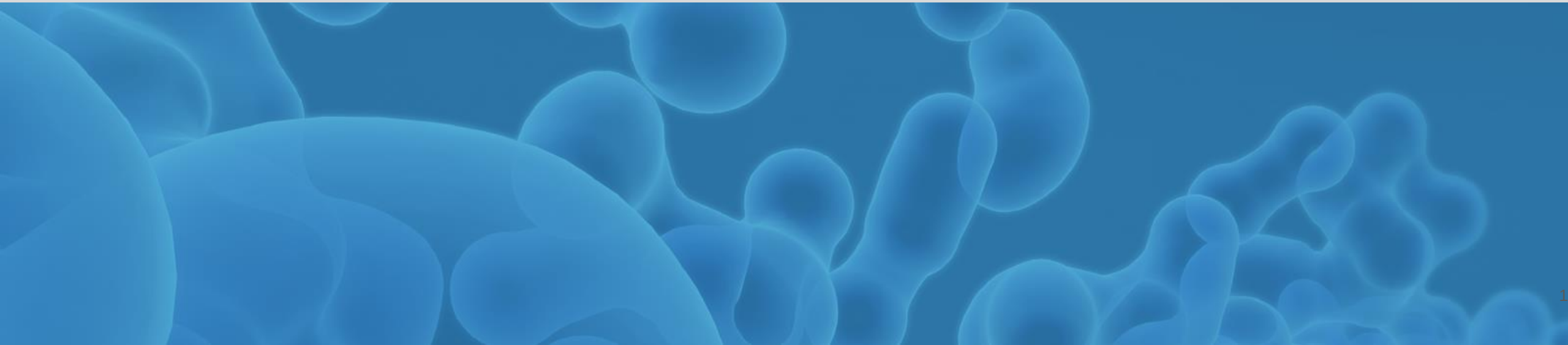
Clinical-Stage Immunotherapy

2021



Forward-Looking Statements

Statements in this presentation that are not descriptions of historical facts are forward-looking statements within the meaning of the “safe harbor” provisions of the Private Securities Litigation Reform Act of 1995. We have attempted to identify forward-looking statements by terminology including “anticipates,” “believes,” “can,” “continue,” “could,” “estimates,” “expects,” “intends,” “may,” “plans,” “potential,” “predicts,” “should,” or “will” or the negative of these terms or other comparable terminology. Forward-looking statements are based on management’s current expectations and are subject to risks and uncertainties that could negatively affect our business, operating results, financial condition and stock price. Factors that could cause actual results to differ materially from those currently anticipated are risks relating to: our growth strategy; results of research and development activities; uncertainties relating to preclinical and clinical testing; our dependence on third party suppliers; our ability to obtain, perform under and maintain financing and strategic agreements and relationships; our ability to attract, integrate, and retain key personnel; the early stage of products under development; our need for substantial funds; government regulation; patent and intellectual property matters; competition; as well as other risks described in our parent company’s SEC filings. We expressly disclaim any obligation or undertaking to update or revise any statements contained herein to reflect any change in our expectations or any changes in events, conditions or circumstances after the date of this presentation.

Corporate Overview

- Developing novel immunotherapies to prevent and control very common virus: Cytomegalovirus (CMV)
  - Potential for lower toxicity versus anti-virals with enhanced immune recovery and limited dosing
  - Programs licensed from City of Hope National Medical Center (Duarte, Ca)

- Two Novel Biologics
  - **Triplex**: Multi-Antigen Modified Vaccinia Ankara (MVA) vaccine for CMV **control**
    - Induces CMV-specific T cell response (pp65 + IE1 + IE2)
    - Phase 1: safe, highly immunogenic in healthy volunteers, n=24
      - Presented at **ASH**, published in **Blood**
    - Phase 2: met primary endpoint in allogenic stem cell transplant, n=102
      - Presented at **EBMT** in March 2019, publication by 1Q2020
    - Multiple other studies ongoing, planned: haplo-, donor vax, pediatric, kidney, liver
  - **ConVax**: Multi-Antigen MVA Vaccine for CMV **prevention** and **control**
    - Induces humoral and cellular response to CMV (pentamer + gB + pp65 + IE1)
    - Non-clinical development ongoing; IND filing in 2020
    - Stable Expression of Up to 8 Antigens

Investment Highlights

1. Novel biologic immunotherapies targeting lucrative markets (no approved immunotherapy)
2. First-in-Class, Best-in-Class Vaccine for CMV Control (Triplex). Met Primary Endpoint in Phase 2
3. Potential for lower toxicity versus anti-virals with enhanced immune recovery and limited dosing
4. Biologic Exclusivity (Orphan for Triplex); robust IP portfolio
5. Significant grant funding reduces capital requirements, validates approach

Helocyte Leadership

Management

Lindsay A. Rosenwald, M.D. Co-Founder and Executive Chairman	20+ years experience	Life Sciences Entrepreneur and Investor
Frank Taffy, J.D. Co-Founder, President and Chief Executive Officer	18+ years experience	Forest Laboratories, Inc. former Head of Business Affairs
Elizabeth Moore, M.S. Executive Vice President Regulatory Affairs	30+ years experience	Pfizer former Head of Regulatory Affairs (La Jolla, CA)

Board of Directors

Lindsay A. Rosenwald, M.D.
Executive Chairman

Michael S. Weiss, J.D.
Director

Frank Taffy, J.D.
Director

Clinical Development Pipeline

TRIPLEX	Pre-Clinical	Phase 1	Phase 2	Phase 3
Allogenic Stem Cell Transplant (Matched Related, Unrelated Donor)	Phase 3 to Open 1H2020 (n=585)			
Allogeneic Stem Cell Transplant (Haploidentical Donor)	Open (n =108)			
Allogeneic Stem Cell Transplant (Pediatric)	Open (n=80)			
Allogeneic Stem Cell Transplant (Donor Vaccination)	Open (n=20)			
Autologous Stem Cell Transplant (To Drive NK Cell Reconstitution)	Open (n=20)			
CMV-HIV Co-Infection on Anti-Retroviral Therapy (To Reduce Viral Shedding)	To Open in 1H2019 (n=90)			
Kidney Transplant	To Open in 2020 (n=72)			
Liver Transplant	To Open in 2020 (n=72)			
CONVAX				
CMV Prevention & Control	IND by 1H2020			

