Donor-derived CD19-specific CAR+ T-cell therapy after haploidentical hematopoietic stem-cell transplantation

Laurence J.N. Cooper
Hyatt Orlando International Airport Hotel
December 3, 2015 (afternoon)
Some of the technology described was advanced through research conducted at the MD Anderson Cancer Center by Laurence Cooper, M.D., Ph.D. Both MD Anderson Cancer Center and Dr. Cooper have a financial interest in ZIOPHARM Oncology, Inc., and Intrexon Corporation. On May 7, 2015, Dr. Cooper was appointed as the Chief Executive Officer at ZIOPHARM. Dr. Cooper is now a Visiting Scientist at MD Anderson.

Because MD Anderson is committed to the protection of human subjects and the effective management of its financial conflicts of interest in relation to its research activities, MD Anderson has implemented an Institutional Conflict of Interest Management and Monitoring Plan (Plan) to manage and monitor the conflict of interest with respect to MD Anderson’s conduct of this research.
Trial design

• Determine the safety and MTD of infusions of donor-derived genetically modified T cells for patients with B-cell-derived lymphoid malignancies after haploidentical hematopoietic stem-cell transplantation (HSCT)
  – Conditioning regimen – Fludarabine/ Melphalan and 2GyTBI
  – GVHD prophylaxis – Post-transplant Cy, tacrolimus and MMF
  – T cells infused 42 to 84 days after infusion of peripheral blood stem cells (PBSC)
• Non-viral gene transfer using the *Sleeping Beauty* system to express second generation CD19-specific CAR (signaling through CD28 and CD3-ζ with IgG4-based extracellular stalk)
• 8 patients infused
• T-cell dosing (based on recipient body surface area)
  – Starting dose $10^6$/m^2
  – Current dose $10^8$/m^2

Data based on work previously undertaken at MDACC
Redirect T-cell specificity to CD19 using *Sleeping Beauty* system

Singh H & Cooper LJ. *Immunol Rev.* 2014

2nd generation CD19-specific CAR (CD19RCD28)

- scFv
- Modified hinge
- IgG4Fc
- CD28TM
- CD28 → Signal 2
- CD3ζ → Signal 1

Shown as a homo-dimer

Data based on work previously undertaken at MDACC
### Patient characteristics at infusion of haploidentical genetically modified T cells

<table>
<thead>
<tr>
<th>UPN</th>
<th>Age</th>
<th>Histology</th>
<th>Stage at HSCT</th>
<th>Prior lines therapy</th>
<th>Prep. regimen</th>
<th>T-cell Dose Level (per m²)</th>
<th>Wt (kg)</th>
<th>BSA (m²)</th>
<th>Total T cells (x10⁸)</th>
<th>% CAR⁺</th>
<th>WBC at infusion (k/uL)</th>
<th>ALC at infusion (k/uL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P580</td>
<td>31</td>
<td>B-ALL</td>
<td>Refractory, MRD neg</td>
<td>4, allo-HSCTx2</td>
<td>FM</td>
<td>A 10⁶</td>
<td>82</td>
<td>2.03</td>
<td>0.02</td>
<td>70.4</td>
<td>5.8</td>
<td>696</td>
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<tr>
<td>P513</td>
<td>25</td>
<td>B-ALL</td>
<td>Refractory, MRD neg</td>
<td>4, auto-HSCT</td>
<td>FM</td>
<td>A 10⁶</td>
<td>61</td>
<td>1.74</td>
<td>0.02</td>
<td>93.3</td>
<td>3.5</td>
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<tr>
<td>P732</td>
<td>36</td>
<td>B-ALL</td>
<td>CR2, MRD pos</td>
<td>2</td>
<td>FM</td>
<td>B 10⁷</td>
<td>81</td>
<td>2.04</td>
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<td>3.8</td>
<td>190</td>
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<tr>
<td>P671</td>
<td>52</td>
<td>Follicular</td>
<td>Transformed DLBL, PET neg</td>
<td>4</td>
<td>FC-TBI2</td>
<td>B 10⁷</td>
<td>91</td>
<td>2.2</td>
<td>0.21</td>
<td>95.2</td>
<td>6.1</td>
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<tr>
<td>P723</td>
<td>23</td>
<td>B-ALL</td>
<td>PIF in CR, MRD neg</td>
<td>2</td>
<td>FM</td>
<td>B 10⁷</td>
<td>93</td>
<td>2.04</td>
<td>0.21</td>
<td>58.8</td>
<td>2.8</td>
<td>756</td>
</tr>
<tr>
<td>P771</td>
<td>46</td>
<td>B-ALL</td>
<td>CR1, MRD neg</td>
<td>1</td>
<td>FM-TBI2</td>
<td>C 5 x 10⁷</td>
<td>86</td>
<td>1.92</td>
<td>0.96</td>
<td>56.8</td>
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<tr>
<td>P783</td>
<td>21</td>
<td>B-ALL</td>
<td>PIF, MRD pos</td>
<td>3</td>
<td>MTF</td>
<td>D 10⁸</td>
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<td>90.3</td>
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<tr>
<td>P788</td>
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<td>B-ALL</td>
<td>Refractory, MRD neg</td>
<td>4, allo-HSCT</td>
<td>FM-TBI2</td>
<td>D 10⁸</td>
<td>64</td>
<td>1.74</td>
<td>1.14</td>
<td>83.8</td>
<td>2.9</td>
<td>522</td>
</tr>
</tbody>
</table>

Data based on work previously undertaken at MDACC
Persistence of haploidentical genetically modified T cells

Data based on work previously undertaken at MDACC
Average time of T-cell persistence within autologous and allogeneic recipients after infusion determined by ddPCR

