“Cancer immunotherapy: an old idea that finally has its day!”

Carl June
March 25, 2016
History of cancer immunotherapy: December 2013
Advances in Health Care: Cardiac Surpasses Cardiac Mortality
Cancer Epidemic: The need for curative therapies

% Survival

Time

Chemotheray
Targeted Therapy
Immunotherapy
Combination?
The Case for Immunotherapy

- Immunotherapy is a “living drug”
- Immune system can evolve to treat the tumor
- Immunotherapy can cure cancers

http://www.cancerresearch.org/
Hallmark of cancer: induction of immune tolerance

Immune therapy can overcome tolerance:

Using Synthetic Biology to Overcome Tolerance
Creation of Bi-specific CAR T cells

**First Generation**
- CD4 / CD8z CARs

**First Generation**
- scFv CARs

**Second Generation**
- scFv CD28z CARs

**Second Generation**
- scFv BBz CARs
- scFv CD27z CARs
- scFv ICOS CARs

**Design of CAR T Cells**

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Irving & Weiss, 1991
Letourneur, 1991
Romeo, 1991
Kuwana, 1987
Eshhar, 1993
Roberts, 1995
Finney, 1998
Maher, 2002
Finney, 2003
Imai, 2004
Milone, 2009
Carpentino, 2009
Song, 2012
Guedan, 2014
Duong, 2013
CAR T Cell Breakthrough: Hype = Reality?

Porter, 2011
Grupp, 2013
Maude, 2014
Garfall, 2015

July 31, 2010
1st CART19 Infusion

Patient Donates Cells

Pediatric Oncology

Cytokine Release Syndrome

Hematologic Malignancies

T cell transfusion

Genetic engineering

Synthetic Biology

Cell Manufacturing

Expand T cells
CAR T CELL THERAPIES

• Durable responses in leukemia, lymphomas myeloma, melanoma

• First example of “synthetic immunity”

• Immunotherapy is a “living drug”

• Immune system can evolve to treat the tumor

• Immunotherapy can “cure” cancers

Jan 31, 2015
Deep Pipeline of Immunotherapies

Nature Reviews Drug Discovery (2016) doi:10.1038/nrd.2015.35
Health Care Challenges:
New Cell Therapy Industry

CAR T Issues:
- Patient specific “n of 1”
- Universal cells?
- Reimbursement models?

Chris Mason et al, Regen Med. 2011
Levine and June, Nature. 2013
Evolving Cellular and Biologic Therapeutics in Oncology

Basic Science

Translational Research

Clinical Science

Clinical Subspecialty

Pre-clinical Development
Process Development
Regulatory Approval
CGMP-Compliant Manufacturing
Clinical Trials Implementation
Summary: Cancer immunotherapy

- Synthetic biology is adding to the “toolbox” for cancer therapies:
  - Engineered herpesvirus (Amgen)
  - CAR T cell pivotal trials underway (Novartis, others)
- Combinatorial trials with other targeted therapies will be synergistic: thousands of combinations need to be tested
- Moonshot initiative may accelerate the “cure” of cancer
Abridged history of cancer immunotherapy: Disappointing until recently

2011: Ipilimumab shows overall survival benefit in melanoma
2012-2014: PD1 and PD-L1 blockade has benefit in melanoma and lung cancer
2011-2014: CAR-modified T cells show durable remissions in leukemia
Advances in Health Care: Cardiac Mortality vs Cancer Mortality
Advances in Health Care: Cardiac Mortality vs Cancer Mortality

Figure 4.1 Mortality rates for major diseases in the United States, 1900–2005

The Case for Cancer Immunotherapy

• No new truly curative anticancer cytotoxic drugs or targeted therapies developed in the last 20 yrs
  – Too many escape routes?
• The immune response is designed to identify and disable “escape routes” that cancers employ
• Immunotherapy can cure cancers
Breakthrough of the Year 2013