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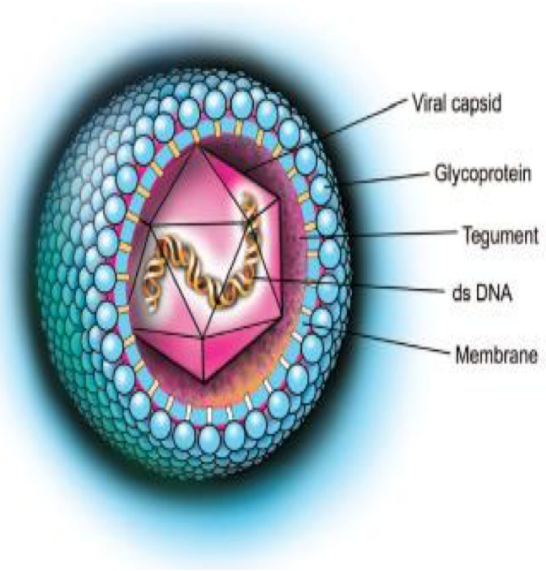
CMV Overview

- CDC estimates 50-80% infected with CMV by age 40
  - Easily transmitted: saliva, urine and in utero
  - Life-long infection, asymptomatic in healthy individuals

- Life-threatening in those with weak immune systems
  - Allogeneic Hematopoietic Stem Cell Transplant (“HSCT”)
  - Solid Organ Transplant (“SOT”)
  - Developing Fetus or Newborn Children

- Standard of Care: often toxic, moderately effective antivirals (often with extended dosing regimens)

- Relevance of Helocyte Vaccines
  - Triplex: control of CMV (in transplant) is cell-mediated
  - ConVax: prevention of CMV requires humoral immunity



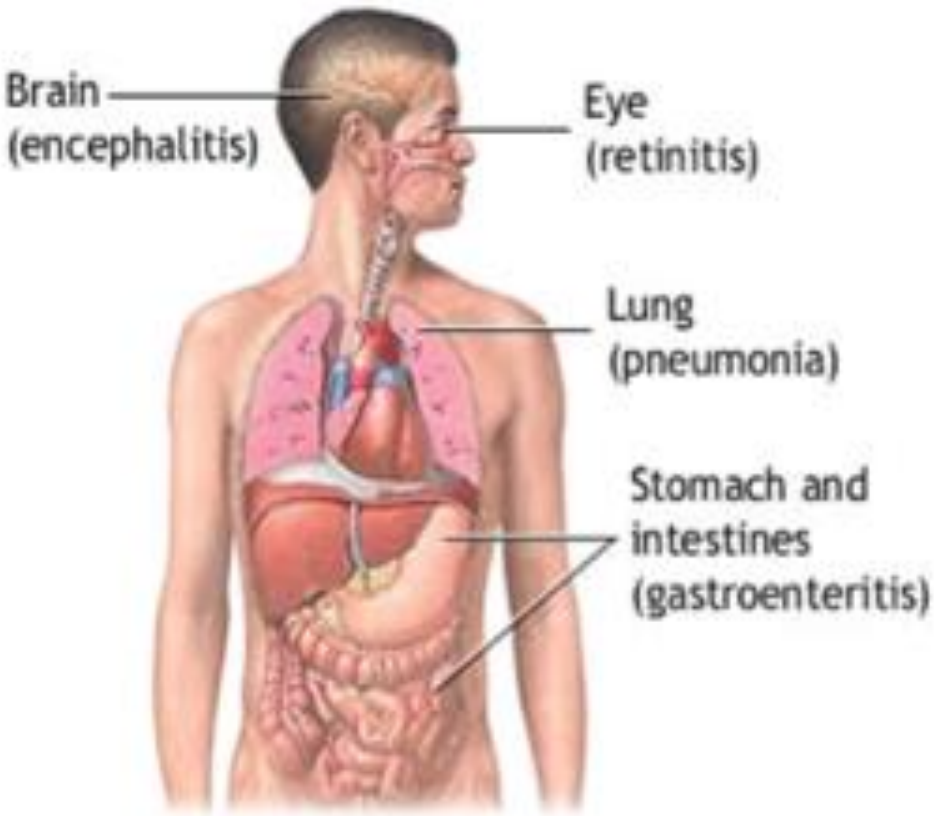
Complications of CMV

Direct Effects

- Viral Syndrome: fever, malaise, myalgia, leukopenia, thrombocytopenia
- Tissue Invasion (End Organ Disease): hepatitis, colitis, nephritis, pancreatitis, retinitis, encephalitis, pneumonia
- Other: bacteremia, fungemia, graft versus host disease

Occurrence

- Early and late after allogeneic HSCT and SOT
  - Late CMV (after Day 100) following antiviral use
  - Measured weekly through Day 100 in HSCT
- Evident at birth upon transmission from mother to fetus



Unmet Needs in Post-Transplant CMV Control Addressed by Triplex

01 Treatments with Reduced Toxicity

02 Treatments that Promote Immune Reconstitution

03 Treatments that are Durable, Reduce Rate of Late CMV (after Day 100)

04 Treatments with More Convenient, Less Frequent Dosing

05 Treatments that do not Promote CMV Resistance (like antivirals)

Triplex: Significant Commercial Opportunity

Antivirals: Standard of Care for CMV Control in Post-Transplant Setting

- Moderately effective, often toxic (*Black Box Warning for Preemptive*)
- Mechanism: merely suppress CMV during course of treatment
  - Delay immune reconstitution, “late CMV” after discontinuation
- Preemptive: upon CMV detection (weekly via PCR)
- Prophylactic: upon transplant, see Prevymis™ (approved 11/2017)
  - WAC Price: $19,500 for oral, $27,000 for injectable for 14-week (100 day) course of therapy
- Overall Burden: ~$140K per patient to manage CMV, up to $800K total for HSCT*

**based on interviews with payors (including Medical Director @ United Health)*

Procedure	US Incidence	EU Incidence
Allogeneic Stem Cell Transplant	**~9,000**	**~15,000**
Solid Organ Transplant (Kidney)	**~20,000**	**~27,000**
Solid Organ Transplant (Liver)	**~8,000**	**~10,000**

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Triplex: Overview

- Universal Multi-Antigen MVA-based CMV Vaccine

- Mechanism: Cellular Immunity to Primary CMV Proteins
  - CD4 & CD8 T Cell Response to: pp65 + IE1 + IE2

- Indication: CMV Control in HSCT & SOT

- Phase 1 in 24 Healthy Volunteers
  - Safe, Well-Tolerated at Three Dose Levels
  - Robust, Durable Immunogenicity
  - Presented at **ASH** (12/2015), Published in **BLOOD** (11/2016)

