TARGETED GENE INTEGRATION
TO TRANSFORM LIVES

Rewriting genetic therapies with precision and efficiency

39th Annual J.P. Morgan Healthcare Conference
January 11, 2021

Josh Lehrer, M.Phil., M.D.
Chief Executive Officer
What if we could find and replace any gene?
Huge potential for gene correction – and beyond

- **Precision gene integration for monogenic diseases**
  - HbS
  - HbA

- **Permanent therapeutic protein delivery**

- **Curative therapies in outpatient setting**

- **Next-generation cell therapies**
Rapidly building a next generation gene editing company

<table>
<thead>
<tr>
<th>Leveraging high-efficiency targeted gene integration</th>
<th>Initiating best-in-disease Phase 1 sickle cell program</th>
<th>Advancing pipeline of gene integration programs</th>
<th>Implementing focused strategy</th>
<th>Building deeply-experienced team</th>
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</thead>
<tbody>
<tr>
<td>• Fix, replace, insert genes</td>
<td>• First-in-industry approach to <strong>correct</strong> sickle mutation and <strong>restore</strong> normal adult hemoglobin</td>
<td>• SCID-X1: gene replacement</td>
<td>• Multiple near-term clinical milestones</td>
<td>• Founded by Stanford gene editing pioneers</td>
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<tr>
<td>• Gene integration above curative ranges</td>
<td>• Gaucher: targeted gene insertion</td>
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<td>▪ Establish POC</td>
<td>• Seasoned management</td>
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<td>• Discovery programs: prevalent diseases</td>
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<td>▪ Expand patient eligibility</td>
<td>• World-class investors &amp; board</td>
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<td></td>
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<td>▪ Leverage platform across indications &amp; cell types</td>
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January 11, 2021 39th Annual J.P. Morgan Healthcare Conference
Powered by pioneers in genetic medicine; Led by seasoned management and board

Matthew Porteus  
M.D., Ph.D.

Maria Grazia Roncarolo  
M.D., Ph.D.

Josh Lehrer, M.D.  
CEO

Katherine Vega Stultz  
COO

Philip Gutry  
CBO, Head Finance/IR

Danny Dever, Ph.D.  
Co-Founder / Head, Translational Science

Investors

Perry Karsen  

Joe Jimenez  

Management

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CBO, Head Finance/IR

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Co-Founder / Head, Translational Science

Board

Perry Karsen  

Joe Jimenez  

Graphite Bio
Targeted Gene Integration to Transform Lives

Platform Technology
Highly differentiated targeted gene integration platform

**Targeted integration**
- Replace defective genes
- Insert genes
- Maintain native control

**Non-targeted integration (e.g., lenti)**
- Insertional oncogenesis risk
- Variable and non-native gene expression

**CRISPR**
- Limited to knocking out genes

**Base editing**
- Single base edits only
- Off-target concerns
From dream to reality: High-efficiency targeted gene integration in hematopoietic stem cells

Unleashing the full potential of stem cells to cure disease

**Hematopoietic Stem Cell (HSC)**

**Multi-potent:**
- Differentiate into multiple blood and immune cell lineages

**Permanent:**
- Can reconstitute blood and immune system for a lifetime

**POC for dozens of genetic diseases via allogeneic HSC transplant (HSCT)**

- Sickle Cell
- SCID-X1
- Gaucher
- MPS
- Beta Thalassemia
- PNH
- Krabbe

**Realizing HSCs’ full therapeutic potential**

**Engineering autologous HSCs:**
- Safe, matched, no GVHD
- Permanent production of virtually any protein

**Applying mild conditioning:**
- Significantly expands eligible populations

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1. Orphanet.
2. Center for international blood and marrow transplant research.
Our strategy

- SCID-X1, moderate SCD, Gaucher, Hemophilia, A1AT, PKU
- >10,000 patients
  - Demonstrate POC for ex vivo targeted integration in HSCs
- >250,000 patients
  - Leverage protein production platforms
  - Expand utility with mild conditioning

