Immuno-Oncology Scientific Updates: An Introduction to CAR T-Cell Therapy

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Faculty

Andrew Fesnak, MD
Assistant Professor of Clinical Pathology and Laboratory Medicine
University of Pennsylvania
Perelman School of Medicine
Speaker Disclosures

In the past 12 months, the following speakers have not had a significant financial interest or other relationship with the manufacturer(s) of the product(s) or provider(s) of the service(s):

Andrew Fesnak, MD

Learning Objectives

• Basic understanding of CAR T cell…
  – Biology and design
  – Current targets
  – Manufacturing
  – Future directions
What are CAR T cells?

- A Chimeric Antigen Receptor is an artificial molecule that combines B cell-derived and T cell-derived domains and functions.
What are CAR T cells?

- T cell activation

What are CAR T cells?

- B cell activation

Opsonization
Neutralization
Fixation
What are CAR T cells?

- T cell activation

[Diagram showing T cell activation process]
What are CAR T cells?

- T cell activation

What are CAR T cells? – Putting it all together

- Highly specific
- MHC independent
- Durable activation

Beyond CD19: Hematologic CAR Targets

Most frequent CAR cell targets in liquid malignancies (except CD19)

- CD138
- CD38
- CD123
- CD33
- BCMA
- CD30
- CD22
- CD20

Diverse Solid Tumor CAR Targets

Most frequent CAR cell targets in solid malignancies

- GPC3
- CEA
- mesothelin
- GD2
- EGFR
- MUC-1
- PSMA
- EpCAM
- HER-2

### Common and Challenging Features of Targets

**Table 1: Examples of chimeric antigen receptor T cell clinical trials**

<table>
<thead>
<tr>
<th>Target</th>
<th>Indications</th>
<th>Clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD20 or CD20-deleted cells</td>
<td>Leukemia</td>
<td>NC-2000, NCX-1001, METX-005, NCX-1020</td>
</tr>
<tr>
<td>CD19 or CD19-deleted cells</td>
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</tr>
<tr>
<td>CD19 or CD19-deleted cells</td>
<td>Multiple myeloma</td>
<td>NCX-1010, NCX-1011</td>
</tr>
</tbody>
</table>

**Adapted from a clinical trial of CAR T cell therapy**

- Varied
- Extracellular
- Conserved/specific

**Fesnak et al. 2016. Nature Reviews Cancer**

### How are CAR T cells manufactured?

1. **Apheresis**
2. **T cell enrichment**
3. **Quality control**
4. **Expansion**
5. **Activation, modification**
6. **Final engineered T cell product**
7. **Leukapheresis**
8. **Counterflow centrifugal filtration**
9. **Bioreactor**

**Reinfusion**

**Fesnak et al. 2016. Nature Reviews Cancer**

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Evolving Cell Manufacturing Technology

- Run-to-run variability
- Continuous technologic improvement
- Can be costly
What will next-gen CAR T cells look like?

• More effective
CAR T cells will be more specific

- Safer – enhanced specificity

CAR T cells will be better controlled in vivo

- Safer – in vivo control
Some CAR T cells will be Allogeneic

- Allogeneic
  - Endogenous TCR -> GVHD?
  - Endogenous HLA -> rejection?

Universal CAR T cells in Action

- Pilot - 2017
  - TALEN-mediated disruption of endogenous TCR, CD52
  - Lentiviral TDN with CD19-directed CAR
  - Molecular remission by day 28
  - Skin and marrow GVHD, controlled
  - Bridge to allo-transplant
- UCART19 - 2018
  - 6/6 patients with CR d28-42
  - 6/6 developed CRS; 3/6 neurotoxicity
  - 3/6 prolonged cytopenia
  - 1/6 acute cutaneous GVHD
- UCART123 – 2018
  - First BPDCN patient developed CRS + capillary leak syndrome and died on day 9 post infusion
  - First AML patient developed CRS + capillary leak syndrome which resolved with treatment by day 12
  - Clinical hold (Sept 4, 2017)
  - Decrease dose of UCART, conditioning; change to inclusion criteria to select for more stable patients
- UCART22 – IND submitted May 2018
- UCARTCS1 – expect mfg in 2018
- UCART38 – preclinical development
Rethinking CAR T Design

- More effective
- Safer
- Allogeneic

Basic understanding of CAR T cell...

- Biology and design
  - Highly specific
  - MHC independent
  - Durable activation

- Manufacturing
  - Run-to-run variability
  - Continuous technologic improvement
  - Can be costly

- Current targets
  - Varied
  - Extracellular
  - Conserved/specific

- Future developments
  - More effective
  - Safer
  - Allogeneic
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