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# Rational design of a fully synthetic nanoparticle-based vaccine for smoking cessation

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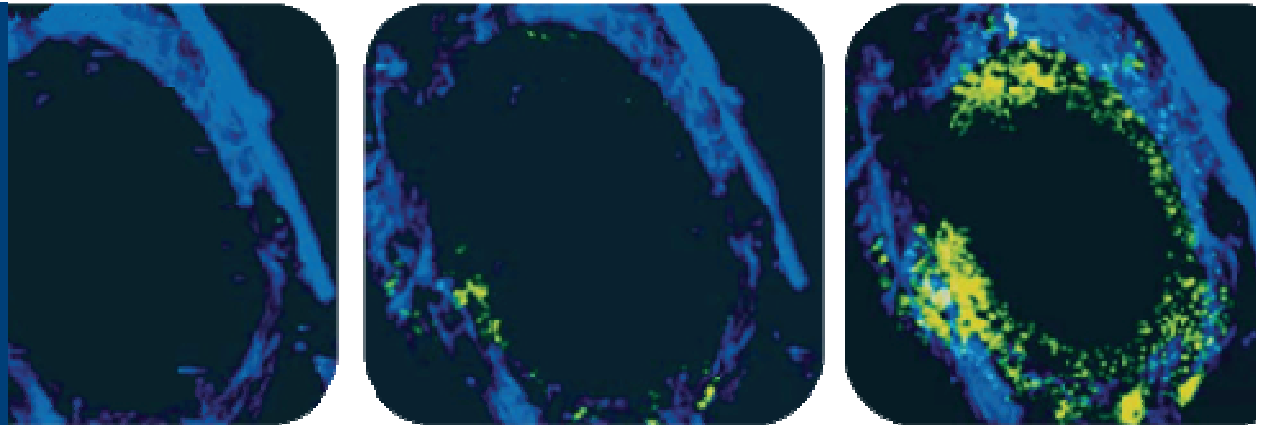
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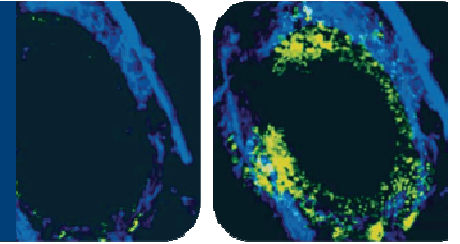
# Rational Design of Synthetic Vaccines

ECI Vaccine Technology  
Portugal  
May 2012



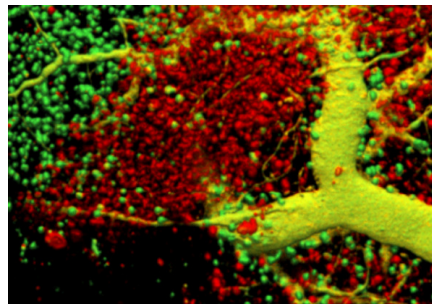
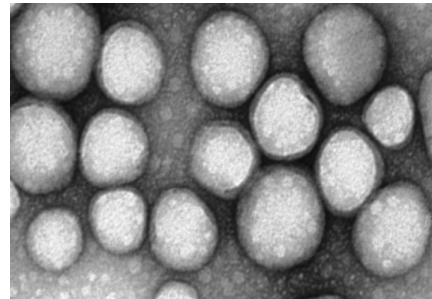
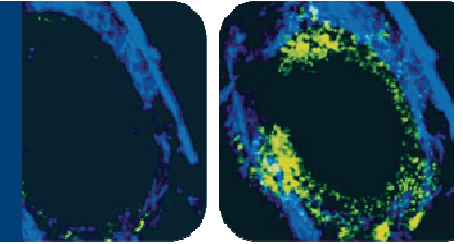
## Shaping the Immune Response

# Outline



- 1) Targeted Synthetic Vaccine Particles (tSVP)**
- 2) SEL-068 – Anti-nicotine vaccine for smoking cessation**

# The Intersection of Immunology and Nanotechnology



**Robert Langer, ScD**  
Institute Professor  
MIT



**Omid Farokhzad, MD**  
Associate Professor  
Harvard Medical  
School

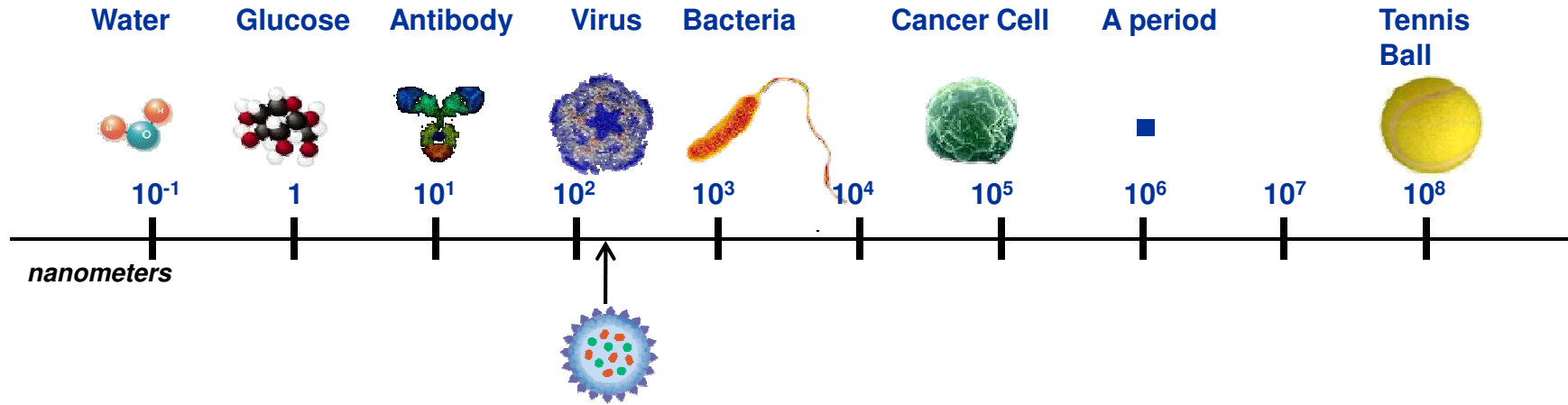
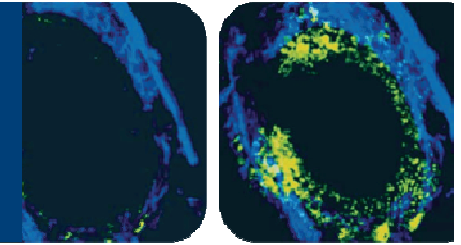


