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

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Signs of our times…

O'Hare Airport, Mar 2010

San Diego Airport, Jan 2010

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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

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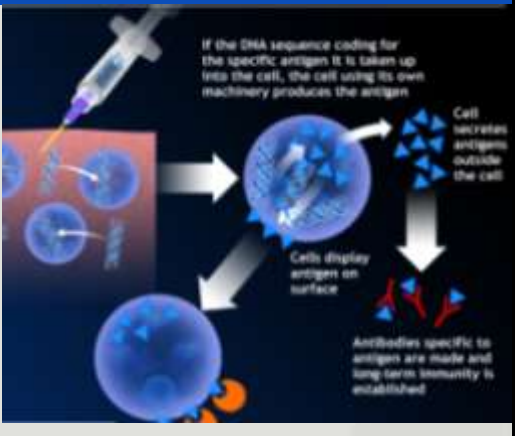
Attractiveness of DNA Vaccines

- 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

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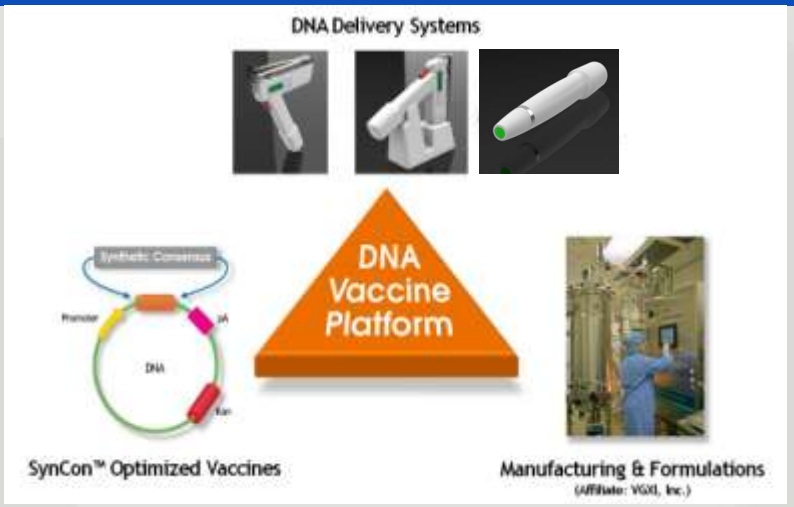
INO: Fulfilling the Promise of DNA Vaccines



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

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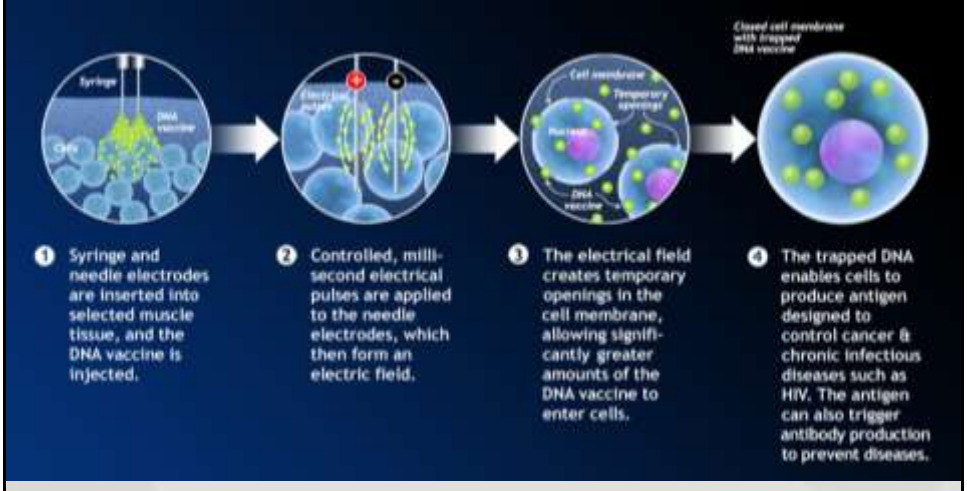
How Electroporation Delivers DNA Vaccines



