MGTA-145 in Combination with Plerixafor Rapidly Mobilizes High Numbers of Hematopoietic Stem Cells and Graft-Versus-Host Disease Inhibiting Myeloid Derived Suppressor Cells in Nonhuman Primates

Patrick C. Falahee, PhD
Magenta Therapeutics
Cambridge, MA
MGTA-145 + Plerixafor Enables Rapid and Robust Mobilization of HSCs

**Limitations to current Standard of Care**
- Requires 4-6 days
- Unpredictable yields
- Associated adverse events
- Contraindicated for certain diseases

**Benefits of novel mobilization regimen**
- Mobilize more HSCs
- Shorten time required for mobilization
- Fewer adverse events

65,000 transplants annually
70% use mobilized peripheral blood

G-CSF Induced Mobilization

Magenta Mobilization

65,000 transplants annually
70% use mobilized peripheral blood
MGTA-145 and Plerixafor Work Synergistically to Rapidly Mobilize HSCs

**Novel mobilization agent:**

MGTA-145 (GroβT) + plerixafor (AMD3100)

- **CXCR2 agonist**
- **CXCR4 antagonist**

**Key features:**

- Rapid & robust mobilization of HSCs in mice
- Well-tolerated
- Mimics physiological response

**Cell**

**Rapid Mobilization Reveals a Highly Engraftable Hematopoietic Stem Cell**

**Authors**

Jonathan Hoggatt, Pratibha Singh, Tiffany A. Tate, ..., Dwight M. Morrow, David T. Scadden, Louis M. Pelus
MGTA-145 + Plerixafor Mobilizes Large Numbers of Long-Term HSCs in Mice

**IN VIVO MOBILIZATION**

- 3-fold increase in LT-HSC per mL
- *p < 0.05*

**WEEK 16 IN VIVO ENGRAFTMENT**

- 7-fold increase in Relative CRU
- *p < 0.05*

LT-HSC = Lin- c-kit+ Sca-1+ CD150+ CD48-

CRU = Competitive Repopulating Unit
A Single Injection of MGTA-145 + Plerixafor Rapidly Mobilizes Large Numbers of HSCs into Peripheral Blood in Nonhuman Primates

<table>
<thead>
<tr>
<th>CD34+ CELLS</th>
<th>CD34+CD90+CD45RA- CELLS</th>
<th>COLONY FORMING UNITS</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Graph" /></td>
<td><img src="image2.png" alt="Graph" /></td>
<td><img src="image3.png" alt="Graph" /></td>
</tr>
</tbody>
</table>

- **MGTA-145 + plerixafor**
- **plerixafor**
- **G-CSF (5 Days)**

*n=3-13 NHP per treatment*
MGTA-145 + Plerixafor Leads to a Significant Increase in CD34\textsuperscript{dim} Cells in Peripheral Blood of Nonhuman Primates

**Representative Mobilization of CD34\textsuperscript{dim} Cells**

<table>
<thead>
<tr>
<th>Unmobilized</th>
<th>MGTA-145 + Plerixafor</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD34\textsuperscript{dim}</td>
<td>2.3%</td>
</tr>
<tr>
<td>CD90</td>
<td>HSPC 0.02%</td>
</tr>
<tr>
<td>CD34</td>
<td></td>
</tr>
</tbody>
</table>

**CD34\textsuperscript{dim} Cells Suppress T Cell Activation In Vitro**

Unstimulated Beads vs. Beads + CD34\textsuperscript{dim}

- CFSE Count
- CD11b+ 93%
- CD14+ 63%

\[ p < 0.05 \]
MGTA-145 + Plerixafor Mobilized Graft is Distinct from G-CSF in Nonhuman Primates

COMPOSITION OF THE MOBILIZED GRAFT

- CD34<sup>dim</sup> cells
- B cells
- T cells
- Neutrophils

How would this graft perform following allogeneic transplantation?
MGTA-145 + Plerixafor Mobilizes an Immunosuppressive Graft

**EXPERIMENTAL DESIGN**

**MOBILIZATION**

Unmobilized
MGTA-145 + plerixafor
plerixafor
G-CSF (5 Days)

*n=3-5 per regimen*

**ISOLATE PBMCs**

**XENO TRANSPLANTATION IN NSG MICE**

6x10⁶ PBMCs per mouse

NSG mice
200 cGy

*n = 13-16 per regimen*

**XENO TRANSPLANTATION**

- Unmobilized (n=13)
- MGTA-145 + plerixafor (n=16)
- Plerixafor (n=16)
- G-CSF (n=16)

*p < 0.0001
#p < 0.05

* Compared to Unmobilized
* Compared to plerixafor
A Single Injection of MGTA-145 + Plerixafor Rapidly Mobilizes Sufficient CD34+ Cells for Transplant in Four Hours

EXPERIMENTAL DESIGN

In collaboration with Dr. Hans-Peter Kiem

MOBILIZATION & LEUKAPHERESIS

MGTA-145 + plerixafor

CD34+ SELECTION

AUTOLOGOUS TRANSPLANTATION

1080 cGy

MOBILIZATION & COLLECTION

APHERESIS PRODUCT

POST ENRICHMENT

Cells Harvested

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD34+</td>
<td>2.3x10⁶ / kg</td>
</tr>
<tr>
<td>CD34+CD90+CD45RA-</td>
<td>0.9x10⁶ / kg</td>
</tr>
</tbody>
</table>

Cells Infused

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD34+</td>
<td>1.8x10⁶ / kg</td>
</tr>
<tr>
<td>CD34+CD90+CD45RA-</td>
<td>0.8x10⁶ / kg</td>
</tr>
</tbody>
</table>
MGTA-145 + Plerixafor Mobilized CD34+ Cells Rapidly Engraft Following Autologous Transplantation in Nonhuman Primate

**AUTOLOGOUS TRANSPLANT**

**Neutrophil Engraftment**

- Neutrophils ($\times 10^3/\mu L$)
- Days post transplant

**Platelet Engraftment**

- Platelets ($\times 10^3/\mu L$)
- Days post transplant

- Neutrophil recovery
- GCSF
- Platelet recovery
- Blood transfusion
A Single Injection of MGTA-145 + Plerixafor Mobilizes Large Numbers of Engraftable HSCs and Immunosuppressive Monocytes

**BENEFITS OF MGTA-145 + PLERIXAFOR**

- **Rapid and robust mobilization of HSCs**
- **Mobilization of CD34\textsuperscript{dim} monocytes capable of suppressing GvHD**
- **Rapid engraftment in large animal transplant model**

**MGTA-145 + plerixafor is moving into the clinic in the first half of 2019**
Acknowledgments

MAGENTA RESEARCH TEAM
Kevin Goncalves
Sharon Hyzy
Shuping Li
Junia Dushime
Jennifer Proctor
Anthony Boitano
Dwight Morrow
John Davis
Michael Cooke

FRED HUTCHINSON CANCER RESEARCH CENTER
Stefan Radtke
Hans-Peter Kiem