Spring 5-22-2012

Cervical cancer immunotherapy: Induction of HPV specific CTLs in human volunteers after VGX-3100 immunization

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Inovio Pharmaceuticals

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revolutionizing vaccines

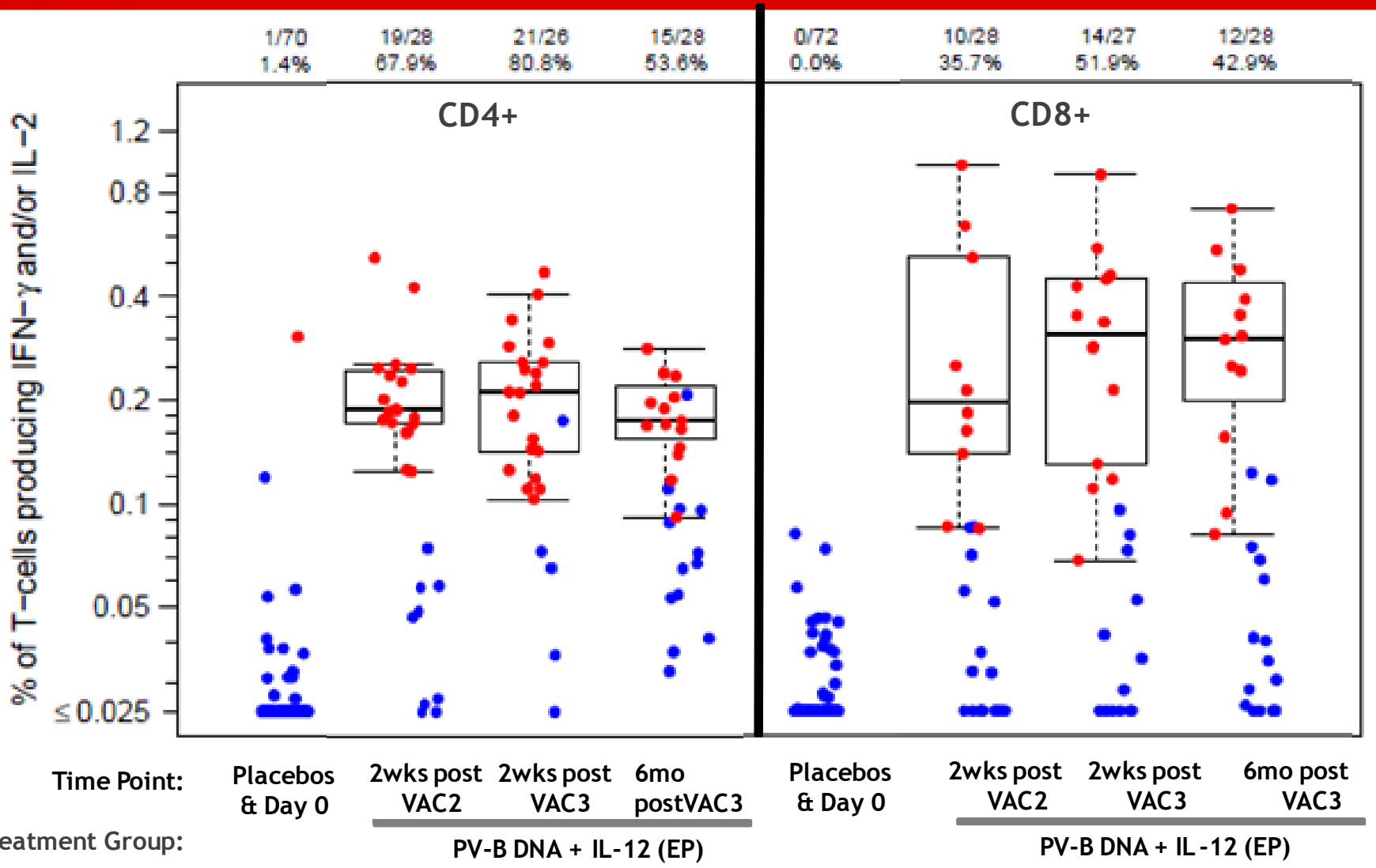
Induction of HPV Specific CTLs in Humans After VGX-3100 Immunization

May 22, 2012

Albufeira, Portugal

Vaccine Technology IV

Best Vaccine Induced CD4+ and CD8+ T-Cells (Humans): HVTN 080 ICS Responses Against HIV Peptides



Ref: HVTN-080 Study; Kalams et al. 2011 HVTN Annual Meeting

HIV Vaccines Comparison: Humans (HVTN Data)

Inovio DNA-EP: Better & faster CD8+ T cell responses than viral vectors and/or complex prime-boost regimens

Vaccine	Details	Components	Immunization Schedule (Days)	% CD4 Response	% CD8 Response
HVTN 073-SAAVI	DNA', MVA-C boost	D, D, D, M, M	0, 28, 56, 112, 140	70	33
HVTN 205-GeoVax	DNA',MVA-B	D, M, M, M	0, 56, 112, 140	73	27
HVTN 077-VRC	Ad35. Ad5	Ad35, Ad5	0, 168	16	35
	DNA', Ad5	D, D, D, Ad5	0, 28, 56, 168	45	47
(Ad5 sero-)	DNA', Ad35	D, D, D, Ad35	0, 28, 56, 168	23	36
(Ad5 sero+)	DNA', Ad35	D, D, D, Ad35	0, 28, 56, 168	23	12
INOVIO's DNA+EP	DNA/IL-12/EP	D, D, D	0, 28, 84	81	52

>90%

Source: McElrath - Compilation of HVTN study results

HIV Therapy: PENNVAX™-B Phase I Study (HIV-001)

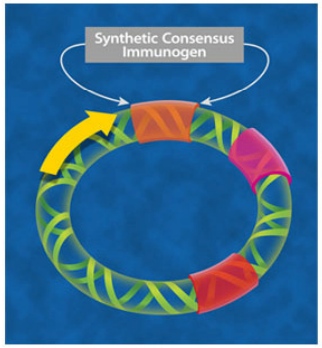
- Open label Phase I clinical trial (therapy) - UPenn
- Four vaccinations over 4 months (0, 4, 8, 16 weeks)
- 12 vaccinated subjects:
  - PENNVAX™-B (1 mg each of EnvB, Gag, Pol) + IM EP
  - On HAART; Undetectable plasma viral load (< 75 copies/mL)
  - CD4 T lymphocyte counts > 400 cells/uL with nadir > 200 cells/uL

T-cell Responses by IFN-g ELISpot Assay	
Vaccine induced T-cell responses (2 SD above prevacc. ELISpot levels)	**Vaccine + EP**
At least 1 Ag	**75%** (9/12)
2 or more Ag	**50%** (6/12)
Responses predominantly CD8+ T Cells	

- T-cell immune responses superior to previously-tested HIV DNA vaccines in HIV+ population

Integrated Synthetic Vaccine Platform:

DNA Delivery Systems



SynCon™ Optimized Vaccines

DNA Vaccine Platform

Manufacturing & Formulations
(Affiliate: VGXI, Inc.)

Revolutionizing Vaccines Through:

- Unparalleled safety profile
- Greater potency than viral vectors in primates and in humans (T-cells & Abs)
- Only platform to yield CD8+ effector T-cells in humans without anti-vector serology
- No vector induced responses – repeat boosts; multiple/combination vaccines; older/younger people
- Manufacturing advantages: Rapid, scalable, stable, stockable

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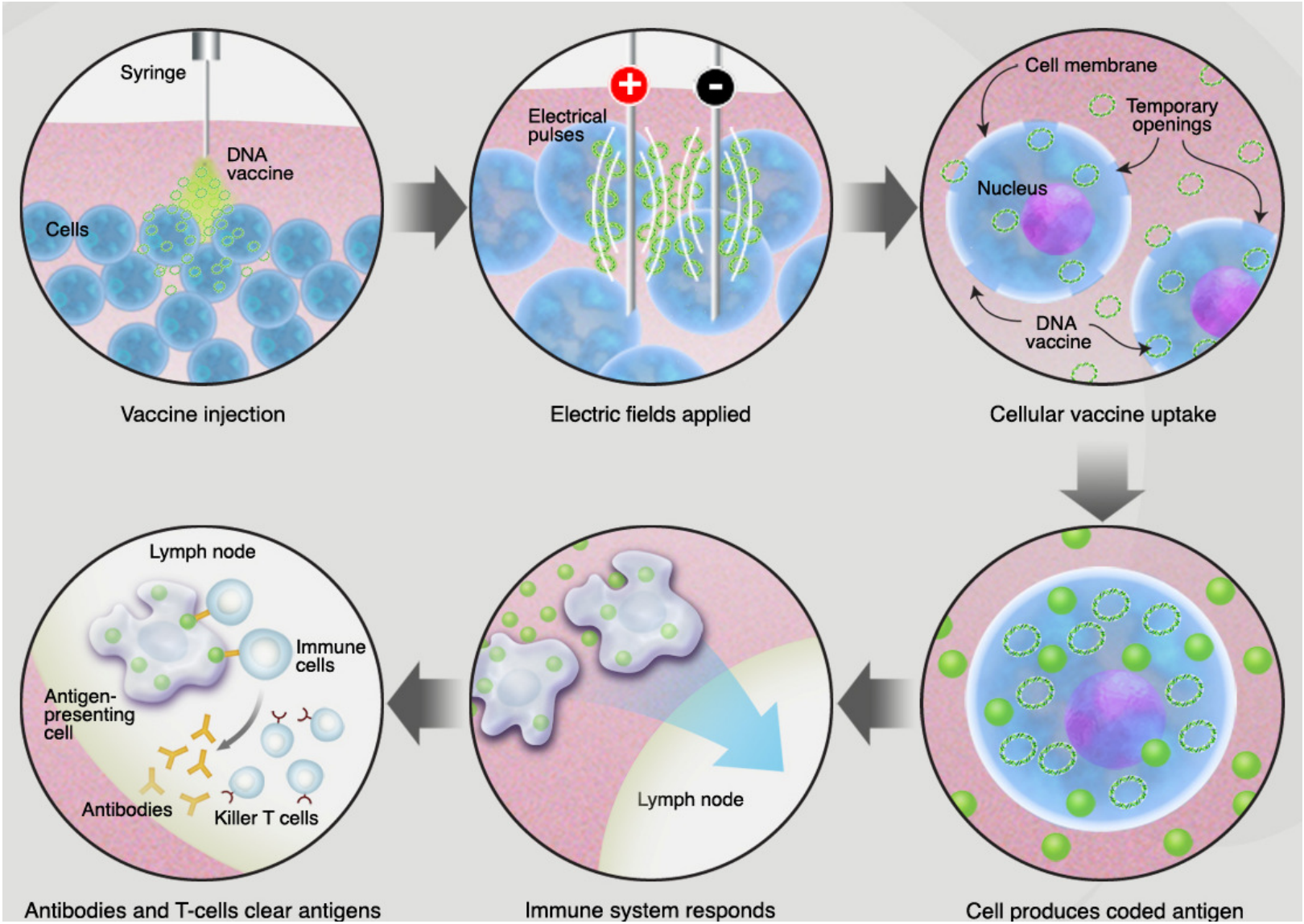
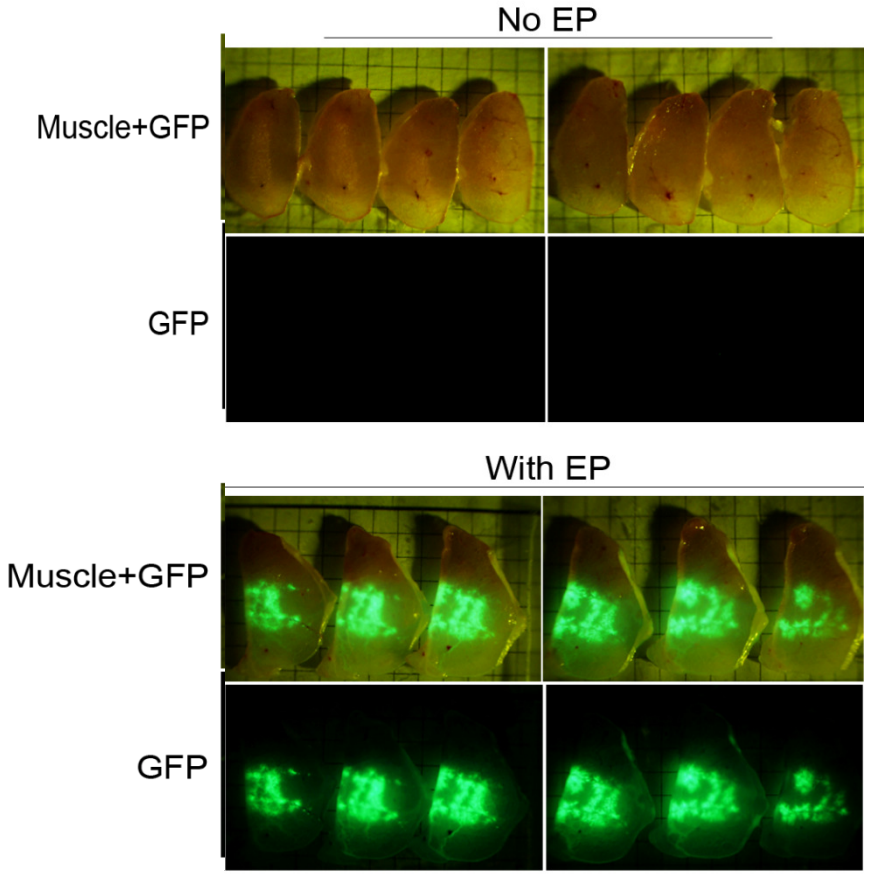
Superior Vaccine Delivery Using Electroporation



