**Company Presentation** 

February, 2016





Innovative solutions for wound & burn care

Nasdaq: MDWD

Gal Cohen, President & CEO

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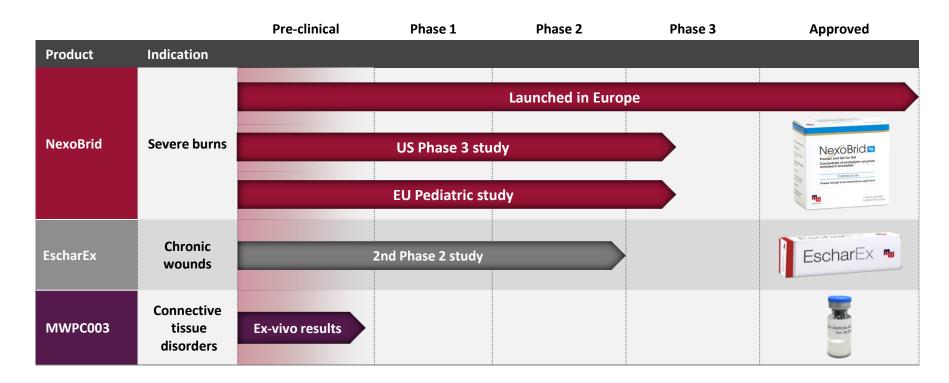
### Who we are

- Fully integrated, biopharmaceutical company developing, manufacturing and commercializing innovative products for wound and burn care
- Nasdaq [MDWD]
- Strong proprietary proteolytic enzymes technology, with 1<sup>st</sup> drug approved and launched
- State of the art, EMA certified and cGMP compliant manufacturing facility for sterile pharmaceutical products
- Strong management team with deep industry experience

...Our goal is to provide
healthcare professionals and
patients with an innovative, burn
and wound eschar removal agent
allowing direct visual assessment of
the wound bed thereby enabling
precise diagnosis of wound severity
and an informed treatment plan...



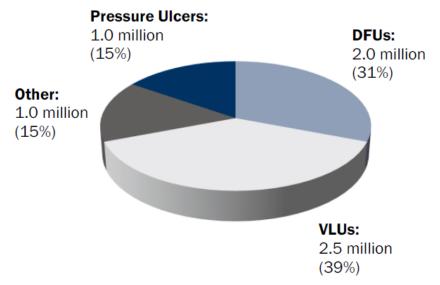
### Introducing disruptive solutions for wound and burn care





### **Chronic wound treatment - large and growing market**

### **U.S. Chronic Wound Cases per Year<sup>1</sup>**



6.5 million U.S. Chronic Wound Cases per Year

### 8% growth:

aging, obesity and diabetes

### \$25 B burden

to the U.S. healthcare system



### **Complementary to many wound healing therapies**

### Debridement



### Healing

**NPWT** 



Skin substitutes

foams





Johnson Johnson

**Interactive dressing** 

collagen



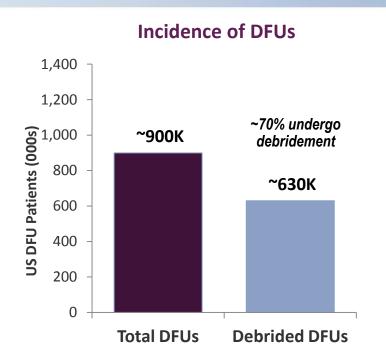


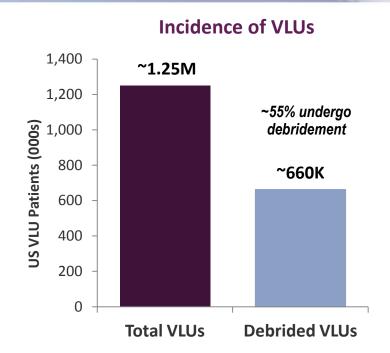


hydrogel

honey

### Significant opportunity in DFU & VLU debridement





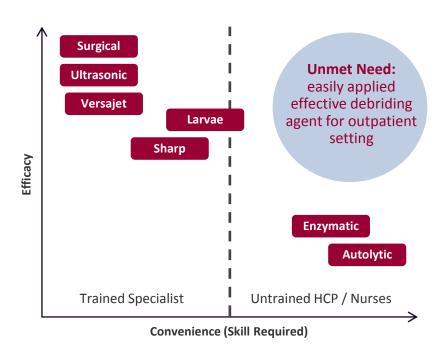
Over \$1B market potential in DFU's and VLU's in the US alone



### Current standard of care limitations create unmet medical needs

### **Sharp Debridement**

- Fast and effective
- Specialist time Pain / anesthesia Bleeding risk



### **Enzymatic/Autolytic Debridement**

- Nurse/self applied
- Limited efficacy Multiple nurse/office visits for 6-8 weeks



### Addressing unmet need in debriding chronic wounds



- **Biological drug** containing a sterile mixture of proteolytic enzymes
- **Easy to use,** non-surgical topical application for outpatient setting
- Effectively debride chronic wounds in less than a week
- **Clinical evidence**
- **IP** protection



### Promising results in a Phase II feasibility study

### **Diabetic Foot Ulcer (3 months old)**

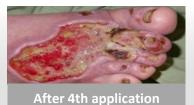




Result: Wound debridement in 2 applications

#### (3) Post traumatic (6 weeks old)





**Result**: Wound debridement in 4 applications

### Venus Ulcer (11 months old)





**Result**: Wound debridement in 1 application

### Pressure Sore (4 months old)





Before

After 2nd application

**Result**: Wound debridement in 2 applications

### **Objectives**



- Prove effective debridement
- Assess safety
- Select indication for pivotal studies

### Design





- Randomized
- Controlled (EscharEx vs. Gel)
- Multi-Center
- Sample size: 73 patients
- Indications: Hard to heal VLUs, DFUs and post surgical

### **Endpoints**



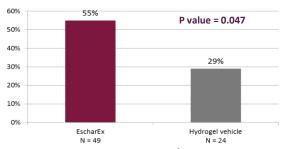
- Eschar removal
- Wound closure
- Pharma-co-economic measurements



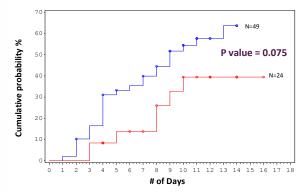
### Phase 2 top-line results

- The study met its primary endpoint with statistical significance
- Significantly higher incidence of complete debridement compared with patients treated with the hydrogel vehicle
- Clear trend (p=0.075) that strongly suggests that debridement occurred earlier in the group treated by EscharEx
- No deleterious effect on wound healing was observed
- Safety profile comparable to current standard of care