- First Phase 2 (n=102): Matched Related, Unrelated HSCTs
  - Safe, Immunogenic, Efficacious (Met Primary Endpoint)
  - Topline data presented at **EBMT** (03/2019)
  - End of Phase 2 Meeting by 1H2020

Triplex: Phase 1 Summary

Phase 1 Data: Presented at <u>ASH</u> and Published in *<u>Blood</u>*

- 24 Healthy Volunteers (3 Dose Levels)
- Safety: well tolerated, no SAE or dose-limiting toxicities
- Immunogenicity: robust, durable T cell responses observed even in
  - CMV-negative subjects with no prior immunity
  - CMV-positive subjects with low baseline immunity

ASH | 57th Annual Meeting & Exposition
Orlando, FL • December 5-8, 2015

3108 Safety, Maximum Tolerated Dose and Immunogenicity of CMV-MVA-Triplex in Healthy Volunteers with or without Prior Immunity to CMV and Vaccinia

Clinical Allogeneic Transplantation: Conditioning Regimens, Engraftment and Acute Transplant Toxicities
Program: Oral and Poster Abstracts
Session: 721. Clinical Allogeneic Transplantation: Conditioning Regimens, Engraftment and Acute Transplant Toxicities: Poster II

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Leading the way in experimental and clinical research in hematology

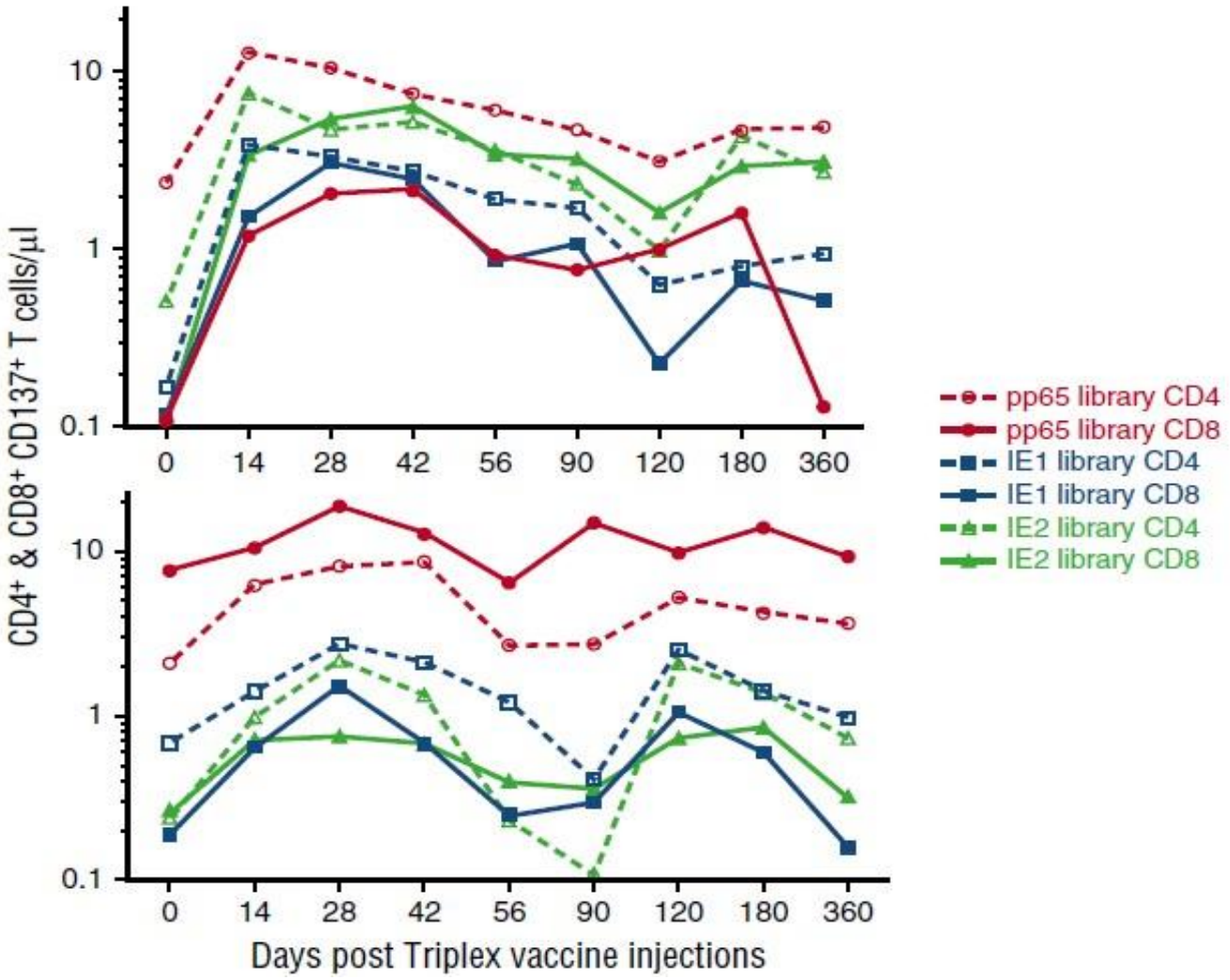
Safety, Maximum Tolerated Dose and Immunogenicity of CMV-MVA-Triplex in Healthy Volunteers with or without Prior Immunity to CMV and Vaccinia

Don J. Diamond, Corinna La Rosa, Jeffrey Longmate, Joy Martinez, Qiao Zhou, Theodora Kaltcheva, Jennifer Drake, Mary Carroll, Sanjeet Dadwal, Ibrahim Aldoss, Ryotaro Nakamura and John A. Zaia

Blood 2015 126:3108;

Triplex: Key Phase 1 Data (published in *Blood*)

Representative CD4 & CD8 T cell responses of two healthy volunteers to each of three CMV proteins targeted by Triplex, durable to 360 days



Triplex: Phase 2 in Allo-HSCT (Lead Indication)

- First Phase 2: CMV control in Allo-HSCT (matched related, unrelated donors)
  - Multi-center, double-blinded Study in 102 patients, randomized (1:1) vaccine / placebo
  - 3 clinical sites: top transplant centers in U.S.
    - City of Hope (PI, Nakamura): primary site, opened June 2016
    - Dana Farber (PI, Baden): opened November 2016
    - MD Anderson (PI, Ariza-Heredia): opened February 2017
  - Primary Endpoint Met: Reduction in CMV Events Thru Day 100
  - Final DMC review: no safety issues, no adverse impact on GvHD, relapse, survival (stopping rules)
  - Secondary Endpoints: late CMV, duration of viremia, anti-viral use; ***data presented at EBMT in 03/2019***

