Generation of robust immunity following DNA vaccination enhanced by intradermal electroporation

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Vaccines: Safety vs. Efficacy

Safety concerns prohibit development of live-attenuated AIDS vaccines. The majority of AIDS vaccine candidates in clinical trials are based on replication-defective viral vectors, including viral vectors, inactivated viruses, nonreplicating viral vectors, proteins, and naked DNA. *Named for Edward Jenner, the father of vaccination, these vaccines are based on animal viruses that are related to the disease-causing human viruses.
Inovio: Fulfilling the promise of DNA Vaccines

DNA Delivery Systems

DNA Vaccine Platform

SynCon™ Optimized Vaccines

Manufacturing & Formulations
(Affiliate: VGXI, Inc.)
Enhanced DNA Delivery: *in vivo* Electroporation

1. DNA vaccine delivered into muscle or skin.
2. Electroporation: millisecond electrical fields applied.
3. Temporary pores in cell membrane; significant cellular uptake of vaccine.
4. Cell membrane reseals. Cellular machinery uses the DNA code to produce one or more of the disease antigens coded by the DNA vaccine.
5. Antigen-presenting cells engulf the antigens and carry them to lymph nodes.
6. Antibodies or killer T-cells that can eliminate cancerous or infected cells are produced.
**Muscle EP Device – In the clinic: CELLECTRA®-5P**

**IM-Electroporation**

- Skin
- Skeletal Muscle

**Number patients treated**: 520+
**Total immunizations**: 1300+

**Phase II efficacy:**
- Lesion regression + viral clearance
  - **VGX-3100**: 40.2%
  - **Placebo**: 14.3%

**Phase III Device**

**Therapeutic Phase I**
- HPV-001 Inovio
- HPV-002 Inovio
- HIV-001 UPenn – PennVax B
- HPV-004 Inovio (open IND)
- HPV-005 Inovio (open IND)
- HPV-006 Inovio (Open IND)

**Prophylactic Phase I**
- HIV-080 HVTN – PennVax B
- FLU-001 Inovio (US)
- FLU-001 Inovio (Korea)
- RV-262 Army – PennVax B and G

**Therapeutic Phase II**
- HPV-003 Inovio Cervical Dysplasia

**Prophylactic Phase II**
- FLU-001 Inovio (US)
- FLU-001 Inovio (Korea)
- RV-262 Army – PennVax B and G
Skin EP Device – preclinical: SEP

Surface EP System

Intradermal Electroporation

ID injection + SEP procedure:

1. Mantoux injection to admin. pDNA

2. EP to allow pDNA transfection
Surface EP specifically targets the Epidermis

K10/RFP/Hoescht

Smith TRF et al, Mol. Ther. – Methods & Clinical Dev. In press
Advantages of vaccinating in the skin

Accessibility

Monitoring

Tolerability:

Immunocompetence:

Diehl MC et al, Hum Vacc. Imm. 2013
Proposed Mechanism

Diagram showing interactions between epidermis, dermis, dendritic cells, afferent lymphatic, lymph node, and lymphocytes.
Directly transfecting Dendritic Cells

Epidermis:

Dermis:

GFP positive dendritic cell

Dendritic cell staining in dermis:

GFP

MsGp2

Color merged

IMARIS-3D Rendered

Kinetics of DC migration into the dermis

Number of GFP+ cells in the dermis:
GFP+ cells in the draining lymph nodes

**CD4/GFP/Dapi**

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

![Image of GFP+ cell in the T cell zone of the cortex in the inguinal lymph node]

![Graph showing number of GFP+ cells over time]

No. GFP+ cells / lymph node

Hours: 0, 6, 12, 24, 48, 72

**Significance levels**
Treatment site excision and host immune responses
Summary

- Transfection of epidermal DCs
- Migration into dermis
- Traffic to the DLN
- Prime Immune Response

Vaccine Indications:
- Influenza
- Ebola
- Travel vaccines
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SynCon® DNA vaccine helps the immune system to recognize and break tolerance of cancer antigens/cells or achieve universal protection against multiple existing or newly emergent virus strains.

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Inovio combines optimized DNA with safe & effective delivery to generate significant T cells with killing activity.

Diverse strains/variants of a target virus/cancer

Assess gene sequence of selected antigen from chosen strains/variants of the virus/cancer

Synthetically create optimal consensus gene sequence for the selected antigen

 Manufacture SynCon® DNA vaccine

Insert synthetic consensus gene sequence for selected antigen into DNA plasmid

Deliver vaccine into muscle or skin tissue using electroporation

Protective universal antibodies and killer T-cells produced by immune system against diverse strains of a virus

**SynCon® DNA vaccine helps the immune system to recognize and break tolerance**
Epidermis
Overall Histopathologic Regression* and Virological (HPV Type 16 or 18) Clearance Incidence Per-Protocol** Population (N=142)
Inovio: Fulfilling the promise of DNA Vaccines

Diverse strains/variants of a target virus/cancer → Assess gene sequence of selected antigen from chosen strains/variants of the virus/cancer → Synthetically create optimal consensus gene sequence for the selected antigen → Insert synthetic consensus gene sequence for selected antigen into DNA plasmid → Manufacture SynCon® DNA vaccine → Deliver vaccine into muscle or skin tissue using electroporation → Protective universal antibodies and killer T-cells produced by immune system against diverse strains of a virus.
Surface EP System

Intradermal Electroporation

1. Mantoux injection to admin. pDNA

2. EP to allow pDNA transfection

GFP expression on skin surface

- EP
+ EP

GFP expression in epidermis

- EP
+ EP