#### Incidence of complete debridement w/i 10 daily applications



Time to complete debridement w/i 10 daily applications\*

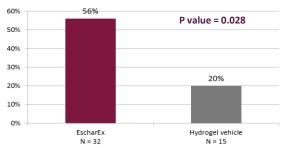


\*Kaplan-Meier survival analysis with log rank p-value

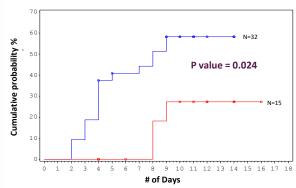
### Phase 2 - DFUs and VLUs post-hoc analysis

- Incidence of complete debridement compared with patients treated with the hydrogel vehicle is higher in DFUs and VLUs
- Debridement occurred significantly earlier in the group treated by EscharEx
- 93% of the patients who completed debridement with EscharEx were debrided within seven days after four to five applications, on average

#### Incidence of complete debridement w/i 10 daily applications



Time to complete debridement w/i 10 daily applications\*



\*Kaplan-Meier survival analysis with log rank p-value

Thank you

www.mediwound.com





Innovative solutions for wound & burn care



## **Preventing Blood Clots without Bleeding**

Neil J. Hayward, Ph.D. President and CEO

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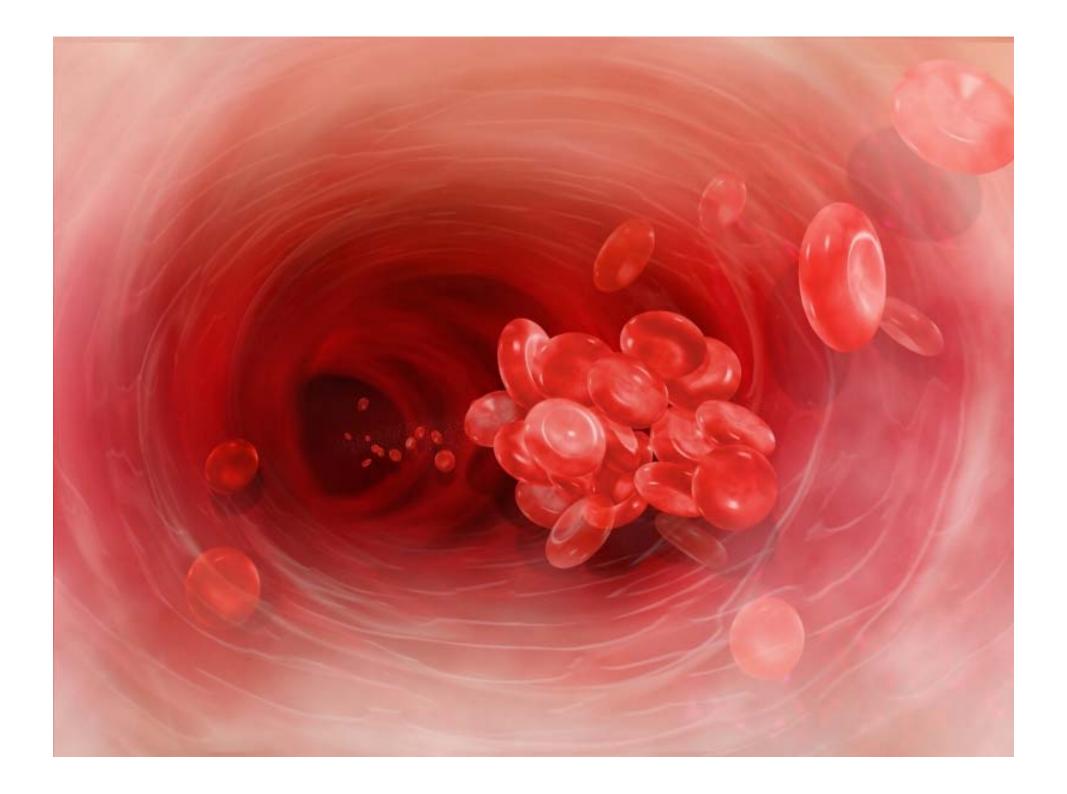
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## DVT/PE: ≈ 1,000,000 people in the US, every year, suffer from a clot



# eXIthera Pharmaceuticals (Shareholders: CBI & Schooner Capital)

### -Mission-

## Develop a <u>new generation</u> of anti-thrombotics with <u>no</u> bleeding complications, unlike the first and second generation agents

- ALL approved anti-thrombotics, including new thrombin and Factor Xa inhibitors, can cause unpredictable bleeding in patients. If major bleeding is uncontrolled death results.
- Factor XI has emerged as a key enzyme for coagulation (thrombosis) without impacting bleeding (hemostasis):
  - Genetic data supports the view that Factor XIa inhibitors will afford efficacy with low bleeding risk
  - Recently confirmed by Phase 2 PoC results injectable Factor XI antisense candidate (Ionis-FXI)
- eXIthera's **EP-7041** is a novel, potent and selective *small molecule* Factor XIa inhibitor
  - On demand treatment window for immediate use before, during and post surgery
  - Stellar preclinical results confirming anti-coagulation potential with no bleeding risk
  - On track to initiate Phase 1 studies in June 2016