	Design	Dosing Schedule	1° Endpoint	2° Endpoint(s)
Phase 2 (Fully-Accrued)	Multi-Center, Randomized (1:1), Double-Blinded Study in 102 Allogeneic HSCT CMV(+) Recipients (MRD, MUD)	Two IM Vaccinations After Transplant: • Day 28 • Day 56	CMV Reactivation through Day 100 as monitored by PCR	• Immune Response • Viremia Duration • Antivirals Use • Relapse, Survival

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Triplex: Phase 2 in Allo-HSCT (Top-Line Data)

- Oral Presentation at European Society for Blood and Marrow Transplantation (EBMT) Conference in Frankfurt, Germany (03/2019)
  - Summary: safe, well-tolerated; significantly better than placebo in preventing viremia, with improved CMV T cell reconstitution
  - See https://www.professionalabstracts.com/ebmt2019/iplanner/#/presentation/725)

- **Safety**
  - Independently Monitored
  - Safe, well-tolerated; no significant difference in grade 3-4 AEs or SAEs between arms (balanced patient characteristics)
  - No adverse impact on any transplant-related outcome (GvHD, relapse or survival)

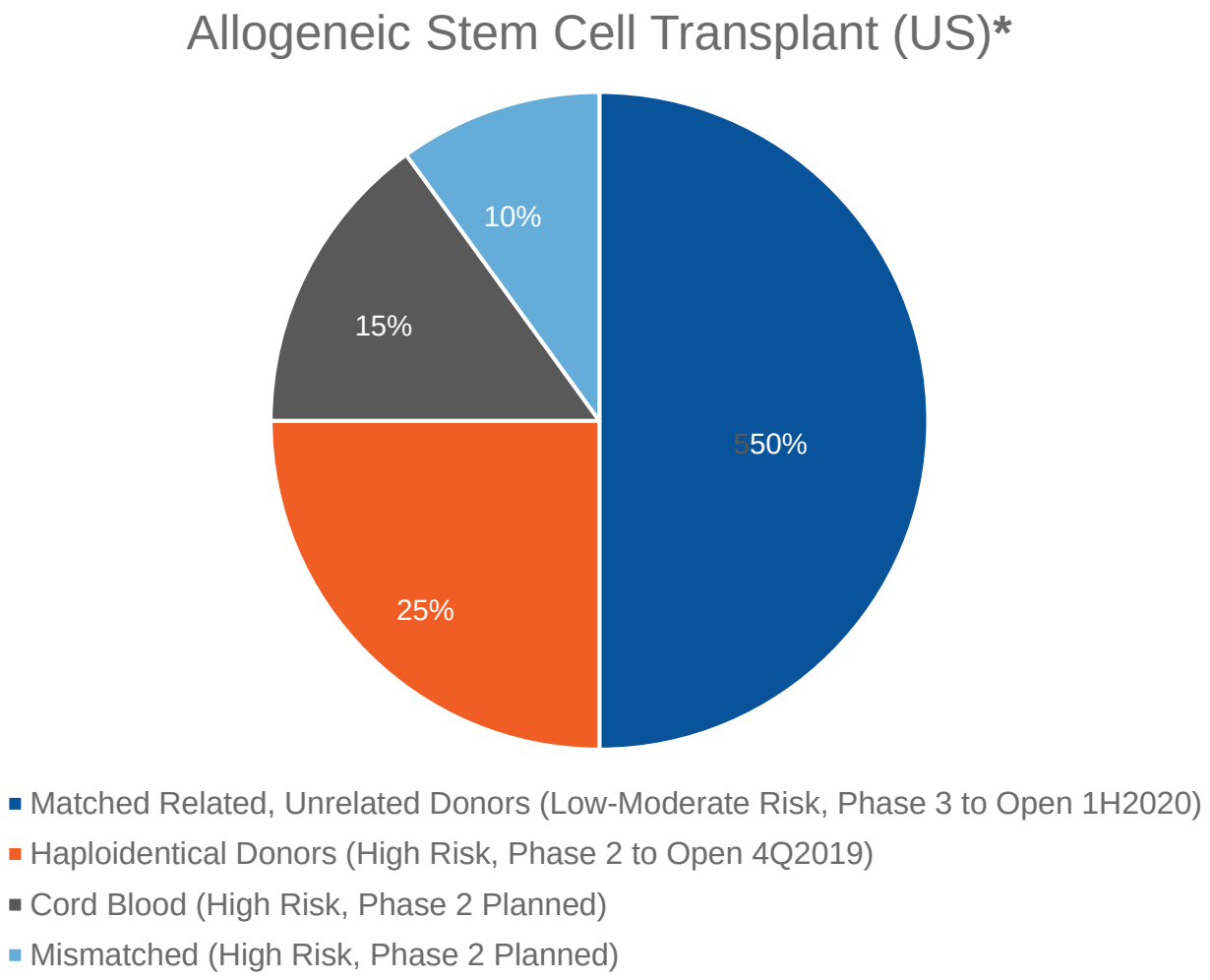
- **Immunogenicity**
  - Recipients with *both* CMV(-) and CMV(+) donors showed strong reconstitution of CD4 and CD8 CMV-specific immunity
  - Immune response initiated soon after first injection and elevated for at least 100 days post-HSCT

- **Efficacy**
  - Primary Endpoint Met: 50% reduction in CMV Events versus placebo through Day 100
    - 5 CMV Events in Vaccine Arm (9.8%) versus 10 in Placebo Arm (19.6%) (one-sided 0.10 p=0.08)
  - Powered by at least 90% at one-sided 0.10 level of significance to detect decrease in events from 30% to 10% or from 40% to 15%
    - Number of CMV Events Anticipated (30 to 40 total) versus Observed (15 total)

Triplex Versus Hookipa (HB101)

