- E LINEAGE CELLTHERAPEUTICS

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Lineage Cell Therapeutics

- Lineage is a leading cell therapy company
- The company manufactures and transplants specific types of cells to treat injuries and disease
- Three clinical-stage programs:
 - Phase 1/2 in dry age-related macular degeneration (Dry AMD)
 - Phase 1/2 in spinal cord injury (SCI)
 - Phase 1 in oncology (non-small cell lung cancer, NSCLC)
- Patent estate of ~850 cell therapy-related patents and pending applications worldwide





Manufacturing and Transplanting Cells to Treat Injuries and Disease

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Cell Therapy Platform Technology

- The Lineage Platform starts with normal pluripotent cell lines, which avoids risks from genetic modifications
- These cells have the capacity to become any human cell type, offering many potential indications
- A cell's lineage is controlled to generate only the desired cell type
- The cells have high proliferative capacity and can produce material for the largest patient populations



CURRENT CLINICAL PROGRAMS



Clinical-Stage Pipeline

| Cell Therapy Programs | Phase I | Phase II | & External Funding |
|---|---------|----------|---|
| OpRegen® Dry Form Adult Macular Degeneration with GA (Dry AMD) | | | רשות החדשנות ג ג א ג ג א ג ג א ג ג א Israel Innovation Authority \$16M |
| OPC1 Spinal Cord Injury (SCI) | | | CRLIFORNIRY JTEM CELL RGENCY >\$14M |
| VAC2 Non-Small Cell Lung Cancer (NSCLC) | | | CANCER RESEARCH UK >\$10M in-kind |





Cell Therapy for Dry AMD

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8 Image adapted from scienceofamd.org

Dry Age-related Macular Degeneration (Dry AMD)

- A common eye disorder causing impaired central vision
- A leading cause of blindness in those over 60 years old
- Retina damage occurs from the accumulation of waste material called drusen and the loss of photoreceptor cells
- Retinal pigment epithelium (RPE) cells help clear away drusen
- Loss of RPE cells impairs drusen clearance and results in photoreceptor damage in the macula and increasing vision loss





9 Image adapted from scienceofamd.org

OpRegen[®] - Treating the Pathology of Dry AMD

- OpRegen is a suspension of RPE cells grown from a cell line
- RPE cells are injected directly into the sub-retinal space
- Potential benefits of replacing lost RPE cells include:
 - RPE reorganization
 - Drusen reduction
 - Photoreceptor recovery
 - Preserved or improved sight

Photoreceptor recovery OpRegen **RPE** cells



In-House GMP Manufacturing of RPE Cells

The lineage of an established line of pluripotent cells can be controlled to create a population of substantially pure RPE cells



In-House GMP Production

Extensive experience directing the lineage of pluripotent cells into terminallydifferentiated, specific cell types (such as retina cells, glial cells, etc.)

- Cell banking and handling
- Process development
- Manufacture of clinical material
- Scale-up into multi-liter bioreactors
- Multiple clean rooms for parallel GMP production runs





Engraftment and Survival of RPE Cells

- OpRegen cells were counter-stained with DAPI (red line)
- OpRegen cells form a sustained monolayer in multiple species



RCS Rat

NOD-SCID Mouse 2 months post transplantation



anti- human Nuclei

Pig 2 months post transplantation



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Improved Visual Acuity in RCS Rat Model

Dose-dependent rescue of vision can be observed via optokinetic nystagmus



OpRegen - Phase 1/2a Trial Design





<u>Purpose</u>: To evaluate the safety and efficacy of sub-retinally transplanted RPE cells in patients with advanced dry AMD with geographic atrophy

PART 2 (ONGOING) (moderate visual impairment)

 Cohort 4
 12 Patients
 100,000 cells

 BCVA 20/64 to 20/250
 100,000 cells
 100,000 cells

<u>Design</u>: Open label, single-arm, and multi-center (US and Israel)

Dose and Administration: One 50ul dose of cells injected into the subretinal space



Phase 1/2a Patient Data: Cell Engraftment

Stable engraftment of OpRegen RPE cells in a human subject



A large region of geographic atrophy is present (lighter circular area)

In areas of cell administration (upper green box), pigmentation is similar to normal retinal appearance, suggesting successful engraftment of cells



Baseline

Month 4

Phase 1/2a Patient Data: Drusen Reduction

- Drusen accumulation is observed at pre-treatment (wrinkled white line)
- A reduction or change to drusen is observed through month 9 in some patients

Treated

Untreated





Visual Acuity Case Study (Subject 602)