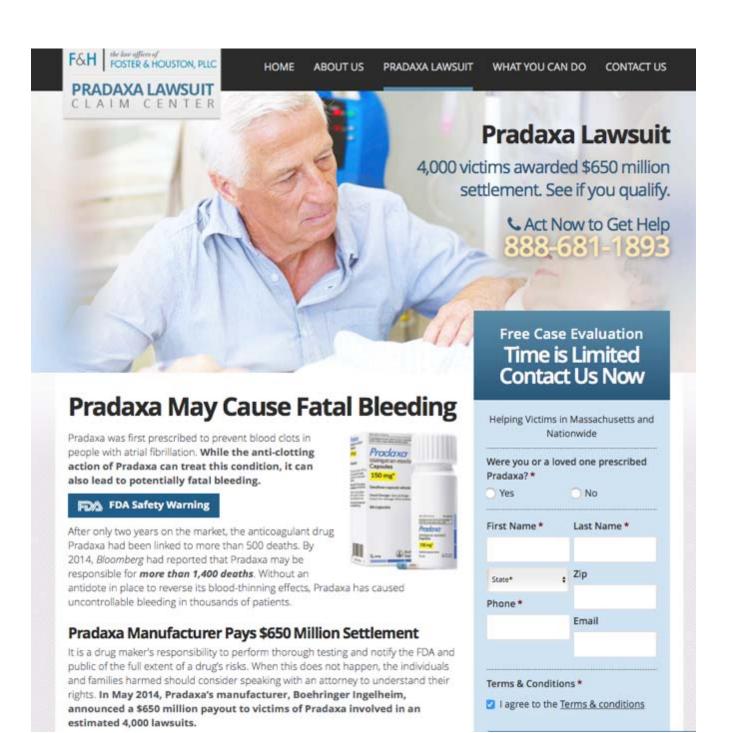


## 1<sup>st</sup> and 2<sup>nd</sup> Generation Drugs

Drug	COUMADIN. (warfarin)	Pradaxa (dabigatran)	(rivaroxaban)	ELIQUIS. (apixaban)
FDA approval	Pre-1982	2010	2011	2012
Onset	slow	rapid	rapid	rapid
Food Effect	yes	no	take with food	no
Routine Lab Monitoring	yes	no	no	no
Bleeding Risk	yes	yes	yes	yes

2<sup>nd</sup> Generation agents have clear advantages over Coumadin BUT still cause bleeding





## All new anticoagulants = "lawsuits"

Xarelto, Pradaxa and Eliquis were hailed as the "next generation" of anti-coagulants. There were few interactions to worry about and dosage was easily determined on a "one-size-fits-all" basis. They were also very profitable for the manufacturers. Whereas warfarin costs around \$80 – \$100 per year, Xarelto carries an annual price tag of \$3,000.

All three of these "next generation" anti-coagulants also have serious side effects. In the case of Xarelto and Pradaxa, the most serious of these is uncontrolled hemorrhaging.









## **Anti-thrombotic Product Landscape**

- Large Market: ≈ \$29.6B 2020
- 2<sup>nd</sup> generation inhibitors are now on the market
  - Direct Thrombin Inhibitor: Pradaxa (BI)
    - \$2.3B sales in 2014
    - FDA warning of internal bleeding complications
    - Antidote approved Q4, 2015: Praxbind (BI)
  - Factor Xa Inhibitors: Xarelto & Eliquis



• \$2.1B sales of Xarelto in 2015



- Antidote in development (Portola) for bleeding latches onto Factor Xa inhibitors, disarming their activity (i.e. patient no longer protected from clots)
- Sales in 2020 to hit \$6.4B and \$3.7B for Xarelto (#8) & Eliquis (#28)





## Genetic Evidence Factor XI Inhibition Supported by Deficient Individuals

• An experiment of nature:



Reduced incidence of ischemic stroke in patients with severe factor XI deficiency

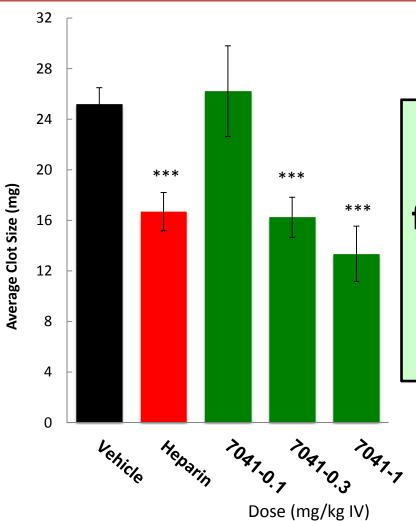
Ophira Salomon, David M. Steinberg, Nira Koren-Morag, David Tanne and Uri Seligsohn

- Factor XI deficient individuals are at *little or no risk* of developing ischemic stroke [Salomon et al. (2008) Blood, 111: 4113-7]
- Factor XI deficient patients have little or no bleeding liability
- [ People with elevated levels of Factor XI in the blood, suffer more frequently from stroke, thrombosis and pulmonary embolism ]
- Factor XI inhibitors expected to be safer than both old and new generations of anti-thrombotics with no antidote required to reverse effects



### EP-7041: Pre-clinical data

### - Inhibition of Thrombus Formation -



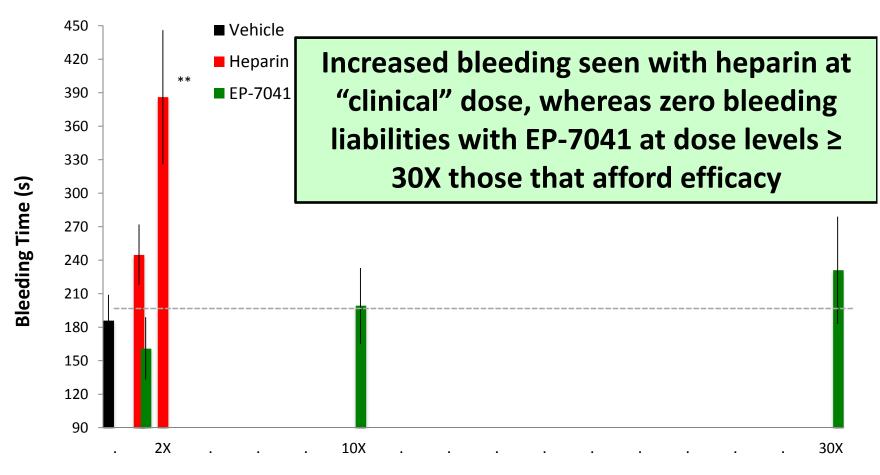
EP-7041 as potent as heparin in inhibiting clot formation in an established rat model of thrombosis

rapid onset & dose-related



## **Zero Bleeding Liability: EP-7041**

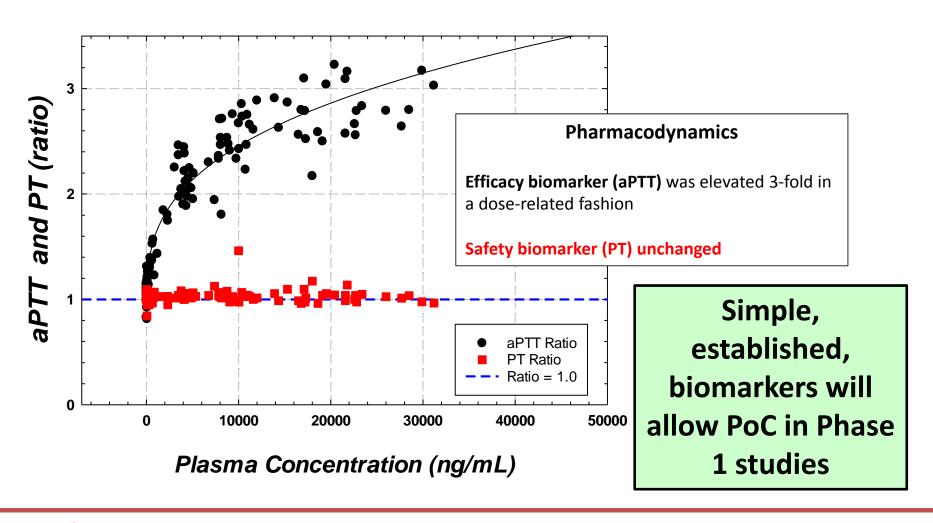
### - Factor XIa Inhibition does not affect Hemostasis -