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

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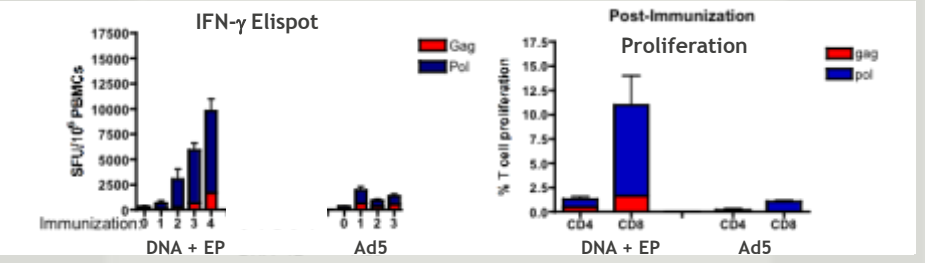
SynCon™ DNA Vaccines + EP: Strong T-Cell & Antibody Responses

SIV vaccine model (NHP)

UPenn/Merck/Inovio



Ref: Weiner et al. Molecular Therapy, August 2010

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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					
Avian Influenza	VGX-3400X					
Universal Influenza	Pandemic/ Seasonal Flu					
HIV Preventive	PENNVAX™-B					HIV Vaccine Trials Network
	PENNVAX™-G					NIH/NIAID
	PENNVAX™-GP					NIH/NIAID
HIV Therapeutic	PENNVAX™-B					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					ChronTech
Breast/Lung Prostate	V934: hTERT					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/NIAID/DAIDS
- MVI
- DOD, CDMRP
- DTRA

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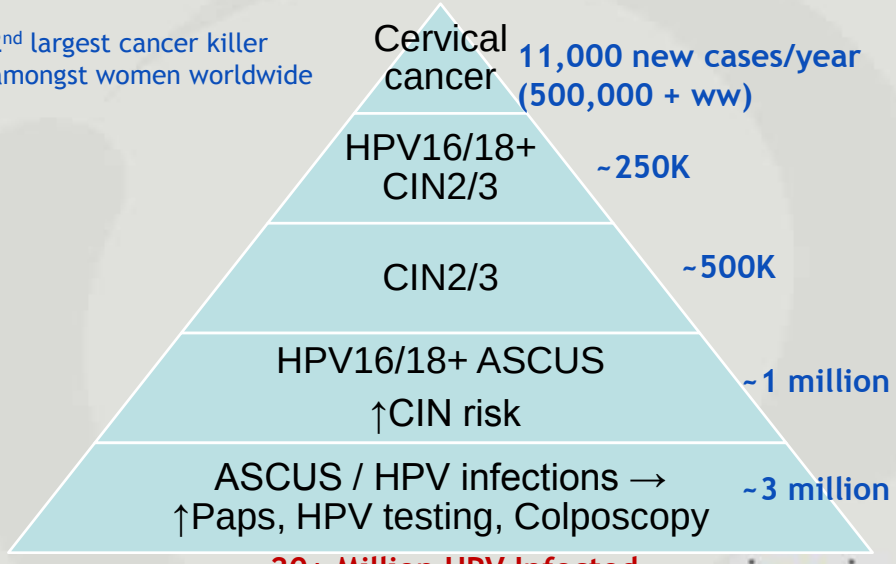
Annual Cervical Disease Burden due to HPV in US

2nd largest cancer killer amongst women worldwide



20+ Million HPV Infected
50+ Million Pap Smears

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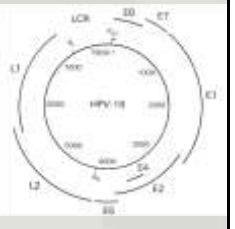
Therapeutic HPV Vaccines for Cervical Cancer Treatment



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.