	Triplex	HB-101
Clinical Stage	Met Primary Endpoint in Multi-Center Phase 2 in difficult-to-treat allogeneic stem cell transplant (HSCT)	Completing Phase 2 in less difficult-to-treat kidney transplant recipients (more immuno-competent than HSCTs)
Vector	Modified Vaccinia Ankara (MVA), dosed safely in over 120,000 (elderly, children included), demonstrated safety and immunogenicity in HSCTs with rapid, robust and durable CD4 & CD8 T cell responses observed	Lymphocytic choriomeningitis (LCM), rodent-borne viral infectious disease; deaths reported from LCM-infected organ donor (see CDC MMWR 05/2005); LCM vector primarily generates CD8 T cells, but reduced CD4 T cell memory (Flatz, 2010)
Immune Targets	pp65 + IE1 + IE2	pp65 + gB
Relevance of Targets	Prevention of CMV viremia critically dependent on reconstitution of pp65-specific T cells (Walter, 1995); IE gene with decisive role in CMV reactivation, IE2 indispensable to CMV replication (Paulus, 2009)	CMV humoral immunity to gB is not required for control of CMV viremia after HCT (Bowden, 1991); gB failed to prevent viremia in kidney transplant (Astellas, ASP0113)
CD8 T Cell Responses	CD8 T cells exert rapid antiviral effects against CMV (Feuchtinger, 2010); Triplex induced robust, durable CD8 T cells in HSCTs early post transplant in Phase 2	In CMV(-) healthy volunteers, two injections of Triplex induced rapid, robust pp65-specific CD8 response (max ~2.3%) compared to three injections of HB101 (max ~0.3%); see Appendix for additional data
CD4 T Cell Responses	CD4 T cells provide physiological, sustained immune response to CMV (Feuchtinger, 2010); Triplex induced robust, durable CD4T cells in HSCTs early post transplant in Phase 2	In CMV(-) healthy volunteers, two injections of Triplex induced rapid, robust pp65-specific CD4 response (max ~2%) compared to three injections of HB-101 (max ~0.02%); see Appendix for additional data
Valuation	Privately-Held (No Equity Financing To Date)	Public (NASDAQ: HOOK); Leerink 5/13 analyst report values HB101 alone at ~$200M (prior to Phase 2 data)

HSCT Market: Addressed By Triplex



**Figures are approximate and based on available market info and feedback from physicians*

ConVax Overview

- Universal Multi-Antigen MVA-based CMV Vaccine

- Mechanism: Humoral + Cellular Immunity
  - Neutralizing Antibody Response to: Pentamer, gB
  - T Cell Response to: pp65 + IE1

- Indication: CMV Prevention **and** Control
  - Vaccinate adolescents, women of child-bearing age, others
  - Deploy as next generation of Triplex in transplant

- Development Status:
  - IND-enabling studies *in progress*
  - Immune responses in mice, rabbits, rhesus macaques
  - IND filing anticipated by 1H2020

Congenital CMV Overview

- CMV Most Common Congenital Infection: 0.5%-2% of all pregnancies (38K in US / year)
  - Institute of Medicine ranks new vaccine as “Highest Priority”
  - Severe Complications (10-15%): hearing loss, mental retardation, retinitis

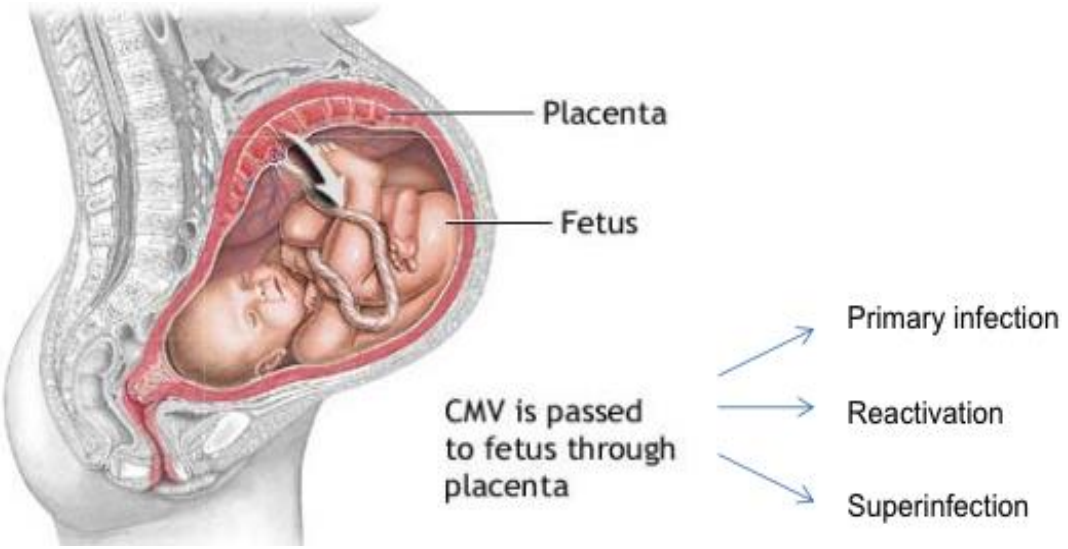
- Prevention requires humoral (NAb) immunity (*vs.* cellular immunity for control in transplant setting)

The New York Times

HEALTH

CMV Is a Greater Threat to Infants Than Zika, but Far Less Often Discussed

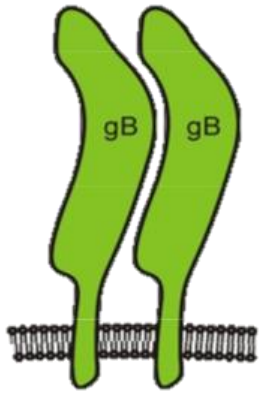
By CATHERINE SAINT LOUIS OCT. 24, 2016



CMV Transmission Pathway

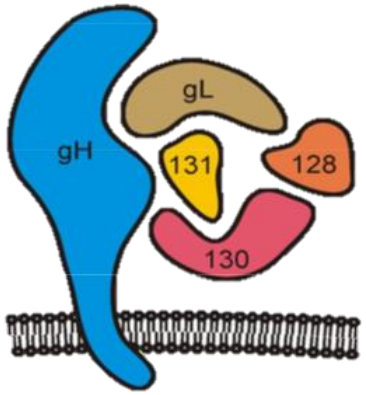
Glycoprotein B (gB)

- Essential for Virus Entry into Host Fibroblasts
- Target of Neutralizing Antibodies (NAbs)
- Fusion protein of, and triggered by, Glycoprotein H (gH)
- Recombinant gB Subunit Vaccine (Sanofi)
  - Only ~50% Efficacy in Preventing Primary Infection



gH/gL complex (gH/gL-PC)

- Pentamer (gH, gL, UL128, UL130, UL131)
- Allows Entry into Epithelial/Endothelial Cells (Epi/EC)
- Major target of NAbs
- Absent in Lab Strains (AD169, Towne)