**Ulrich von Andrian,  
MD, PhD**  
Professor  
Harvard Medical  
School

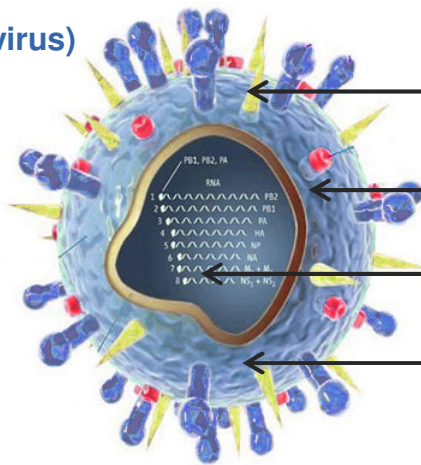
## Need for new vaccine technology

- Rapidly mutating pathogens (e.g. HIV, malaria)
- Immunosenescence
- Chronic infections
- Cancer
- Autoimmune diseases and allergies
- Other chronic diseases (e.g. Alzheimer's disease, cardiovascular disease, smoking cessation)

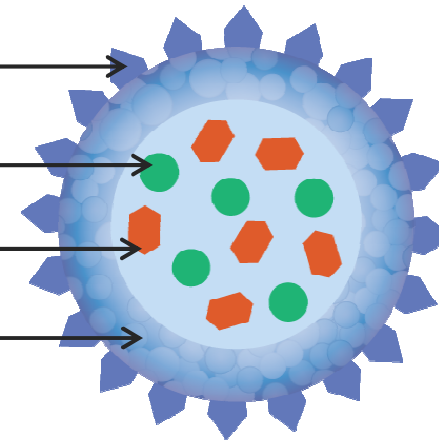
# Rational Design of *targeted* Synthetic Vaccine Particles (*tSVP*)



**Virus**  
(e.g. influenza virus)



***tSVP***



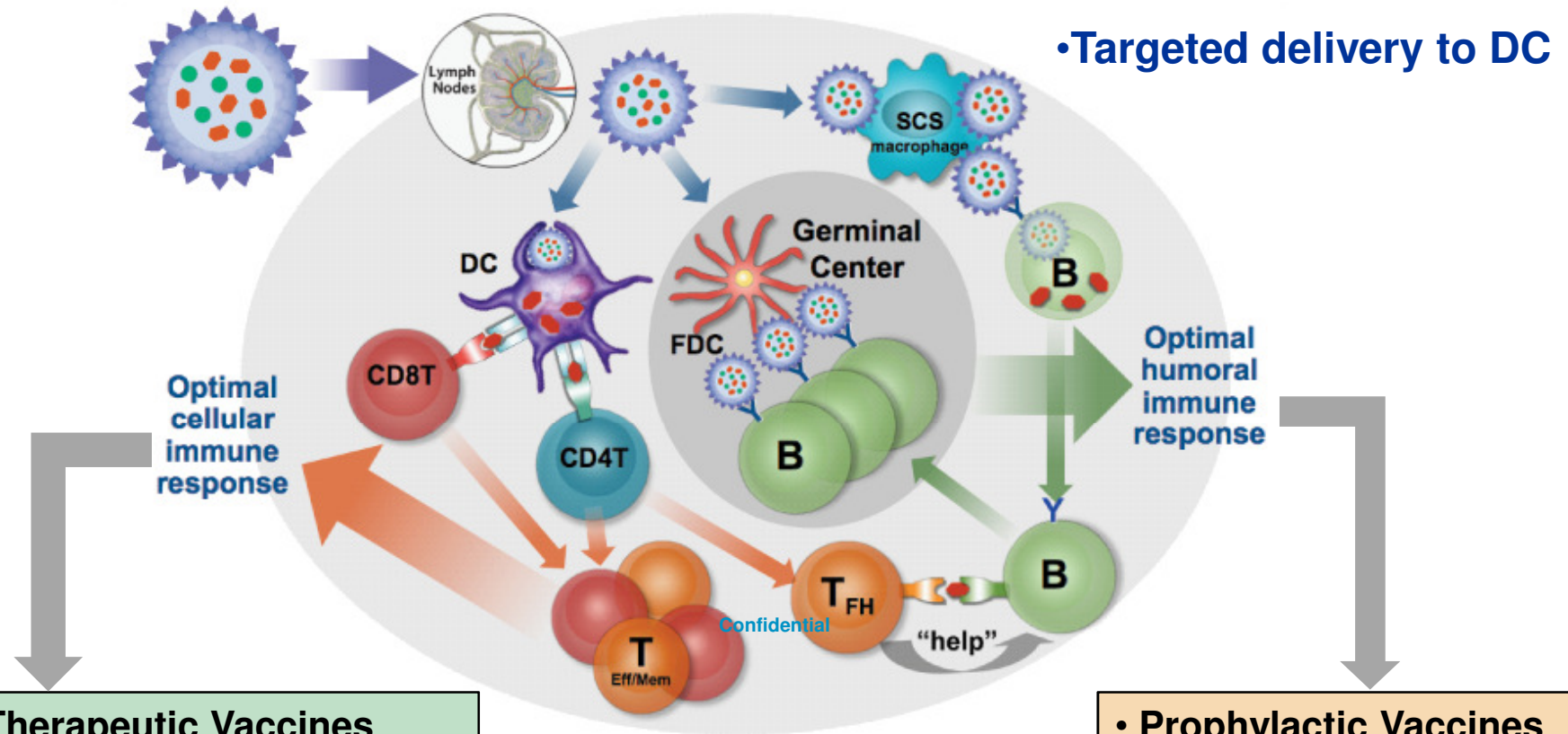
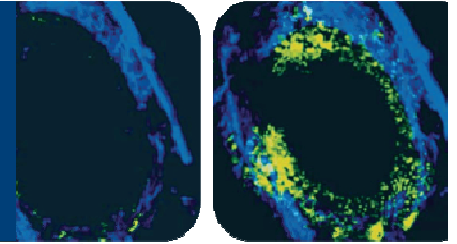
B-Cell Antigen