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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.**

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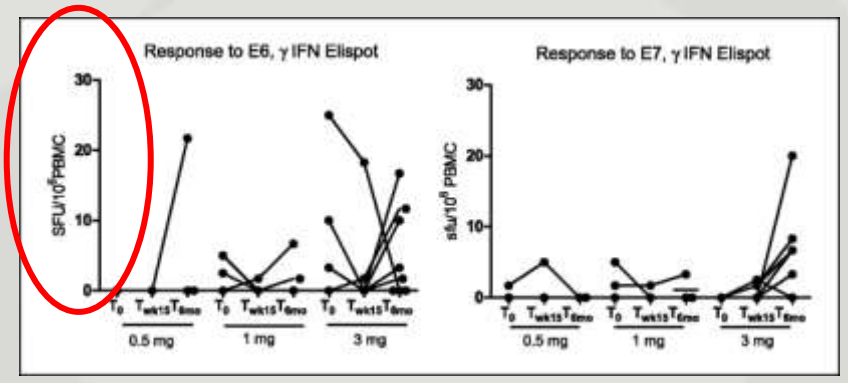
Historical Data: HPV16 E6 and E7-specific T cell responses induced by a HPV DNA vaccine in humans



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

Trimble C L et al. Clin Cancer Res 2009;15:361-367

Clinical Cancer Research

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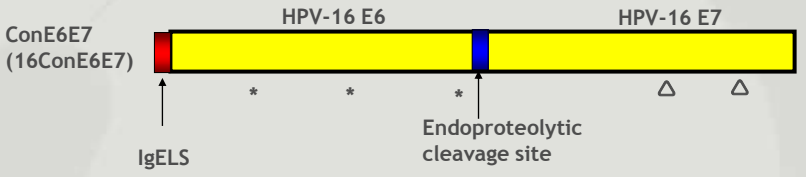
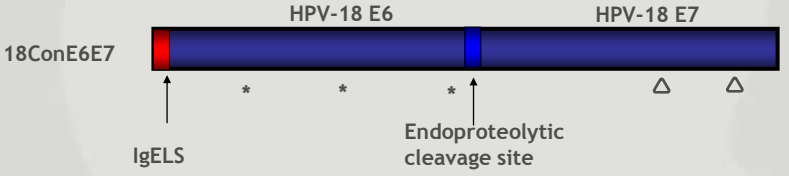
VGX-3100: SynCon™ Immunogen Design





* Deletions or mutations important for p53 binding and degradation

△ Mutations in Rb binding site

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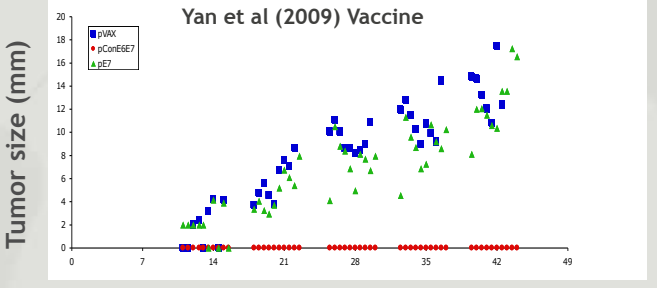
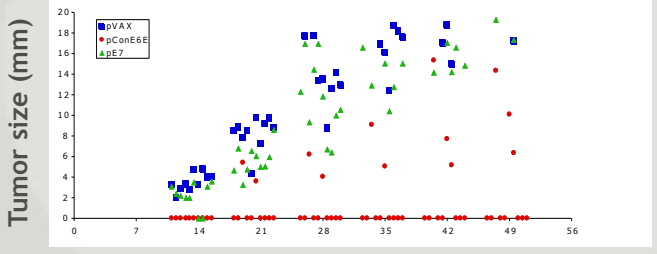
Vaccination with pConE6E7 delays/prevents tumor growth



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

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High Concentration, High Purity Formulations

