

# VGX-3100: Induction of Potent Immune Responses in Post-LEEP CIN 2/3 Following Immunotherapy with HPV 16 & 18 Syncon™ DNA Vaccines

Niranjan Y. Sardesai, Ph.D.  
Sr. Vice President, Research & Development

Vaccines Renaissance Conference IV  
Providence, RI  
October 21, 2010

inovia

Page 1

## Signs of our times...



O'Hare Airport, Mar 2010



San Diego Airport, Jan 2010

inovia

Page 2

## Points to Consider

- Not enough attention to vaccines
  - US GDP = \$14.2 Trillion
  - Total healthcare spending = 15.3% of GDP
    - Of which US govt. covers 45.8%
  - HHS budget = 879 Bn
  - Global Pharmaceutical Market Size = \$773 Bn (2008)
  - Global vaccine sales = \$20 Bn
- Development cost of an average drug = \$ 1.32 Bn (2006)
- Vaccine innovation is critical
  - Low hanging fruit have been plucked
  - New technologies are needed

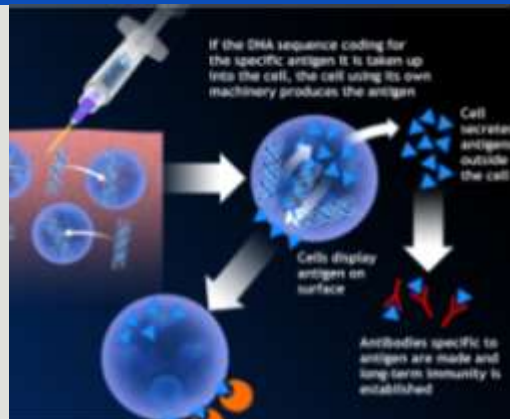
References: 2009 WHO Statistics on Global Healthcare Expenditure;  
PhRMA 2010 Profile; Sci. Am. Pathways 2010

inovia

Page 3

## Attractiveness of DNA Vaccines

- Safety - eliminate vector induced responses
- Able to boost repeatedly
- Generate T-cell and/or antibodies
- Greater potency than viral vectors in primates and in humans
- Combination vaccines possible
- Development speed
- Ease of manufacture & storage



**Electroporation is a key enabling technology eliminating the need for complex viral or lipid vectors**

inovia

Page 4

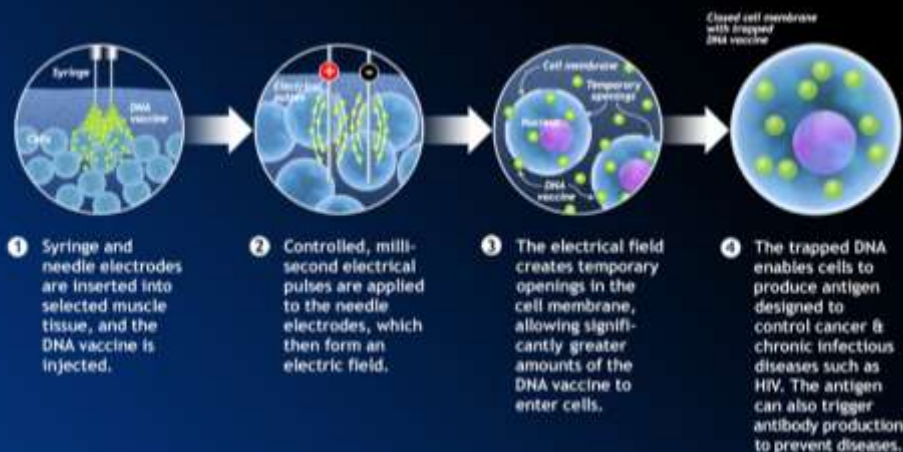
# INO: Fulfilling the Promise of DNA Vaccines



No vector induced responses - repeat boosts; multiple/combination vaccines  
 Greater potency than viral vectors in primates and in humans  
 Manufacturing advantages