Phase 1/2a Clinical Trial Highlights

- Treatment with OpRegen has been well-tolerated
- Some patients show signs of structural improvement in the retina and decreases in drusen density
 - Photoreceptor layer and ellipsoid zone assumed a more regular structural appearance in areas of the transition zone where cells were administered
- Recent data from patients with earlier-stage disease and better baseline vision is encouraging
 - Evidence of durable transplantation and & structural improvement within the retina
 - Some improvements in visual acuity noted
- No unexpected adverse events or treatment-related systemic serious adverse events reported through 15 patients
 - One retinal detachment (successfully repaired) was not able to be assigned as related to treatment, procedure, or to the combination
 - Current subjects are being dosed with an improved delivery device (Orbit SDS), eliminating the need for a vitrectomy and retinotomy



Subretinal Delivery Challenges

- Current standard (transvitreal) techniques reach the subretinal space by vitreous removal (vitrectomy) and incision of the retina (retinotomy)
- Vitrectomy complications include retinal tear/detachment and cataract formation
- Transvitreal delivery complications may include:
 - enlarged retinotomy at bleb area;
 - efflux of delivered cells (during injection, needle removal, or retinotomy)
 - significant dose variability; and
 - significant surgeon and patient variability





Subretinal Delivery Solution

- Lineage has an exclusive option with Orbit Biomedical to utilize a vitrectomy-free subretinal injection device (originally developed by Janssen)
 - For subretinal delivery of RPE cells for the treatment of all stages of dry AMD including geographic atrophy
- Device provides access to the subretinal space via a suprachoroidal route
- A microneedle within a flexible cannula is advanced into the subretinal space
- Procedure avoids puncturing the retina and creates a stable bleb of therapeutic agent





Significant Market Opportunity

- AMD afflicts ~11 million people in the United States
 - 90% of AMD patients have the dry form
 - 100% of Wet AMD is preceded by Dry AMD
 - ~\$6B in sales of approved Wet AMD therapies²: Lucentis^{*} and Eylea^{*}
 - Currently, there are no approved therapies for Dry AMD





Sources: (1) Pennington and DeAngelis, Eye and Vision, 2016 3:34; (2) JM Seddon, Epidemiology of age-related macular degeneration. (AP Schachat, S Ryan eds.) Retina, 3rd ed. St. Louis, MO: Mosby; 2001;1039-50 and (3) 2016 product sales summary based on publicly reported revenue figures for Lucentis and Eylea.



Cell Therapy for Spinal Cord Injury

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Lucas' Story



Lucas Linder, an OPC1 clinical trial participant, was paralyzed from the neck down following an accident. The next year, he threw out the first pitch at a Major League Baseball game.



Spinal Cord Injury (SCI)

- SCI creates a significant burden for patients and caregivers*
 - 60% of cases result in some degree of tetraplegia
 - 67% of patients are unemployed 10 years post-injury
 - Lifetime direct healthcare costs can reach \$5 million for one patient
- Motor level improvements can translate into clinically significant improvements in self-care and reductions in cost of care
- The therapeutic goal is to restore arm, hand, and finger function, increasing independence and quality of life





OPC1 Overview

- OPC1 is a population of non-patient derived oligodendrocyte progenitor cells (OPCs)
- OPCs are precursors to the cells which provide electrical insulation for nerve axons in the form of a myelin sheath
- OPC1 has RMAT and Orphan Drug Designations from the FDA
- Program has received significant support from CIRM (>\$14M to date)



OPC1 Injection Procedure



OPC1 Potential Mechanisms of Action

Myelination of axons



Secretion of neurotrophic factors



Prevention of Cavitation





OPC1 Development in Spinal Cord Injury

Pre-Clinical

28 Animal Studies

- Survives in the spinal cord
- Greatest activity in subacute injury
- Improves locomotor activity
- Reduces parenchymal cavitation
- Migrates up to 5cm in spinal cord
- No distribution outside of CNS
- Does not increase mortality
- Does not induce systemic toxicity
- Does not produce teratomas
- Not highly susceptible to direct immune responses

Clinical

Phase 1 Thoracic Study

- 5 subjects administered 2M cells
- Long-term follow up has shown no evidence of adverse changes in any subjects

Phase 1/2a Cervical Study

- 25 subjects received up to 20M cells
- Evidence of durable cell engraftment
- Increased motor recovery
- No serious adverse events (SAEs)



Safety and Efficacy from OPC1 Phase 1/2a Study

Cell Engraftment

(cohorts 2-5 at 12 months, n=22)

Motor Function Gain

(cohorts 2-5 at 12 months, n=22)



To date, there have been no serious adverse events related to the OPC1 cells



Motor Recovery in Cohorts 2-5*

| | 2 Motor Levels | | UEMS Improvement | |
|-------------|----------------|-----------|------------------|-------------|
| | 6 Months | 12 Months | 6 Months | 12 Months |
| Cohort 2 | 2/6 | 4/6 | 9.7 | 12.3 |
| Cohort 3 | 1/6 | 1/6 | 6.0 | 9.2 |
| Cohort 4 | 1/6 | 1/6 | 5.5 | 6.7 |
| Cohort 5 | 0/4 | 1/4 | 5.8 | 6.8 |
| Cohorts 2-5 | 4/22 | 7/22 | 6.8 | 8.9 +/- 4.2 |

- The two worst performing subjects (with an average UEMS improvement of 3.5) experienced cord compression without intervention. C4 patients (a higher level of injury) generally had less recovery than C5-C7. Both can be addressed in next trial.
- A subset analysis excluding cord compression or C4 baseline injury shows a UEMS improvement of 10.2 +/- 3.9 at 12 months.