T-Cell Antigen

Adjuvant

Biocompatible Matrix

# Nanoparticles Enable Targeted Delivery of Immunological Instructions to the Lymph Node



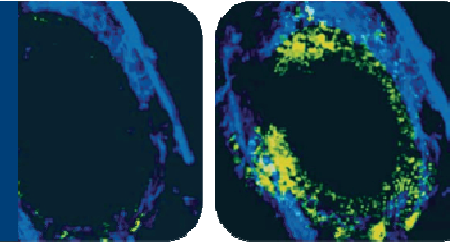
## • Therapeutic Vaccines

- Cancer
- HIV
- HCV
- Other chronic Infections

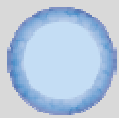
## • Prophylactic Vaccines

- Infectious diseases
- Therapeutic Vaccines
- Addiction
- Cancer

# Self-assembling Manufacturing Process of Synthetic Vaccines



## Components



PLGA



PEG



B antigen



Adjuvant



T antigen

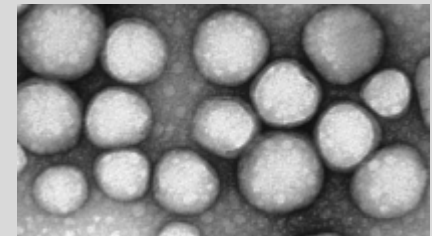
## Production



- Nanoparticle Formation Vessel for 10 g scale (~10,000 doses)
- Total batch time <10h (w/o drying and filling)

Self-assembly

## Finished Particles



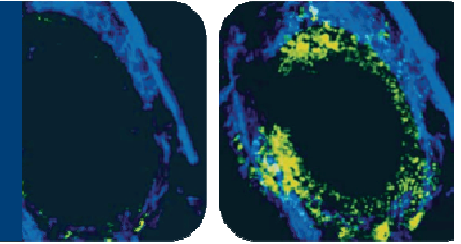
- High Batch consistency

## Advantages of synthetic tSVP production :

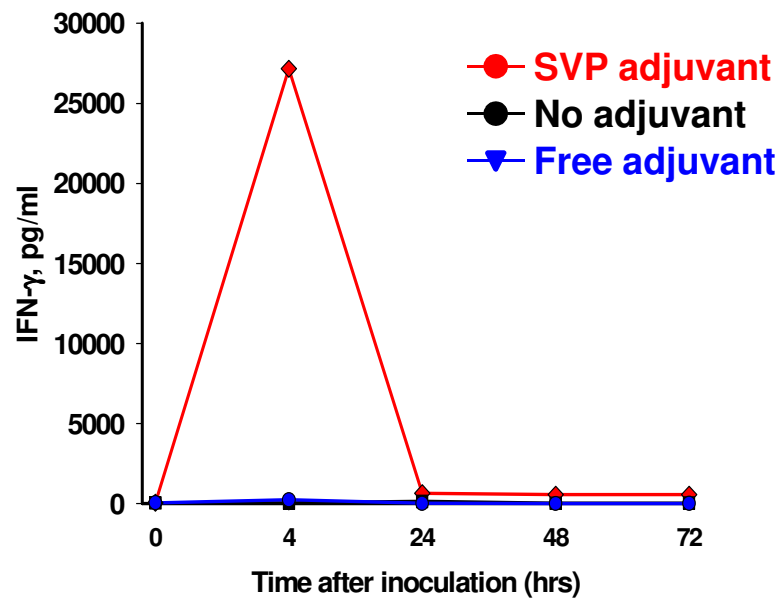
- Scalability
- Stable and Reproducible
- Fast to the clinic
- Cost efficient

**Successful GMP manufacturing demonstrated to support Ph 1 trial**

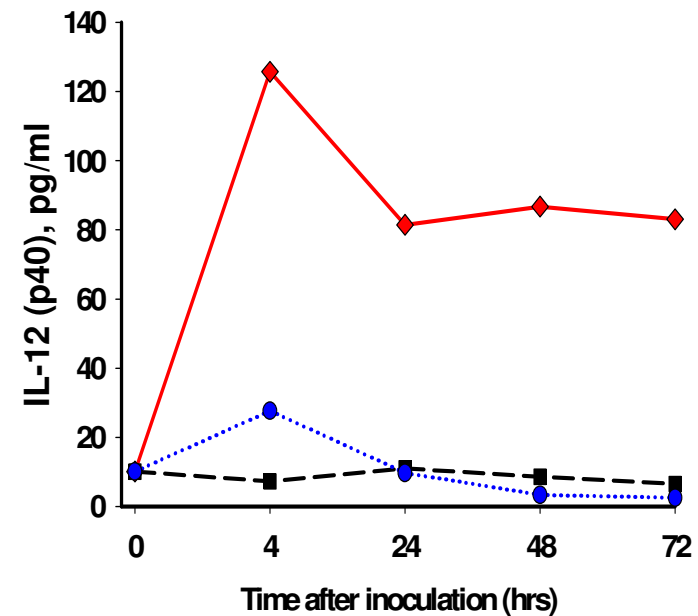
# tSVP-Encapsulated Adjuvant is Targeted to the Draining Lymph Node