# How Electroporation Delivers DNA Vaccines



## Electroporation (electrical field)-based DNA delivery:

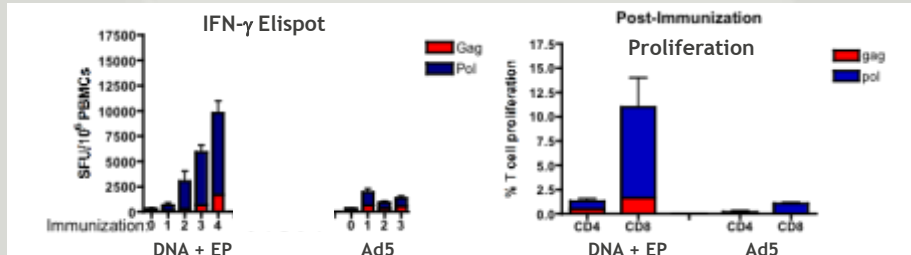
- Efficient: 1000X increase in DNA uptake
- No residual carrier/vector to lead to toxicity/vector immunity
- Elicits T cell and antibody immune responses



# SynCon™ DNA Vaccines + EP: Strong T-Cell & Antibody Responses

## SIV vaccine model (NHP)

UPenn/Merck/Inovio



Ref: Weiner et al. Molecular Therapy, August 2010

inovio

Page 7

# Key DNA Vaccine Development Programs

## Proprietary DNA Vaccines Delivered Using Electroporation

Indication	Product	R&D	Pre-Clin	IND	Ph I	Partner/Funding
Cervical Cancer Therapeutic	VGX-3100	Completed	Completed	Completed	In Progress	
Avian Influenza	VGX-3400X	Completed	Completed	Completed	In Progress	
Universal Influenza	Pandemic/Seasonal Flu	Completed	Completed	Completed	In Progress	
HIV Preventive	PENNVAX™-B	Completed	Completed	Completed	In Progress	HIV Vaccine Trials Network
	PENNVAX™-G	Completed	Completed	Completed	In Progress	NIH/NIAD
	PENNVAX™-GP	Completed	Completed	Completed	In Progress	NIH/NIAD
HIV Therapeutic	PENNVAX™-B	Completed	Completed	Completed	In Progress	University of Pennsylvania

## License Partners & Collaborators Using Inovio's Electroporation Technology

Indication	Product	R&D	Pre-Clin	IND	Ph I	Partner/Funding
Hepatitis C Virus	NS3/4A	Completed	Completed	Completed	In Progress	ChironTech
Breast/Lung Prostate	V934: hTERT	Completed	Completed	Completed	In Progress	Merck

■ Completed    ■ In Progress

## Preclinical Programs

- Dengue fever, CHIKV
- Malaria: funded by MVI PATH (Gates Found. NGO)
- Next-gen HCV (PA-CARE grant)
- HIV: NIH/DAIDS - HVDDT Contract

## Govt./NGO Funding

- NIH/NIAD/DAIDS
- MVI
- DOD, CDMRP
- DTRA

inovio

Page 8

## Annual Cervical Disease Burden due to HPV in US

2<sup>nd</sup> largest cancer killer  
amongst women worldwide

Cervical cancer 11,000 new cases/year  
(500,000 + ww)

HPV16/18+  
CIN2/3 ~250K

CIN2/3 ~500K

HPV16/18+ ASCUS  
↑CIN risk ~1 million

ASCUS / HPV infections →  
↑Paps, HPV testing, Colposcopy ~3 million

20+ Million HPV Infected  
50+ Million Pap Smears

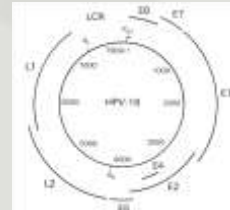
inovia

Page 9

## Therapeutic HPV Vaccines for Cervical Cancer Treatment

### Prophylactic vaccines

- Aimed at inducing natural immunity against HPV infection. They generate serum-neutralizing antibodies.
- Anti-L1-directed vaccines are designed for preventive purpose (Merck; GSK)



### Therapeutic vaccines

- Focused on women with active disease/HPV exposure.
- Aimed at eliminating or controlling existing infection or disease progression.
- Induction of strong cell-mediated responses.
- HPV E6 and E7 proteins are good targets for therapeutic vaccines as they are expressed in most of the HPV-related (pre) cancerous tumors.
- A vaccine/therapeutic including types 16 and 18 could potentially treat 70+% of cervical cancers.