Better Delivery = Improved Immune Responses



1000x enhancement in expression

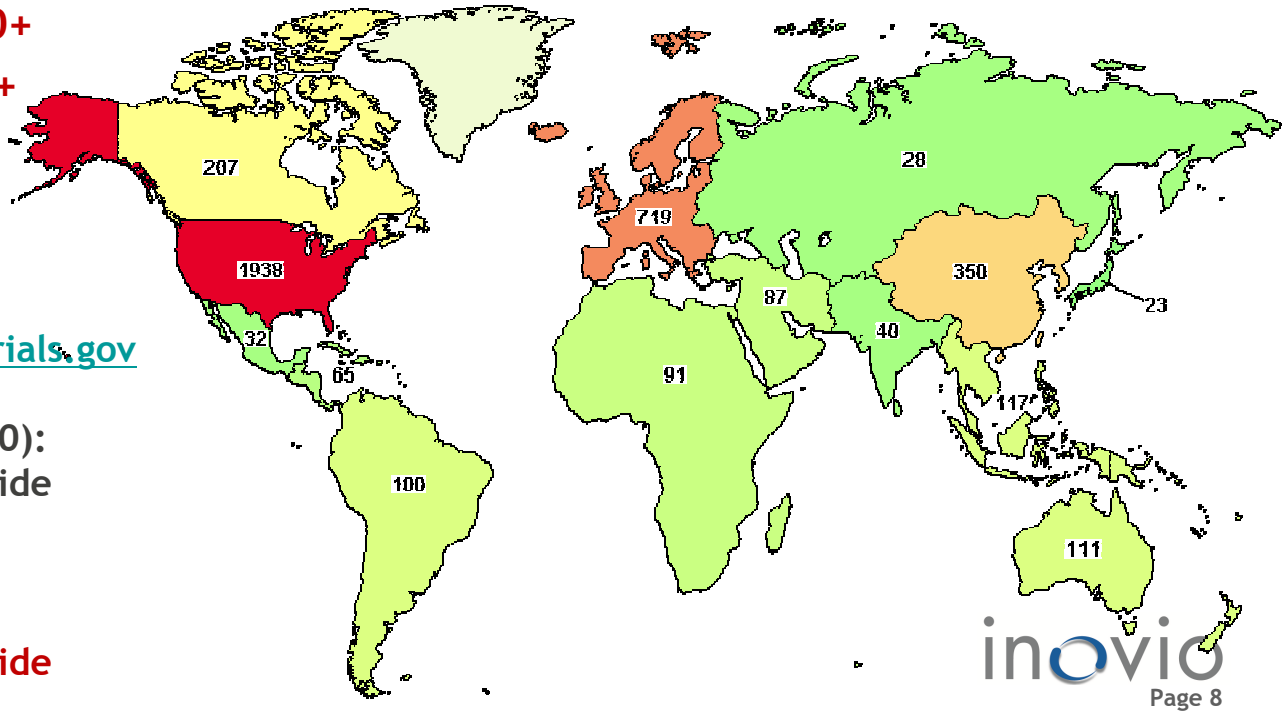
> 10-100x enhancement in immunogenicity

Display of Green Fluorescence Protein (GFP) gene expression after electroporation delivery into rabbit muscle

Ref: Sardesai & Weiner Curr. Opin. Immunol. 2011

DNA/EP by the Numbers

- Number of DNA Trials: > 3,600
- Number of study participants: Est. > 50,000+; > 150,000 Imm.; decades of follow up
- Number of DNA + EP Trials: 32
- Number of DNA + EP study participants: >1,600 (enrolled/scheduled)
- Number of EP vaccinations: > 4,800+ (estimated)
- Inovio Figures (**enrolled**); **# Vaccinations**:
  - IM EP: **300+**; **1000+**
  - ID EP: **120+**; **280+**



U.S. FDA website,
http://www.clinicaltrials.gov

Keyword DNA (2/2010):
2612 studies worldwide
1466 US; 530 EU

2/2012:
3631 studies worldwide
1938 US; 719 EU

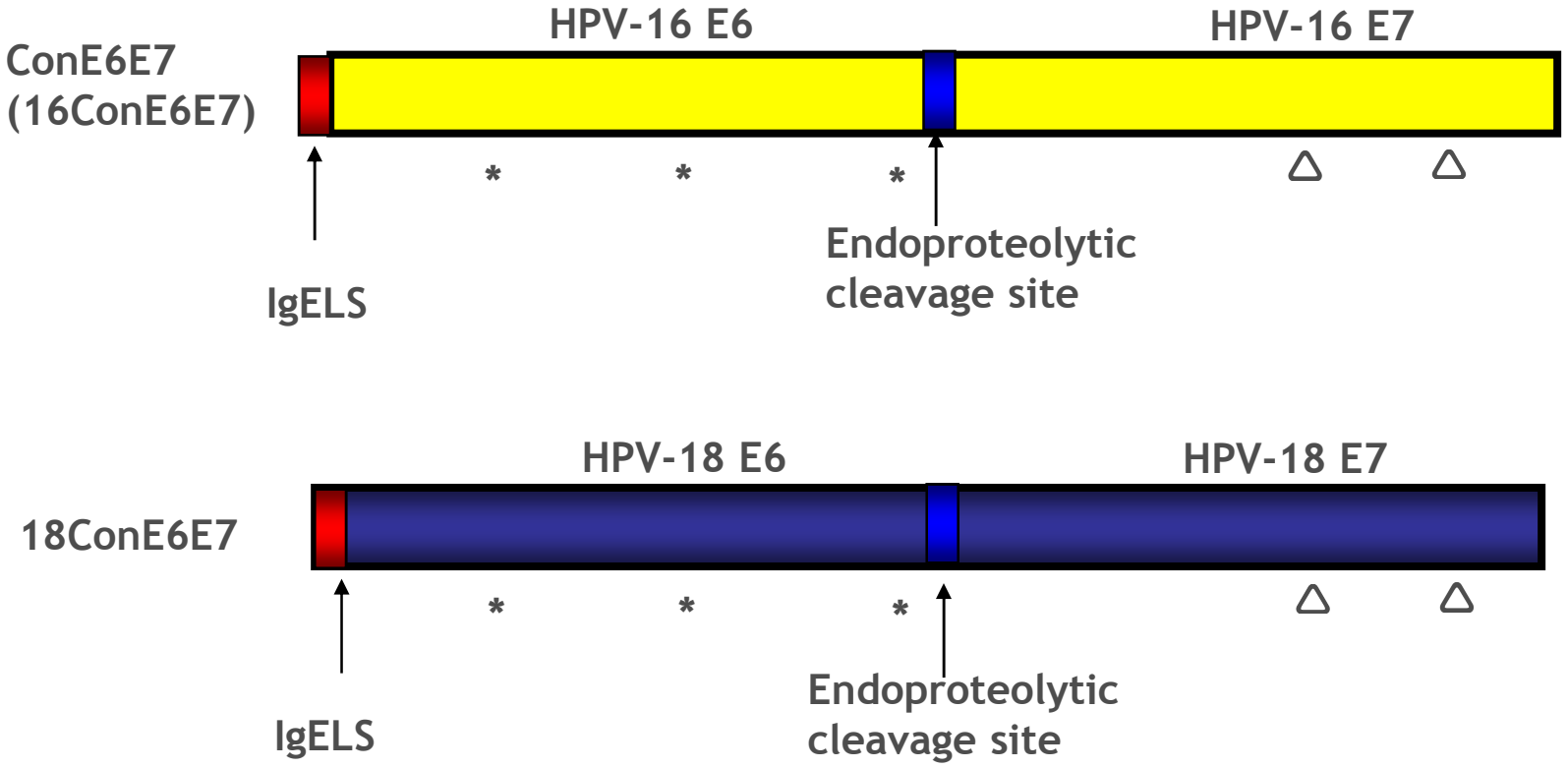
HPV & HPV Associated Cancers

- **USA: Annual incidence of HPV associated cancers**
  > 20,000 in women; > 11,000 in men
- Cervical Cancer > 99% HPV associated (> 70% are 16/18)
  - Merck (Gardasil) & GSK (Cervarix): **>$1.5 B in annual sales**
  - Worldwide: Annually
    - **~500,000 new cases cervical cancer – 50% fatal**
    - **2nd largest cancer killer of women > 250k deaths**
  - USA: Annually
    - 3M ASCUS (atypical cells) with HPV
    - 250K CIN 2/3 (stage prior to cancer) with HPV16/18
    - 13,000 cervical cancer; 5,000 deaths
    - $6 B spent: cervical cancer diagnosis and treatment
    - Surgery/ablation invasive + feared impact on childbirth

  Need for less-invasive, more readily distributable treatment of cervical dysplasia and cancer
- Head and Neck (HNSCC) ~ 23.5% – 35.6% associated with HPV
  - HPV 16 (68-86%); HPV 18 (1-8%)
  - USA Annually: >40,000 new cases; >7,800 deaths
  - 5 year survival: 26.5% - 81.8% (median 59.1%)

