The editors of Science magazine have chosen Cancer Immunotherapy as their Breakthrough of the Year for 2013. The magazine cover image features work done in the Cancer Research Laboratory at Berkeley in the 1990s by Jim Allison and colleagues. See the December 20th issue of Science for more details or read about the groundbreaking cancer research done in the CRL, The Story of Yervoy (Ipilimumab).

Strategic intervention to enhance/suppress the immune response
Examples: Checkpoint blockade...Chimeric Antigen Receptors...Bispecific antibodies
After decades of investigation establishing principles in animal models, it has become possible to treat and cure some diseases in humans by interventions that target immunological functions. Immunotherapy, described by Science magazine as the ‘Breakthrough of the Year’ in 2013, has led to major changes in the standard of care for some diseases and is particularly useful in infectious disease, autoimmunity, allergy/asthma, and especially cancer.

The Goal
The Human Immunology and Immunotherapy Initiative will develop needed infrastructure, train future scientific leaders, and recruit faculty to complement existing strengths, with the goal of establishing preeminence in human immune system-targeted therapies.

Existing Strengths
The integrated campus with outstanding facilities for biomedical research, patient care, medical education and biotechnology provides an exceptionally strong foundation from which the existing immunology and clinical programs can expand their focus to become an internationally recognized center for human immunology and immunotherapy.
Inhibitory (checkpoint) receptors constrain the immune response

TCR Signal 1
(TCR recognizes MHC-Ag on APC)

Signal 2
interaction with co-stimulatory molecule CD80/86
(+ CD28 or - CTLA-4)

APC displaying processed antigen peptide in MHC

Tumor antigen

Tumor

Activation
cytokines, proliferation, migration...

if (+) Signal 2 dominates

PD-1 expressed and traffic to tumor

Inhibition
PD-1 interaction with PD-L1 results in T cell death...

Acronym key
APC – Antigen-Presenting Cell
Ag – Antigen
CD28 – Cluster of Differentiation 28
CD80/86 – Cluster of Differentiation 80/86
CTLA-4 – Cytotoxic T Lymphocyte-Associated Antigen-4
PD-1 – Programmed cell Death protein-1
PD-L1 – Programmed cell Death Protein-1 Ligand
TCR – T Cell Receptor

modified from 2013 American Association for Cancer Research
Negative signals affect T cell activation: removing the brakes

Molecules on the antigen-presenting cell (on the left side of the figure) interact with specific receptors on the T cell (right side of the figure)

Stimulation through these receptors leads to a positive (+) response, such as cell activation (arrows with a ◦) OR a negative (-) response, such as inhibition (arrows with a ◦)

Blockade of inhibitory receptors enhances T cell activation and killing of tumor cells
### Candidate therapeutics for checkpoint inhibitor blockade

<table>
<thead>
<tr>
<th>Target</th>
<th>Biological function</th>
<th>Antibody or Ig fusion protein</th>
<th>State of clinical development*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTLA4</td>
<td>Inhibitory receptor</td>
<td>Ipilimumab</td>
<td>FDA approved for melanoma, Phase II and Phase III trials ongoing for multiple cancers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tremelimumab</td>
<td>Previously tested in a Phase III trial of patients with melanoma; not currently active</td>
</tr>
<tr>
<td>PD1</td>
<td>Inhibitory receptor</td>
<td>MDX-1106 (also known as BMS-936558)</td>
<td>Phase I/II trials in patients with melanoma and renal and lung cancers</td>
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<td></td>
<td></td>
<td>MK3475</td>
<td>Phase I trial in multiple cancers</td>
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<tr>
<td></td>
<td></td>
<td>CT-011†</td>
<td>Phase I trial in multiple cancers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AMP-224§</td>
<td>Phase I trial in multiple cancers</td>
</tr>
<tr>
<td>PDL1</td>
<td>Ligand for PD1</td>
<td>MDX-1105</td>
<td>Phase I trial in multiple cancers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple mAbs</td>
<td>Phase I trials planned for 2012</td>
</tr>
<tr>
<td>LAG3</td>
<td>Inhibitory receptor</td>
<td>IMP321‖</td>
<td>Phase III trial in breast cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple mAbs</td>
<td>Preclinical development</td>
</tr>
<tr>
<td>B7-H3</td>
<td>Inhibitory ligand</td>
<td>MGA271</td>
<td>Phase I trial in multiple cancers</td>
</tr>
<tr>
<td>B7-H4</td>
<td>Inhibitory ligand</td>
<td></td>
<td>Preclinical development</td>
</tr>
<tr>
<td>TIM3</td>
<td>Inhibitory receptor</td>
<td></td>
<td>Preclinical development</td>
</tr>
</tbody>
</table>

A variety of antibodies or immunoglobulin (Ig) fusion proteins have been produced to target specific receptors and thereby modulate the immune response.

**Example:** CTLA4 is an inhibitory receptor expressed on T cells that when blocked by the therapeutic ipilimumab unleashes the immune system to attack the tumor.
Chimeric Antigen Receptors
Homogenize Antigen Specificity of “killer” T cells...bringing more soldiers to the fight

T cells are isolated from the patient’s blood and modified to express a receptor specific for a target antigen expressed by the tumor cells. These cells are then infused into the patient where they attack the tumor.

This type of immunotherapeutic is called ‘Chimeric Antigen Receptor T cells’ or CAR-T cells

The ‘chimeric antigen receptors’ (CARs) on the T cells (shown on the right) are composed of an extracellular portion called an scFv (single-chain Fragment variable) that is specific for the target of interest on the tumor cells. The intracellular portion of the CAR contains amino acid sequence motifs that upon receptor interaction nucleate the transduction of signals to kill.

CAR-T cells were originally developed for CD19+ B cell lymphoma and chronic lymphocytic leukemia
**Bispecific T cell Engager (BiTE)**

**Antibodies to Redirect T Cell Specificity Toward the Tumor**

BiTEs are antibodies with two specificities; one specificity at each end that are linked so that they bridge the T cell and the target tumor cell, holding the killer cell and the target cell together.

One end is a single chain fragment antibody specific for an antigen expressed on the tumor cells and the other end is a single chain fragment antibody specific for an antigen, CD3, expressed on the T cell. CD3 is a molecule that is part of the T cell receptor that when bound (in this case by the BiTE) will activate the T cell, resulting in destruction of the target or the tumor cell.
Some BiTE antibodies in clinical trials

A variety of BiTE antibodies have been produced to simultaneously bind specific antigens on T cells to specific antigens on tumors (or other tissues)

Example: Blincyto is a BiTE that simultaneously binds CD19 (an antigen present on all B cells, including cancers of B cell origin) and CD3 (an antigen present on all T cells) leading to activation of the T cell and destruction of the adjacent CD19+ B cell
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Activities of the HI³

Develop needed infrastructure

- Establish human immune monitoring and mass cytometry facility
- Facilitate translational research by promoting networking and access to human tissues
- Provide huSCID preclinical models
- Enable GMP production of immunotherapeutics
- Provide clinical research support

Recruit new faculty

Train the next generation of scientists