inovia

10

Page 10

## Therapeutic HPV Vaccines for Cervical Cancer Treatment

### Previous Studies:

- MVA - based HPV E6/E7 vaccines
  - Transgene/Roche: Phase IIa (n = 21) completed; Phase IIb (n = 200) recruiting
- Ad5, SFV (Semliki Forest virus)-based HPV E6/E7 vaccines
- Protein/Peptide-based vaccines
- *Listeria*-based vaccines
- DNA-based vaccines (TC Wu)
  - Use gene gun techniques to introduce HPV DNA vaccines directly into APCs.

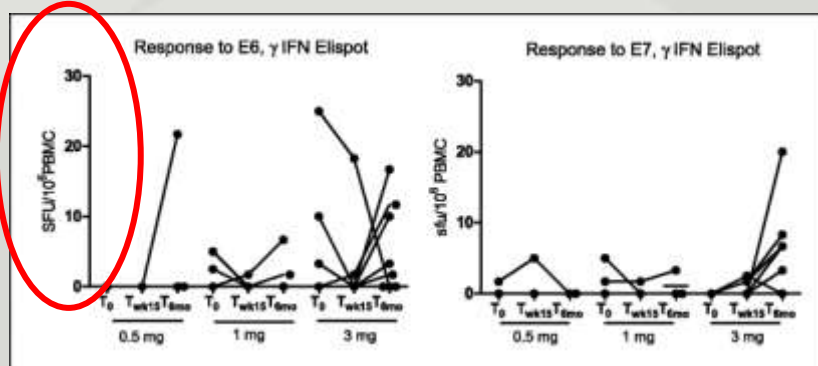
### However...

- Safety and immune interference issues were reported
- Vaccination with HPV DNA vaccines was able to induce low HPV-specific CTL
- In E6/E7 transgenic mice could not overcome immune tolerance.
- **Low immune responses observed in human clinical trials**
  - cultured elispots needed to see cellular responses
  - no antibody responses induced.

inovia

Page 11

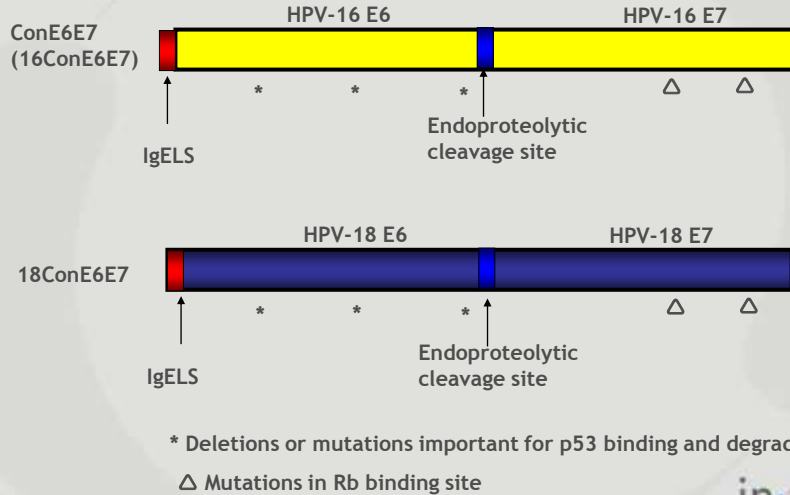
## Historical Data: HPV16 E6 and E7-specific T cell responses induced by a HPV DNA vaccine in humans



IM injection: **5/15** patients showed E7-specific responses, **2/15** patients showed E6-specific responses, the T cell immune responses **required several days of culture to be observed.**

