MGTA-456, A First-in-Class Cell Therapy Produced from a Single Cord Blood Unit, Enables a Reduced Intensity Conditioning Regimen and Enhances Speed and Level of Human Microglia Engraftment in the Brains of NSG Mice

Kevin A. Goncalves, PhD

Magenta Therapeutics
Cambridge, MA
Most Inherited Metabolic Disorders (IMDs) Are Characterized by Defective Enzyme Function In Patients

**DEFECTIVE ENZYME FUNCTION IN PATIENTS WITH IMDs**

- Wild-Type Cell
- Enzyme-Deficient Cell
- Accumulation of Toxic Substrates
- Cell and Tissue Death Leading to Neurological Defects

**Therapeutic Goal**

- Restore Functional Enzyme Levels

**HEMATOPOIETIC STEM CELL (HSC) TRANSPLANT AS A STANDARD OF CARE FOR SELECTED IMDS**

- Mucopolysaccharidosis I, II, IIIA and B, and VI
- Metachromatic Leukodystrophy
- Globoid Cell Leukodystrophy
- Cerebral Adrenoleukodystrophy

**Cross Correction of Disease**
CROSS-CORRECTION OF DISEASE BY DONOR-DERIVED MYELOID CELLS IN BRAIN POST-TRANSPLANT

HSC Transplant Is A Standard Of Care in IMD Indications Where Cross-Correction Can Occur

STRATEGIES TO CROSS-CORRECT

Allogeneic HSC Transplant
- > 2000 transplants performed since 1980 with documented disease-modifying capabilities
- Cord blood is the preferred source of HSCs
- Cord blood inventory provides rapid access to patients

Autologous Gene Therapy
- Limited by challenging manufacturing processes
- Unknown effects of transduction efficiency and dose
HSC Transplant is Disease-Modifying, but Graft Failure Remains High

### ENHANCED FOLLOWING TRANSPLANT IN CEREBRAL ADRENOLEUKODYSTROPHY

<table>
<thead>
<tr>
<th>Pre-Transplant</th>
<th>Post-Transplant (Day 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Pre-Transplant Image]</td>
<td>![Post-Transplant Image]</td>
</tr>
</tbody>
</table>

### CIBMTR OUTCOMES IN PATIENTS WITH IMDs

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Hurler Syndrome</th>
<th>Adrenoleukodystrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil Engraftment (Day 28)</td>
<td>84% (95% CI: 79-89%)</td>
<td>80% (95% CI: 73-86%)</td>
</tr>
<tr>
<td>Graft Failure (1 year)</td>
<td>21% (15-27)%</td>
<td>24% (95% CI: 17-32%)</td>
</tr>
</tbody>
</table>

Lund et al. ASH 2018 Abstract #4628

How Can Patient Outcomes Be Further Improved?
Increased Cell Dose Leads to Increased Hematopoietic and Brain Engraftment

**EXPERIMENTAL SCHEMA**

Cord Blood CD34+ Cells

- 3,000 cells
- 10,000 cells
- 30,000 cells

Transplanted per mouse

**PERIPHERAL BLOOD ENGRAFTMENT**

<table>
<thead>
<tr>
<th>Number per mouse</th>
<th>3,000</th>
<th>10,000</th>
<th>30,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number per kg</td>
<td>150,000</td>
<td>500,000</td>
<td>1,500,000</td>
</tr>
</tbody>
</table>

**BRAIN ENGRAFTMENT**

<table>
<thead>
<tr>
<th>Number per mouse</th>
<th>3,000</th>
<th>10,000</th>
<th>30,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number per kg</td>
<td>150,000</td>
<td>500,000</td>
<td>1,500,000</td>
</tr>
</tbody>
</table>
MGTA-456: Aryl Hydrocarbon Receptor (AHR) Antagonism as a Mechanism of HSC Expansion

**METHOD TO EXPAND HUMAN HSCs**

SR1 directly binds and inhibits the AHR, blocking induction of CYP1B1 and HSC differentiation.

**NUMBER OF CD34+ CELLS**

Modified from Wagner et al., Cell Stem Cell 2016
MGTA-456 Has Been Clinically-Validated in Hem/Onc Patients

**WITH MYELOABLATIVE CONDITIONING**

MGTA-456
100% Engraftment
n = 21/21 patients
Median: 12 days

Historical Control
83% Engraftment
Median: 26.5 days

**WITH NON-MYELOABLATIVE CONDITIONING**

MGTA-456
100% Engraftment
n = 9/9 patients
Median: 8 days

Historical Control
94% engraftment
Median: 17.5 days

Rationale for Ph2 Clinical Trial in IMDs

1. Accelerate engraftment
2. Prevent graft failure
3. Potentially accelerate and increase donor-derived microglia engraftment?

Wagner et al., ASH 2017
MGTA-456 Leads to Enhanced Hematopoietic Engraftment in NSG Mice Compared to Standard of Care

**EXPERIMENTAL SCHEMA**

Cord Blood CD34+ Cells

Unexpanded → MGTA-456

Transplant

200 cGy

At 3 Months Post-Transplant:

- hCD45 Frequency in Peripheral Blood
- Microglia in Brain by Flow Cytometry and IHC

**CD34+ FOLD EXPANSION OVER 10 DAYS**

<table>
<thead>
<tr>
<th></th>
<th>Unexpanded</th>
<th>MGTA-456</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cells</td>
<td>200,000</td>
<td>600,000</td>
</tr>
<tr>
<td>Frequency (%)</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

