CARs for Pediatric Cancers

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Presenter Disclosure Information

Nathan Singh

The following relationships exist related to this presentation:

No relationships to disclose
Childhood cancer

ALL
- 80-85% 5y EFS
- ~21% of pediatric oncology deaths

Neuroblastoma
- ~45% 5y EFS
- ~15% of pediatric oncology deaths
Chimeric Antigen Receptors

- "CART19"

- GD2 CAR
# T-cell engineering

<table>
<thead>
<tr>
<th>Permanent</th>
<th>Transient</th>
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<tbody>
<tr>
<td><strong>Method</strong></td>
<td><strong>RNA electroporation</strong></td>
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<tr>
<td>Lentiviral transduction</td>
<td></td>
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<tr>
<td><strong>Benefits</strong></td>
<td><strong>Short-term toxicity</strong></td>
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<tr>
<td>Sustained activity</td>
<td>Cheap(er)</td>
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<td>Potential memory response</td>
<td></td>
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<tr>
<td><strong>Limitations</strong></td>
<td><strong>Limited activity</strong></td>
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<tr>
<td>Persistent toxicity</td>
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<tr>
<td>Expensive</td>
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<td>? Insertional mutagenesis?</td>
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Xenograft model of ALL

NOD/SCID/γc−/− (NSG)

CD19+ ALL

7d

Lenti CART19 cells OR RNA CART19 cells

Multiple infusions?
Lymphodepletion?

Barrett DM et al.
Human Gene Therapy. 2011
RNA CARs: role of lymphodepletion

1 x 10^7 RNA CART19 cells on days 7, 14, 28 or 1 x 10^7 Lenti CART19 cells on day 7

19-BBz RNA no cytoxan median overall survival: 28d
19-BBz RNA + cytoxan median overall survival: 56d
RNA CARs: role of lymphodepletion
RNA CARs: dose splitting

RNA CART19 cells
1 dose on day 7 or
3 doses on days 7, 14, 28

RNA CART19 cells
2 x 10^7 on day 7
5 x 10^6 on days 14 and 21

p<0.0001
Neuroblastoma
Xenograft model of neuroblastoma

1. GD$_2$+ NB S.Q.
2. 2W
3. 3 doses GD$_2$ RNA CAR T-cells

1. GD$_2$+ NB I.V.
2. 1-2W
3. 1 dose GD$_2$ Lenti CAR T-cells OR
4. 3 doses GD$_2$ RNA CAR T-cells
GD2 RNA CARs for flank NB

5 days after first CAR T-cell administration I.T.
GD2 RNA CARs for disseminated NB

Day 7
Day 11

CART19

GD2 CAR

T-cell administration
CD19: 5 x 10^6 (>97% CAR+)
GD2: 5 x 10^6 (>97% CAR+)

CD19: 5 x 10^6 (>97% CAR+)
GD2: 5 x 10^6 (>97% CAR+)
GD2 RNA CARs for disseminated NB

Day 8: 5 x 10^6
Day 22: 1.5 x 10^7
Day 29: 1.5 x 10^7
GD2 Lenti CARs for disseminated NB

CART19

Day 13

Day 21

GD2 CAR

↑ T-cell administration
CD19: $1 \times 10^7$ (55% CAR+)
GD2: $1 \times 10^7$ (11% CAR+)
GD2 Lenti CARs for disseminated NB

T-cell administration
CD19: $1 \times 10^7$ (55% CAR+)
GD2: $1 \times 10^7$ (11% CAR+)

p<0.001
Conclusions

- Permanently-modified CAR T-cells can have significant impact on both liquid and solid tumors

- Transiently-modified CAR T-cells can mediate successful anti-tumor responses in liquid and solid tumors
  - Multiple doses
  - Lymphodepletion between doses
  - Dosing schedule
Acknowledgments

Grupp Lab
Stephan Grupp
David Barrett
Jessica Hulitt
Junior Hall
Tiffaney Vincent
Terri Ryan
Alix Seif
David Teachey
Shannon Maude
Jessica Lee

June Lab
Carl June
Yangbing Zhao
Xiaojun Liu
Shuguang Xiang
Carmine Carpenito
John Scholler

Penn ITMAT
Emma Meagher
Garrett Fitzgerald

Supported by NIH T32 TL1 RR024133, Alex’s Lemonade Stand Foundation POST grant, ASH TRA grant