**Vaccination did not elicit antibody responses**

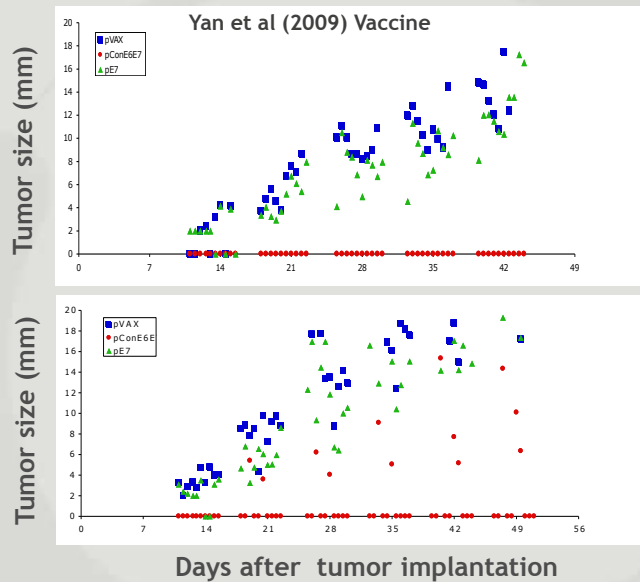
# VGX-3100: SynCon™ Immunogen Design



inovia

Page 13

## Vaccination with pConE6E7 delays/prevents tumor growth



Prophylactic model - mice

- Groups
1. pVAX
  2. pConE6E7
  3. pE7

Therapeutic model - mice

Note: TC1 Challenge model - Lung Epit. Cell line with HPV-16 - E6, E7

inovia

Page 14

# High Concentration, High Purity Formulations

Test	VGX-3100 (HPV)	
	pGX3001	pGX3002
Nucleic Acid Concentration	6.0 mg/mL	6.0 mg/mL
Purity (A260/280)	2.0	2.0
Host-Cell RNA	≤ 0.1%	1%
Host-Cell Protein	≤ 0.1%	≤ 0.1%
Host-Cell DNA	≤ 0.001%	≤ 0.001%
Endotoxin	≤ 0.1 EU/mg	≤ 0.1 EU/mg
Microbial Limits	Absent	Absent

Test	VGX-3400 (Influenza)		
	pGX2001	pGX2002	pGX2003
Nucleic Acid Concentration	9.2 mg/mL	8.1 mg/mL	8.5 mg/mL
Purity (A260/280)	2.0	2.0	1.9
Host-Cell RNA	≤ 0.06%	≤ 0.08%	≤ 0.07%
Host-Cell Protein	≤ 0.03%	≤ 0.04%	≤ 0.04%
Host-Cell DNA	≤ 0.001%	≤ 0.001%	≤ 0.001%
Endotoxin	1.1 EU/mg	≤ 1.2 EU/mg	≤ 1.9 EU/mg
Microbial Limits	Absent	Absent	Absent



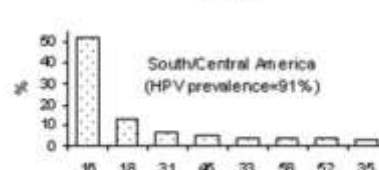
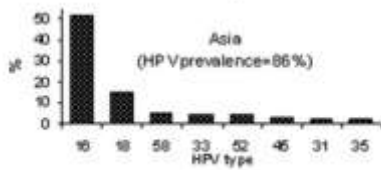
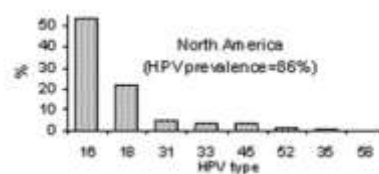
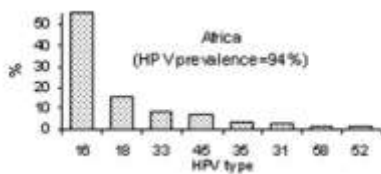
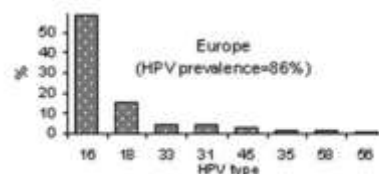
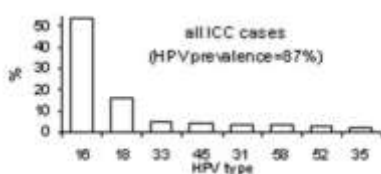
Now routinely achieve upwards of 10+ mg/mL to support multi-plasmid formulations

inovia

Page 15

# HPV Distribution in Invasive Cervical Cancer

HPV types 16 or 18 account for > 70% ICC and > 55% HSIL worldwide

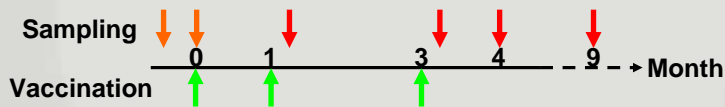


Ref: Smith et al Int. J. Cancer (2007)