VGX-3100: Cervical Dysplasia/Cancer Therapy

- VGX-3100 targets E6 + E7 oncogenes which transform HPV-infected cells into precancerous & cancerous cells
  - HPV Types 16 and18

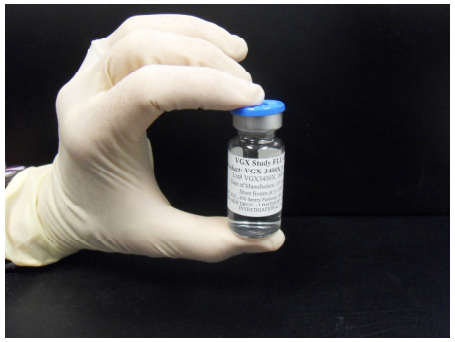


*** Deletions or mutations important for p53 binding and degradation**

△ Mutations in Rb binding site

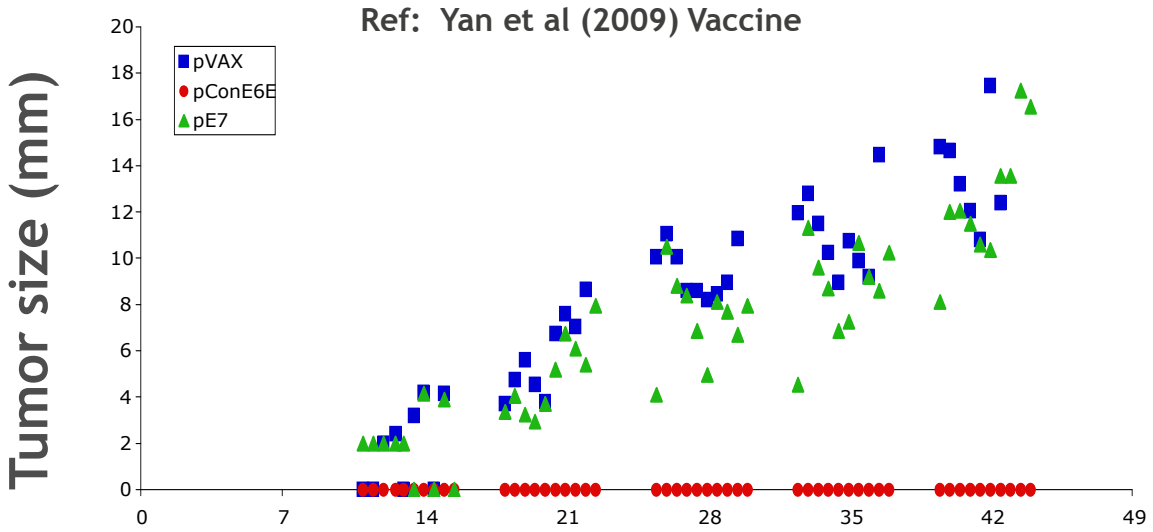
High Concentration, High Purity Formulations

	VGX-3100 (HPV)		VGX-3400 (Influenza)		
Test	**pGX3001**	**pGX3002**	**pGX2001**	**pGX2002**	**pGX2003**
Nucleic Acid Concentration	6.0 mg/mL	6.0 mg/mL	9.2 mg/mL	8.1 mg/mL	8.5 mg/mL
Purity (A260/280)	2.0	2.0	2.0	2.0	1.9
Host-Cell RNA	≤ 0.1%	1%	≤ 0.06%	≤ 0.08%	≤ 0.07%
Host-Cell Protein	≤ 0.1%	≤ 0.1%	≤ 0.03%	≤ 0.04%	≤ 0.04%
Host-Cell DNA	≤ 0.001%	≤ 0.001%	≤ 0.001%	≤ 0.001%	≤ 0.001%
Endotoxin	≤ 0.1 EU/mg	≤ 0.1 EU/mg	1.1 EU/mg	≤ 1.2 EU/mg	≤ 1.9 EU/mg
Microbial Limits	Absent	Absent	Absent	Absent	Absent

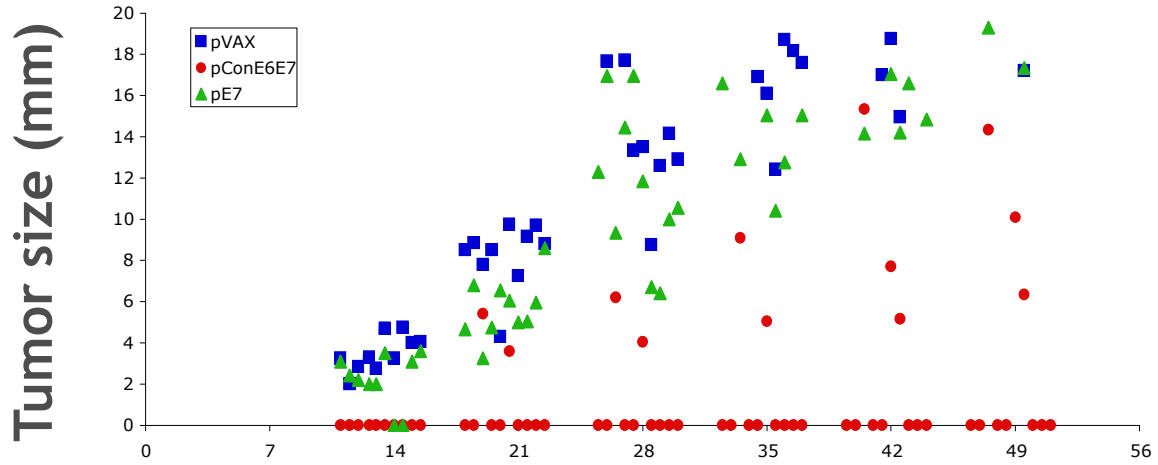


Now routinely achieve upwards of 10+ mg/mL to support multi-plasmid formulations

Vaccination with pConE6E7 delays/prevents tumor growth



Prophylactic model - mice



Groups
1. pVAX
2. pConE6E7
3. pE7

Therapeutic model - mice

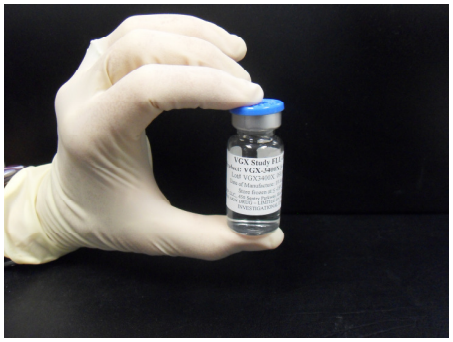
Days after tumor implantation

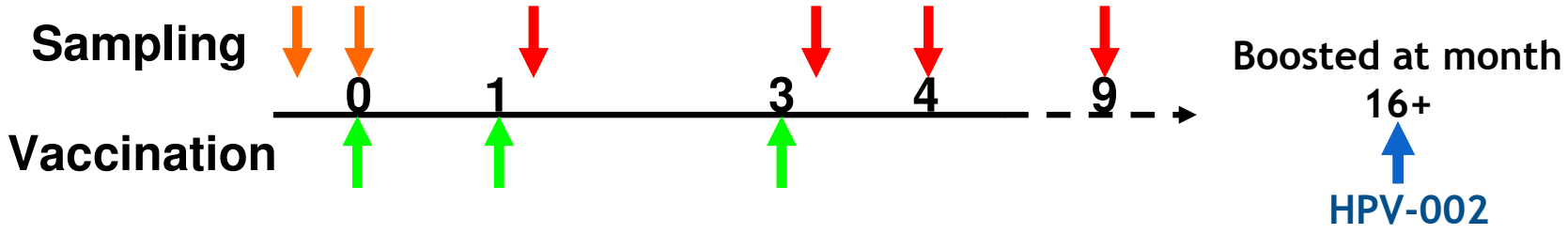
Note: TC1 Challenge model - Lung Epit. Cell line with HPV-16 - E6, E7

HPV-001/002: Phase 1 Study - Safety & Immunogenicity

- Combination of HPV DNA vaccine delivered IM using Cellectra® EP device - HPV 16, 18 (E6 + E7)
- Indication: Treatment of HPV types 16 and/or 18 associated CIN2/3

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



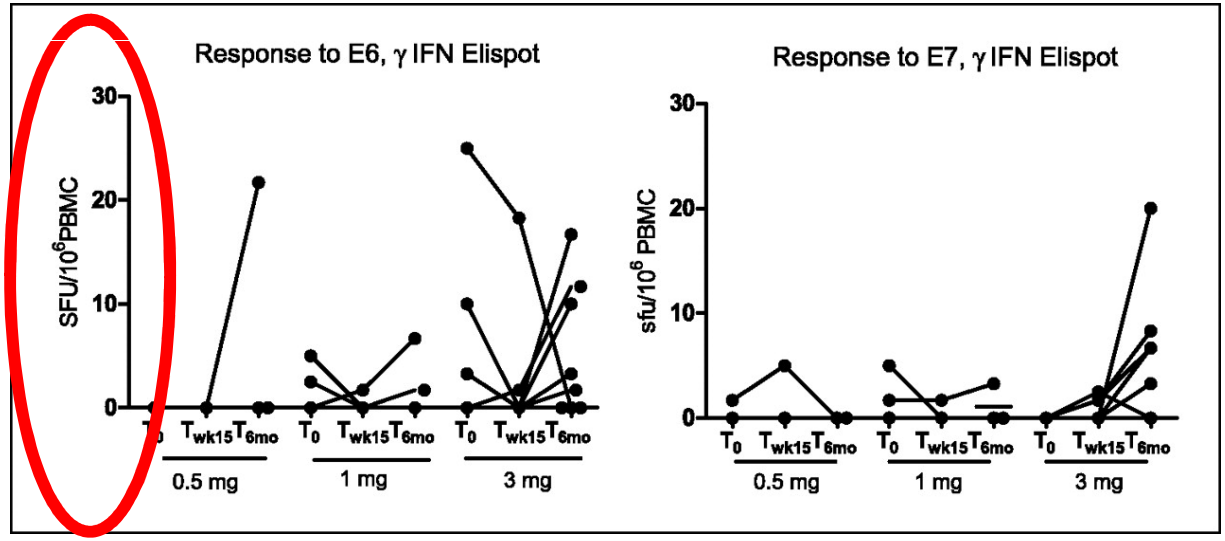


Patients with a history of CIN 2/3 previously treated by LEEP procedure were vaccinated 3x at 0, 1, 3 mo.
Serum and PBMC samples collected at multiple time points before and post immunization to evaluate immune responses.