'Multiples of the Efficacious Dose'



# EP-7041: Plasma Levels vs. Biomarkers (Dog PD: Efficacy & Safety)





## eXIthera's Trajectory

- Strong Corporate Position
  - Capitalized through Phase 1a/1b clinical program, with \$14m raised to date
  - Issued patents covering scaffolds
  - Experienced development team and top advisors in the field

Neil J. Hayward

President & CEO











Dennis I. Goldberg

VP Regulatory









Phillip M. Friden

VP R&D









**Eric Morrel** 

VP Clinical











## eXIthera's Trajectory

- Factor XI Competitive Environment
  - Ionis Pharmaceuticals FXI (antisense) SC injectable
    - Limitation due to long pre-dosing requirement before surgery
    - Partnered with Bayer (\$150m upfront) following Phase2a PoC
  - BMS, Bayer and other big Pharma groups have internal Factor XIa programs
  - eXIthera compounds have potential to be best in class
- eXIthera's IV Product for Acute Hospital Care: EP-7041
  - Submit regulatory dossier in Q2 2016
  - Commence PoC Phase 1a/1b clinical trials in Q2 2016
    - Primary efficacy endpoint increase in aPTT
    - Primary safety endpoint no change in PT
  - Initial read out expected Q4 2016
- Goal for strategic partnership to coincide with EP-7041 clinical data
  - All players in the anti-thrombotic arena will need a Factor XIa inhibitor to compete





Discovery of novel NMDAr modulators for neurodevelopmental and psychiatric diseases

Introduction for TASE | 23 February 2016

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## Luc Therapeutics: vision and identity

### **Vision**

 To discover and develop breakthrough, first-in-class therapies for neurodevelopmental and psychiatric disorders by modulating NMDA receptors to restore synaptic plasticity and dynamic network connectivity

### **Identity**

- Seeded in 2010 pharma-experienced NMDAr pharmacology, medicinal chemistry
- In 2014, recruited leadership to further scale company new CEO, CSO
- In 2015, partnered lead negative allosteric modulator (NAM) selective for NR2B with Novartis (rapid acting agent for depression)
- Now: Positive allosteric modulators (PAMs) for cognitive impairment in schizophrenia

## Luc Therapeutics team

### Vanessa King, Ph.D. – President and CEO

- 20+ years leadership experience in pharma/biotech, including Novartis, Amgen, and in leading scientific institutions (Venter Institute)
- Led business development at deCODE, yielding 2012 Amgen acquisition

### Timothy Piser, Ph.D. - CSO

- 20 years scientific leadership experience in pharma/biotech, including Astra Zeneca and Forum Pharmaceuticals
- Expertise spans all aspects of in vitro and in vivo neuropharmacology

### Robert Volkmann, Ph.D. -- VP Chemistry

30+ years medicinal chemistry experience at Pfizer

### **David Anderson, Ph.D. -- Head Discovery Operations**

Medicinal chemistry, computational chemistry, HTS at Pfizer

### **Christopher Fanger, Ph.D. – Director In Vitro Pharmacology**

Ion channel drug discovery at Astra Zeneca, Hydra Biosciences

### Steve Leiser, Ph.D. -- Head Translational Science

Translational biomarker research, neurophysiology at Lundbeck, Astra Zeneca, Wyeth

## The unmet medical need is profound Treatment-resistant Major Depressive Disorder

### High unmet need

- 31% of patients do not reach remission even after their 4th treatment
- High costs for those with inadequate response to treatment
  - Direct costs:\$22,784 vs. \$11,733;
  - Indirect costs: \$12,765 vs. \$6,885\*

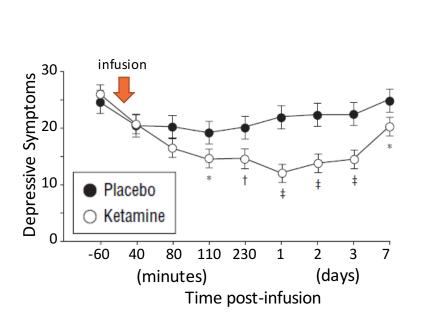
### **Competitive landscape**

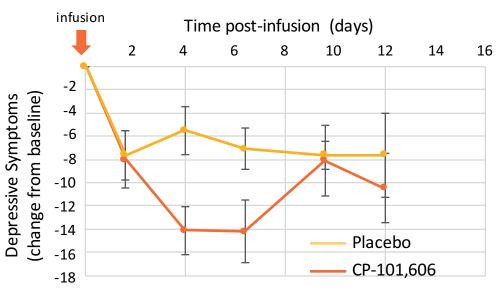
- No NMDAr therapies approved for Treatment Resisistant Depression
  - Pfizer: rapastinel (GLYX-13), Ph3
  - J&J: esketamine, Ph3
  - Cerecor: CERC-301, Ph2
- Novartis is strong partner for Luc

† Rush, AJ et al, Acute and Longer Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR\*D Report, Am J Psychiatry 2006; 163: 1905-1917

## The benefit to patients has been demonstrated Rapid response in treatment-resistant depression

### Capitalizing on the ketamine revolution in clinical neuroscience



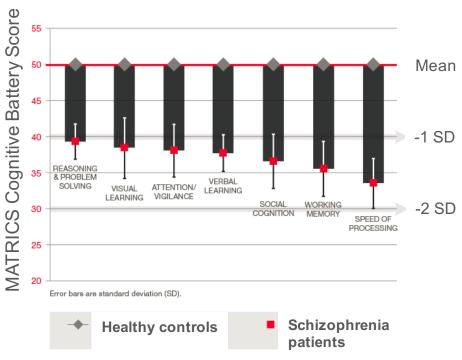


- Ketamine: anesthetic NMDA receptor channel blocker used off-label for severe treatment resistant depression
- CP-101,606: Pfizer's GluN2b-selective NAM
- Luc GluN2B NAMs partnered with Novartis