ConVax: CMV Prevention & Control

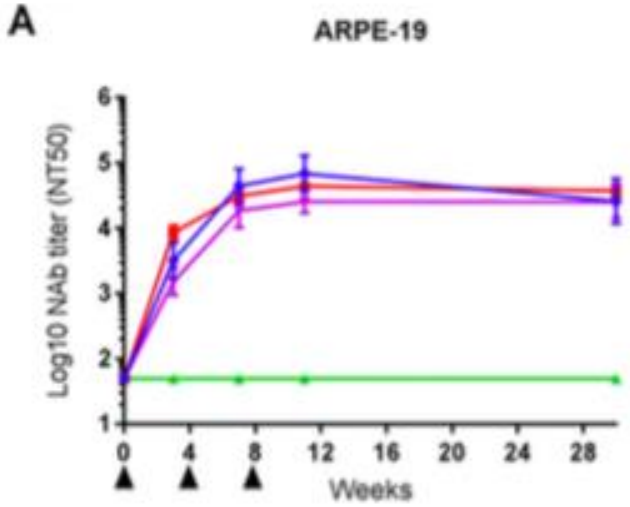
Development Candidates (3)

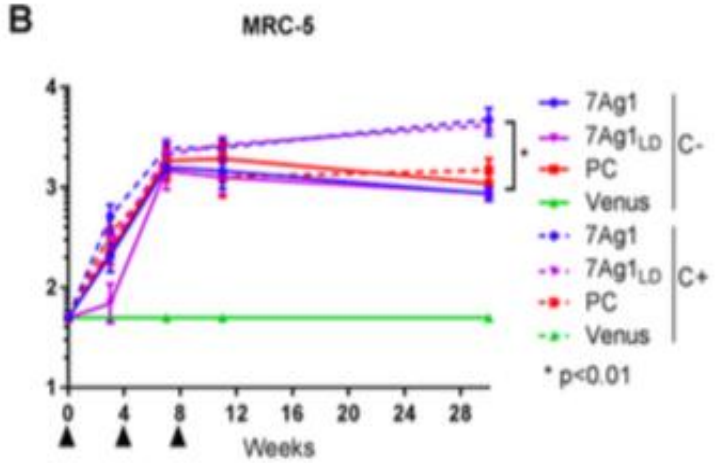
- First Vaccine Candidate (**Pentamer**)
  - Stable expression of six antigens (pentamer + gB)
- Second Vaccine Candidate (**Heptamer**)
  - Stable expression of seven antigens (pentamer + gB + pp65)
- Third Vaccine Candidate (**Octamer**)
  - Stable expression of eight antigens (pentamer + gB + pp65 + IE1)

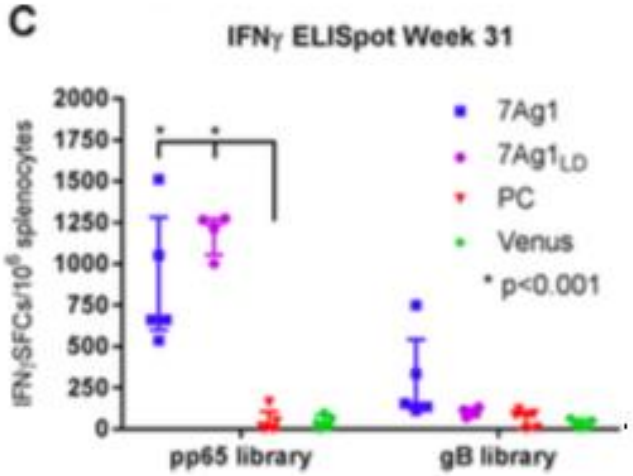
- Development Status
  - Tested in mouse models, rabbits, rhesus macaques
  - Robust, durable immune responses observed
  - IND filing (Octamer) anticipated by 1H2020

ConVax: Key Preclinical Data (published in *J. Virology, 2018*)

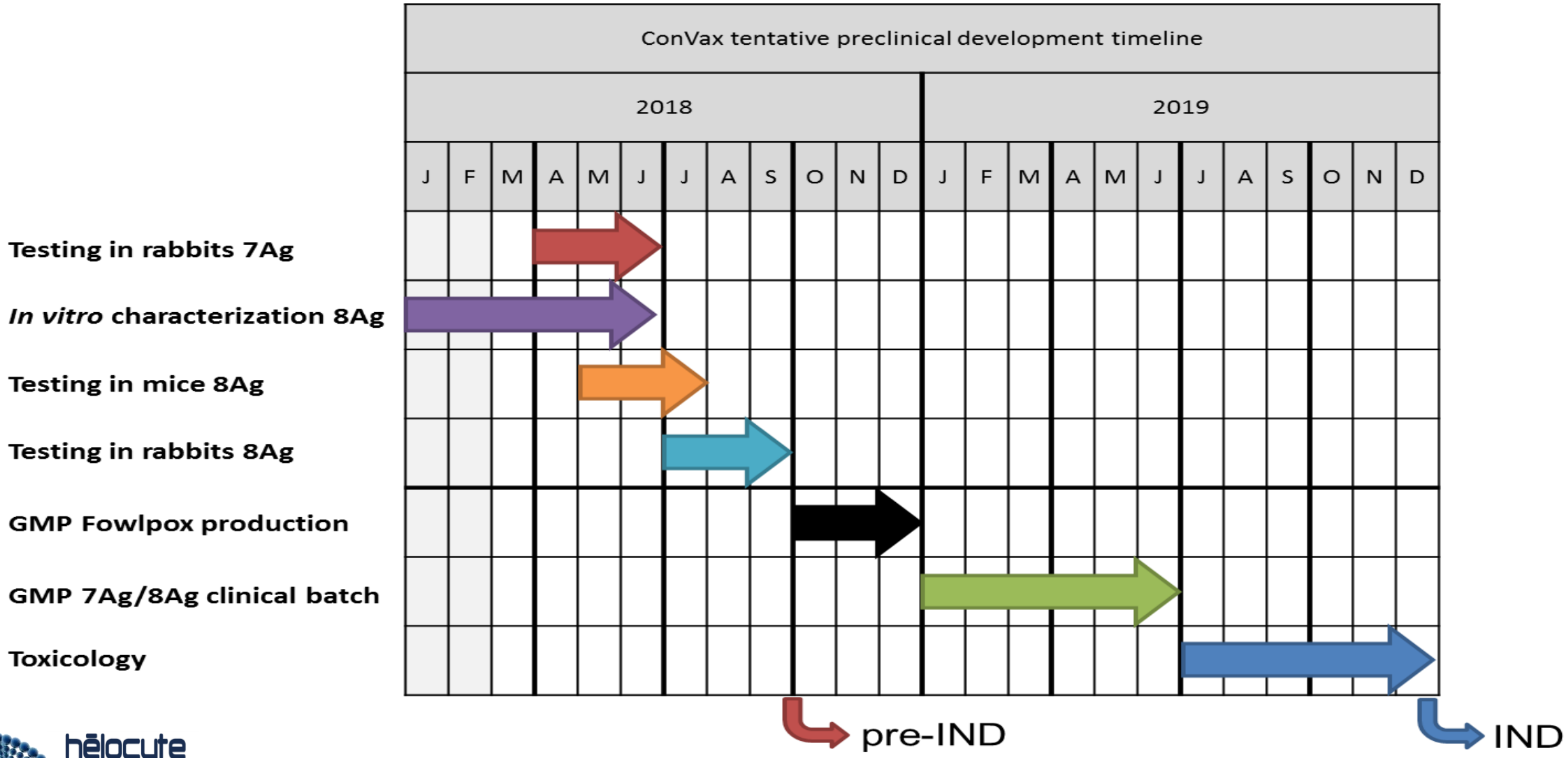
Robust <u>and</u> Durable Humoral <u>and</u> Cellular Responses to Next-Generation (7-antigen) Construct
(*to be used in both prevention <u>and</u> control of CMV*)