HPV: Therapeutic Vaccines

HPV Clinical Reports - Previous Studies:

- MVA – based HPV E6/E7 vaccines from Transgene: Phase IIa (n = 21) completed; Phase IIb (n = 200) near completion
- Ad5, SFV (Semliki Forest virus)-based HPV E6/E7 vaccines
- Protein/Peptide-based vaccines – Recent encouraging data in VIN (Malief et al)
- *Listeria*-based vaccines
- DNA-based vaccines (TC Wu) - Use gene gun techniques to introduce HPV DNA vaccines directly into APCs; However…
- **Low immune responses observed - cultured ELISpots needed to see cellular responses**
  - **no antibody responses induced**

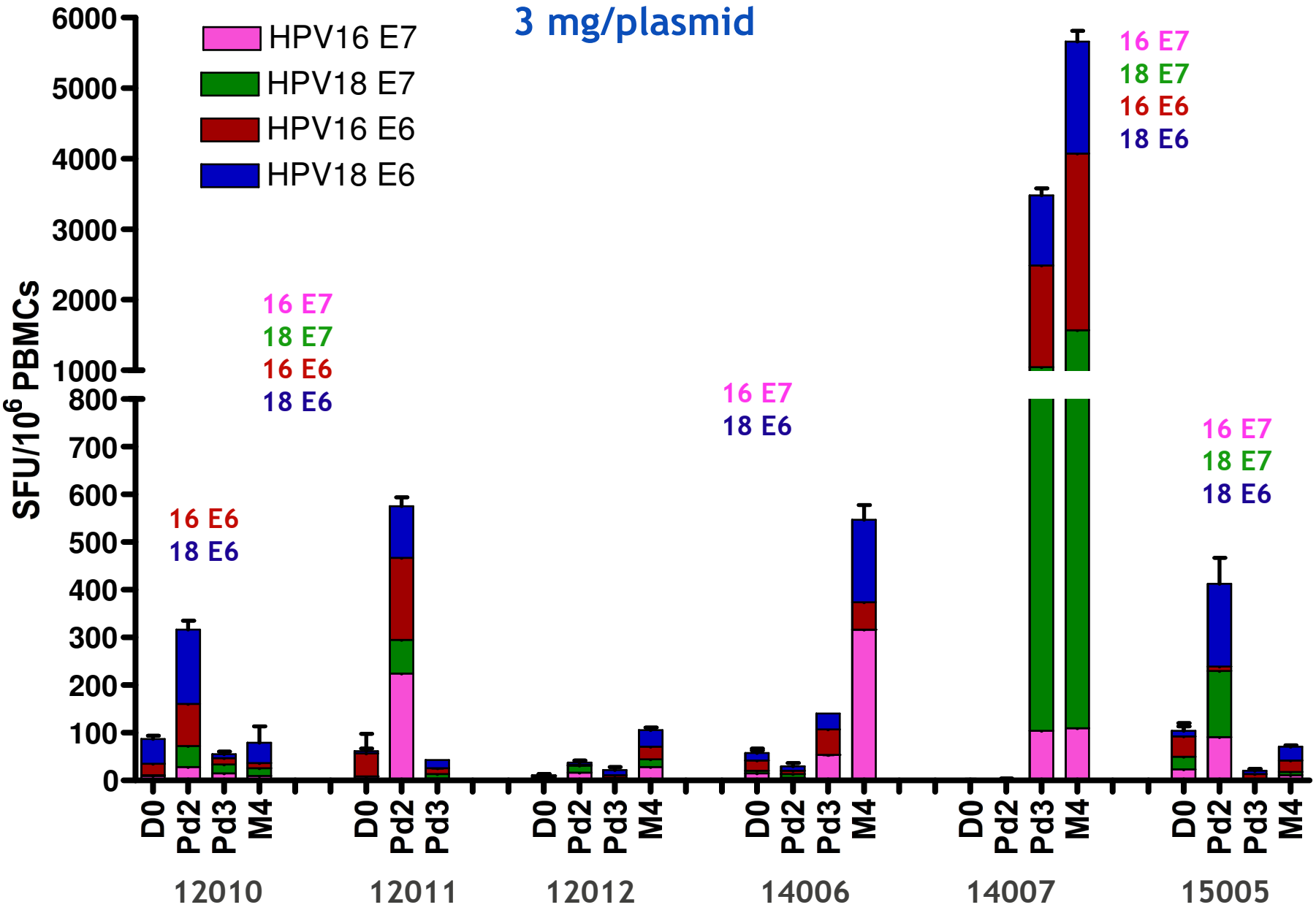


IM injection: 5/15 patients showed E7-specific responses, 2/15 patients showed E6-specific responses, the T cell responses required culture to observe. Vaccination did not induce Abs

Improving Immune potency important

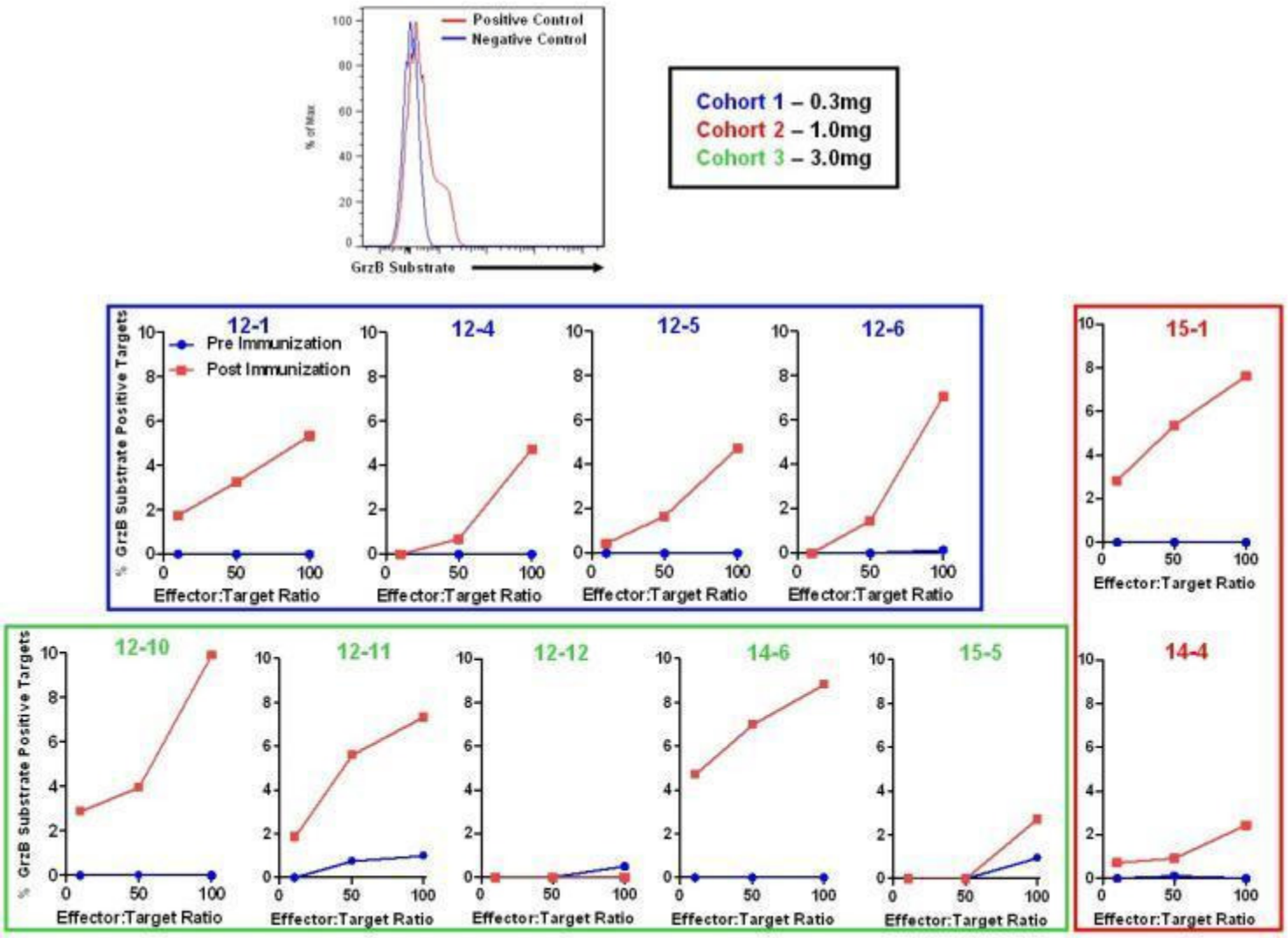
Trimble C L et al. Clin Cancer Res 2009;15:361-367

HPV001: Best Vaccine Induced IFN-γ ELISpot Responses to HPV Peptides and HPV-Specific CTL Activity (GrzB Assay) (Humans)



Flow Cytometry – HPV-001 Quantitative Killing Assay

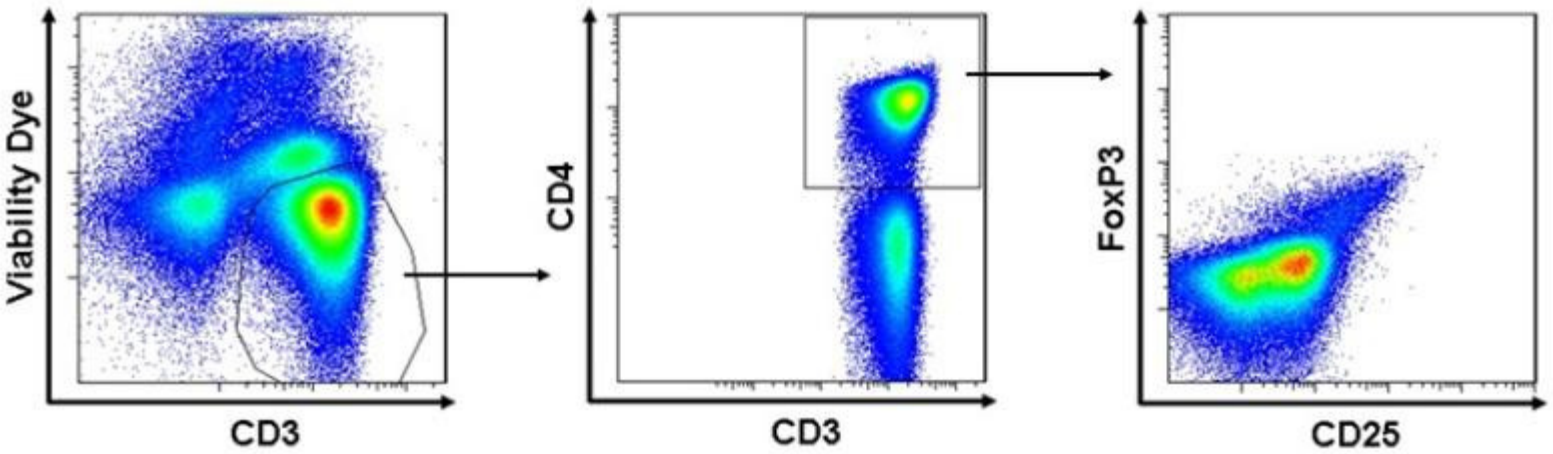
Morrow, Inovio

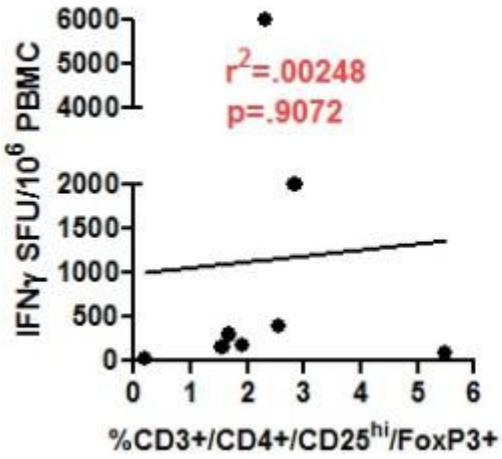


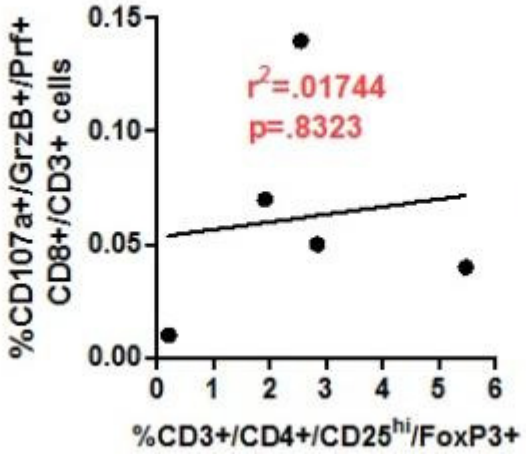
Whole PBMCs are effectors. Killing Magnitude scales with the number of CTLs.