<table>
<thead>
<tr>
<th>T-cell Dose Level and recipients (allo versus auto)</th>
<th>Number of patients infused</th>
<th>Average time (days) transgene detected</th>
<th>Maximum time (days) transgene detected</th>
</tr>
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<tbody>
<tr>
<td>MSD (allo)</td>
<td>10</td>
<td>52</td>
<td>90</td>
</tr>
<tr>
<td>Haplo (allo)</td>
<td>8</td>
<td>54</td>
<td>180</td>
</tr>
<tr>
<td>All Auto patients</td>
<td>7</td>
<td>201</td>
<td>360</td>
</tr>
<tr>
<td>All Allo patients</td>
<td>19</td>
<td>51</td>
<td>180</td>
</tr>
</tbody>
</table>

MSD = matched-sibling donor

Data based on work previously undertaken at MDACC
PFS and OS after haploidentical HSCT

N=8 pts treated and 6 alive in CR

All patients tolerated the infusions with no significant increase in incidence of GVHD

Data based on work previously undertaken at MDACC
Patient outcomes following infusion of haploidentical genetically modified T cells

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<th>Prior lines therapy</th>
<th>Prep. regimen</th>
<th>T-cell Dose Level (per m²)</th>
<th>Relapse or progression after T-cell infusion</th>
<th>Disease status after T-cell infusion</th>
<th>Response duration (days) at last follow up</th>
<th>Toxicity</th>
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<td>FM</td>
<td>A 10⁶</td>
<td>No</td>
<td>CCR</td>
<td>544</td>
<td>None</td>
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<td>No</td>
<td>CCR</td>
<td>216</td>
<td>aGVHD skin</td>
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<td>2</td>
<td>FM</td>
<td>B 10⁷</td>
<td>Yes</td>
<td>Alive</td>
<td>136</td>
<td>None</td>
</tr>
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<td>No</td>
<td>CCR</td>
<td>402</td>
<td>None</td>
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<td>CCR</td>
<td>81</td>
<td>None</td>
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Data based on work previously undertaken at MDACC
Donor-derived CD19-specific CAR$^+$ T cells infused for primary refractory DLBCL

- 52 yo man (UPN P671) with history of FL transformed to DLBCL in 2013
- Treatment prior to haplo-HSCT and donor-derived CD19-specific T cells
  - R-CHOP x 6 followed by progression
  - R-ICR x 2 followed by progression
  - R-DHAP x 2 followed by progression
  - R-hyperCytoxan & XRT with partial response
- At haplo-HSCT and donor-derived CD19-specific CAR$^+$ T cells in 2014
  - Refractory to chemotherapy
  - Bulky disease in the mesenteric area
- Haplo-HSCT from son after Flu/Cy/TBI
- Donor-derived $10^7$/m$^2$ T cells infused 45 days after peripheral blood stem cells
- No aGVHD or cGVHD
- In CR at 6 months – off immunosuppression with 100% donor chimerism

Data based on work previously undertaken at MDACC
Haplo-HSCT and donor-derived CAR+ T cells for primary refractory bulky DLBCL

Initial intra-abdominal mass size 7x16x15 cm

At Diagnosis

Post chemo

Day 30 post SCT

Day 90 post SCT
50 days after CAR

Post XRT

Complete response

Data based on work previously undertaken at MDACC
Second infusion of haplo CD19-specific CAR\(^+\) T cells

- UPN P671 then relapsed in 2015
  - PET/CT – multiple LN – R axilla, L axillar, neck, abdomen
  - Biopsy R axilla showed recurrent CD19\(^+\) FL
- Re-infusion of CAR\(^+\) T cells 5x10\(^7\)/m\(^2\) in 2015 without lymphodepleting chemotherapy
- Repeat PET scan one month after T-cell infusion
  - Clearance of disease from all sites except R axilla
  - Improvement in SUV uptake in the R axilla from 13.0 to 7.9 SUV
- Repeat R axilla LN FNA and core biopsy 2 months after T-cell infusion
  - No evidence of lymphoma

Data based on work previously undertaken at MDACC
Disease relapse at day +402 (left) and after repeat infusion of CAR⁺ T cells (right)

Data based on work previously undertaken at MDACC
Next-generation technology
Improving therapeutic potential of CAR$^+$ T cells by co-signaling through cytokine receptor

Membrane-bound IL15 (mIL15)

Provide “signal 3”

Data based on work previously undertaken at MDACC
Stable co-expression of mIL15 & CAR

Data based on work previously undertaken at MDACC
**mIL15^+CAR^+** T cells persist in the absence of CAR activation and have **T<sub>SCM</sub>**-like phenotype

Persisting T-cell Phenotype (*in vitro*)

Data based on work previously undertaken at MDACC

Superior \textit{in vivo} activity of CAR co-expressed with mIL15

Data based on work previously undertaken at MDACC
Conclusions

• *Sleeping Beauty* system can be used to generate CAR\(^+\) T cells to target CD19\(^+\) malignancies after HSCT
• Infused haplo-identical CAR\(^+\) T cells persist after infusion
• Evidence of anti-tumor effects
  – 75% CR at median 5.2 month follow up
• No increase in GVHD despite up to 10\(^8\)/m\(^2\) of donor-derived T cells being infused
  – Supports further development of off-the-shelf CAR\(^+\) T-cell therapy
• Next-generation *Sleeping Beauty* trial safe-to-proceed (IND 16474, clinical trial.gov NCT02529813) at MDACC

Additional information presented by Dr. Kebriaei at 5:15 pm on December 7, 2015, ASH abstract 862, Session 723
Acknowledgments

• MDACC SCTCT
  – Partow Kebriaei
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• Ziopharm Oncology
• Intrexon