• "Xenogenized" Tumor Cells (Virally-infected Cells)
• Exposure of Cryptic Antigens
Antigenic Peptides from Tumor Antigens
Autologous Tumor Cells Vaccine for Glioblastoma Multiforme

April, 2012

50% increase in survival time (48 weeks vs 33 weeks)
Minimal side reactions
40 Patients


A phase 2 multicenter trial of about 40 patients with recurrent glioblastoma -- an aggressive brain cancer that typically kills patients within 15 months of diagnosis -- showed that the vaccine safely increased average survival to nearly 48 weeks, compared with about 33 weeks among patients who didn't receive the treatment. The six-month survival rate was 93 percent for the vaccinated group, compared with 68 percent for 86 other glioblastoma patients, who were treated with other therapies.
Applications of Monoclonal Antibodies

Monoclonal Antibody Diagnosis and Tumor-Imaging

• Prostate-specific Antigen (PSA)
• Carcino-embryonic Antigen (CEA)
• Colon Carcinoma A33 Antigen

Monoclonal Antibody Targeting

• Immuno-toxins
• Monoclonal antibodies directed to tumor cell surface markers
  – Can inhibit the cancer cell function
  – Can target the cancer cell for destruction by the immune response
Imaging on Metastatic Colon Carcinoma with Radioactive-Iodine-Labelled Monoclonal Ab to A33 Ag
Lloyd Old, Scientific American, August, 1996, p. 138)
Anti-CD20 Monoclonal Antibodies in Treatment of B-Cell Lymphoma/Leukemia

Rituxan#, Zevalin# (Yttrium 90 Radio-isotope Beta-emitter), and Bexxar* (Iodine-131 Radio-isotope Beta and Gamma Emitter)

# IDEC Pharmaceuticals. *Corixa and Glaxo Smith Kline

Rituxan binds CD20 cell surface markers on pre-B and B cells. The drug also induces antibody-dependent, cell-mediated cytotoxicity and complement-mediated cytolysis in vitro.
Herceptin: Genentech

Anti-HER2/Neu Growth Factor Receptor in Breast Cancer

Avastin:

Antibody to Vascular-Endothelial Growth Factor Receptor (Anti-angiogenesis Therapy)

Erbitux

Antibody to Epidermal Growth Factor Receptor

(See page 141, Immunology, 6th Edition)
IMMUNE SYSTEM has a safety mechanism that prevents a mature T cell from mounting an immune attack against its host. Before a T cell can attack, it must receive two signals. The first is the binding of an antigen to the T cell’s receptor. The second is typically the secretion and binding of a protein, B7, for example (left). If a T cell is exposed to a self-protein that is presented on a nonstimulatory cell, the T cell will die or become inactive (right).

Role of CD28 Antigen: Costimulatory Signals
STIMULATION by two molecules is needed to activate lymphocytes. The diagrams depict a CD8 T cell and a macrophage. Without the presence of antigens, the T cell is dormant (left). Yet antigen alone cannot induce T cell function (center). In this way, a response to the body’s own antigen does not occur; in fact, this first signal turns off the T cell. If the macrophage is infected, it will produce a molecule called B7, which acts on the T cell’s CD28 surface protein (right). Only when an antigen and the B7 molecule are present on the same cell does the T cell proliferate.

Co-Stimulation by Antigen-presenting Cells of T-Cells
CANCER CELLS can elude attack by lymphocytes even if they bear distinctive antigens. That absence of immune response may occur because cancerous cells lack the proper costimulatory molecules (left). Researchers are attempting to induce the body to fight tumors by inserting the molecule B7 into cancer cells (center). When B7 engages CD28, a complementary molecule on the surface of T cells, it generates a signal that instigates an assault on the cancer cells (right).

Co-Stimulatory Signals in T-Cell Mediated Tumor Cell Cytotoxicity
Chekpoints and chekpoint inhibition

A Suppression of T-Cell Activation in Lymph Node

B Activation of T Cell by Antibody Blockade of CTLA-4

Figure 3: T-cell activation in the lymph node.
Figure 1. T-cell Activation in the Lymph Node.