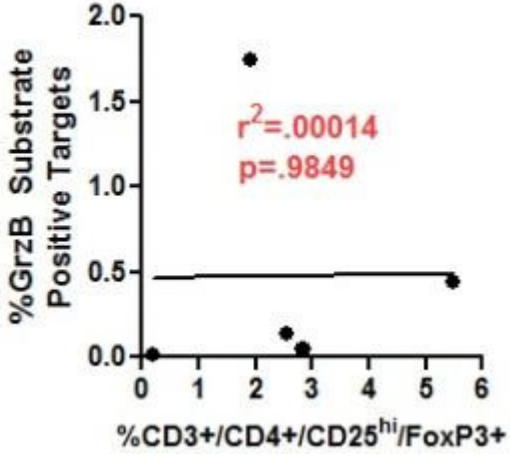
Flow Cytometry – HPV-001 Identification and Analysis of Tregs

Morrow, Inovio









No association between Tregs (PBMC CD4/CD25hi/FoxP3+) present pre-vac. and response rate in ELISpot, CTL ICS or Quantitative Killing

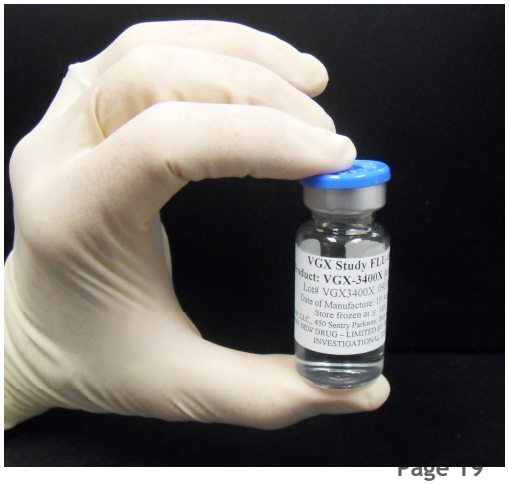
VGX-3100/EP Phase 1 Study Summary

- IM VGX-3100 + CELLECTRA™ EP Safety
  - **No safety concerns to date, well tolerated**
  - No discontinuations or related SAEs or Gr 3 or 4 AEs
  - Mean VAS 6.2/10 decreases to 1.4/10 within 10 mins
- Antibodies against all 4 antigens with high titers in 15/18 (83%) and Western Blot confirmation in all persist to 9 mos
- Antigen-specific cellular responses to HPV16,18 E6, E7
  - **13/18 (72%) POS by IFN-γ ELISpot (>50 SFU/10^6 PBMC)**
  - Increase w/ dose up to > 2500 SFU/10^6 PBMC for 1 Ag, > 5,670 SFU/10^6 PBMC for all 4 antigens
  - 5 subjects responded to all 4 antigens
  - **Responses persist to 9 months after primary series**
  - **4th dose boosts T cell responses up to > 2 years**
  - HLA DR+ / CD38+ CD8+ T cells release Granzyme B / perforin for cell killing – more sensitive than ELISpot?

Phase II Study Design for VGX-3100 (CIN2/3)

- Randomized, blinded study: VGX-3100/IM EP vs. placebo
- Patients: CIN2/3 (high grade cervical dysplasia)
- + HPV16 and/or 18 (cause 70% of cervical cancers)
- 1˚endpoint: CIN 2/3 or CIN 3 lesion clearance to CIN 1 or less 6 months post 3rd dose (based on biopsy)
- 80% Power to detect efficacy >25% difference in regression rate between Vaccine and Placebo : ~150 patients, 3:1 Vaccine/placebo
- Timeline: total duration: ~2 ½ years

- Launched: 2Q 2011
- Enrollment:1 – 1½ years
- ~18 month protocol: 3 month treatment + 6 month endpoint + 9 month LTFU



Product Opportunities for HPV Serotypes Beyond 16/18

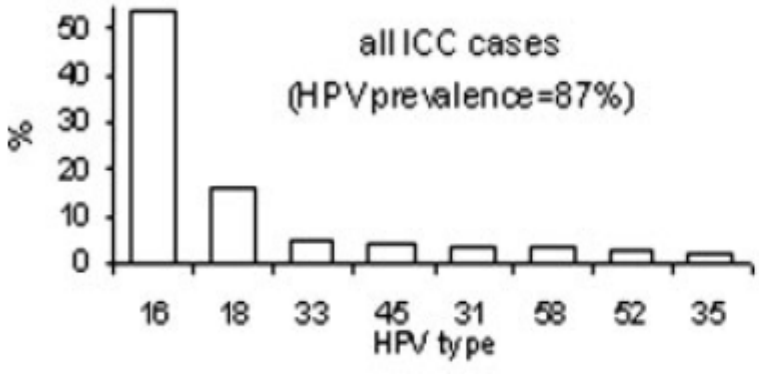
HPV 33, 45 - Cancer

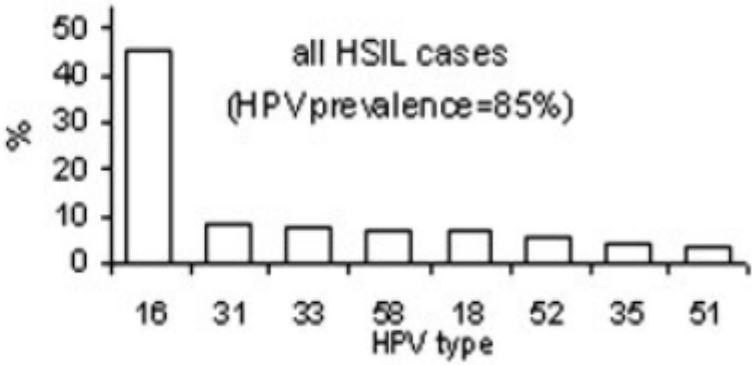
HPV 6, 11 – Genital Warts

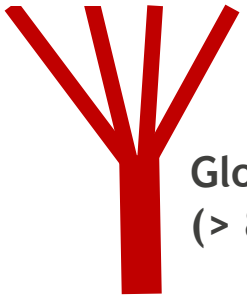
Potential for Broader and/or Targeted Coverage

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

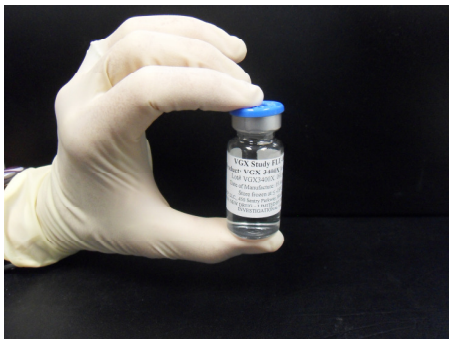
Ref: Smith et al Int. J. Cancer (2007)

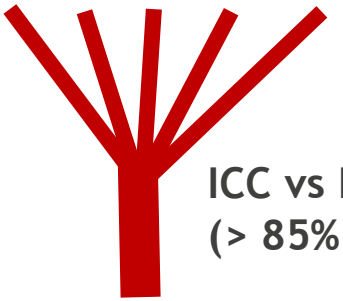




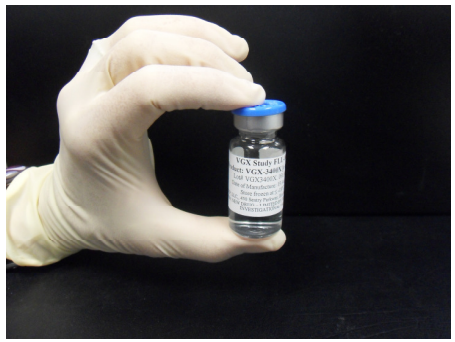


Global Cervical Cancer Vaccine
(> 85% Coverage)





ICC vs HSIL
(> 85% Coverage)



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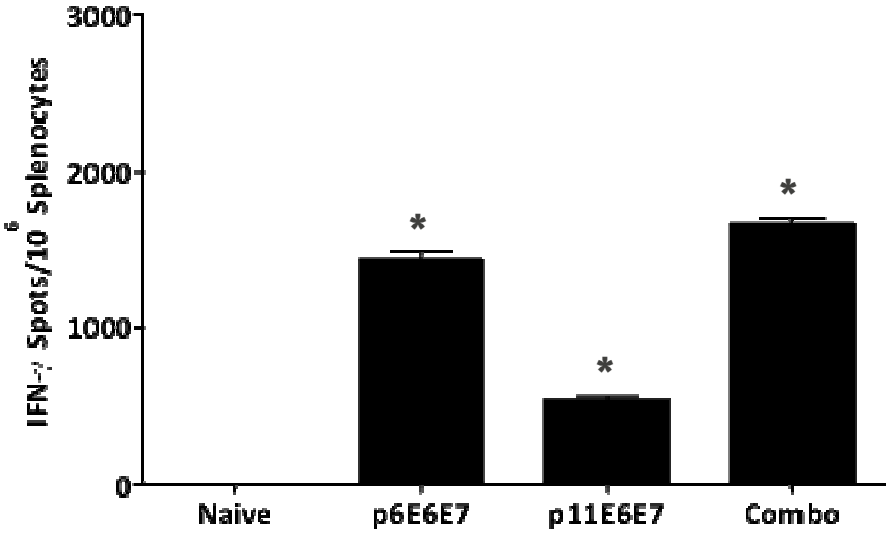
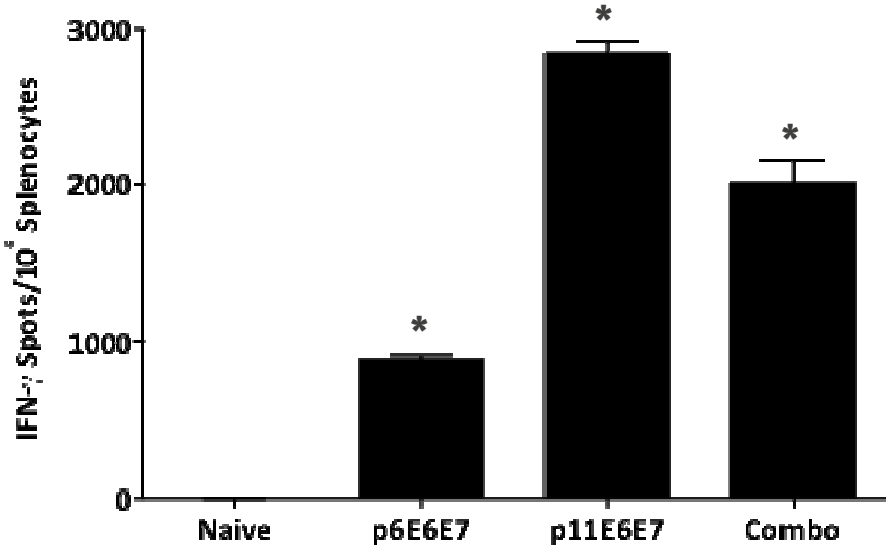
Potent T-Cell ELISpot Responses to HPV 6, 11 Vaccines