CANCER IMMUNOTHERAPY

NOVARTIS ONCOLOGY
Hallmarks of Cancer: Immune Escape and Tolerance

# History of Cancer Treatment Modalities

<table>
<thead>
<tr>
<th>Approach</th>
<th>Surgery</th>
<th>Radiation</th>
<th>Chemotherapy</th>
<th>Targeted Drugs</th>
<th>Immunotherapy</th>
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</thead>
<tbody>
<tr>
<td>Since</td>
<td>1800s</td>
<td>early 1900s</td>
<td>late 1940s</td>
<td>2000s</td>
<td>2010s</td>
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<tr>
<td>Limitations</td>
<td>Many inaccessible tumors ineligible; limited effectiveness if tumor has already begun to spread</td>
<td>Limited effectiveness if tumor has already begun to spread; potentially dangerous for tumors near vital organs</td>
<td>High toxicity and often does not destroy the whole tumor, leading to high rates of recurrence</td>
<td>Limited tumor types eligible; high efficiency but short durability driving high rates of recurrence</td>
<td>Applicable to all tumors at all stages of disease including metastatic tumors; responses are highly durable; potential for lower toxicity profiles; synergistic with other treatments</td>
</tr>
</tbody>
</table>
Personalized Medicine

- Cytokines
- DNA/Peptide Vaccines
- Tumor Cell Antigens
- Adenoviral vectors
- Dendritic cells
- Synthetic Antibodies
- Adoptive B/T cell Therapy
- Synthetic Antibodies
- Adoptive B/T cell Therapy
- DNA/Peptide Vaccines
- Cytokines
- Tumor Cell
Novel Combinations

- Vaccines
- Immune checkpoint modulators
- Metabolism modulators
- Treg inhibitors
- Cancer inflammation modifiers
- Cancer stem cells - targeting NMEs
- Targeting cytokines

Designed to address unmet medical needs

NMEs = new molecular entities

http://www.ionc.com/mashup/
"...The curse of medical education is the excessive number of schools. The situation can improve only as weaker and superfluous schools are extinguished." Abraham Flexner, 1910

In a muckraking style, Flexner revealed the discrepancies between school catalogue descriptions of courses and clinical opportunities and the realities of medical training in schools throughout the nation. Flexner argued strongly for placement of medical education within the structure of American universities, away from strict control of practitioners, and he emphasized the need to close substandard schools. For Flexner, the desired ideal was truly academic training, with clinical teaching in close geographical association with university science departments.
CD28 Family of Receptors Control Immunologic Tolerance: 1995

Adoptive Cell Therapy: 3 Approaches in Advanced Development

Science Trans Med, 2015
Essential factors for augmenting adoptive immunotherapy

Which Lymphocyte Subset?

Synthetic Biology: Genetic Reprogram

Optimize Ex Vivo Expansion
Synthetic biology: “putting the immune system on steroids”

- An emerging interdisciplinary field with the common approach of manipulating or engineering properties of biological systems from biological ‘parts’ or synthetic components to create functions or systems not found in nature.

- For the Biomedical researcher: An approach and set of tools to improve our knowledge of biological systems and engineer novel therapies.

- Examples:
  - “artificial life (Craig Ventner),
  - bacteria producing biofuels,
  - CAR T cells!

*Pigs Might Fly*
– Damien Hirst
CAR T cells: personalized “serial killer” cells

- Gene transfer technology is used to stably express CARs on T cells, conferring novel antigen specificity\(^1,2\)
- CART19 therapy takes advantage of the cytotoxic potential of T cells thereby killing tumor cells in an antigen-dependent manner\(^1,3\)
- Persistent CART19 cells consist of both effector (cytotoxic) and central memory T cells\(^3\)
- T cells are non-cross resistant to chemotherapy
- Responses are cytolytic: no swelling!

Adult Chronic Leukemia Study Overview*


* ClinicalTrials.gov #NCT01029366
93% CR rate for r/r ALL after CTL019

>200 patients with CLL, ALL, NHL, MM have gotten CTL019

- 59 r/r pediatric ALL pts: 55 in CR at 1 mo (93%)
- 6 went to subsequent transplant
- 6-month RFS: 76%
- No relapses past 1 year
- 13 patients in remission beyond 1 year, 10 without further therapy
Please excuse Emily from school - she was with me!