ConVax: Non-Clinical Development Timeline



Grant Partners

Phase 2 study in Allogeneic HSCT
(matched related, unrelated donors)

Phase 1 study in Autologous HSCT
(NK cell reconstitution to improve relapse, survival)

Phase 2 study in in Allogeneic HSCT
(vaccination of HSCT donor, followed by recipient)

Phase 2 study in Adults Co-infected with CMV-HIV on potent anti-retroviral therapy (ART)

Regulatory & IP Exclusivity

Regulatory

Orphan Exclusivity (applicable to Triplex): 7 Years (US), 10 Years (EU)

Biologic Exclusivity (applicable to Triplex & ConVax): 12 Years (US), 11 Years (EU)

Triplex IP

HCMV Antigens Expressed in MVA, Methods (7,163,685), expires 2024

rMVA Vaccines and Methods of Prep Thereof (14/075,975), expires 2030

rMVA Vaccines and Methods of Prep Thereof (8,580,276), expires 2031

Other applications relating to MVA construct extend protection to 2033

Patent Term Adjustment, Patent Term Extension possible

ConVax IP

MVA Vaccine UL128 Complex, Methods (PCT/US2013/32554)

Additional IP covering new constructs filed (not yet published)

Near-Term Target Development Milestones

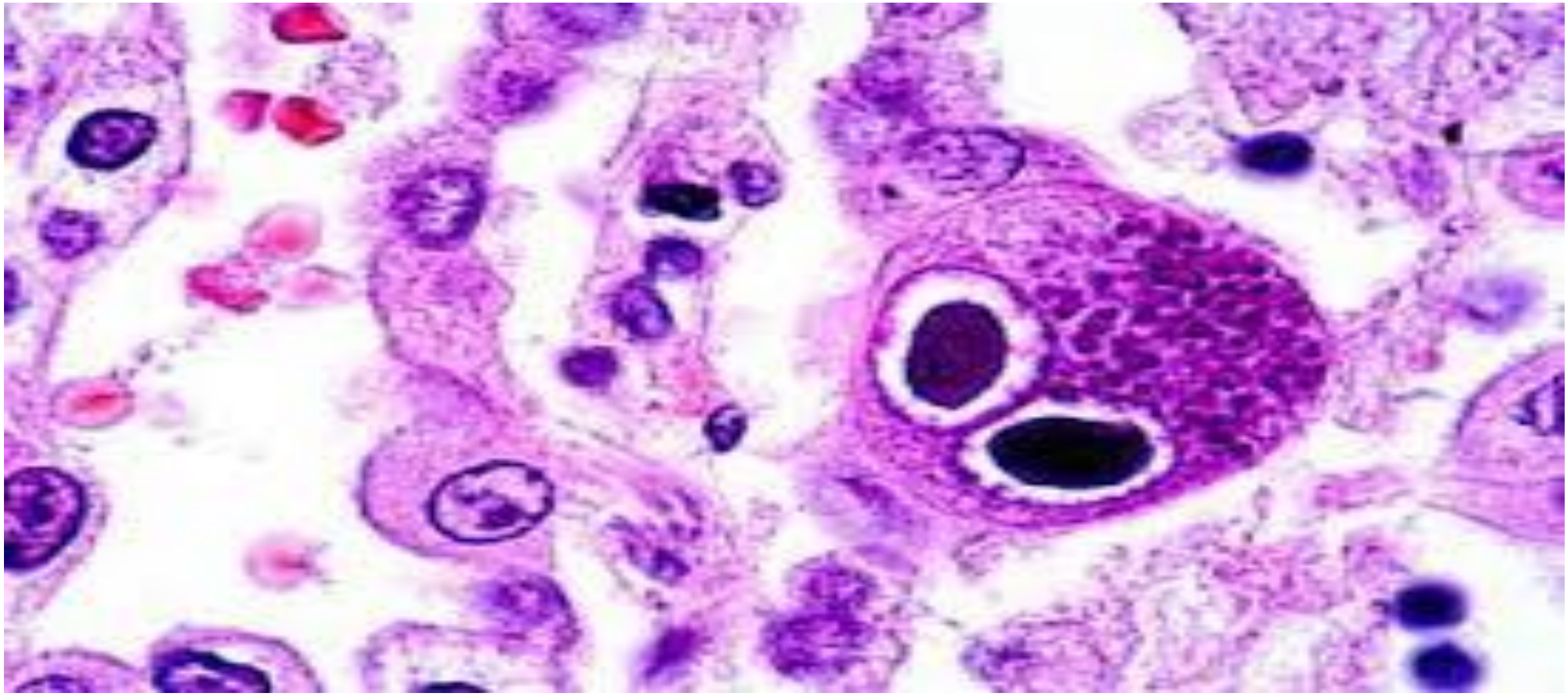
- Triplex
  - Complete End of Phase 2 Meeting with FDA by 1Q2020
  - Initiate Phase 3 Study (matched related, unrelated donors) in 1H2020