## HPV-001: Phase 1 Study - Safety & Immunogenicity

- Combination of HPV DNA vaccine delivered IM using Collectra® EP device - HPV 16, 18 (E6 + E7)
- Study Population: Patients with a history of CIN 2/3 previously treated by LEEP procedure
- Sites: North Carolina, Pennsylvania, Puerto Rico

Cohort	Number of Patient	Dose(mg)
1	6	0.3 X 2 Plasmids
2	6	1 X 2 Plasmids
3	6	3 X 2 Plasmids



Patients were vaccinated 3x at 0, 1, 3 mo.  
Serum and PBMC samples collected at multiple time points before and post immunization to evaluate immune responses.

inovia

Page 17

## HPV-001 Summary of AEs by Grade and Cohort

Grade	Injection Site Reactions (Subject Count)				Adverse Events (Subject Count)			
	1	2	3	4	1	2	3	4
Cohort 1 (0.6mg) (n=6)								
Vaccination 1	6	2	0	0	4	1	1 <sup>a</sup>	0
Vaccination 2	6	0	0	0	5	2	0	0
Vaccination 3	6	1	0	0	4	1	1 <sup>b</sup>	0
Cohort 2 (2mg) (n=6)								
Vaccination 1	6	1	0	0	4	0	0	0
Vaccination 2	5	2	0	0	2	1	0	0
Vaccination 3	6	1	0	0	1	0	0	0
Cohort 3 <sup>c</sup> (6mg) (n=6)								
Vaccination 1	6	3	0	0	3	1	1 <sup>d</sup>	0
Vaccination 2	4	1	0	0	1	0	0	0
Vaccination 3	4	1	0	0	0	0	0	0

<sup>a</sup> Grade 3 tension headache assessed by investigator as not related to study drug

<sup>b</sup> Grade 3 gastroenteritis viral assessed by investigator as not related to study drug