## Lymph Node IFN- $\gamma$

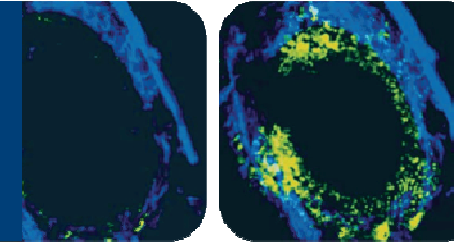


## Lymph Node IL-12(p40)

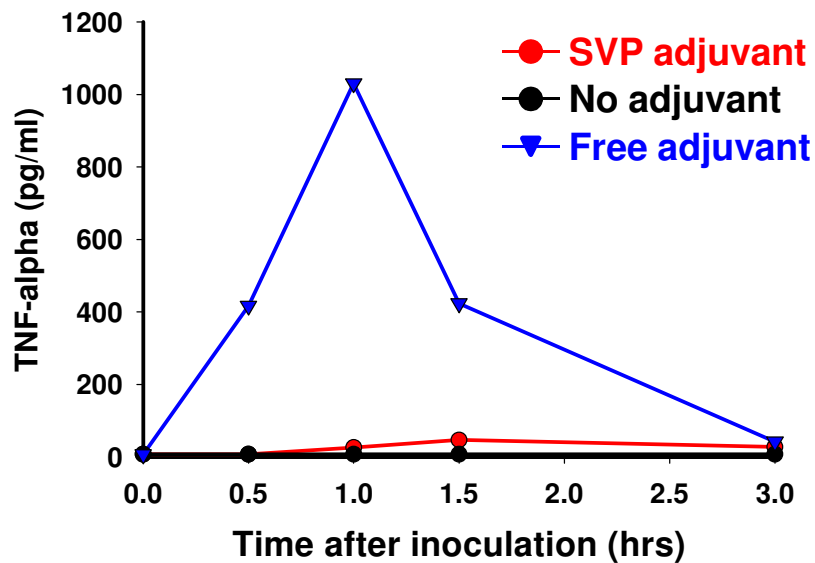




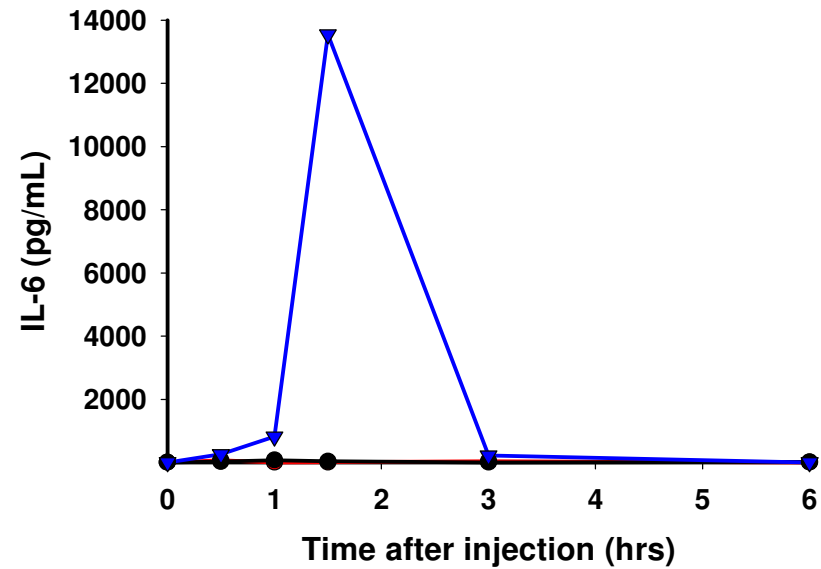
# tSVP-Encapsulated Adjuvant Minimizes Systemic Cytokine Production



## Plasma TNF- $\alpha$

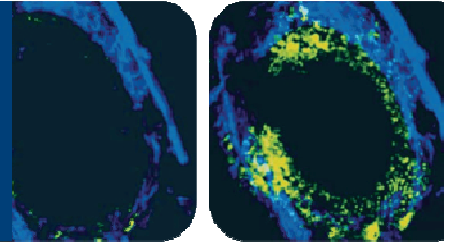


## Plasma IL-6



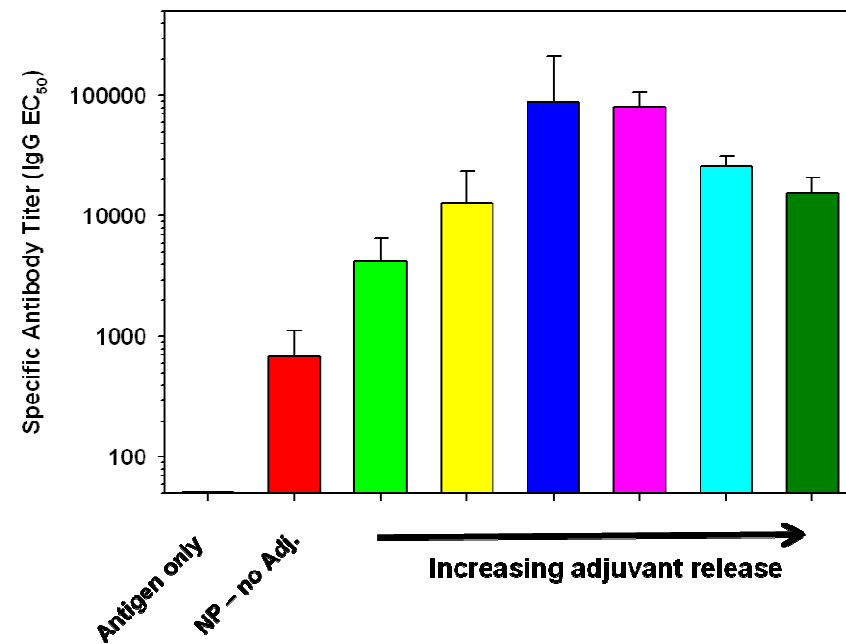
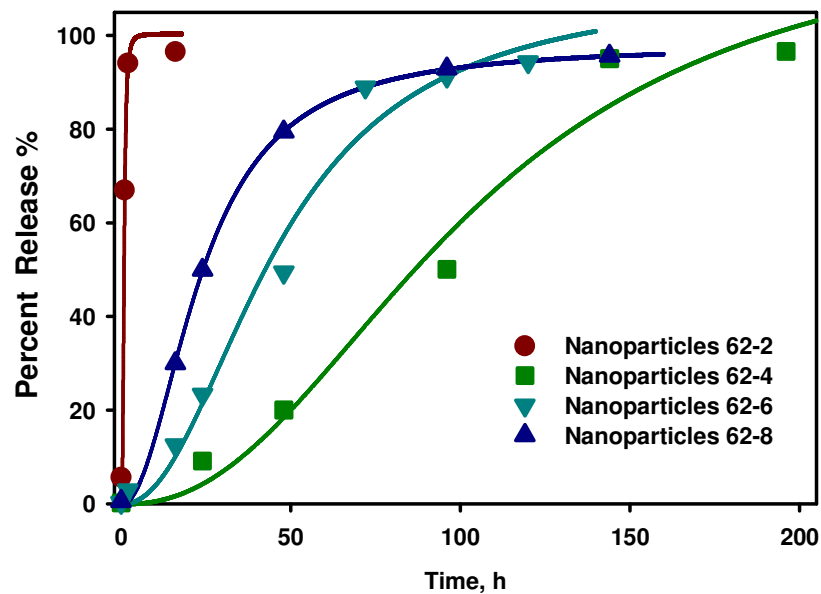
•tSVP encapsulation of TLR agonist minimizes systemic cytokine secretion