Zarate 2006 Arch Gen Psych; Preskorn 2008 J Clin Psychopharmacol

# Focus of Luc's internal program: A therapeutic for cognitive impairment in schizophrenia

#### Global cognitive impairment



# Cognitive impairment in Schizophrenia

- Persists over patient lifetime
- Cause of severe disability (e.g., unemployment, inability to live independently)
- No approved treatments



# Why Luc's approach, today

# 1. Extensive target validation

#### Previous approaches

- Putative animal models of disease
- 2. Unprecedented NMDA receptor pharmacology
- NMDr antagonists and glycine site activators

- 3. Translatable neuro-physiological biomarkers
- Not used or only 'target engagement'
- Patient population defined only by clinical assessment

#### Our approach

- Strong platform of clinical evidence for therapeutic hypothesis
- Proprietary assay protocols
- Drug-like NMDAr positive allosteric modulators (PAMs)
- Disease- and target-related clinical biomarkers enabling translation

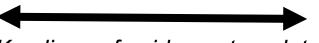
# Platform of clinical evidence for Luc's therapeutic approach

#### Decreased cognitive function in schizophrenic patients



#### Clinical Evidence

- Pharmacology
- EEG Biomarkers
- Cognitive Physiology
- Neuroanatomy
  Proteomics/Genomics
- Genetics



Key lines of evidence translate

#### Non-clinical Evidence

Translational Pharmacology



Disease-relevant measures of cortical function

Therapeutic hypothesis: Luc drugs will normalize function of the brain safely improving cognition in schizophrenic patients



# Luc compounds enhance synaptic currents in increasingly native systems

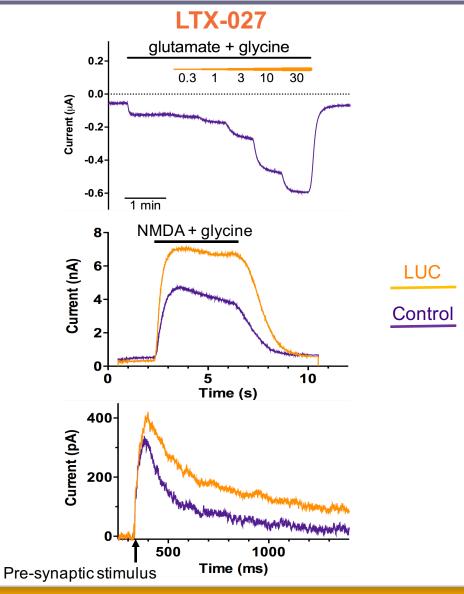
Glutamate/glycineevoked currents in oocytes expressing human GluN1 and GluN2B



NMDA/glycineevoked currents in cultured rat cortical neurons



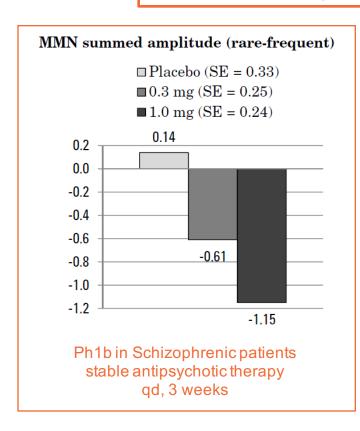
Synaptic currents in **rat brain slices** 

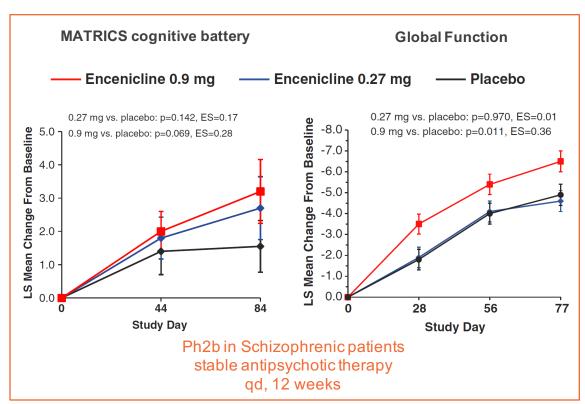




# Translatable EEG biomarkers enable Luc's development path

Consistent with direct measurement of cortical pathophysiology, effects on MMN predict effects on cognitive and global function





Preskorn 2014 J Psych Practice Keefe 2015 Neuropsychopharmacol



\*FORUM Ph3 design accepted by FDA (Special Protocol Assessment)

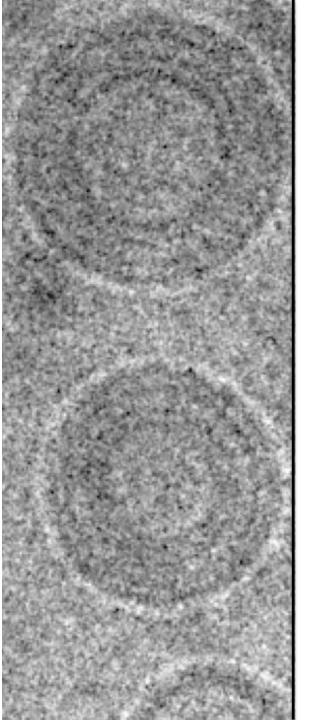
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- Now: Positive allosteric modulators (PAMs) for cognitive impairment in schizophrenia





# Vedantra Pharmaceuticals Inc.

Precision Immunotherapeutics for Cancer and Infectious Disease

One Kendall Square, Suite 14303, Cambridge, MA 02139 USA +1 617-945-2077

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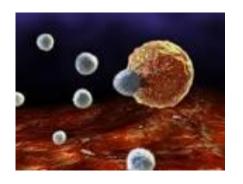
# The Next Leap Forward in Precision Immunotherapy

# **Vedantra Pharmaceuticals Inc.**

- An immunotherapeutic company founded on nanotechnology from Dr. Darrell Irvine's Lab (MIT, Koch Institute, Ragon Institute, HHMI)
- Vedantra labs located in Kendall Square, Cambridge, MA
- \$7.6 MM invested to date (\$6 MM Clal, 78% equity)
- Two immune potentiating technologies licensed from MIT
- Unprecedented immune responses against cancers and infectious diseases
- Operating in stealth mode until recent completion of 2<sup>nd</sup> license from MIT



# Current Landscape in Immunotherapy for Cancer



It's all about specific CD8 T cell responses. A potential \$30 BB market!

