Jill O’Donnell-Tormey, Ph.D.
Cancer Research Institute

WELCOME
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• Bay Area Cancer Connections
• Coalition for Clinical Trial Awareness
• Colon Cancer Alliance
• Cancer Support Community
• Fight Colorectal Cancer
• Focused Ultrasound Foundation
• FORCE

• GI Cancers Alliance
• Head and Neck Cancer Alliance
• Imerman Angels
• Immunotherapy Foundation
• Let Life Happen
• Parker Institute for Cancer Immunotherapy
• Patient Empowerment Network
• UCSF Helen Diller Family Comprehensive Cancer Center
Our Guest Faculty

Scientific Experts

**Ezra Cohen, M.D.**
University of California San Diego

**Lewis Lanier, Ph.D.**
University of California San Francisco

**Aaron Miller, M.D., Ph.D.**
University of California San Diego

**Stanley Riddell, M.D.**
Fred Hutchinson Cancer Research Center

Patient & Caregiver Experts

**Janie Ferling**
Melanoma Survivor

**Johanna Packard**
Caregiver (Prostate Cancer)

**Philip Prichard**
Kidney Cancer Survivor
Lewis Lanier, Ph.D.
UCSF Helen Diller Family Comprehensive Cancer Center
Parker Institute for Cancer Immunotherapy

IMMUNOTHERAPY BASICS
Cut ‘em, Burn ‘em, Poison ‘em

We now have a new weapon against cancer – your immune system
The New York Times

*Patient's Cells Deployed to Attack Aggressive Cancer*

The Washington Post

Health & Science

*New therapies raise hope for a breakthrough in tackling cancer*
Paul Ehrlich (1909) Concept of cancer immunosurveillance. Predicted that cancer would occur at "incredible frequency" if host defenses did not prevent the outgrowth of continuously arising cancer cells.

Lewis Thomas (1957) “primary function of cellular immunity….is to protect from neoplastic disease”

Macfarland Burnet (1957) “It is by no means inconceivable that small accumulations of tumour cells may develop and because of their possession of new antigenic potentialities provide an effective immunological reaction with regression of this tumor and no clinical hint of its existence”
Spontaneous Tumors in Immunocompetent and Immunodeficient Mice

Mice without T and B cells

Mice without T and B cells and unable to respond to interferons
Cancer Immunotherapy

In the beginning... Dr. William Coley 1890s

Treating cancer with bacterial products to stimulate the patient’s immune system
Immunity to Cancer – The Players

Antibodies
– made by your B cells or given as drugs

Myeloid cells
– good ones stimulate the immune system (dendritic cell) and kill tumors (macrophages)
– bad ones suppress immune responses

T cells and Natural Killer cells
– good ones kill tumors (cytotoxic and helper T, NK)
– bad ones suppress immune responses (Treg)
Monoclonal antibody coats tumor cells

Natural Killer cells and macrophages with Fc receptors bind to the tail (Fc) of the antibody and kill the tumor

Rituximab – targets CD20 on B cell tumors
Trastuzumab – targets her2 on breast cancer
Daratumumab – targets CD38 on myeloma
CetuximAb – targets EGFR on colon cancer
Using Antibodies to Boost the Immune Response to Cancer

Monoclonal Antibody
Anti-myeloma activity

Myeloma Cell

Surface Marker
eg CD38

Monoclonal Antibody
eg Daratumumab

NK Cell

Fc Receptor
Immune Cells Are Controlled by a Balance of Activating and Inhibitory Signals

T cells and Natural Killer cells

Activating protein

Activating receptor

Inhibitory protein

Inhibitory Receptor

Tumor cells

Kill & expand

Inhibit

Killing & expansion

Fail-safe prevents immune cells from attacking healthy self tissues (autoimmunity)
Activating protein T cells and Natural Killer cells

Activating receptor

Inhibiting protein

Inhibitory Receptor

Tumor cells

Block the inhibitory signal - Enhance tumor killing!

"Checkpoint Blockade" - Use Antibodies to Block the Inhibitory Receptors to Boost the Immune Response
Checkpoint Inhibitors – Antibodies to Inhibitory PD-1 Receptor

PD-L1/PD-1 binding inhibits T cell killing of tumor cell

Blocking PD-L1 or PD-1 allows T cell killing of tumor cell
CTLA-4 Blockade: Anti-Tumor Immunity, but Autoimmunity

The good news...

Lung

The bad news...