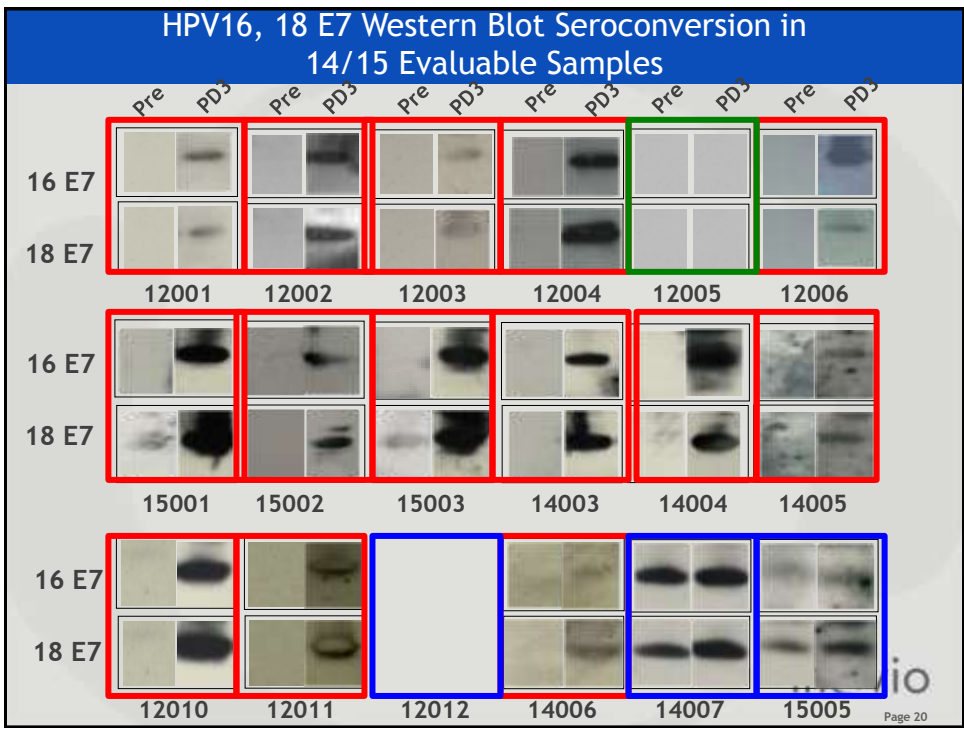
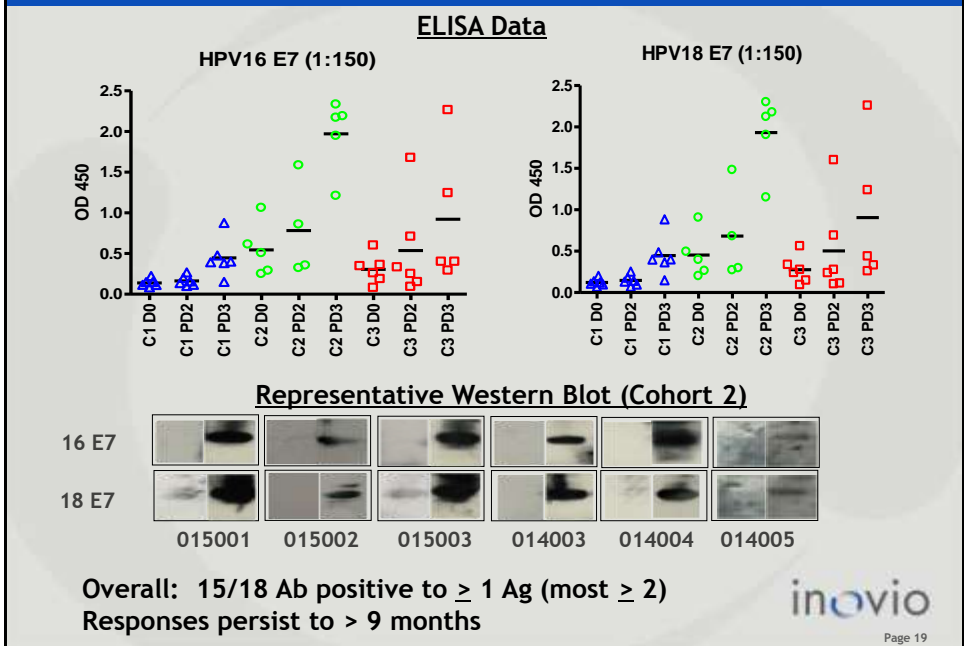
<sup>c</sup> All data is current through September, 2010 with no subjects in Cohort 3 having received vaccination 3

<sup>d</sup> Grade 3 wrist fracture assessed by investigator as not related to study drug