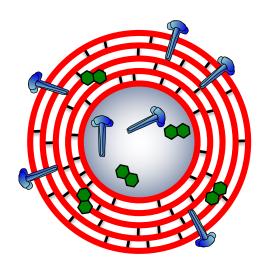
# Mechanisms for anti-tumor therapy:

- Vaccines
  - Whole tumor lysates and oncolytic viruses (T-vec)
  - Antigenic peptides (Neon)
  - Live vectors (Advaxis, Aduro)
  - Dendritic cell vaccines (e.g. Provenge)
  - DNA vaccines
- Adoptive cell therapy (e.g. CAR-T: Juno, Kite, Novartis)
- Checkpoint inhibitors (target PD-1, CTLA4, CD-40)



# Vedantra's Core Immunotherapeutic Technologies

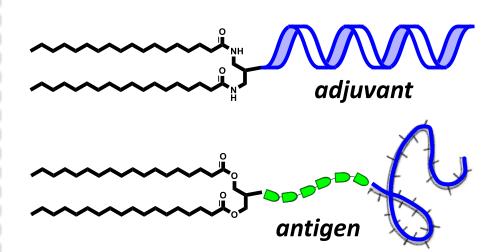
#### **ICMV Vaccines**



<u>Interbilayer-Crosslinked</u> *Multilamellar Vesicles* 

- Lymph node targeting
- Ideal for whole-protein antigens
- Generates CD8 T-cells for cancer
- Generates antibodies to block infectious diseases

#### **Amphiphile Vaccines**

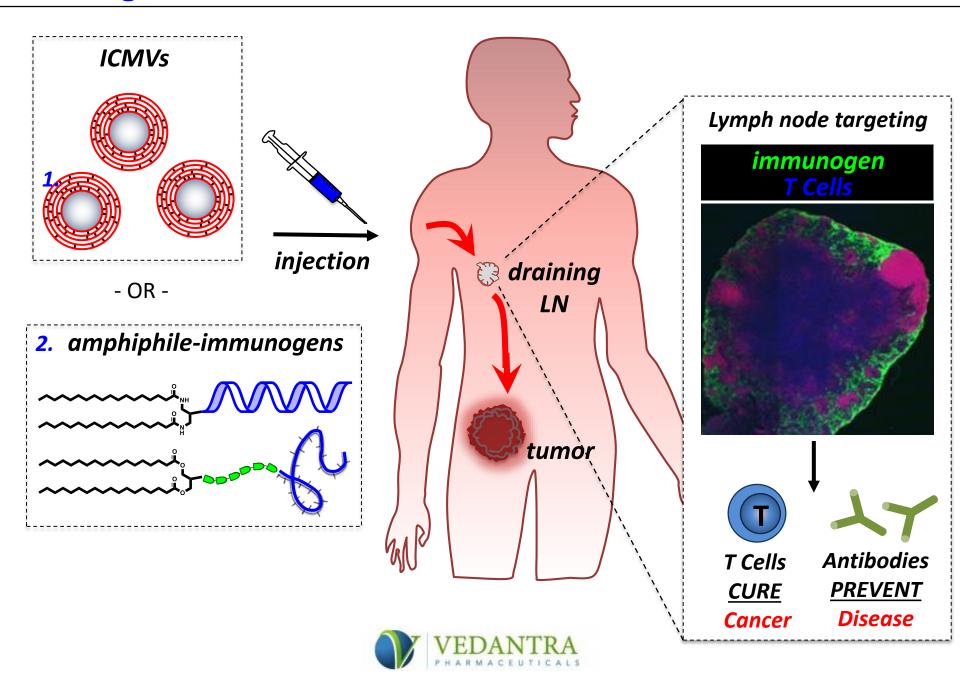


Antigen / adjuvant amphiphile conjugates

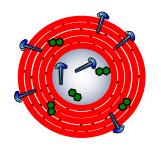
- Lymph node targeting via albumin
- Ideal for peptide antigens
- Generates CD8 T-cell for cancer



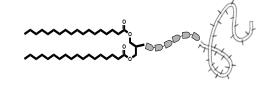
# **Creating T-cells to kill tumors**



#### **Vedantra's Core Immunotherapeutic Technologies**



#### **Vedantra's Advantage:**



- Targeted delivery to lymph nodes creates unprecedented levels of tumor targeting CD8 T cells
- Toxicity of adjuvants minimized or eliminated by reduced systemic exposure
- Vedantra's delivery systems are not neutralized by immune system.....can give multiple booster shots to increase activity
- Can be made on a production scale



# ICMV therapy for HPV-induced Cancers

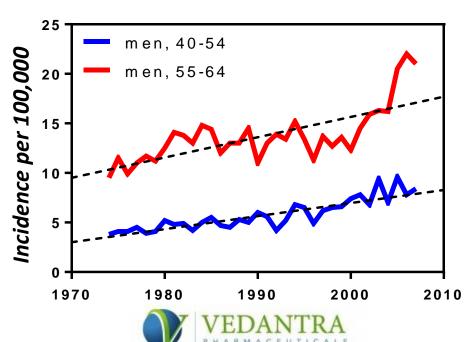
#### **Market Opportunity**

- 20 million currently infected in the US,
  6.2 million new infections each year
- HPV-induced cervical cancer (500k/year), ano-genital (89k/year) cancer, head and neck cancer (115k/year)

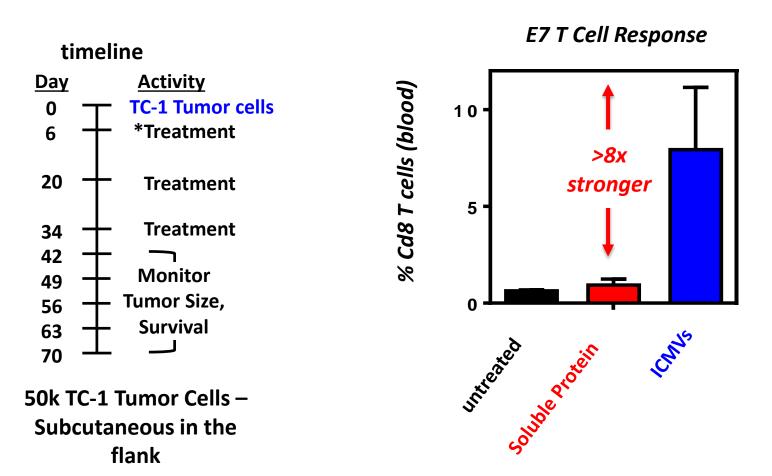
#### **Current Strategies**

- only 32% of eligible women are receiving the licensed prophylactic vaccines
- prophylactic vaccines cannot cure existing infection or implicated cancers

#### HPV-related head and neck cancer incidence



# ICMVs induce strong + effective T cells against HPV tumors

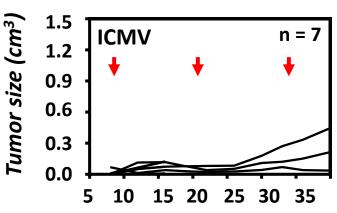


Addition of adjuvant can raise CD8+ T-cell response to 30%!!!