HPV 6 Vaccine



Mice model

HPV 11 Vaccine



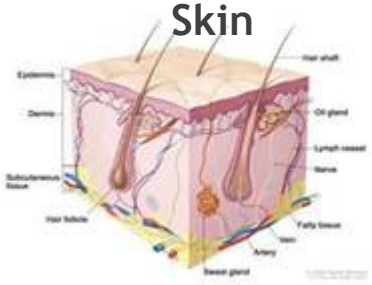
CD8+ Ag Specific T-cells (By ICS)

Ref: Shin et al. Hum. Vaccines Immunotherapy 2012

Broad Applicability of INOVIO's Electroporation Platform

Muscle

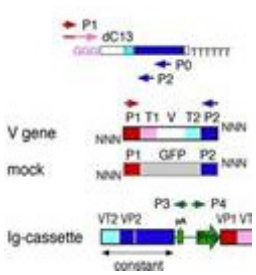
Skin

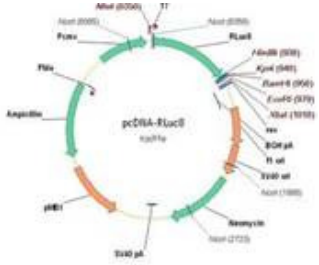


EP Target Tissue

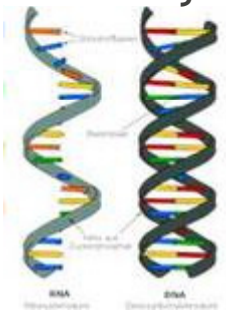
INOVIO's

Electroporation Technology





Nucleotide Delivery

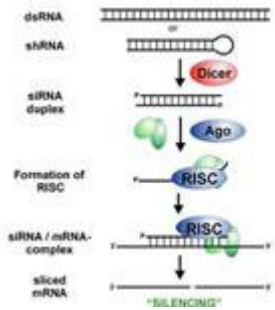


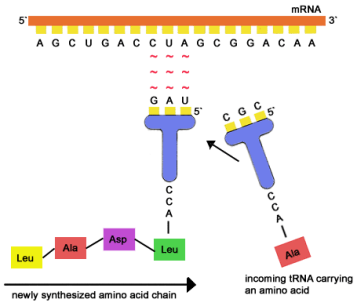
DNA

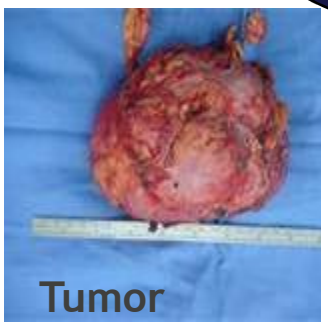
Plasmid
PCR product
Linear Expression Cassette
Cosmids

RNA

mRNA
siRNA
srRNA







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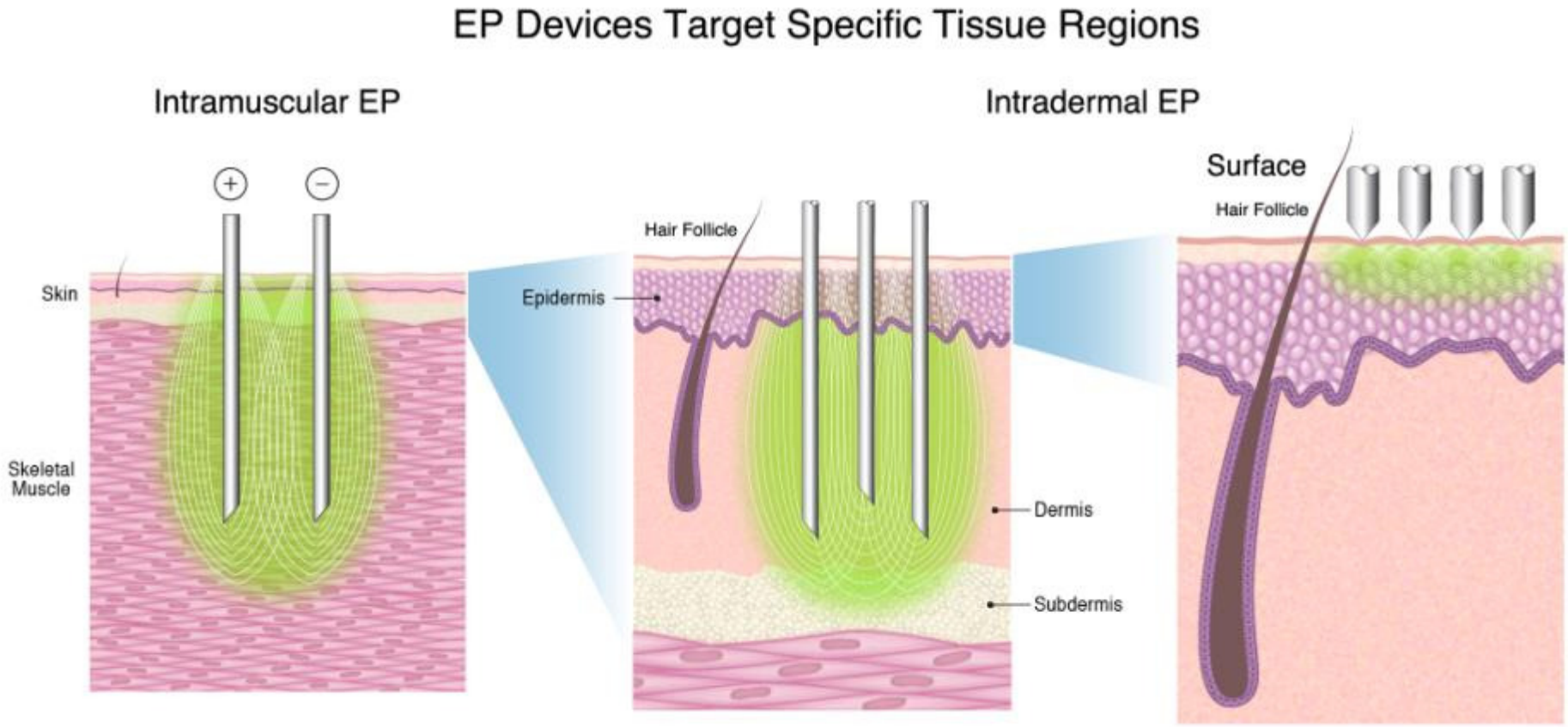
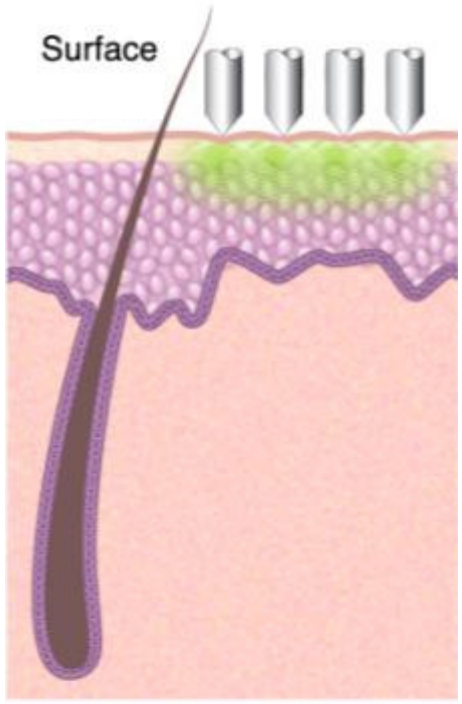
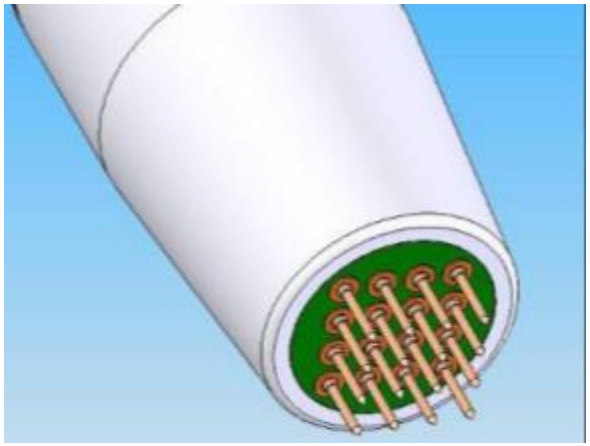
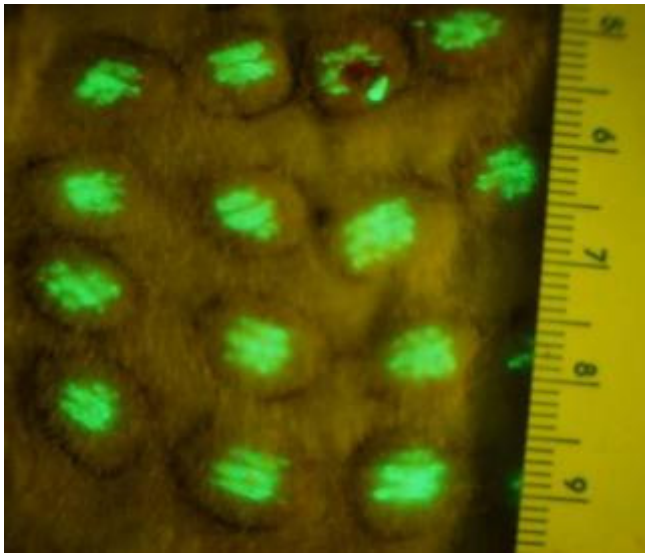
Next Generation DNA Delivery Systems for T- and B-cell Targets and Prophylactic Vaccination