# Controlled Adjuvant Release



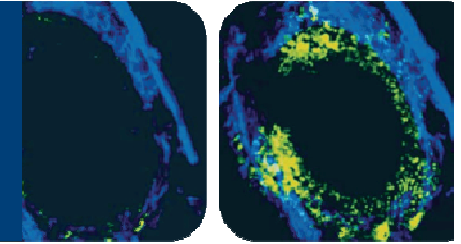
Adjuvant can be released at a wide range of targeted rates

Percent Adjuvant Release, 37 C



Ideal immune response is correlated with duration of TLR receptor stimulation

# Universal T-Help Antigen to Boost Response and Enable Universal Vaccines

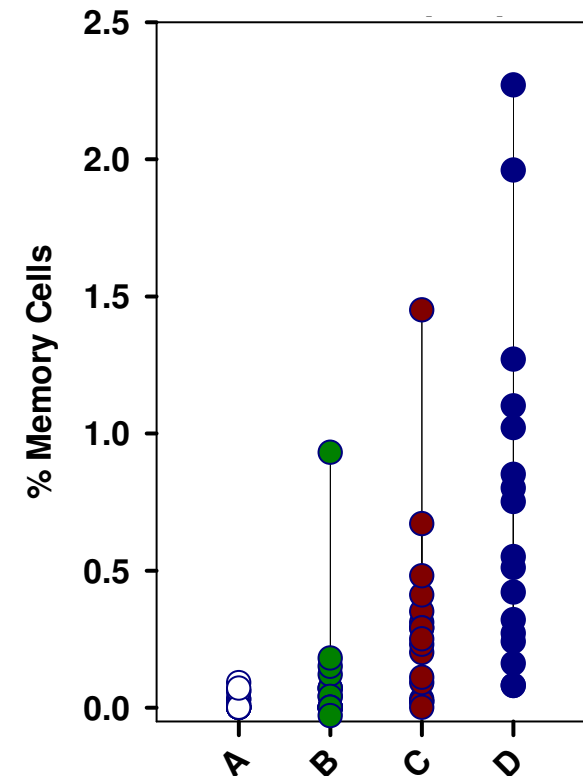


## Algorithm to identify promiscuous MHC class II-binding peptides

### Predicted crossreactivity

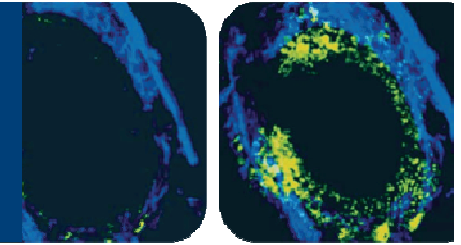
Allelic variant	Allele frequency	Peptide D
HLA-DRB1*0101	5.4	4.99
HLA-DRB1*0301	13.7	3.81
HLA-DRB1*0401	4.6	2.02
HLA-DRB1*0404	3.6	1.79
HLA-DRB1*0405	6.2	4.94
HLA-DRB1*0701	13.5	0.5
HLA-DRB1*0802	4.9	0.7
HLA-DRB1*0901	6.2	0.36
HLA-DRB1*1101	11.8	3.13
HLA-DRB1*1302	7.7	1.7
HLA-DRB1*1501	12.2	3.02

### Human PBMC recall response

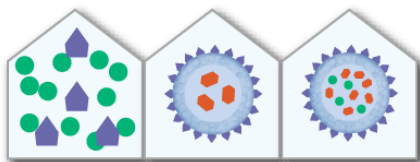
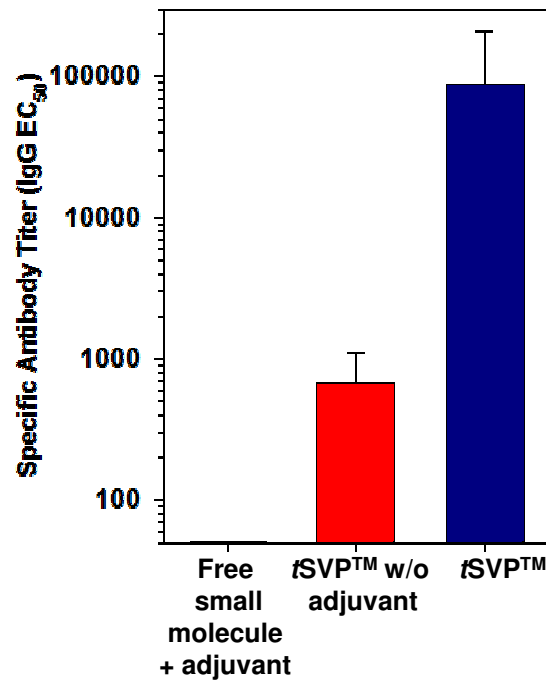