Skin

Colon

Colon

CD3

Liver

Phan et al. PNAS (2003) 100:8372
New immunotherapy drug behind Jimmy Carter's cancer cure

Former president given pembrolizumab, one of the most promising new drugs in the treatment of cancer
Using Antibodies to Block Inhibitory Receptors or Stimulate Activating Receptors Boosts Immune Responses

Nature. 2011 480:480-9
Activating and Co-Stimulatory Receptors

- T cells and NK cells
- Kill & expand
- Boosts
- Activating receptor
- Activating receptor
- Costimulatory Receptor
- Agonist antibody to Costimulatory Receptor
- Enhances Immune Response
- Tumor cells
Combined PD-1 and CTLA-4 Blockade in Melanoma Pts

PFS Among BRAF WT Patients

- PFS among BRAF MT patients (8.5 mo for NIVO + IPI, 2.7 mo for IPI monotherapy) was similar to that observed among BRAF WT patients

HR = hazard ratio
## Combination Therapies in Trials

### Table 3 Clinical trials of combination therapies with molecularly targeted drugs

<table>
<thead>
<tr>
<th>Combination</th>
<th>Tumor</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-1 mAb (Nivolumab)</td>
<td>LAG3 (BMS-986016)</td>
<td>Solid Tumors</td>
</tr>
<tr>
<td>PD-1 mAb (Nivolumab)</td>
<td>B7-H3 (Enoblituzumab)</td>
<td>Solid Tumors</td>
</tr>
<tr>
<td>PD-1 mAb (Pembrolizumab)</td>
<td>B7-H3 (Enoblituzumab)</td>
<td>Solid Tumors</td>
</tr>
<tr>
<td>PD-1 mAb (Nivolumab)</td>
<td>KIR (Lirilumab)</td>
<td>Solid Tumors</td>
</tr>
<tr>
<td>PD-L1 mAb (MEDI4736)</td>
<td>OX40 (MEDI6383)</td>
<td>Solid Tumors</td>
</tr>
<tr>
<td>PD-1 mAb (Nivolumab)</td>
<td>4-1BB (Urelumab)</td>
<td>Solid tumors and B-cell non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>PD-1 mAb (Nivolumab)</td>
<td>ICOS (JTX-2011)</td>
<td>Solid Tumors</td>
</tr>
<tr>
<td>Pd-1 mAb (PDR001)</td>
<td>GITR (GWN323)</td>
<td>Solid Tumors and Lymphomas</td>
</tr>
<tr>
<td>PD-1 mAb (Nivolumab)</td>
<td>CD27 (Variliumab)</td>
<td>Solid Tumors</td>
</tr>
<tr>
<td>PD-L1 mAb (Atezolizumab)</td>
<td>CD27 (Variliumab)</td>
<td>Solid Tumors</td>
</tr>
<tr>
<td>PD-1 mAb (Nivolumab)</td>
<td>GM.CD40L (vaccine for NSCLC)</td>
<td>Lung (NSCLQ)</td>
</tr>
<tr>
<td>PD-L1 mAb (Atezolizumab)</td>
<td>VEGF inhibitors (Bevacizumab cediranib)</td>
<td>Ovarian Cancer</td>
</tr>
<tr>
<td>PD-L1 mAb (MEDI4736)</td>
<td>PARP inhibitors (Olaparib)</td>
<td>S tumors</td>
</tr>
<tr>
<td>PD-L1 mAb (MEDI4736)</td>
<td>Multi-kinase inhibitor (Sunitinib)</td>
<td>Solid tumors</td>
</tr>
<tr>
<td>PD-1 mAb (Pembrolizumab) with SBRT</td>
<td>Multi-kinase inhibitor (Sunitinib)</td>
<td>TKI refractory mRCC*</td>
</tr>
<tr>
<td>PD-L1 mAb (Durvalumab)</td>
<td>EGFR inhibitor (Osimertinib)</td>
<td>Lung (NSCLQ)</td>
</tr>
</tbody>
</table>

*Tyrosine kinase inhibitor refractory metastatic renal cell cancer
Autoimmunity Caused by Checkpoint Blockade
- combinations can increase toxicity

CTLA-4  CTLA-4  + PD-1  PD-1  PD-1

Bar chart showing incidence per 1,000 person months for various side effects:
- Increased ALT
- Colitis
- Hyperthyroidism
- Hypophysitis
- Hypothyroidism
- Pneumonitis

