Enhanced delivery of DNA-based vaccines and immunotherapeutics through next-generation electroporation devices

Stephanie Ramos, Ph.D.
Inovio Pharmaceuticals

Cell & Gene Therapy, 2015
London, UK
August 10, 2015
Attractiveness of DNA Vaccines

Safer than live virus vaccines
- Cannot cause disease
- No significant side effects

Prevent and treat
- Vastly expands market size
- Generate T cell & Antibody responses

Faster development

Easier to manufacture

Combination vaccines possible

Key limitation of delivery being recently overcome with electroporation

Electroporation is a key enabling technology
Enhanced DNA Delivery: Electroporation
Electroporation Enhanced Transfection

Sardesai & Weiner, Curr Opin Immunol 2011
INOVIO: Fulfilling the Promise of DNA Vaccines

DNA Delivery Systems

SynCon™ Optimized Vaccines

DNA Vaccine Platform

Manufacturing & Formulations
(Affiliate: VGXI, Inc.)
Muscle EP Device in the Clinic: CELLECTRA®-5P

**Prophylactic Phase I**
- FLU-001 US (Flu)
- FLU-001 Korea (Flu)
- HIV-080 (HIV)
- RV-262 (Ebola)
- EBOV-001 (Ebola)

**Therapeutic Phase I**
- HIV-001 (HIV)
- HPV-001 (HPV-associated CIN)
- HPV-002 (HPV-associated cancers)
- HPV-004
- HPV-005
- HPV-006 (breast, lung, pancreatic cancers)
- TRT-001 (prostate cancer)
- PCa-001
- VGX-6150-01 (chronic HepC)
- HBV-001 (chronic HepB)

**Therapeutic Phase II**
- HPV-003 (HPV-assoc cervical dysplasia)
- EORTC-1411 (HPV-associated cervical cancer)

Number of total patients treated - 550+
Number of total immunizations - 1450+
Combination HPV16/18 E6/E7 DNA immunotherapy

Two DNA plasmids delivered simultaneously via IM injection followed by IM electroporation (CELLECTRA®-5P)

Capitalizes on Inovio’s ability to drive the body’s own immune system to seek and destroy pre-cancerous cells

*pDeletions or mutations important for p53 binding and degradation

△Mutations in Rb binding site
VGX-3100 Phase II: Generation of Robust HPV-16 and HPV-18 T Cell Responses

*IFN-γ ELISpot Analysis*

- **VGX-3100 Specific T Cells (SFU/10⁶ PBMCs Above Baseline)**
- **Study Week**
- **Treatment at wks 0, 4 & 12**

*Statistically significant; bars are 95% CI. IFN = interferon.

Inovio Pharmaceuticals: Proprietary Data
VGX-3100 Phase II: Clinically Significant Efficacy in the Treatment of Cervical Dysplasia

- Significant disease regression and viral clearance
- First report of clinical efficacy with a therapeutic naked DNA vaccine using electroporation delivery

Inovio Pharmaceuticals: Proprietary Data
Enhanced DNA Delivery to the Skin via Surface Electroporation

- **Surface Electroporation**
- **Tethered Surface EP System**
- **Surface EP System**

GFP expression on skin surface:
- EP
- + EP
- - EP
- x20
- x40

+ EP

**inov**
Evolution of Surface EP to a Multi-head Device

McCoy, *Hum Vacc Immunother* 2014
Expression Kinetics in Skin following SEP

- Surface Expression
- Cellular Expression
- Monocyte/Granulocyte Infiltration

<table>
<thead>
<tr>
<th>No EP</th>
<th>1 Hr</th>
<th>2 Hr</th>
<th>4 Hr</th>
<th>6 Hr</th>
<th>8 Hr</th>
<th>24 Hr</th>
<th>48 Hr</th>
<th>Day 3</th>
<th>Day 7</th>
<th>Day 12</th>
<th>Day 14</th>
<th>Day 21</th>
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Mendoza, Vaccines 20
Directly Targeting the Epidermis with SEP

Smith, Mol Ther Methods Clin Dev 2014
Directly Transfecting Keratinocytes with SEP

Mendoza et al, Hum Vacc Imm 2013
Directly Transfecting Dendritic Cells with SEP

Amante, *Hum Gene Ther* Method
Transfected Cell Migration into Draining Lymph Nodes

GFP positive cell in the T cell zone of the cortex in the inguinal lymph node

*Smith, Mol Ther Methods Clin Dev 2014*
Minimally Invasive Dermal Electroporation – CELLECTRA®-3P

- **Tethered 3P System**
- **Next Gen Tethered 3P System**
- **Portable Cordless 3P System**

**ID Electroproporation**

**Skin surface**

**Skin underside**

**No EP**

**3P-EP**
CELLECTRA®-3P targets a wide range of cell types in the skin

Keratinocytes after 1 hour

Fibroblasts

Langerhans Cell

Keratinocytes after 24 hours

Adipocytes

Myocytes

Amante, Hum Gene Ther Methods 2015
Same target tissue, different biological effect.....

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<tr>
<th>DNA Injection Only (No EP)</th>
<th>SEP</th>
<th>CELLECTRA-3P</th>
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<tr>
<td>Skin Surface</td>
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<tr>
<td>Skin Underside</td>
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<td><img src="image4.png" alt="Image" /></td>
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<td>Skin Section (DAPI stained)</td>
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<td><img src="image6.png" alt="Image" /></td>
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<tr>
<td>Skin Section (H&amp;E stained)</td>
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<td><img src="image8.png" alt="Image" /></td>
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<td>Skin Section (TUNEL stained)</td>
<td><img src="image9.png" alt="Image" /></td>
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- Epidermal Transfection
  - SEP: +
  - CELLECTRA-3P: ++++

- Dermal/Subdermal Transfection
  - SEP: -
  - CELLECTRA-3P: ++++

- Epidermis : Dermis Transfection Ratio
  - SEP: 1:0
  - CELLECTRA-3P: 5:0
  - SEP: 3:5

- Necrosis
  - SEP: -
  - CELLECTRA-3P: +

- Apoptosis
  - SEP: -
  - CELLECTRA-3P: +++

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Acknowledgments

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