Our vision

- >10MM patients
  - Leverage technology across endothelial cells, iPSCs, MSCs
- Autoimmune, CNS, oncology, regenerative
- Severe Sickle Cell Disease, Gaucher
- >10,000 patients
  - Apply our technology to enable one-time outpatient cures across a range of genetic and other diseases
- >10MM patients
Targeted Gene Integration to Transform Lives

Sickle Cell Disease Program: Correcting Sickle Globin and Restoring Normal Adult Hemoglobin
SCD unmet need

- Among most prevalent monogenic diseases\(^1\)
  - (A→T base mutation codon 6 of HBB gene)
  - 100,000 U.S. patients

- 30-year reduced life expectancy in US\(^2\)

- Most mortality from organ damage; noncurative treatments ineffective

- Annual treatment cost >$250K for severe patients\(^3\)

- Allo SCT curative, but rarely used (~150/yr US)\(^4\)
  - HLA match requirement and safety risks

Our goal

Correct the Sickle Globin gene to **restore normal hemoglobin** - so SCD patients can live normal lives

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4. Center for international blood and marrow transplant research.
Gene correction is the optimal approach

>250 million people live normal lives with Sickle trait (one normal, one sickle gene)
Selected by evolution by decreasing malaria severity

From the first molecular disease to the first molecular correction

Sickled Red Blood Cells

HbS  HbS

Corrected Red Blood Cells
(normal/trait)

HbA  HbAS
Curative gene correction has been achieved at GMP clinical scale

Sickle stem cells produce sickle RBCs

HSCT 5-20% normal stem cells sufficient for cure\(^1\)

GPH101 GMP scale cell drug product 55% cell correction (42% of alleles)\(^2\)

1. Fitzhugh et al. At least 20% donor myeloid chimerism is necessary to reverse the sickle phenotype after allogeneic HSCT. Blood. 2017 Oct 26;130(17):1946-1948.
2. Corrected cells average (55%) = 1.3× proportion of corrected alleles (42%, Graphite engineering runs).
Sickle mutation correction in patient cells and engraftment into mice

Correct mutation in SCD patient HSPCs

Measure HSC ex vivo function

Measure disease modification in mouse SCD model

Gene correction efficiency in SCD patient derived HSPCs exceed curative threshold

RBC differentiation ex vivo, >90% normal hemoglobin

Elimination of sickling and restoration of normal RBC lifespan


1. HSPCs - CD34+ hematopoietic stem and progenitor cells.
4. Background HbF not included for ease of comparison.
“The ultimate challenge to treat SCD is to genetically correct the HbS mutation”

John Tisdale, M.D., NIH SCD genetic therapy pioneer
>$1B market opportunity for SCD curative cell therapy, assuming 5-10% of severe patients treated

1. >100,000 patients with sickle cell disease in U.S.
2. ~20% patients with severe disease
3. >$1 million USD cost of curative therapy
4. Lifetime medical costs of up to $9 million per severe SCD patient
5. Mild bone marrow conditioning dramatically expands eligible patients

3. Analyst estimates and Headlands Consulting Analysis of approved Gene therapies
>10,000 patients
Demonstrate curative potential of gene corrected HSCs

>10MM patients
Leverage protein production platforms
Expand utility with mild conditioning

>10MM patients
Leverage technology across endothelial cells, iPSCs, MSCs

Autoimmune, CNS, oncology, regenerative

SCID-X1, moderate SCD, Gaucher, Hemophilia, A1AT, PKU

Severe Sickle Cell Disease, Gaucher

Our vision
Apply our technology to enable one-time outpatient cures across a range of genetic and other diseases
SCID-X1 gene replacement: demonstrating power and broad utility of platform while meeting critical unmet need