- ConVax
  - File IND by 1H2020
  - Initiate Phase 1 Study in 2020

Investment Highlights

1. Novel biologic immunotherapies targeting billion dollar markets (no approved immunotherapy)
2. First-in-Class, Best-in-Class Vaccine for CMV Control (Triplex). Primary Endpoint Met in Phase 2
3. Potential for lower toxicity versus anti-virals with enhanced immune recovery and limited dosing
4. Biologic Exclusivity (Orphan for Triplex); robust IP portfolio
5. Significant grant funding reduces capital requirements and validates approach

Backup Slides



CMV in Hematopoietic Stem Cell Transplant (HSCT)

Hematopoietic Stem Cell Transplant

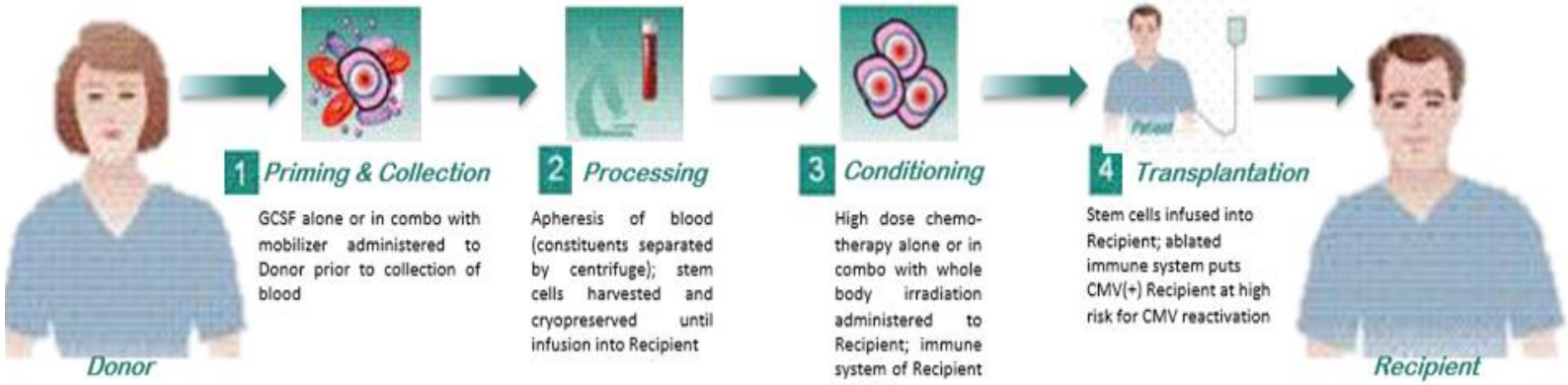
Leading therapy for hematological malignancies (chronic, acute leukemias)
Trend towards increased use (particularly in EU) as outcomes improve
Allogeneic: stem cells transplanted from healthy donor

Process

Conditioning: prior to transplant; high-dose chemo +/- radiation
Ablates bone marrow, cells needed to fight infection (CMV)
Immunosuppressants often administered to prevent rejection of graft, GvHD
Engraftment: occurs two to four weeks after transplant
Stem cells travel to bone marrow, produce WBCs, RBCs, platelets
Recovery of immune function can take 1-2 years in allogeneic HSCTs

CMV Incidence

Rate: ~30% btwn Days 40 to 100 after transplant; ~15% after Day 100 ("late CMV")
Most at Risk: seropositive allogeneic Recipient (R+), regardless of Donor status (D+/-)



Adapted from http://biomed.brown.edu

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CMV in Solid Organ Transplant (SOT)

Solid Organ Transplant

Recipients receive immuno-suppressants to prevent organ rejection, GvHD

Process

Organ collected from Donor and cryopreserved until transplantation

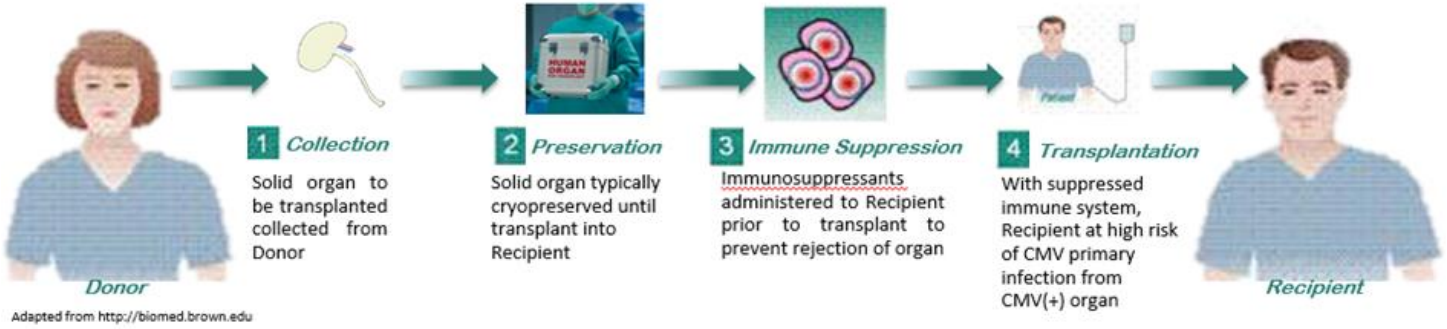
Preserved, allogeneic organ transplanted into immunosuppressed Recipient

CMV Incidence

Rate: >50%, most common infectious complication after SOT

Most at Risk: seropositive Donor (D+), seronegative Recipient (R-); results in primary infection

Risk Factors: size of organ transplanted (viral load); level of immunosuppression (type, dose)



MVA as Delivery Vehicle

- Vaccinia strain *Ankara* passaged 570x in CEF (re-named Modified Vaccinia *Ankara)*
  - Propagates only in CEF but replicates DNA and prolific expression in eukaryotes
  - Head-head comparison to ALVAC™ shows superior immunogenicity (*Zhang et al, JVi 2007)*
- Human MVA studies conducted in Germany in 1970's
  - 120K+ individuals (children, elderly) vaccinated
  - No significant adverse events reported
- Recent study by VRC shows safety in healthy vaccinia naïve and immune adults
- European study shows safety after immunization in HIV-infected adults
- Pre-clinical studies in immuno-suppressed R. macaques shows no propagation, pathogenesis
- PK studies shows rapid disappearance of the viral DNA within 6 weeks of administration