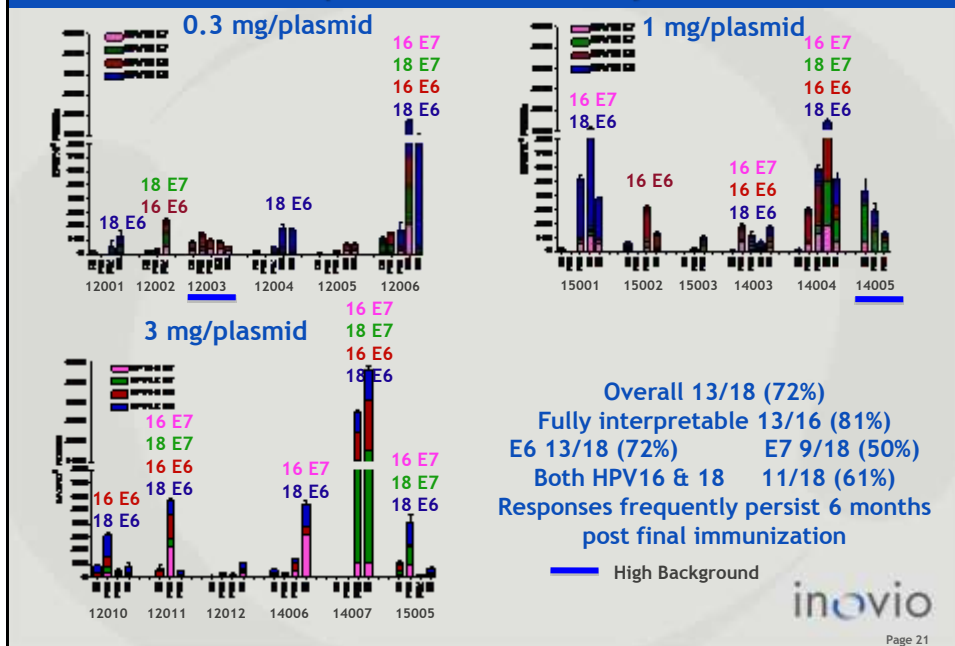
inovia

Page 18

# HPV 16 & 18 E7 Abs by Cohort and Vaccination



## Cellular Responses Induced by VGX3100/EP



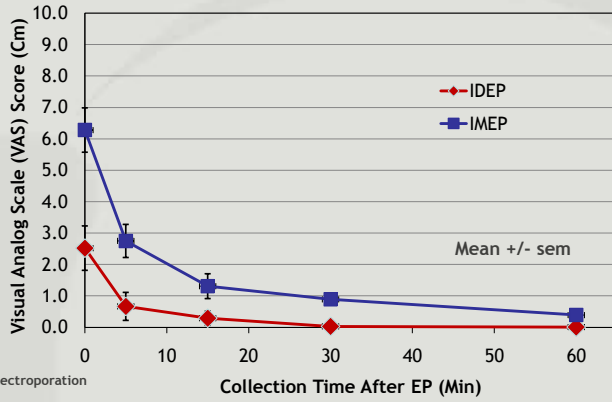
## VGX-3100 Phase I Study Conclusions

- IM administration of VGX-3100 by EP with CELLECTRA™ device was safe and generally well tolerated.
  - No SAEs or study related grade 3 or 4 AEs reported
  - All subjects completed 3 dose regimen
  - VAS (tolerability scores) averaged 6.2/10 immediately after vaccination and decreased to 1.4/10 within 10 min
- Vaccine induced antigen specific cellular responses to HPV 16 & 18 and E6 and E7 observed
  - 13/18 (72%) positive by IFN- $\gamma$  ELISpot ( $> 50$  SFU/ $10^6$  PBMC)
  - Magnitude increased with dose upto  $> 2500$  SFU/ $10^6$  PBMC for a single antigen and  $> 5,670$  SFU/ $10^6$  PBMC for all 4 antigens
  - 4 subjects responded to all 4 Ags
  - Responses persist to  $>9$  months
- Vaccine induced Ag specific Ab responses observed against all 4 antigens
  - High titers measured in 15/18 (83%) subjects
  - Responses persist to  $> 9$  months
- Phase 2 study in untreated subjects with CIN 2/3 planned

inovia

Page 22

# CELLECTRA™ EP Device Tolerability Scores (IM, MID)

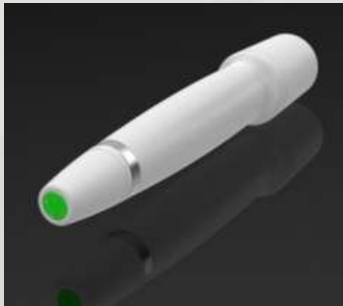


Minimally Invasive Device

Time (Min)	ID-EP			IM-EP		
	Mean	95% CI	Range	Mean	95% CI	Range
0	2.5	3.91-1.14	0.2-6.8	6.28	4.9-7.66	3.5-9.3
5	0.7	1.54-(-0.21)	0.0-4.6	2.75	1.72-3.78	0.6-6.2
15	0.3	0.73-(-0.16)	0.0-2.3	1.31	0.54-2.08	0.1-1.0
30	0	0.07-(-0.01)	0.0-0.2	0.89	0.53-1.25	0.1-1.7
60	0	0.03-(-0.01)	0.0-0.1	0.39	0.21-0.57	0.0-0.8

page 23

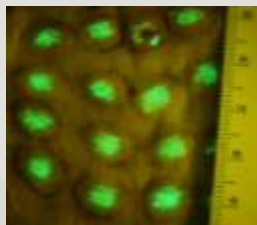
## ID & MID: Next Generation DNA Delivery Systems for B-cell Targets and Prophylactic Vaccination