High unmet need

- IL-2 receptor common gamma (IL2RG) mutations severely impair T/B/NK cell function
- Severe unmet need: lifespan without treatment ~2 years¹
- Allogeneic HSCT is only cure
- 45 births per year in major markets²

Gene replacement approach³
Ideal strategy due to multiple mutations in IL2RG

Unlocks new and larger opportunities

- Auto-inflammatory syndromes
- Beta-thalassemia
- Immunodeficiencies

Mild antibody conditioning

Conduct SCID-X1 clinical trial with novel mild antibody conditioning

2. Wall Street Analyst reports (JPMorgan, Cowen, Leerink, Morgan Stanley, HC Wainwright).
Beyond blood and immune disease: precision engineered stem cells for permanent therapeutic protein production

**CCR5 locus**
(exogenous promoter)

- Targeted gene integration
- Lineage-specific expression
- Organ-specific expression

- Lysosomal storage diseases
  - Gaucher*
  - MPS*
  - Krabbe*
  - Pompe
  - Fabry

- CNS therapeutic protein delivery
  - GBA Parkinson’s
  - Progranulin
  - Antibodies

**Alpha globin locus**
(endogenous promoter)

- Targeted gene integration
- RBC-specific expression

- Lysosomal storage diseases
  - Hemophilia A/B
  - Alpha 1 antitrypsin deficiency
  - Beta-thalassemia*
  - PKU

*Published animal or in vitro data from Porteus lab
Protein production platforms unlock large commercial markets

Potential Market Opportunities

- Phenylketonuria
- Alpha-1 Antitrypsin Deficiency
- Hemophilia B
- Hereditary Angioedema
- Hemophilia A
- Other Lysosomal Storage Disorders
  - Hunter Syndrome
  - Gaucher
  - Pompe
  - Fabry

Source: Evaluate Pharma sales by indication for 2026
SCID-X1, moderate SCD, Gaucher, Hemophilia, A1AT, PKU

Severe Sickle Cell Disease, Gaucher

Demonstrate curative potential of gene corrected HSCs

Autoimmune, CNS, oncology, regenerative

>10MM patients
Leverage technology across iPSCs, MSCs, myeloid cells

>1MM patients
Expand utility with mild conditioning

Leverage protein production platforms

Our vision
Apply our technology to enable one-time outpatient cures across a range of genetic and other diseases
Platform extends across numerous indications and cell types.
Vast potential enabled by efficient targeted integration across wide range of cells


### PROGRAM / INDICATION

<table>
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<tr>
<th>PROGRAM / INDICATION</th>
<th>GENE</th>
<th>DISCOVERY</th>
<th>PRE-CLINICAL</th>
<th>IND-ENABLING</th>
<th>PHASE 1/2</th>
<th>PIVOTAL</th>
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<tr>
<td>GPH101 Sickle cell disease (SCD)</td>
<td>β-globin</td>
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<td>GPH201 X-linked severe combined immunodeficiency syndrome (SCID-X1)</td>
<td>IL2RG</td>
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<td>GPH301 (CCR5 locus) Gaucher disease – Type III</td>
<td>GBA</td>
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<td>GPH301 (CCR5 locus) Gaucher disease – Type I</td>
<td>GBA</td>
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<td>Safe harbor tissue protein production (CCR5) Potential programs: MPS1, Fabry, Pompe</td>
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<td>Safe harbor circulating protein production (alpha-globin) Potential programs: HemA/B, A1AT</td>
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Developing transformative therapies and building value in 2021

**Invest in Research**
- Enhance platform efficiency and generate novel IP
- Discovery projects for novel cell engineering applications

**Best-In-Disease Phase 1 Sickle Cell Program**
- Successfully manufacture and treat patients
- Translational endpoints to demonstrate differentiation
- Drive toward SCD POC (1H’22)

**Pipeline Progress**
- Complete IND enabling studies for SCID-X1 and Gaucher
- CCR5 and alpha-globin - potential program nominations
Thank you!

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