Recall response to peptide D observed in 50 of 50 human donors

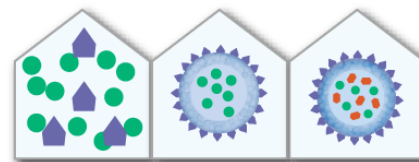
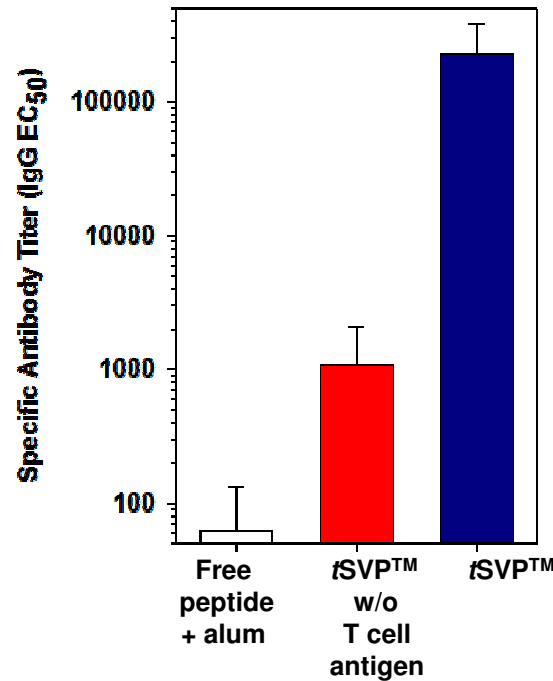
# tSVP Induction of Robust Antibody Responses to Wide Range of Antigens



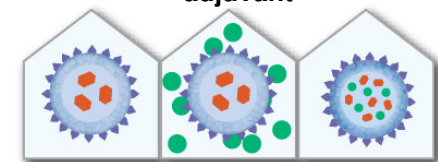
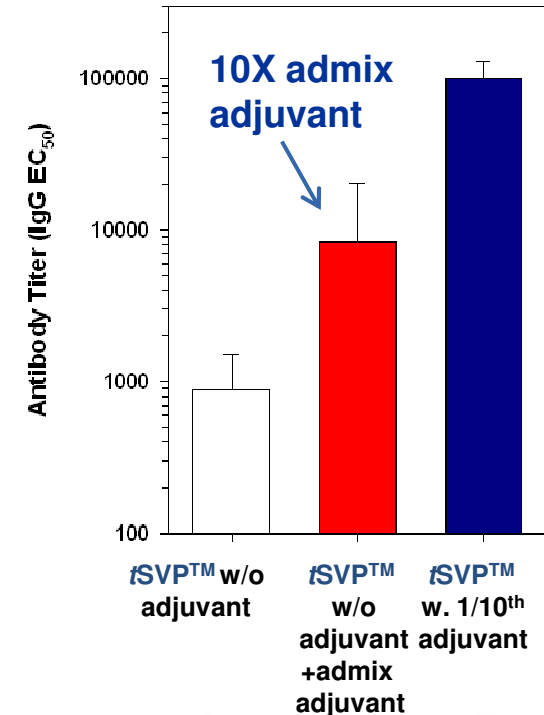
## Small Molecule Antigen\*