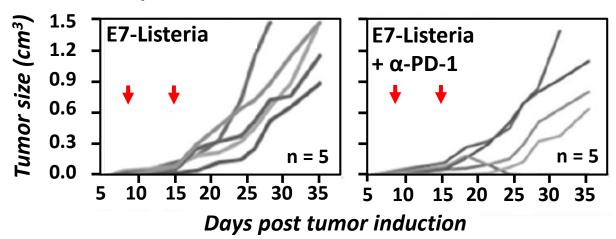
# ICMVs compared to Advaxis Phase 2 Vaccine





Days post tumor induction

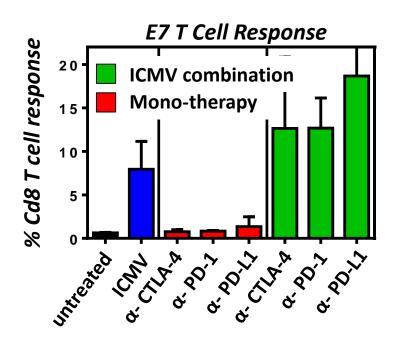
#### Compare to Advaxis Live E7-Listeria with $\alpha$ -PD-1



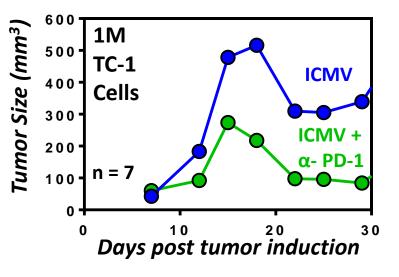
ICMVs outperform Live Vector +  $\alpha$ -PD-1



# **Checkpoint inhibitors work with ICMV therapy**



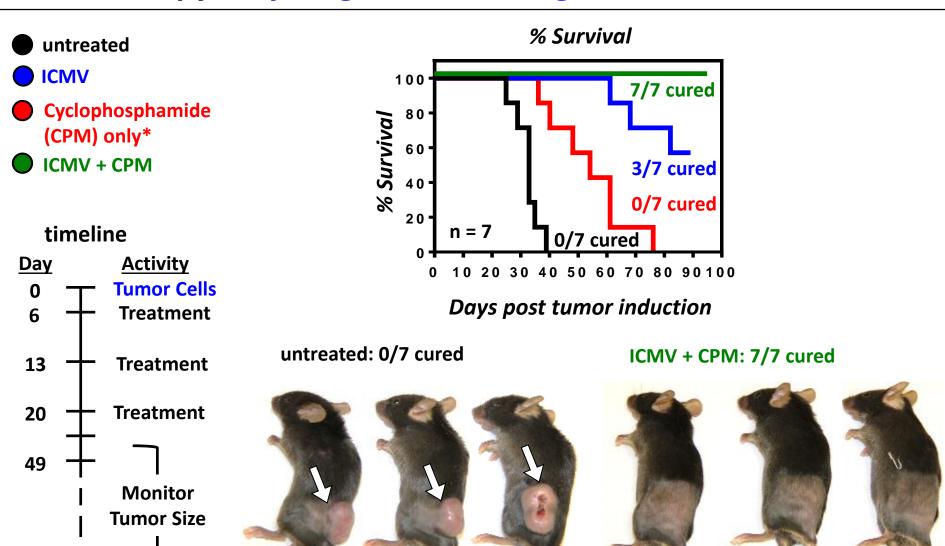
#### Combination therapy in larger tumors



Checkpoint inhibitors amplify ICMV CD8 T Cell response and kill tumors!