Legend:
- Ipilimumab
- Ipilimumab + Nivolumab
- Nivolumab
- Pembrolizumab

Grade 1–2 in light colours and grade 3–5 in darker colours

Source: Boutros et al., Nature Reviews Clinical Oncology, 2016
Tumor Antigens - What the Immune System Recognizes

Tumor-specific “neo-antigens”
- Expressed ONLY by tumors due to genetic mutations

Tumor-associated antigens
- Preferentially expressed by tumors (overexpressed normal proteins due to gene amplification or epigenetics)

Oncofetal antigens
- Expressed by tumors in adult, but also expressed by fetal (not adult) tissues

Viral antigens
- Expressed by oncogenic viruses (HPV, EBV, KSV)
Genetic Mutations Are Frequent in Some Tumors (Melanoma, Lung, etc.) – Rare in Others

Science 2015 – Schumacher & Schreiber
Adoptive T Cell Therapy

T cell with tumor-specific T cell receptor

APC
pMHC
TCR
CD28L
CD28
CD3z

T cell with engineered Chimeric Antigen Receptor (CAR)

Ectodomain
(Antigen recognition)

Linker

Light (or heavy) chain
Heavy (or light) chain
Derived from an scFv or known specificity

Hinge region
Derived from CD8 or IgG4

Lipid bilayer

Transmembrane domain

Co-stimulatory molecule(s)

Endodomain
(Stimulation)

Stimulatory molecule
CD3z chain or CD8 chain

None, one, or more of:
CD27, CD28, ICOS, 4-1 BB, OX40
Adoptive T cell therapy using antigen-specific CD8⁺ T cell clones for the treatment of patients with metastatic melanoma: In vivo persistence, migration, and antitumor effect of transferred T cells

C. Yee*,†, J. A. Thompson*, D. Byrd*, S. R. Riddell*, P. Roche†, E. Celis†, and P. D. Greenberg*

IL-2 Dose:  
(mU/m²/day)

Infusion#:  
T cell Dose:  

Day 0  |  Day 14  |  Day 35  |  Day 56
---|---|---|---
CTL #1 | IL-2 (0.5) | IL-2 (1.0) | IL-2 (2.0)
3.3 x 10⁹/m² | 3.3 x 10⁹/m² | 3.3 x 10⁹/m² | 3.3 x 10⁹/m²
Adoptive “CAR” T cell therapy

• Isolate patient's peripheral blood T cells
• Lentivirus transduced with "CAR" (chimeric antigen receptor)
• CAR – anti-CD19 antibody fragment fused to intracellular domains of potent T cell signaling subunits
• Re-infuse “CAR”-modified T cells into patient
• Successful for treating children with B cell malignancies (toxicity – loss of normal B cells – forever?; cytokine storm)
In Girl’s Last Hope, Altered Immune Cells Beat Leukemia

By DENISE GRADY  DEC. 9, 2012

Emma Whitehead, with her mother, Karla. Last spring, Emma was near death from acute lymphoblastic leukemia but is now in remission after an experimental treatment at the Children’s Hospital of Philadelphia.

Jeff Swensen for The New York Times
Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia

Shannon L. Maude, M.D., Ph.D., Noelle Frey, M.D., Pamela A. Shaw, Ph.D., Richard Aplenc, M.D., Ph.D., David M. Barrett, M.D., Ph.D., Nancy J. Bunin, M.D., Anne Chew, Ph.D., Vanessa E. Gonzalez, M.B.A., Zhaohui Zheng, M.S., Simon F. Lacey, Ph.D., Yolanda D. Mahnke, Ph.D., Jan J. Melenhorst, Ph.D., Susan R. Rheingold, M.D., Angela Shen, M.D., David T. Teachey, M.D., Bruce L. Levine, Ph.D., Carl H. June, M.D., David L. Porter, M.D., and Stephan A. Grupp, M.D., Ph.D.