## Viral Peptide Antigen\*

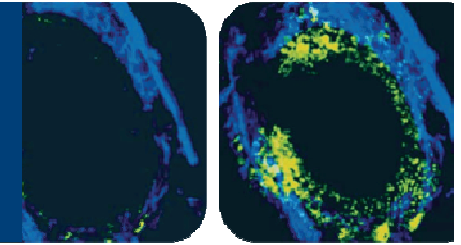


## Adjuvant Sparing with Protein Antigen\*

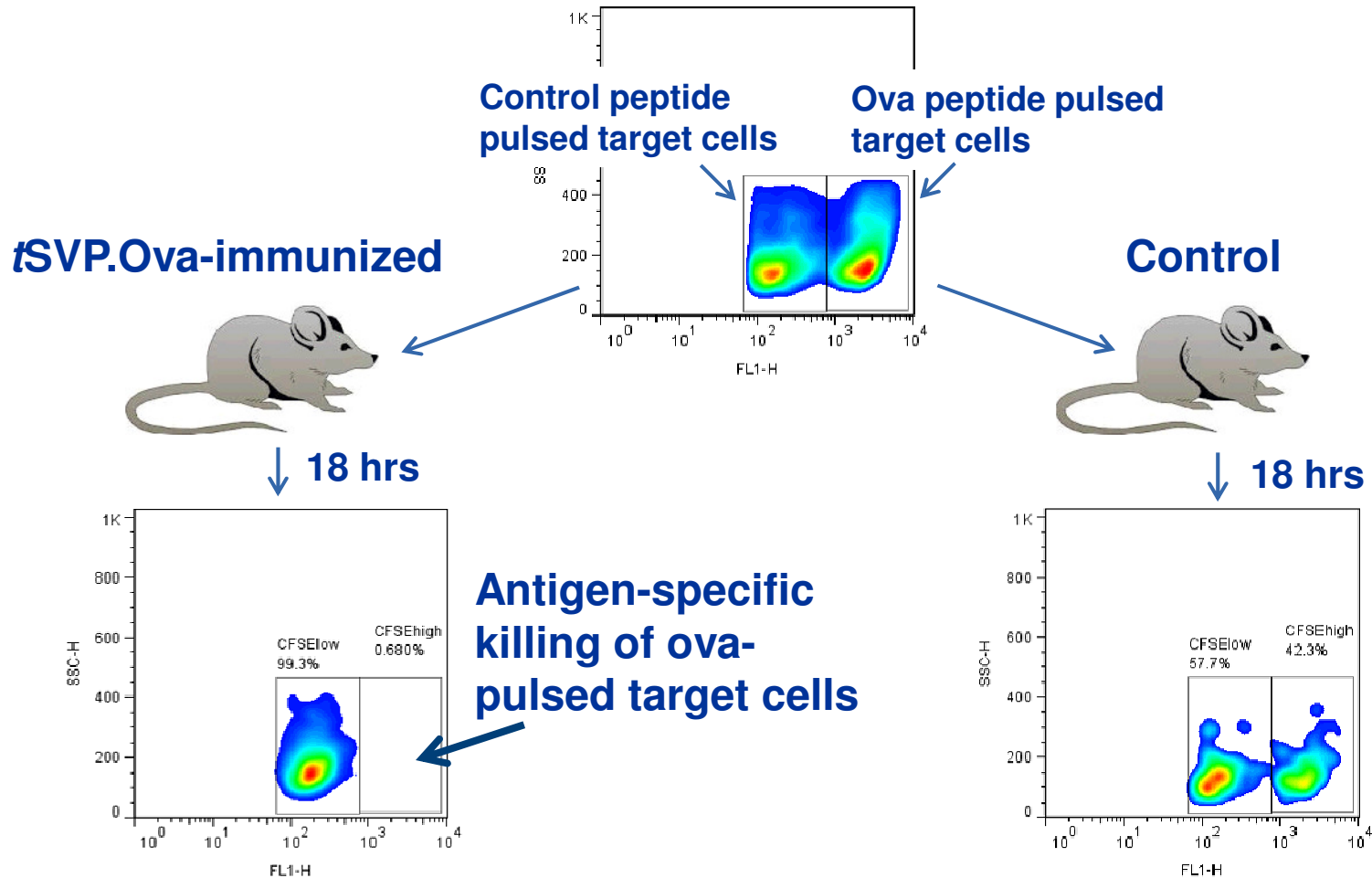


\* Subcutaneous injection in mice

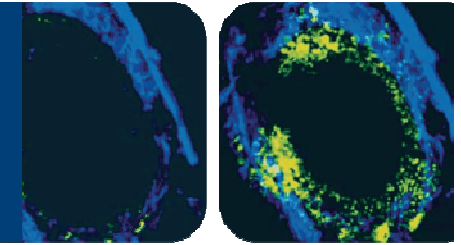
# tSVP Induction of In vivo CTL Responses



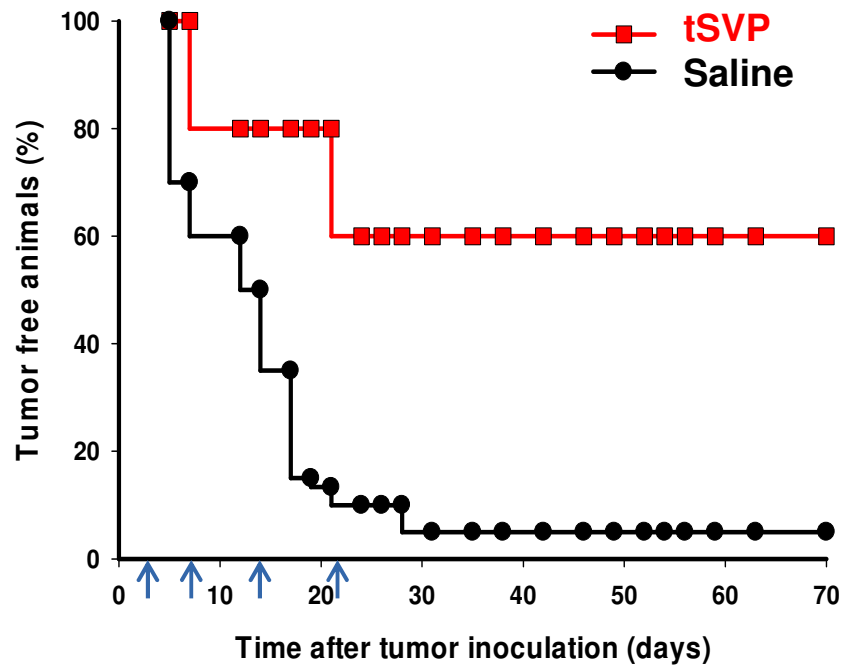
## Fluorescent-labeled target cells



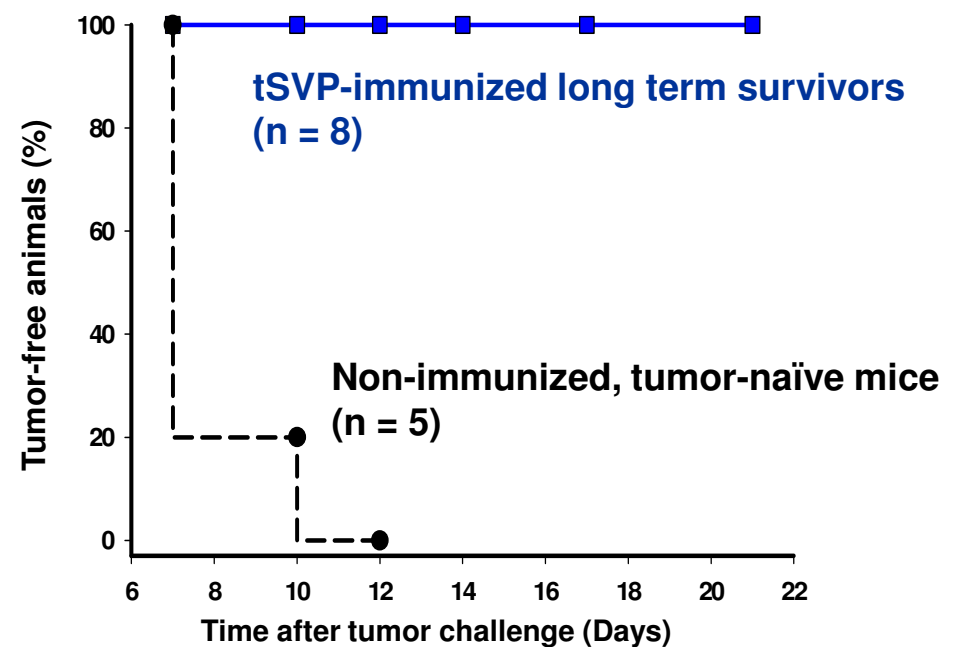
# Efficacy and Memory in E.G7 Tumor Model



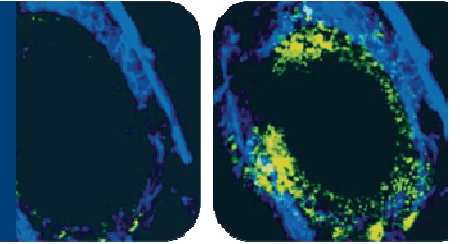
## Therapeutic Dosing Regimen



## Survivors re-challenged with tumor 2-3 months later



# Outline



- 1) Targeted Synthetic Vaccine Particles (tSVP)
- 2) **SEL-068 – Anti-nicotine vaccine for smoking cessation**