	VGX-3100 (HPV)	
Test	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

VGX-3400 (Influenza)		
pGX2001	pGX2002	pGX2003
9.2 mg/mL	8.1 mg/mL	8.5 mg/mL
2.0	2.0	1.9
≤ 0.06%	≤ 0.08%	≤ 0.07%
≤ 0.03%	≤ 0.04%	≤ 0.04%
≤ 0.001%	≤ 0.001%	≤ 0.001%
1.1 EU/mg	≤ 1.2 EU/mg	≤ 1.9 EU/mg
Absent	Absent	Absent

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

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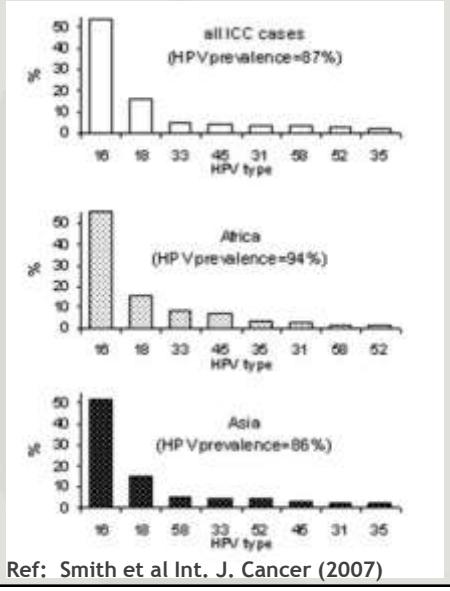
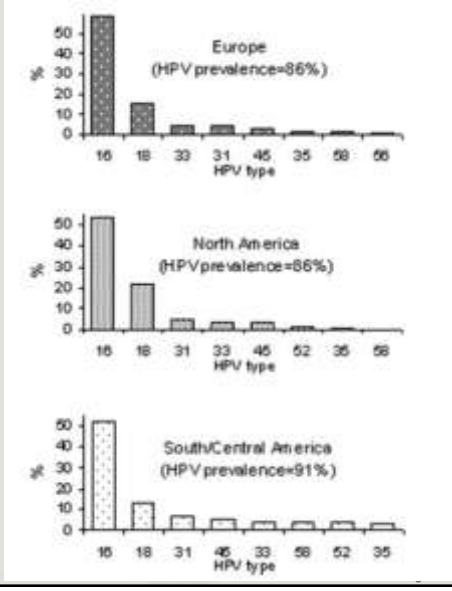
HPV Distribution in Invasive Cervical Cancer

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



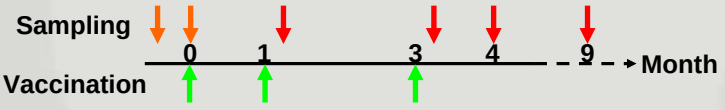


Ref: Smith et al Int. J. Cancer (2007)

HPV-001: Phase 1 Study - Safety & Immunogenicity

- Combination of HPV DNA vaccine delivered IM using Cellectra® 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.

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HPV-001 Summary of AEs by Grade and Cohort

	Injection Site Reactions (Subject Count)				Adverse Events (Subject Count)			
Grade	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Cohort 1 (0.6mg) (n=6)								
Vaccination 1	6	2	0	0	4	1	1[a]	0
Vaccination 2	6	0	0	0	5	2	0	0
Vaccination 3	6	1	0	0	4	1	1[b]	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[c] (6mg) (n=6)								
Vaccination 1	6	3	0	0	3	1	1[d]	0
Vaccination 2	4	1	0	0	1	0	0	0
Vaccination 3	4	1	0	0	0	0	0	0

[a] Grade 3 tension headache assessed by investigator as not related to study drug
[b] Grade 3 gastroenteritis viral assessed by investigator as not related to study drug
[c] All data is current through September , 2010 with no subjects in Cohort 3 having received vaccination 3
[d] Grade 3 wrist fracture assessed by investigator as not related to study drug

