Precision CAR T Cell Therapeutics

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I have the following financial relationships to disclose:
Consultant for: Novartis, Immune Design, Viracta, Carisma
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Grant/Research support and royalties / IPR from: Novartis
Stockholder in: Tmunity Therapeutics, Inc.
Honoraria from:
Employee of:

- and -

I will discuss investigational use in my presentation: CTL019
Cancer Immunotherapy: Overnight sensation 100 years in the making

Checkpoints and CAR T

Various immune checkpoint mAbs and CAR T approved

Sébastien Anguille et al. Pharmacol Rev 2015;67:731-753

WORLD

Nobel Medicine Prize Awarded to American, Japanese Scientists for Cancer Work

Scientists developed a new form of cancer treatment using immunotherapy
CAR T Design: first example of synthetic biology in medicine

**Design of CAR T Cells**

- **First Generation CD4 / CD8z CARs**
- **First Generation scFv CARs**
- **Second Generation scFv CD28z CARs**
- **Second Generation scFv BBz CARs**
- **Second Generation scFv CD27z CARs**
- **scFv ICOSz CARs**

**Yescarta**

- CD28
- 4-1BB

**Kymriah**

- CD27
- ICOS

**References**

- Irving & Weiss, 1991
- Letourneur, 1991
- Romeo, 1991
- Kuwana, 1987
- Eshhar, 1993
- Roberts, 1995
- Finney, 1998
- Maher, 2002
- Finney, 2003
- Imai, 2004
- Milone, 2009
- Carpenito, 2009
- Song, 2012
- Guedan, 2014
- Duong, 2013
- Romeo, 1991
- Letourneur, 1991
CAR T Cell Therapy: a process not a drug

- Autologous T cells
- Allogeneic “3rd party” T cells
  - Cord blood
  - Healthy donor
  - iPSC

https://cen.acs.org/pharmaceuticals/oncology/Controlling-CAR-T-scientists-plan/96/i19
85% of children are cured with intensive chemotherapy and radiation: However: major long term disability from chemoradiotherapy

- The two year survival for twice relapsed pediatric ALL is <2 years
- Tisagenlecleucel (Kymriah™) induced complete remissions in <85% young adults and children with multiply relapsed ALL
- FDA approved August 2017

Hematologic Malignancies:
- CD19 Phase I/II trials at the University of Pennsylvania

<table>
<thead>
<tr>
<th>Disease</th>
<th>Reference</th>
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<tr>
<td>CLL</td>
<td>Porter, 2011</td>
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<td>ALL</td>
<td>Grupp, 2013</td>
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<td>ALL</td>
<td>Maude, 2014</td>
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<td>Myeloma</td>
<td>Garfall, 2015</td>
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<td>DLBCL</td>
<td>Schuster, 2017</td>
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<tr>
<td>ALL</td>
<td>Maude, 2018</td>
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He says he ran up medical bills of $500,000 when he participated in a clinical trial of CAR T cells in 2013, despite receiving the medication for free. (Dr. Keith Eaton)

On the horizon: CAR T Cells for advanced myeloma

Multiple myeloma:
- 2nd most common blood cancer

- Currently considered incurable with uncommon exceptions
- Standard of care is autologous stem cell transplant and biologics
- Over the previous decade, survival increased from 2-3 years to ~8 years
- Chronic, non-curative therapy leads to morbidity
- Myeloma is the most expensive cancer: financial toxicity
- CAR T cells have efficacy in advanced myeloma

=> BCMA CAR T cells are in advanced clinical trials in US and China
Scientific Challenges for CAR T Cells: solid tumors

Solid tumors

• Numerous CARs targeting various surface molecules are being developed for many cancer histologies
• Examples:
  • EGFRviii and IL13Ralpha 2 for glioblastoma
  • PSMA for prostate cancer
  • Mesothelin for ovarian, pancreatic cancer and mesothelioma
  • C-Met and Her2/neu (c-erB2) for breast and other carcinomas
  • FAP to target tumor stroma
Scientific Challenges for CAR T Cells: manufacturing

Current limitations:
- apheresis availability
- GMP suites availability
- Trained labor force limited
- testing of each product
- “Peak serum”

Issues
- Patient specific “n of 1”
- Blood bank model?
- Central manufacturing?

Mason et al, Regen Med. 2011
Levine and June, Nature. 2013
Social Challenges: Geographic disparities and high cost of ultra-personalized genetically engineered cells

Clinical trials.gov search term “chimeric antigen receptor”
305 trials listed as of August, 2018

Rajkumar, ASCO 2018

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THE WALL STREET JOURNAL

The Million-Dollar Cancer Treatment: Who Will Pay?

So far, few patients have received the new drugs, as commercial health plans and Medicare wrestle with how to cover the treatment

- The number of new myeloma patients in the US in 2017: ~30,000
- At current standard of care: total lifetime costs to treat all patients diagnosed in 2017: $22.4B
- The average cost of cancer drugs approved in the US in 2017: 150,000

Clinical trials.gov search term “chimeric antigen receptor”
305 trials listed as of August, 2018

Rajkumar, ASCO 2018
Combinatorial Cancer Immunotherapies: Curative and affordable?

- Vaccines
- Oncolytic viruses
- HSCT
- CAR T Cell Based Therapies
- Antibodies
- Checkpoints, ADC, etc
- Cytokines
- Targeted Small Molecule Drugs
- Chemotherapy
- Ionizing Radiation
- chemotherapy