Portable Cordless System



Portable Tethered System



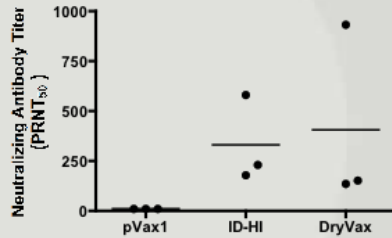
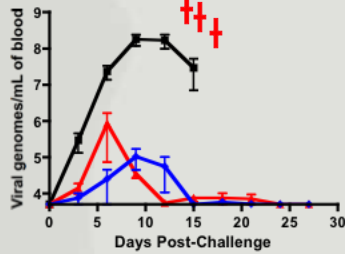
Surface EP System

Flu  
Malaria  
Dengue  
CHIKV  
RSV  
Smallpox  
inovia

Page 24

## NHP Challenge: Impact on Viral Replication

8 Plasmid Small Pox Antigen Formulation  
High concentration; 1 mg/plasmid



### Monkeypox challenge

iv infused with  $2 \times 10^7$  PFU of monkeypox virus NR-523

Neuts by M. Slifka lab  
DNA compared to Dryvax

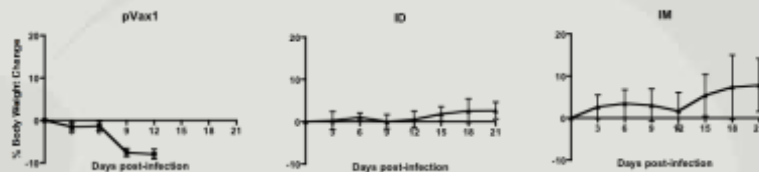
Hirao et al. J. Infect. Diseases (in press)

inovia

Page 25

## NHP Challenge: Impact on Clinical Disease

### Morbidity (% Weight Loss)



### Lesions



Hirao et al. J. Infect. Diseases (in press)

inovia

Page 26

## Conclusions: Enhanced DNA Vaccines

- **Concerted development** of vaccine, formulations, and **delivery** is critical.
- SynCon™ DNA vaccines delivered via Inovio EP drives **improved humoral and cellular** immune responses in many important species
- Responses mimic or can be **superior** to those induced by **live vaccine vectors** - CTL and Antibodies
- Immune phenotypes induced appear **diverse and manipulatable** allowing targeting of **multiple pathogens and disease states**
- **SynCon™ - EP platform** impacts disease or infection in models of SIV, monkeypox, malaria, chikungunya, cancer and influenza
- Preliminary data from **universal influenza and therapeutic HPV** vaccines is **promising**

inovio

Page 27 27

## Acknowledgements

### Inovio

Amir Khan            Kate Broderick  
Maria Wang         Steve Kemmerer  
Xuefei Shen         Feng Lin  
Janice Mendoza     Jay McCoy  
Jessica Lee          Mary Giffear  
Mark Bagarazzi  
J. Joseph Kim



**Funding:**  
NIH/NIAID/DAIDS; MVI-PATH  
DTRA; CDMRP

### University of Pennsylvania

Jian Yan  
Matthew Morrow  
Devon Shedlock  
Jean Boyer  
Karuppiah Muthumani  
David Weiner

### BIOQUAL, Inc.

Mark Lewis  
Hanne Anderson

### VGXI, Inc.

Henry Hebel  
Ying Cai

### SRI


Peter Silvera

### Public Health Agency of Canada

Gary Kobinger  
Ami Patel, Shane Jones

inovio  
Page 28

# Inovio Biomedical



Developing the next  
generation of vaccines to prevent  
and treat cancers and infectious diseases

[investor.relations@inovio.com](mailto:investor.relations@inovio.com)

NYSE Amex: INO