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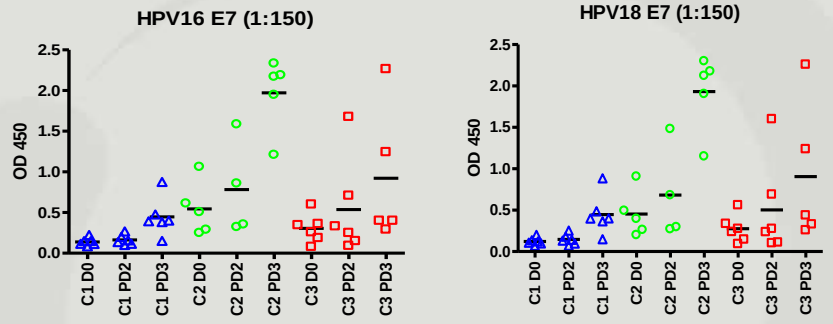
HPV 16 & 18 E7 Abs by Cohort and Vaccination

ELISA Data



Representative Western Blot (Cohort 2)

Overall: 15/18 Ab positive to ≥ 1 Ag (most ≥ 2)
Responses persist to > 9 months

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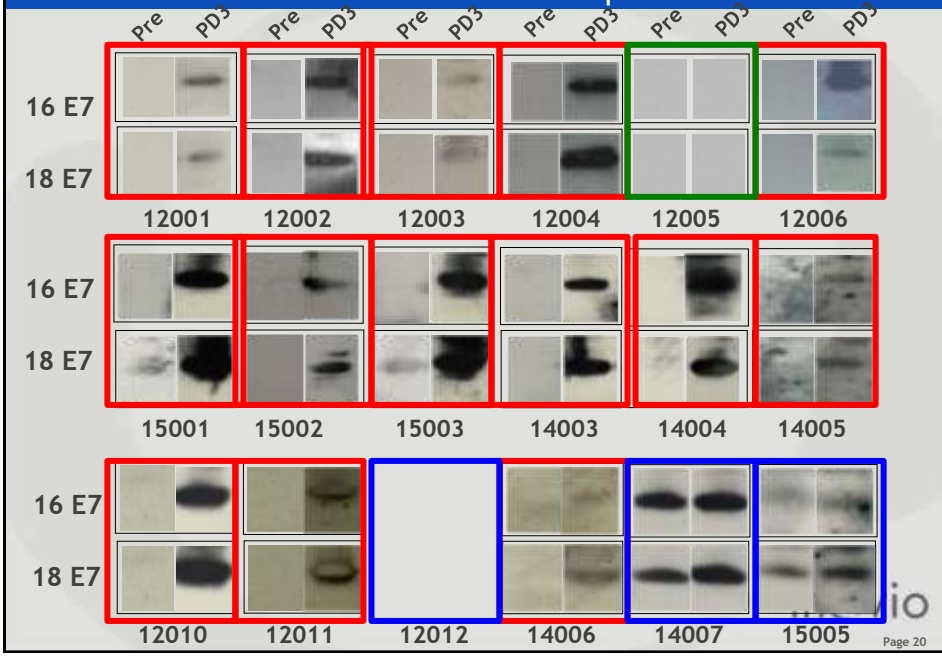
HPV16, 18 E7 Western Blot Seroconversion in 14/15 Evaluable Samples



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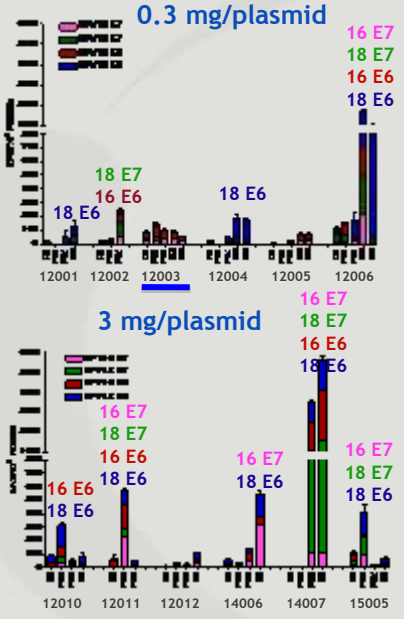
Cellular Responses Induced by VGX3100/EP