- $0.76 \times 10^6$ to $20.6 \times 10^6$ CTL019 cells/kg IV
- 27/30 (90%) children and adults with relapsed ALL achieved complete remission
- All patients developed a cytokine release syndrome
- 73% with relapse-free B cell aplasia.
Active Immunotherapy Vaccination
A decade on, vaccine has halved cervical cancer rate

29 August 2016
Successful Active Vaccination Against Virus-Induced Cancers

- Vaccine to feline leukemia virus for cats
- Vaccine to herpes virus (Marek’s virus) in chickens
- Vaccine to hepatitis B in humans to prevent liver carcinoma
- Vaccination to HPV prevents cervical cancer
How Tumors Escape the Immune System

• Loss of MHC or TAP
• Antigenic variation
• Upregulate inhibitory receptor ligands (e.g. PD-1L)
• Secretion of immunosuppressive factors
  – e.g. TGF-b, IL-10
• T cells don’t penetrate solid tumors efficiently
• Exhausion of T cells
• T regulatory cells suppress anti-tumor responses
Useful resources about cancer immunotherapy

https://www.cancerresearch.org/we-are-cri/what-is-immunotherapy

https://www.mskcc.org/immunotherapy-msk

https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy.html

https://www.mdanderson.org/treatment-options/immunotherapy.html

Panel Discussion

LATEST RESEARCH UPDATE
Scientific Panel

Moderator

Lewis Lanier, Ph.D.

Panel

Ezra Cohen, M.D.
Head and Neck Cancers

Aaron Miller, M.D., Ph.D.
Colorectal Cancer

Stanley Riddell, M.D.
Blood Cancer
Janie Ferling
Melanoma Survivor

PATIENT PERSPECTIVE
Floor 3 - Gallery

LUNCH AND NETWORKING
DEMystifying CLINICAL TRIALS

Brian Brewer
Cancer Research Institute
What Are Clinical Trials?

• Clinical trials are research studies that involve people
• Studies are designed to answer questions about new treatments or ways of using existing treatments better
• Researchers design cancer clinical trials to test new ways to:
  – Treat cancer
  – Find and diagnose cancer
  – Prevent cancer
  – Manage symptoms of cancer and side effects from its treatment
• Through clinical trials, doctors find new ways to improve treatments and the quality of life for people with disease

National Cancer Institute. (October 2016). Taking part in cancer treatment research studies. (NIH Publication No. 16-6249)
Why Are Clinical Trials Important?

- Many treatments today are the results of past clinical trials
- Clinical trials determine whether new treatments are safe and effective and are better than current treatments
- Participating in a clinical trial adds to our knowledge of cancer and helps improve cancer treatment for future patients
- Clinical trials are key to making progress against cancer

National Cancer Institute. (October 2016). *Taking part in cancer treatment research studies.* (NIH Publication No. 16-6249)
What Are Clinical Trial Phases?

Phase 1

Is the treatment safe?

Purpose:
• To find a safe dose
• To decide how the new treatment should be given
• To see how the new treatment affects the human body and fights cancer

Number of people: 15-30

Phase 2

Does it work?

Purpose:
• To determine if the new treatment has an effect on a certain cancer
• To see how the new treatment affects the human body and fights cancer

Number of people: <100

Phase 3

Does it work better?

Purpose:
• To compare the new treatment (or new use of a treatment) with the current standard treatment

Number of people: 100-2k +

National Cancer Institute. (October 2016). *Taking part in cancer treatment research studies.* (NIH Publication No. 16-6249)
Who Can Participate in a Clinical Trial?

• Clinical trials follow strict guidelines that determine who will be able to join the study

• The clinical trial protocol explains what the trial will do, how it will be conducted, and the criteria of who can join

• Common criteria for entering a trial include:
  – Having a certain type or stage of cancer
  – Having received (or not having received) a certain type of therapy in the past
  – Having specific genetic changes in your tumor
  – Being in a certain age group
  – Medical history, current health status
How Can I Find a Clinical Trial?

• Ask your doctor
• Ask another doctor if necessary...
• Contact a patient advocacy organization
  – Seek assistance from a clinical trial navigator, if offered
  – CRI Clinical Trial Finder: 1 (855) 216-0127
• Search online
  – https://www.cancerresearch.org/patients/clinical-trials
  – https://clinicaltrials.gov/
Panel Discussion

IMMUNOTHERAPY CLINICAL TRIALS
Patient and Caregiver Panel

Moderator
Brian Brewer

Panel
Janie Ferling
Melanoma
Johanna Packard
Caregiver (Prostate Cancer)
Philip Prichard
Kidney Cancer
BREAKOUT SESSIONS
Breakout Rooms

Blood Cancers
Stanley Riddell, M.D.

Colorectal Cancer
Aaron Miller, M.D., Ph.D.

Head and Neck Cancer
Ezra Cohen, M.D.

General Networking
Jill O’Donnell-Tormey, Ph.D.

Skyline A, Floor 21
Skyline B, Floor 21
Skyline C, Floor 21
Ballroom (here)
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