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Cell Therapy for Cancer

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VAC Immuno-Oncology (I-O) Program

- VAC platform uses mature dendritic cells (DC) to increase a patient's tumor response
- Treatment is an allogeneic vaccine; cells are manufactured from a pluripotent cell line and not derived from the patient
- Mature dendritic cells are manufactured and loaded with an antigen present in >85% of all cancers and fused to a sequence which aids antigen presentation via MHC proteins, to stimulate CD8+ (cytotoxic) and CD4+ (helper) T cell responses
- Targeted education of T cells increases immune response and tumor cell destruction



Potential Advantages of the VAC2 Approach

| Attribute | VAC2 |
|---|------|
| Single master cell bank for scalability and consistency | Х |
| Available 'off-the-shelf', on demand | Х |
| No known significant off-target effects | Х |
| Low AE-related cost of treatment | Х |
| Lower anticipated COGS than CAR-T | Х |
| In combination with chemotherapy | Х |
| In combination with immune checkpoint inhibitors | Х |

VAC2 was designed to overcome limitations of first-generation I-O combinations and autologous approaches, while providing cost and safety advantages in combination or competition with CAR-T, CTL4, or Immune Checkpoint Inhibitors (ICIs).



VAC2 Clinical Program

- Partnered with Cancer Research UK
- Cancer Research UK is responsible for the costs and conduct of manufacturing and the clinical trial
- Primary endpoint: safety and tolerability
- Secondary objectives: immunological response and survival
- Enrollment is ongoing





Future Directions: VAC2 In Combination with Immune Checkpoint Inhibitors (ICI)

- ICIs make tumors more susceptible to immune function, potentially boosting DC immunotherapy by reducing cancer cell resistance
- Ex vivo functional studies with glioblastoma tissue have shown 4 that PD-1 blockade in combination with DC therapy results in increased survival compared to PD-1 or DC alone⁽¹⁾
- Proof-of-concept for a DC-ICI combination has been demonstrated in humans with multiple myeloma⁽²⁾

Dendritic cell vaccine added to PD-1 blockade rescues the survival benefit in mice with established tumor burden





The VAC Platform has Broad Application

Approach:

In Combination with Checkpoint Inhibitors with or without Chemo **Rationale:**

Stimulate endogenous T cell response to enable ICIs to work better in 'immune cold' tumors

Additional, Targeted, and/or Combination Antigens

Monotherapy in Minimal Residual Disease with High Risk of Relapse

- Allogeneic and autologous platforms can be used to deliver any antigen(s), including neoantigens
- Stimulate T cell response to eliminate residual cancer cells after debulking chemotherapy, surgery, and radiotherapy





Renevia®

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Renevia[®]

- A proprietary cell transplant matrix tested clinically in combination with autologous fat stromal vascular fraction (SVF) cells for facial volume augmentation
- 50-patient, HIV-Associated Lipoatrophy Study
 - Increase in hemifacial volume as measured by 3D image scan at 6 months
 - There were no device or procedural-related serious adverse events reported
- Submitted for CE mark in Europe; response expected 2H 2019





Financial Overview

- Cash and cash equivalents and marketable securities
 \$16.7 million (as of 6/30/2019)
- Value of Equity Holdings in OncoCyte Corporation (OCX)
 - \$21.6 million (based on closing stock price on 8/6/2019)
- Convertible promissory note due <u>from</u> Juvenescence
 - \$22.9 million (as of 6/30/19, matures Aug 2020)
- Market Capitalization
 - ~\$151 million (as of 8/6/2019)
- Employees
 - 73 (as of 8/9/2019)



Investment Highlights

- Lineage Cell Therapeutics is a leading cell therapy company, developing three clinical-stage programs, each transplanting specialized cells to treat unmet medical needs:
 - Dry AMD with GA
 - Spinal Cord Injury
 - Non Small Cell Lung Cancer

• Significant Events:

- Hired new CEO, CFO, CMO, General Counsel, VP of Business Development
- Completed acquisition of Asterias Biotherapeutics, Inc.
- Spun off and completed distribution of AgeX Therapeutics, Inc. (NYSE American: AGE)
- Received \$21.6M in payments from Juvenescence Ltd.
- Received patent for method of reducing cavitation in patients with acute spinal cord injury
- Sold 2.25 million shares of OncoCyte Corporation for gross proceeds of \$4.5 million
- Awarded \$2.5M grant from Israel Innovation Authority for OpRegen development
- Announced new name and corporate relocation (Carlsbad, CA)





The future of cell therapy.

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