P-BCMA-ALLO1 — a non-viral allogeneic anti-BCMA CAR T therapy with potent anti-tumor function for the treatment of multiple myeloma

Maximilian Richter, Stacey A. Cranert, Yening Tan, Min Tong, Christine Domingo, Elvira Argus, Samad A. Ibitokou, Jenessa B. Smith, Christopher Martin, Xinxin Wang, Burton E. Barnett, Eric M. Ostertag, Julia Coronella, Devon J. Shedlock
# Allogeneic CAR-T – The Holy Grail of Cell Therapy

<table>
<thead>
<tr>
<th>AUTOLOGOUS/PATIENT-DERIVED CAR-T</th>
<th>ALLOGENEIC/HEALTHY DONOR-DERIVED CAR-T</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Patient" /></td>
<td><img src="image2" alt="Healthy Donor" /></td>
</tr>
<tr>
<td>MHC I</td>
<td>TCR knock-out</td>
</tr>
<tr>
<td>TCR</td>
<td></td>
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</tbody>
</table>

## EXPERIENCE TO DATE
- Good efficacy in liquid tumor indications including Poseida’s P-BCMA-101
- Outstanding safety driven by non-viral product with T stem cell memory ($T_{SCM}$) phenotype
- Relatively high production cost of an individualized product

## PROMISES AND ADVANTAGES
- Healthy donor material promises better product characteristics
- Off the shelf access and convenience
- Dramatically reduced cost
P-BCMA-ALLO1 – Creating a New Standard for Allogeneic CAR-T

- **High % of $T_{SCM}$** Phenotype through use of piggyBac® technology
  - Growing evidence that $T_{SCM}$ is the desired phenotype for CAR-T
- **Fully allogeneic** approach with Cas-CLOVER gene editing
  - TCR KO to prevent graft versus host disease
  - MHC I KO to prevent host versus graft reaction
- **Addressing TCR deletion liability with Booster Molecule technology**
  - Creating gene edited CAR-T without a loss in functionality
- Robust manufacturing process with the ability to generate **hundreds of doses** per manufacturing run
- Bring our **superior safety profile** from autologous to allogeneic CAR-T
T_{SCM} – The Ideal T Cell for Adoptive Immunotherapy

“The extreme longevity, the robust proliferative potential and the capacity to reconstitute a wide-ranging diversity of the T cell compartment make the T_{SCM} cell type an ideal cell population to employ in adoptive immunotherapy”


- P-BCMA-101 – an autologous T_{SCM} CAR-T
  - \%T_{SCM} correlates with response in patients
  - Gradual expansion of T_{SCM} CAR-T with less toxicity
  - Better duration of response and potential for re-response

![Diagram showing the progression from Stem Cell Memory to Central Memory to Effector Memory to Effector T-Cell, with lesser differentiated cells on the left and more differentiated cells on the right.]

**Stem Cell Memory**
- Self-renewing
- Long-lived
- Multipotent

- T_{SCM} Cell

**Central Memory**
- T_{CM} Cell

**Effector Memory**
- T_{EM} Cell

**Effector T-Cell**
- T_{EFF} Cell
PiggyBac® Produces an Allogeneic CAR-T Product rich in T_{SCM}

- PiggyBac® preferentially transposes naïve/T_{SCM} cells
  - Lentivirus transduced a more differentiated cell population

- Produces P-BCMA-ALLO1 – an allogeneic CAR-T rich in T_{SCM} phenotype
  - Harness the potency and safety benefits already experienced with autologous P-BCMA-101

<table>
<thead>
<tr>
<th></th>
<th>CD62L</th>
<th>CD45RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naive T-Cell</td>
<td>9.4%</td>
<td>89.8%</td>
</tr>
<tr>
<td>T_{SCM} Cell</td>
<td>0.3%</td>
<td>0.6%</td>
</tr>
<tr>
<td>T_{EM} Cell</td>
<td>3.3%</td>
<td>90.2%</td>
</tr>
</tbody>
</table>

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<tr>
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<th>CD45RA</th>
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<tbody>
<tr>
<td>Naive T-Cell</td>
<td>5.5%</td>
<td>90.2%</td>
</tr>
<tr>
<td>T_{SCM} Cell</td>
<td>1.1%</td>
<td>3.3%</td>
</tr>
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</table>
PiggyBac® – High Cargo Capacity Allows Delivery of Additional Safety Features