Overall 13/18 (72%)
Fully interpretable 13/16 (81%)
E6 13/18 (72%) E7 9/18 (50%)
Both HPV16 & 18 11/18 (61%)
Responses frequently persist 6 months post final immunization

High Background

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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-γ 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

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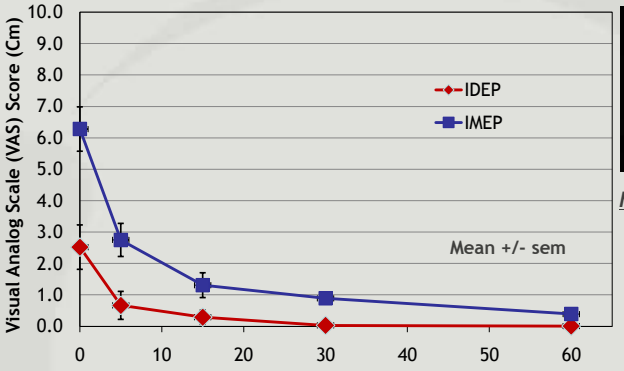
CELLECTRA™ EP Device Tolerability Scores (IM, MID)



EP: Electroporation

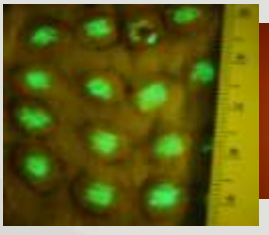
Minimally Invasive Device

	ID-EP			IM-EP		
Time (Min)	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-.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

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

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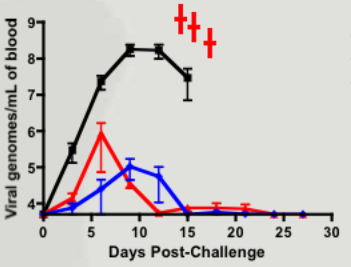
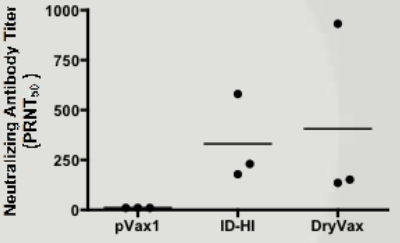
NHP Challenge: Impact on Viral Replication

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





Monkeypox challenge

iv infused with 2 x 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)

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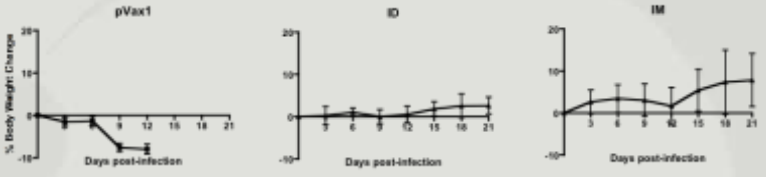
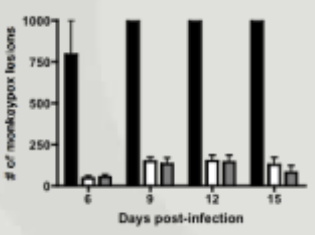
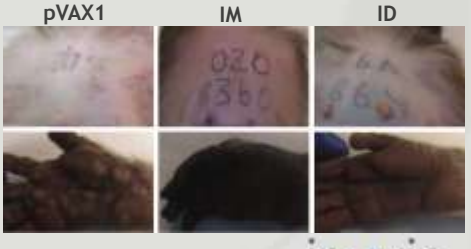
NHP Challenge: Impact on Clinical Disease

Morbidity (% Weight Loss)



Lesions





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

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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**

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

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