Two immunologic signals are required for T-cell activation in the lymph node: stimulation of the T-cell receptor (TCR) by the MHC (immunologic signal 1), and stimulation of CD28 by the B7 costimulatory molecules (immunologic signal 2). However, binding of the B7 costimulatory molecules to CTLA-4 blocks immunologic signal 2, and therefore blocks T-cell activation. Antibody blockade of CTLA-4, for example, by ipilimumab, derepresses signaling by CD28, permitting T-cell activation.
Checkpoint inhibition in the tumor environment

A) Suppression of T-Cell Activation by Tumor

Binding of PD-1 by one of its ligands blocks TCR signaling and therefore blocks T-cell activation.

B) Activation of T Cell by Antibody Blockade of PD-1 Signaling

Antibody blockade of PD-1 (e.g., by pembrolizumab or nivolumab) or one of its ligands permits T-cell activation.
Chekpoint inhibition in the tumor environment

Figure 2. T-cell Activation in Tumor Milieu.
During long-term antigen exposure, such as occurs in the tumor milieu, the programmed death 1 (PD-1) inhibitor receptor is expressed by T cells (Panel A); it suppresses the effect of the TCR on T-cell activation. Blockade of PD-1 or its ligand (Panel B) (e.g., by pembrolizumab or nivolumab) derepresses TCR signaling, thereby permitting T-cell activation.
Combination immunotherapy

**Figure 1 | Receptor–ligand pairs of the immune system that are amenable to pharmacological manipulation with immunostimulatory monoclonal antibodies.** This is a representation of the receptor and cognate ligands on juxtaposed cells forming immune synapses (antigen-presenting cell (APC) on the left and T cell on the right). The co-stimulatory (black pointed arrows) or co-inhibitory (grey inhibitory arrows) outcome of receptor ligation is provided for each interaction. Signal 1 refers to antigen-specific recognition by the T cell receptor (TCR). It is of note that these interactions take place in transient cell-to-cell interactions, named immune synapses¹, in which the surface of interaction between cells is highly structured, permitting complex levels of crosstalk among receptors. B7-H3, B7 homologue 3 (also known as CD276); B7-H4, B7 homologue 4 (also known as VCTN1); BTLA, B lymphocyte and T lymphocyte attenuator; CD28H, CD28 homologue; CD40L, CD40 ligand; CD137L, CD137 ligand (also known as TNFSF9); CEACAM1, carcinoembryonic antigen-related cell adhesion molecule 1; CTLA4, cytotoxic T lymphocyte-associated antigen 4; GITR, glucocorticoid-induced TNFR family-related protein; GITRL, GITR ligand; HHLA2, HERV-H LTR-associating 2 (also known as B7-H7); HVEM, herpes virus-entry mediator (also known as TNFRSF14); Ig, immunoglobulin; LAG3, lymphocyte activation gene 3 protein; LIGHT, HVEM ligand (also known as TNFSF14); MHC, major histocompatibility complex; OX40L, OX40 ligand (also known as TNFSF4); PD1, programmed cell death protein 1; PD-L1, PD1 ligand; TIGIT, T cell immunoreceptor with Ig and ITIM domains; TIM3, T cell Ig mucin domain-containing 3; TNF, tumour necrosis factor; TNFR, TNF receptor; VISTA, V-domain Ig suppressor of T cell activation (also known as PD1 homologue).

Updated figure from REF. 6, Nature Publishing Group.
Currently tested combination approaches
New approaches

Figure 4 | Building immunotherapy combinations on the pillar of PD1 or PDL1 blockade, and steps in the development of an immunotherapy combination. A schematic representation of potential treatment combinations involving programmed cell death protein 1 (PD1) or PD1 ligand (PDL1) blockade. Given the clinical success of PD1–PDL1 blockade in multiple diseases, this pathway will probably become the foundation for immunotherapy combinations. Importantly, data from preclinical models show that PD1–PDL1 blockade acts synergistically with most, if not all, of the other immunotherapy modalities shown. Development and personalization of these PD1–PDL1 blockade combinations should be guided by biomarkers. Additionally, triplets or higher order-of-magnitude combinations have the potential to further increase efficacy. BTLA, B lymphocyte and T lymphocyte attenuator; CTLA4, cytotoxic T lymphocyte-associated antigen 4; GITR, glucocorticoid-induced tumour necrosis factor receptor family-related protein; IDO1, indoleamine-2,3-dioxygenase 1; iNOS, inducible nitric oxide synthase; LAG3, lymphocyte activation gene 3 protein; mAb, monoclonal antibody; TIGIT, T cell immunoreceptor with immunoglobulin and ITIM domains; TIM3, T cell immunoglobulin and mucin domain-containing 3; T_{Reg} cell, regulatory T cell.