THE PRESIDENT
Some of Dr Grupp’s Pediatric Leukemia Patients
At Penn, Biden sets cancer ‘moonshot’

By Don Sapatkin

Vice President Biden met with scientists at the University of Pennsylvania’s Abramson Cancer Center Friday afternoon, officially launching his “moonshot” quest to cure cancer.

“We’re on the cusp of phenomenal breakthroughs,” Biden said, adding that President Obama would be issuing an executive order that would get every federal agency involved in the effort.

Biden asked the researchers to educate him on the challenges and possibilities of genome-based discoveries of the last several years, particularly a type of immunotherapy that has been pioneered by Penn researcher Carl H. June.

Just last month, researchers from Penn and Children’s Hospital of Philadelphia, led by June, announced that an experimental cell therapy that boosts the immune system continues to produce...
Determine Efficacy and Safety of CTL019 in Pediatric Patients With Relapsed and Refractory B-cell ALL (ELIANA)

Stephan Grupp, Children’s Hospital of Philadelphia
Stella Davies, Cincinnati Children’s Hospital
Christian Capitini, University of Wisconsin
Ted Laetsch, Children’s Medical Center of Dallas
Doug Myers, Children’s Mercy Kansas University
Enelda Nemecek, Oregon Heath & Science University
Krysta Schlis, Stanford University
Michael Verneris, University of Minnesota
Alan Wayne, Children’s Hospital Los Angeles
Gary Yanik, University of Michigan
Paul Martin, Duke University
Francoise Mechinaud, Royal Children’s Hospital (Australia)
Henrique Bettencourt, Hospital St. Justine (Canada)

Clinicaltrials.gov  NCT02435849
Lessons Learned

long term attention span
incorporate new technologies
stubbornness: do what you believe!
patients accept “on target” toxicity
details matter: small changes in experimental approach can lead to large changes in outcome
Sometimes luck is a major component of success
Study patient outliers

You can have a career in Immuno-Oncology!
Pharma and Biotech
Take on CAR T cells

• Penn-Novartis Alliance for CAR T cells. August 2012
• Joe Jiminez CEO: “I’ve told the team that resources are not an issue. Speed is the issue”. May 2014
• FDA awards “breakthrough designation” to UPENN for CART19. July 2014
### CAR’s in Clinical Development

**Commercial CARs:** Autolus/UCL, Bellicum, BioNTech, CBMG, Cardio3→Celyad, CARSgen, Celgene/Bluebird, Cellectis/Servier/Pfizer, Cellular Therapeutics Ltd, Juno/Opus, Kite/Amgen, Mustang/COH, Novartis, Sorrento/Conkwest, Takara, Transposagen/J&J/Janssen, TheraVectys, Unum, Intrexon/Ziopharm . . .

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<thead>
<tr>
<th>Academic Institute (US)</th>
<th>Target(s)</th>
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<tbody>
<tr>
<td>Baylor College of Medicine</td>
<td>CD19, GD-2, Her2, CD30, kappa Ig</td>
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<tr>
<td>FHCRC</td>
<td>CD19, CD20, ROR1</td>
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<tr>
<td>MD Anderson Cancer Center (MDACC)</td>
<td>CD19</td>
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<tr>
<td>Memorial Sloan Kettering)</td>
<td>CEA, mesothelin, PSMA</td>
</tr>
<tr>
<td>National Cancer Institute (NCI)</td>
<td>CD19, CD22, CSP4, GD-2, EGFRvIII, mesothelin, VEGFR2</td>
</tr>
<tr>
<td>University of Pennsylvania</td>
<td>CD19, CD123, BCMA, mesothelin, cMet, EGFRvIII</td>
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<th>Academic Institute (non-US)</th>
<th>Target(s)</th>
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<tr>
<td>Chinese PLA General Hospital</td>
<td>CD19, CD20, CD33, CD138, HER2</td>
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<tr>
<td>Christie Hospital NHS Foundation Trust</td>
<td>CD19</td>
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<tr>
<td>Peter MacCallum Cancer Centre, Australia</td>
<td>LewisY</td>
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<tr>
<td>University of Zurich</td>
<td>FAP</td>
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CAR Trials: A special thanks

CVPF
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Patients and Families

The Leukemia & Lymphoma Society
Fighting Blood Cancers

Center for Cellular Immunotherapies

Novartis