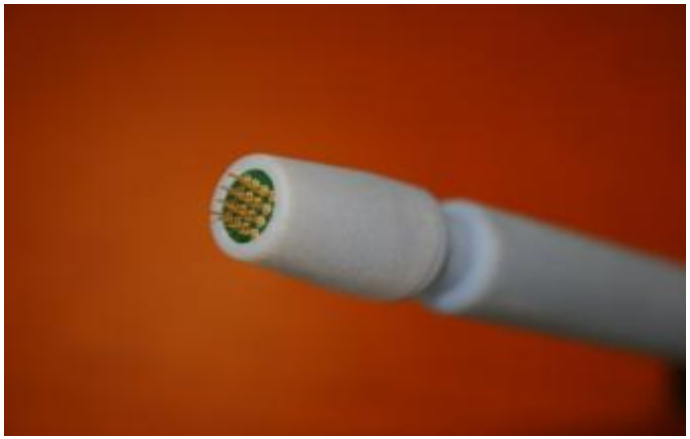


Surface EP Device – Transfection localization



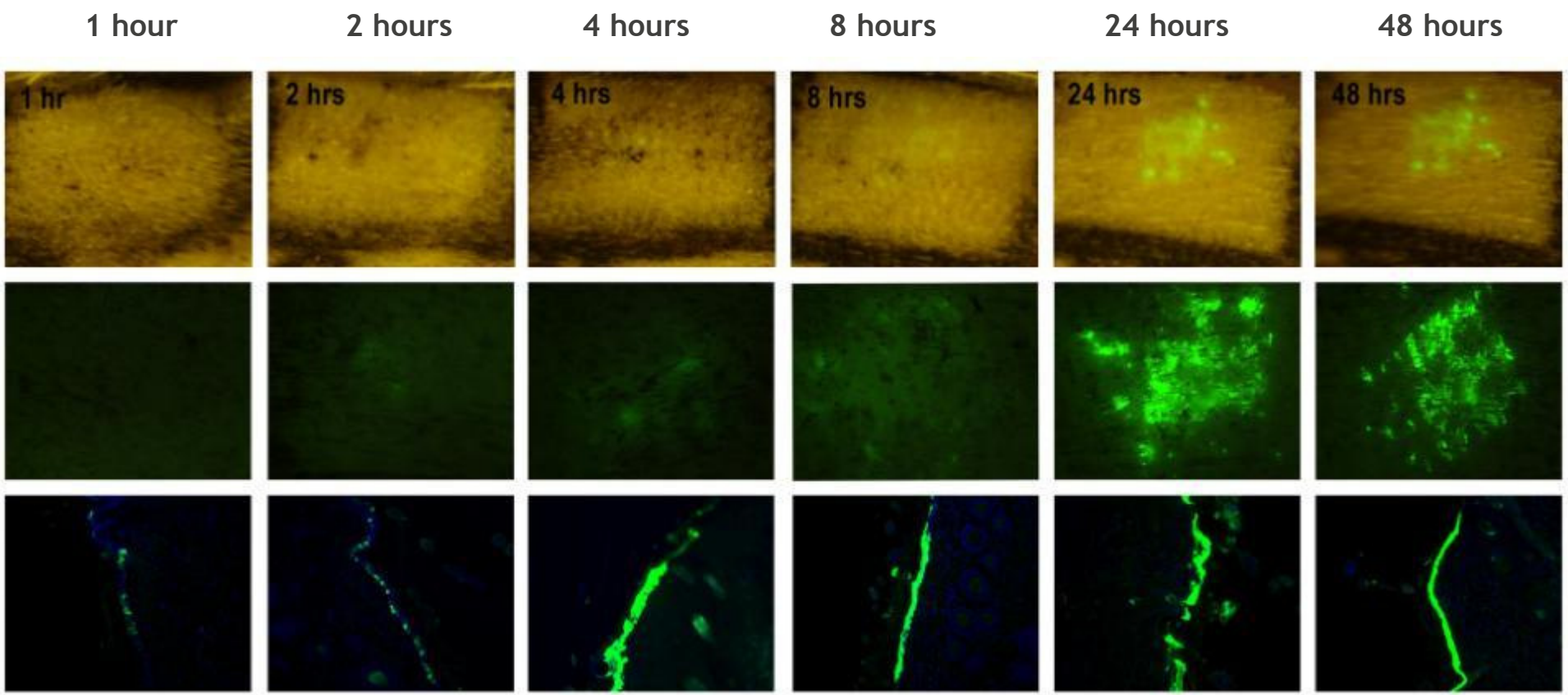






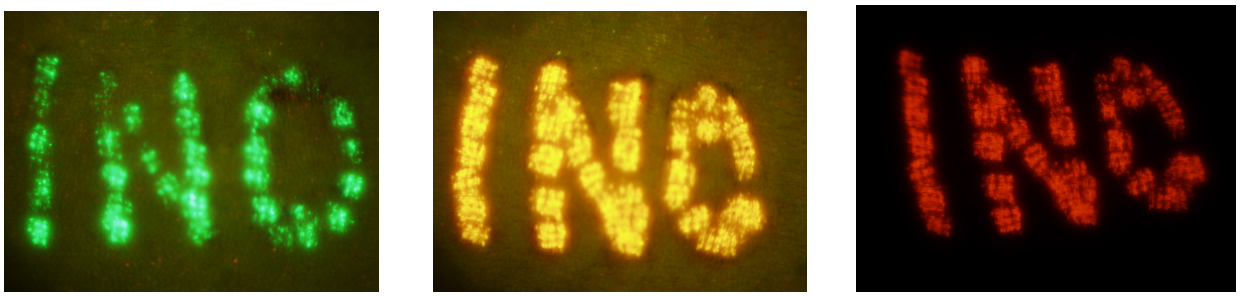
Broderick *et al*, Gene Therapy 2011

SEP Device GFP Expression Kinetics



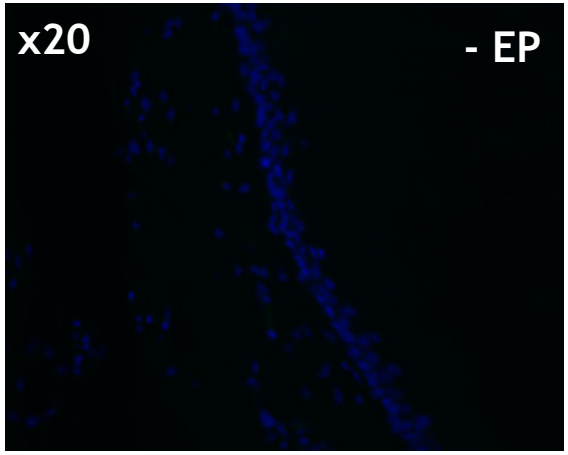
Upper Panel - Gross guinea pig skin
Middle Panel - Magnified guinea pig skin
Lower Panel - Guinea pig skin sections

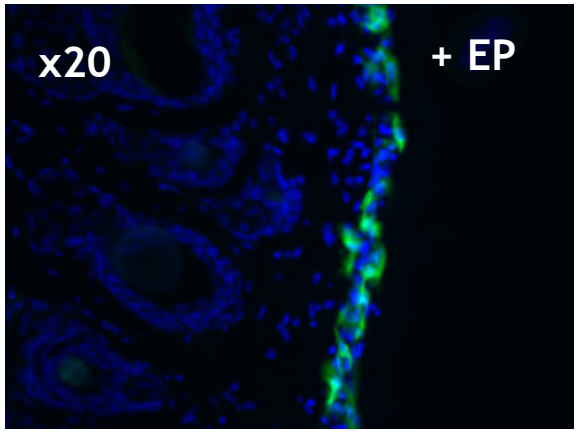
Directed and Targeted EP

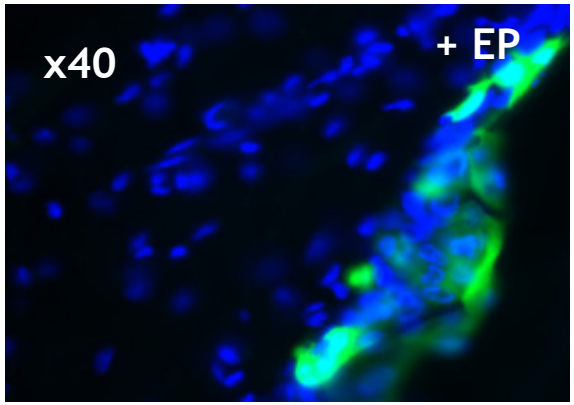


GFP Co-delivery RFP

Guinea Pig Skin



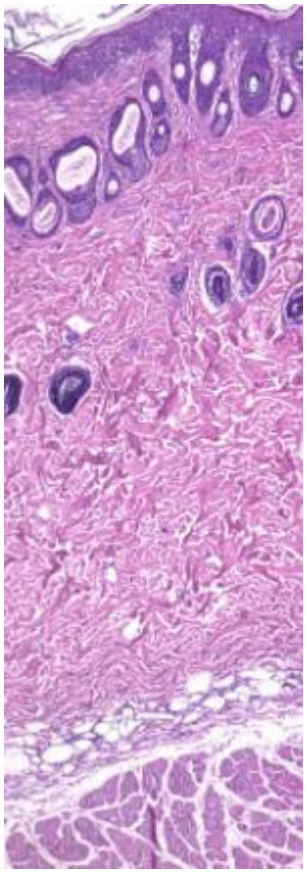




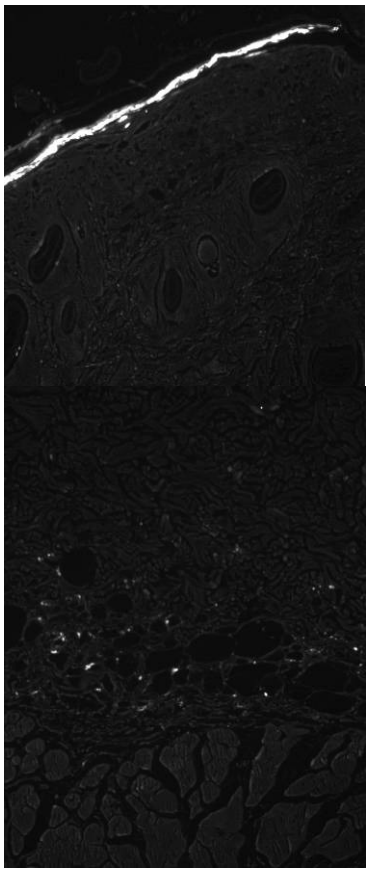
Flu	Smallpox
HIV	Malaria
Lassa	FMD
CHIKV	Dengue
HCV	HBV
CMV	CDiff

inovio

Histology and Immunology



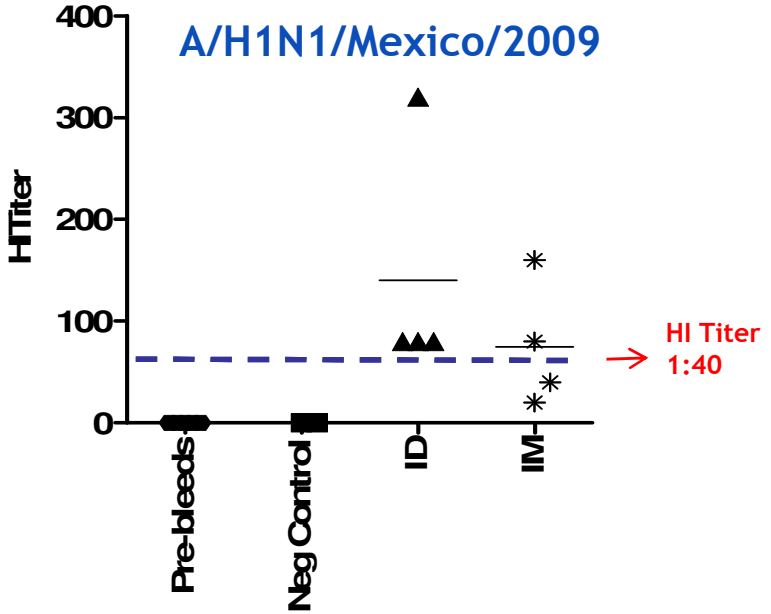
No associated tissue damage in guinea pig skin biopsies removed 3 days post treatment.