**p<0.01**

**hCD45 FREQUENCY IN PERIPHERAL BLOOD**

<table>
<thead>
<tr>
<th></th>
<th>Unexpanded</th>
<th>MGTA-456</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency (%)</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

**p<0.05**

n=8 mice
MGTA-456 Leads to Enhanced Brain Engraftment in NSG Mice Relative to Unexpanded Cells, the Standard-of-Care

**hCD45+CD11b+ NUMBER IN BRAIN**

<table>
<thead>
<tr>
<th></th>
<th>Vehicle</th>
<th>MGTA-456</th>
</tr>
</thead>
<tbody>
<tr>
<td>hCD45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD11b</td>
<td>0.00015%</td>
<td>0.0038%</td>
</tr>
</tbody>
</table>

p<0.01

**Ku80+lba-1+ NUMBER BY IHC**

<table>
<thead>
<tr>
<th></th>
<th>Unexpanded</th>
<th>MGTA-456</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number per brain</td>
<td>[data points and bars]</td>
<td>[data points and bars]</td>
</tr>
</tbody>
</table>

p<0.01

**LOCALIZATION OF Ku80+lba-1+ MICROGLIA**

- Perivascular
- Non-Perivascular

Ku80+lba1+ microglia indicated by magenta arrows

n=8 mice
Busulfan Dosing Enables Enhanced Brain Engraftment Compared To Irradiation

Modified from Capotondo et al. Sci Adv 2017
MGTA-456 Enables A Reduced Intensity Conditioning Regimen and Enhances Level of Human Microglia Engraftment in the Brains of NSG Mice Relative to Standard-of-Care

**EXPERIMENTAL SCHEMA**

- Cord Blood CD34+ Cells
  - Unexpanded
  - MGTA-456
  - Transplant
  - Transplant Progeny

**HEMATOPOIETIC ENGRAFTMENT**

Condition mice with:
- Low Dose BU (20 mg/kg)
- High Dose BU (40 mg/kg)
- 200 cGy Irradiation

**MICROGLIA ENGRAFTMENT**

n=8 mice

- MGTA-456
- Unexpanded
MGTA-456 Enhances Microglial Engraftment As Early As Two Weeks

Which cell type contributes to microglial engraftment?

**HEMATOPOIETIC ENGRAFTMENT**

![Graph showing hematopoietic engraftment](image)

**MICROGLIA ENGRAFTMENT**

![Graph showing microglia engraftment](image)

***p<0.001
n=8 mice
Which Cell Type Is Responsible For Engraftment?

HUMAN HEMATOPOIETIC HIERARCHY

- **HSC** (CD34+ CD90+ CD45RA-)
- **MPP** (CD34+ CD90- CD45RA-)
- **CLP** (CD34+ CD90- CD45RA+)
- **CMP** (CD34+ CD90- CD45RA+)

Lymphoid Cells
Myeloid Cells
Only CD90+ Cells Contribute to Microglial Engraftment

**EXPERIMENTAL SCHEMA**

Cord Blood
CD34+ Cells

Uncultured
MGTA-456

Sort Cells:
CD90+
CD90-
CD34-

Transplant

**UNCULTURED**

<table>
<thead>
<tr>
<th>TIME (DAY EXPANSION)</th>
<th>UNsorted</th>
<th>CD90+</th>
<th>CD90-</th>
<th>CD34-</th>
</tr>
</thead>
<tbody>
<tr>
<td>FREQUENCY (%)</td>
<td>&lt;0.01</td>
<td>1</td>
<td>10</td>
<td>100</td>
</tr>
</tbody>
</table>

**PERIPHERAL BLOOD**

<table>
<thead>
<tr>
<th>TIME (DAYS)</th>
<th>UNsorted</th>
<th>CD90+</th>
<th>CD90-</th>
<th>CD34-</th>
</tr>
</thead>
<tbody>
<tr>
<td>NUMBER PER BRAIN</td>
<td>&lt;1.0</td>
<td>10</td>
<td>100</td>
<td>1,000</td>
</tr>
</tbody>
</table>

**MGTA-456**

<table>
<thead>
<tr>
<th>TIME (DAYS)</th>
<th>UNsorted</th>
<th>CD90+</th>
<th>CD90-</th>
<th>CD34-</th>
</tr>
</thead>
<tbody>
<tr>
<td>NUMBER PER BRAIN</td>
<td>&lt;1.0</td>
<td>10</td>
<td>100</td>
<td>1,000</td>
</tr>
</tbody>
</table>

n=8 mice
MGTA-456 Results in Faster and Greater Hematopoietic and Brain Engraftment

- *Ex vivo* expanded human cord blood CD34+ cells, MGTA-456, significantly improves hematopoietic engraftment and number of human microglia in the brains of NSG mice.
- CD90+ cells are the only cells to contribute to microglia engraftment under these treatment conditions.
- Magenta-sponsored trial for MGTA-456 in patients with IMDs.
### ABSTRACT #3467

Preliminary Phase 2 Results Demonstrate Engraftment with Minimal Neutropenia with MGTA-456, a CD34+ Expanded Cord Blood Product in Patients Transplanted for Inherited Metabolic Disorders

John Wagner, M.D.
Sunday, December 2, 2018 6:00 – 8:00 PM
Acknowledgments

MAGENTA RESEARCH TEAM
Shuping Li
Melissa Brooks
Sharon Hyzy
Anthony Boitano
Michael Cooke

UNIVERSITY OF MINNESOTA
John E. Wagner
Paul J. Orchard
Claudio G. Brunstein
Todd E. DeFor
David McKenna
Darin Sumstad
Bruce R. Blazar
Jakub Tolar
Chap Le