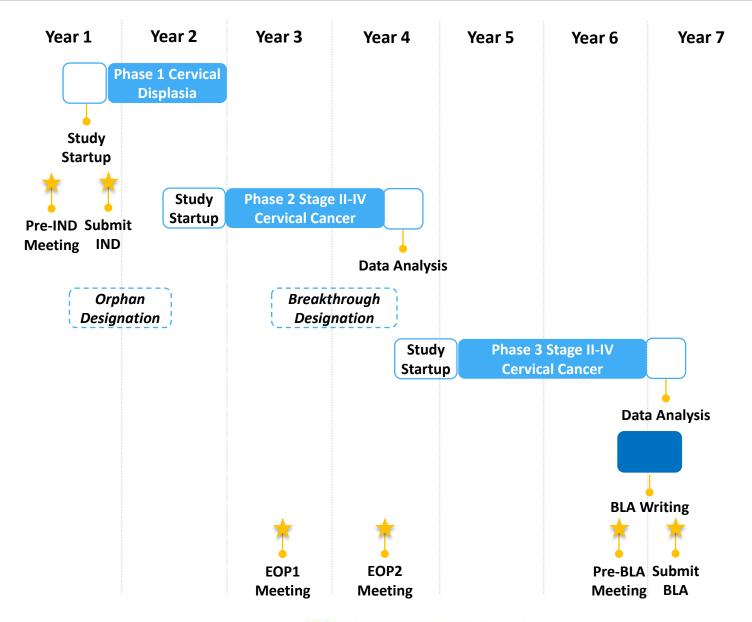


# ICMV therapy is synergistic with Treg inhibition



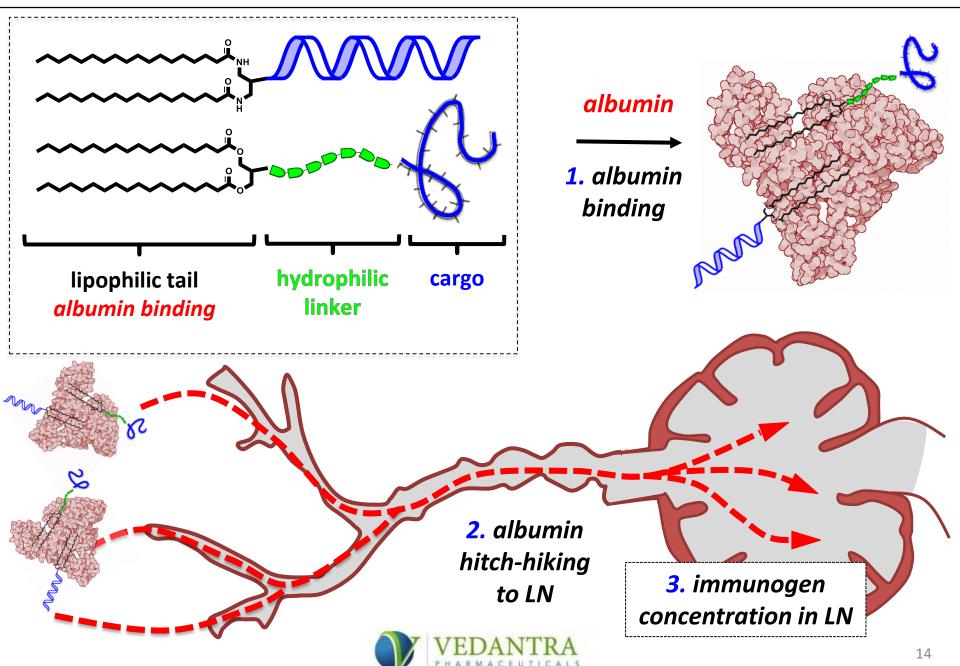


# Clinical program: ICMV therapy for HPV-induced Cancers

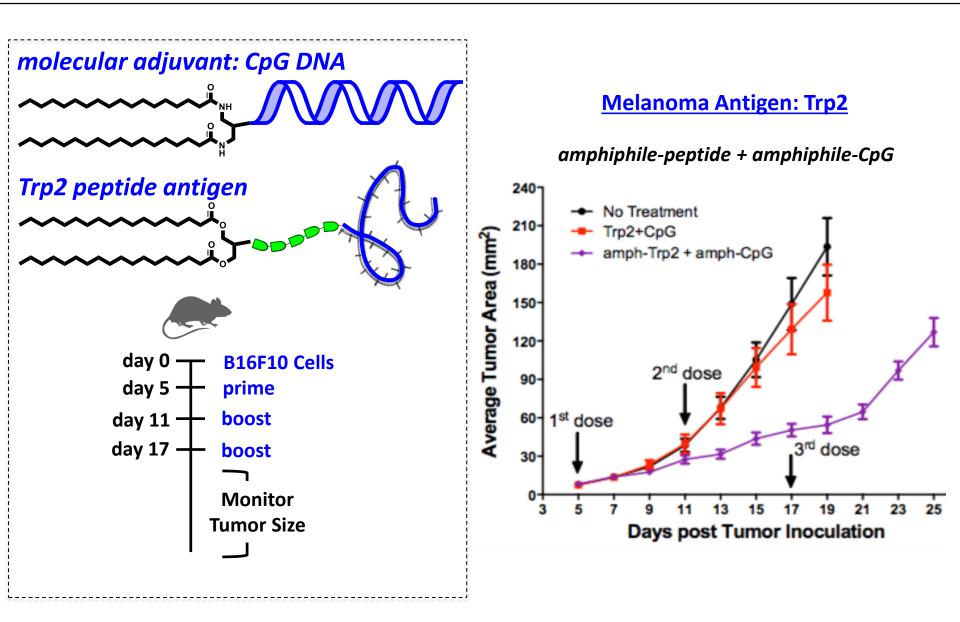




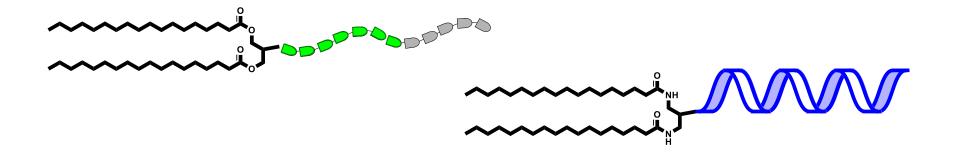
# Amphiphiles hitch-hike on albumin into lymph nodes



### Amphiphile conjugation enhances immunity to peptide antigens



# **Vedantra's Amphiphilic Agents**



- Efficient delivery of peptidic antigens and adjuvants to site of CD8+ T cell activation
- Applications:
  - Targeted delivery of neoantigens
  - Ideally suited to personalized medicine paradigm
  - Improved safety for adjuvant delivery



### **Vedantra Executive Summary**

# An immunotherapy company focused on developing products for cancer and infectious disease.

Two Core Technologies generating strong CD8+ T-cell and antibody responses

#### Three internal candidates moving towards clinical development:

- HPV immunotherapy: preclinical development candidate identified; application: cervical and head/neck cancers
- ALK immunotherapy: IP licensed for protein; discovery candidates identified; application in lung cancer
- Malaria vaccine: non-human primate study on-going at NIH

#### **Collaborative exploratory research** with other companies in:

- Cancer: adjuvant delivery, neoantigen presentation
- Infectious Disease: HIV, HSV, TB



#### **Vedantra's Team**

#### **Board of Directors**

Isaac Kohlberg, MBA

William Koster, PhD (chair) previous SVP, BMS; CEO, Neurogen Corp.

Steven Deitcher, MD CEO, Medeor; Former CEO, Talon

Satish Jindal, PhD Co-founder; Co-founder Verastem; former VP, BMS

**Chief Technology Development Officer, Harvard** 

**University** 

#### **Scientific and Management Team**

William Koster, PhD Executive Chairman

Mark Carthy, MBA Business Advisor to Board, previous Vertex, Cubist

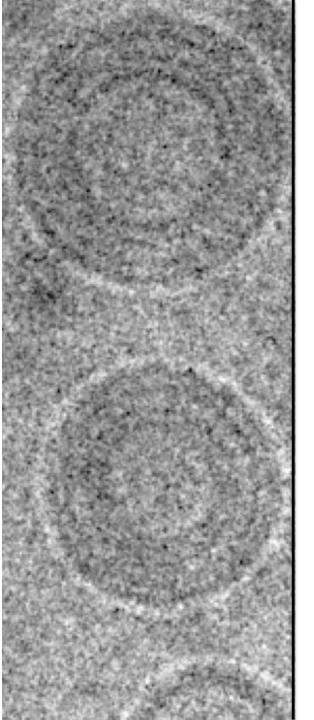
Dan Geffken, MBA Interim CFO; founder and managing

director, Danforth Advisors

Darrell J. Irvine, PhD Founder and Scientific Consultant

George Siber, MD Consultant; former EVP, Wyeth Vaccines







# Vedantra Pharmaceuticals Inc.

Precision Immunotherapeutics for Cancer and Infectious Disease

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