Incorporates proprietary safety switch
- Rapid, dose-dependent elimination of engineered T-cells if needed
- Management of Cytokine Release Syndrome (CRS) or other AEs

Drug resistance gene permits positive selection
- ~100% of T cells in final product express the CAR molecule
- Predicted to result in better therapeutic index

In the diagram:
- **TTAA Insulator**
- **ITR**
- **Promoter**
- **P-BCMA-ALLO1 Transposon**
- **Poly(A)**
- **Insulator**
- **Safety Switch**
- **CAR Molecule**
- **Selection Gene**

**POSEIDA THERAPEUTICS**
Cas-CLOVER Gene Editing for Improved Safety

• Efficient gene editing in resting cells is crucial for generation of $T_{SCM}$ rich allogeneic CAR-T

• Multiplex gene knock out of TCR & MHC class I

• TCR KO purification to generate a safe product unable to mediate GVHD

• No/low off-target cutting increases safety of gene editing
Booster Molecule Increases Yield and Preserves Desirable Attributes of P-BCMA-ALLO1

- Gene editing of TCR can impair allogeneic CAR-T products compared to unedited healthy donor CAR-T — The Allo Tax

- Booster Molecule technology overcomes these limitations, significantly increases production yield while preserving desirable attributes of P-BCMA-ALLO1
Booster-Produced P-BCMA-ALLO1 Functions at Least as well as Unedited Healthy Donor CAR-T Cells *in vitro*

- Booster Molecule *preserves effector function and proliferative potential* even in TCR KO cells

- P-BCMA-ALLO1 at least as potent as donor-matched, unedited CAR-T cells

**Target Cell Killing**

**Cytokine Secretion**

**High Proliferative Capacity**

![Graphs showing target cell killing, cytokine secretion, and high proliferative capacity](image-url)
P-BCMA-ALLO1 Manufacturing Process is Robust Across a Wide Range of Healthy Donors

- piggyBac® gene delivery, Cas-CLOVER gene editing, and Booster Molecule result in highly robust P-BCMA-ALLO1 manufacturing process
- Tens to hundreds of doses per manufacturing run produced from a group of minimally pre-selected donors
- High %T_{SCM} achieved across all donors

*Includes both T_{CM} and T_{SCM} cells in transition
P-BCMA-ALLO1 from Various Donors Shows *in vivo* Activity

- P-BCMA-ALLO1 produced from five healthy donors showed **rapid and durable anti-tumor response** in MM xenograft model across all donors.

- **Anti-tumor effect**, **CAR-T expansion**, and **CAR-T persistence** of P-BCMA-ALLO1 was comparable to unedited anti-BCMA CAR-T cells.

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**Tumor Volume [mm³]**

<table>
<thead>
<tr>
<th></th>
<th>No CAR T</th>
<th>Unedited anti-BCMA CAR-T</th>
<th>Donor 1</th>
<th>Donor 2</th>
<th>Donor 3</th>
<th>Donor 4</th>
<th>Donor 5</th>
<th>P-BCMA-ALLO1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Days post CAR-T infusion</strong></td>
<td>0 7 14 21 28 35 42 49</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tumor Volume [mm³]</strong></td>
<td>0</td>
<td>500</td>
<td>1,000</td>
<td>1,500</td>
<td>2,000</td>
<td>0</td>
<td>500</td>
<td>1,000</td>
</tr>
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**CAR+ cells/µl blood**

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<tr>
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<tr>
<td><strong>Days post CAR-T infusion</strong></td>
<td>Pre 7 14 21 28 35 42 49</td>
<td></td>
</tr>
<tr>
<td><strong>CAR+ cells/µl blood</strong></td>
<td>1</td>
<td>100,000</td>
</tr>
</tbody>
</table>

- NSG mice
- RPMI-8226 s.c. 1x10⁷ per mouse
- 1x10⁷ CAR-T cells per mouse
- Results shown as mean ± SD
Summary

- Highly desirable \( T_{SCM} \)-rich product phenotype
- Allogeneic CAR-T equivalent or better than unedited healthy donor CAR-T \textit{in vitro} & \textit{in vivo}
- Robust non-viral manufacturing process compatible with majority of healthy donors & ability to generate hundreds of doses per manufacturing run
- Superior safety due to \( T_{SCM} \) phenotype, no/low off-target gene editing, and safety switch
- Results support rapid advancement of P-BCMA-ALLO1 into the clinic for treatment of MM