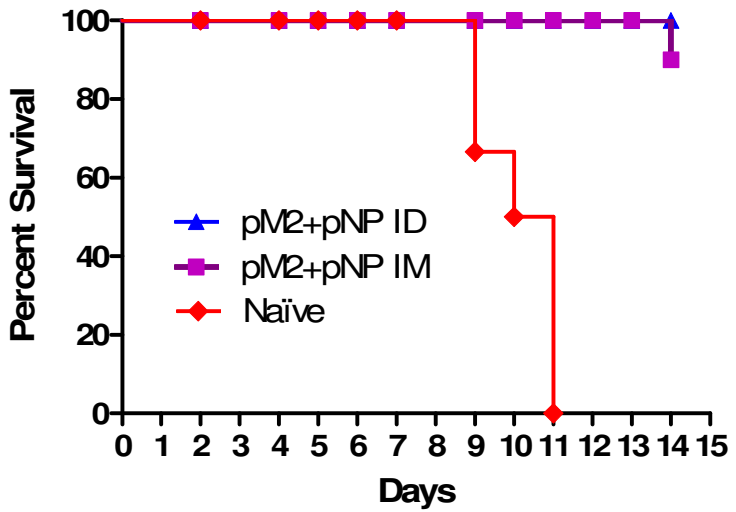
Majority of GFP transfection was observed in upper layers of epidermis.

Broderick *et al*, Gene Therapy 2011

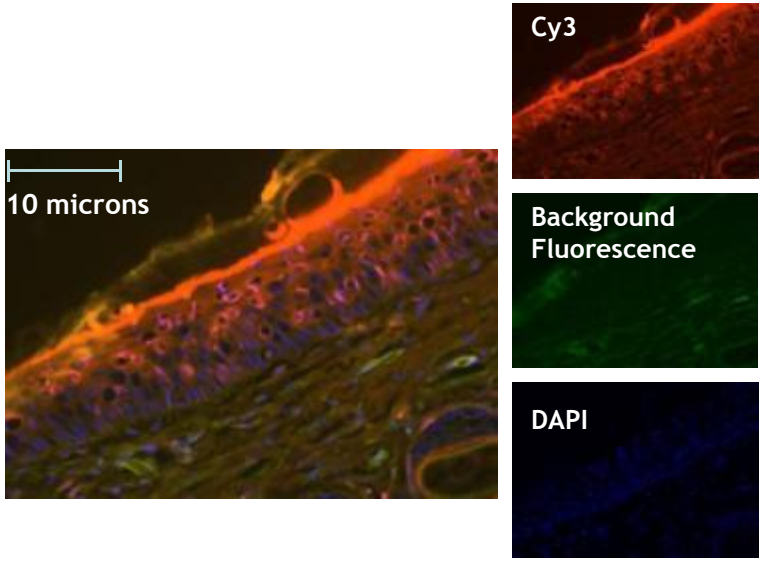
HAI titers following immunization with the surface ID device in NHP's

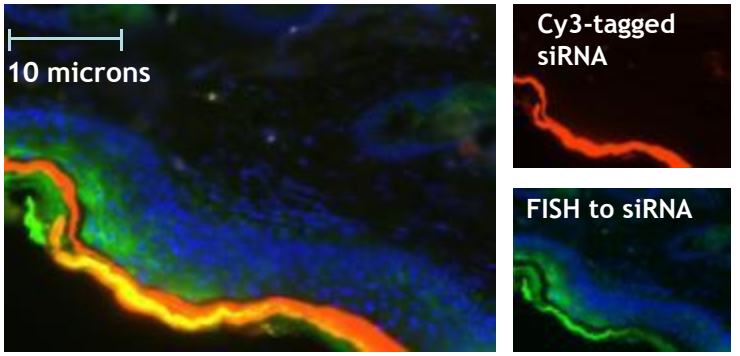


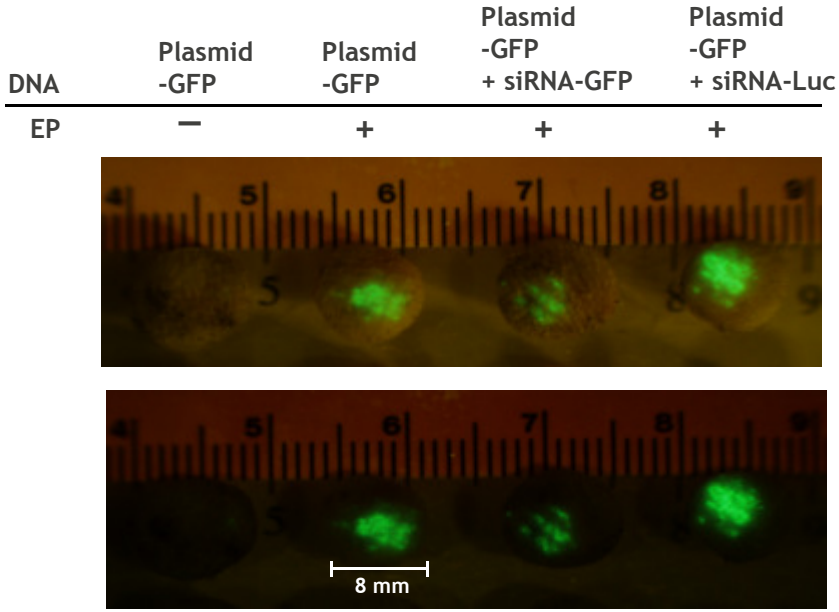
Percent survival following immunization with the surface ID device in mice

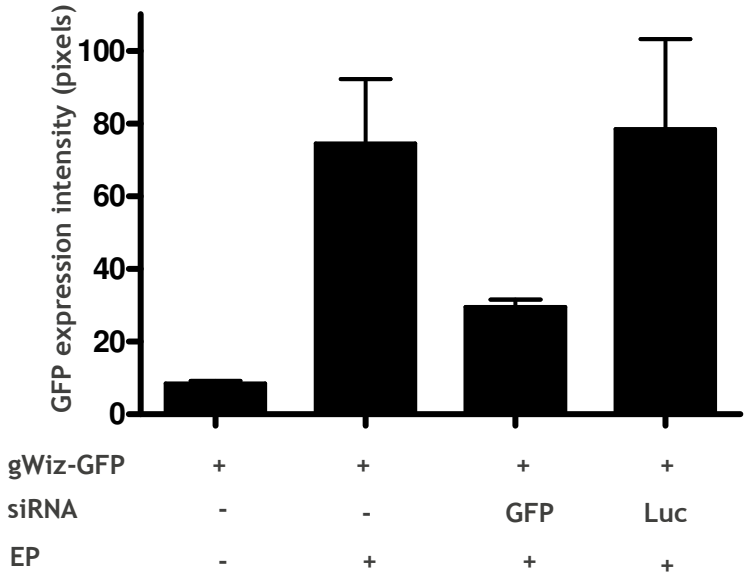


Not just plasmid DNA – Successful delivery of siRNA









Broderick *et al*, Molecular Therapy 2012

Some Issues of Conventional Vaccine Technologies

Conventional Vaccines

- Attenuation is an art form - ?
- Safety – Goldilocks paradox
- Atypical responses following vaccination (RSV, Measles)
- STEP: Serology issues not understood
- Manufacturing complexity
- Cell substrates (Egg limitations, Cell line contamination, etc)
- Raw materials
- Product Analytics - Complex
- Stability and Formulation
- Filling models – What is in the vial
- Building production plants at risk

Some Novel At Risk Populations

- Eczema
- Autoimmune Diseases (treated – TNF inhibitors etc.)
- Pregnancy
- Increased elderly population
- Elderly travelers (Unique)
- HIV +, Immune suppressed patients
- Transplant patients

Cancer Immune Therapies

- Older patients many vector immune (Ad, pox, many others)
- Poorer ability to control live replication
- Poorer responses to non live antigens

Development of new vaccine technologies (DNA) are an important driver of

Competitive Advantage!

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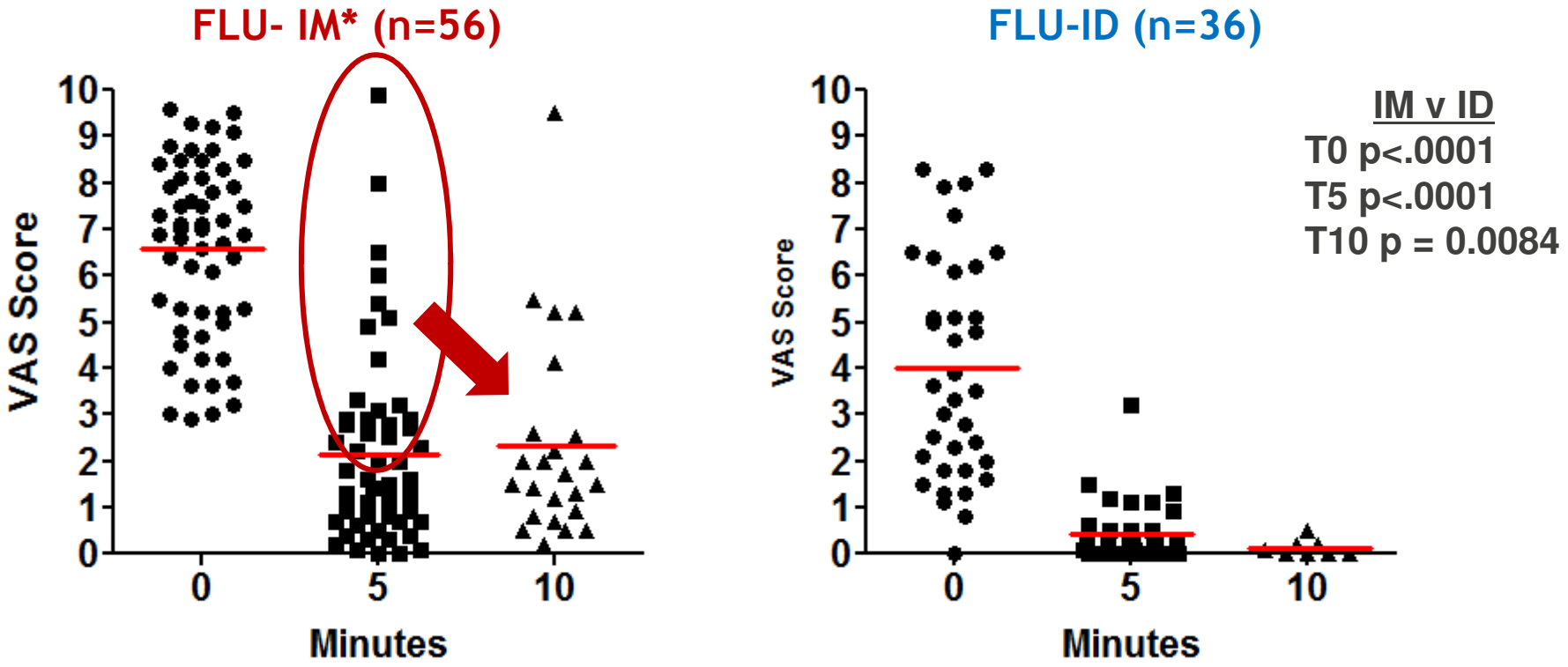
IM v. ID EP: Clinical Tolerability Data (FLU-001/002)

FLU study: Interim data from volunteers who received 2x IMEP Prime followed by 2x IDEP Boost



Inovio DNA-EP:

- Generally well tolerated
- No Grade 3 or 4 AEs/SAEs related to vaccine
- No biodistribution/integration concerns noted to-date