# Smoking Cessation



## High prevalence with worldwide smoking population >1B

- 46 million adult smokers in USA – 70% desire to quit (CDC)
- Smoking costs the US \$97.6 billion/yr in direct healthcare costs
- 50% of smokers live in BRIC countries

## High remaining unmet medical need

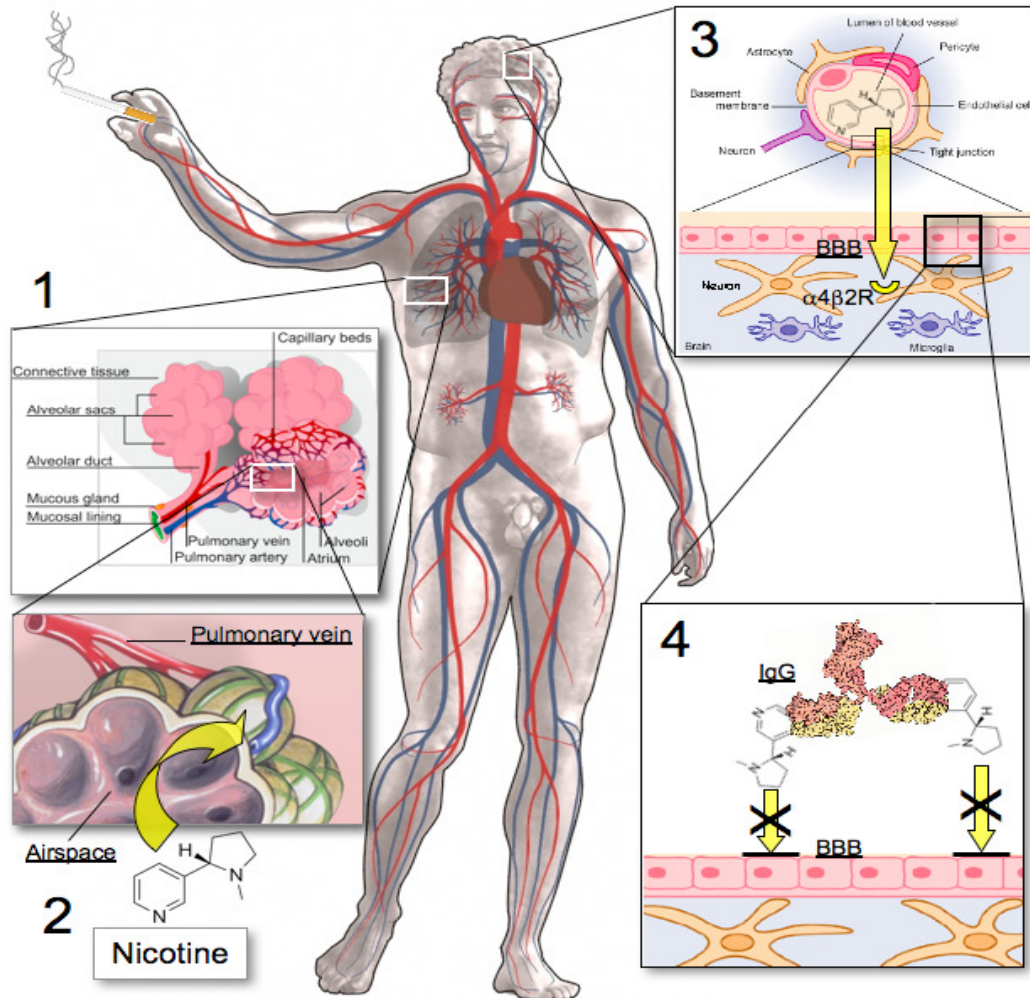
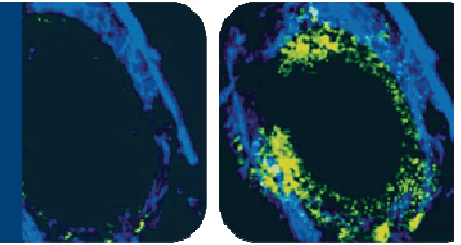
- 12 months abstinence rates for current treatment just over 20%
- High relapse risks

## Smoking cessation is a worldwide priority for health care providers

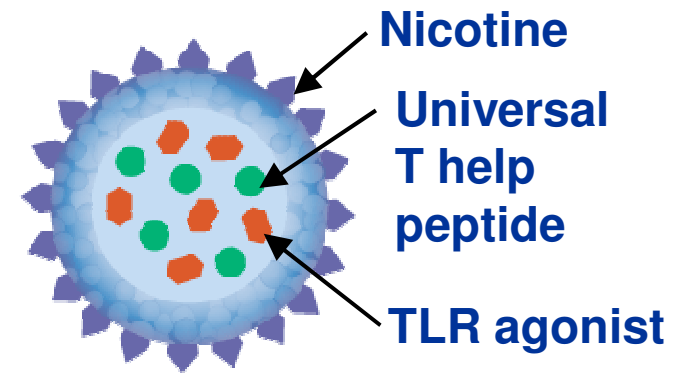
- Fast track status for smoking cessation products in the US
- Favorable health economics for smoking cessation products (costs per year of life saved)
- High market growth from current \$3.8B to over \$5.0B in next 5 years



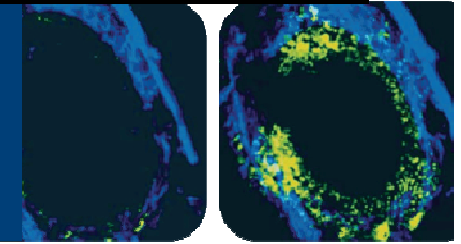
# Nicotine Vaccine for Smoking Cessation and Relapse Prevention (SEL-068)



Nicotine vaccine creates nicotine specific antibodies that bind free nicotine and prevent it from crossing the blood-brain barrier

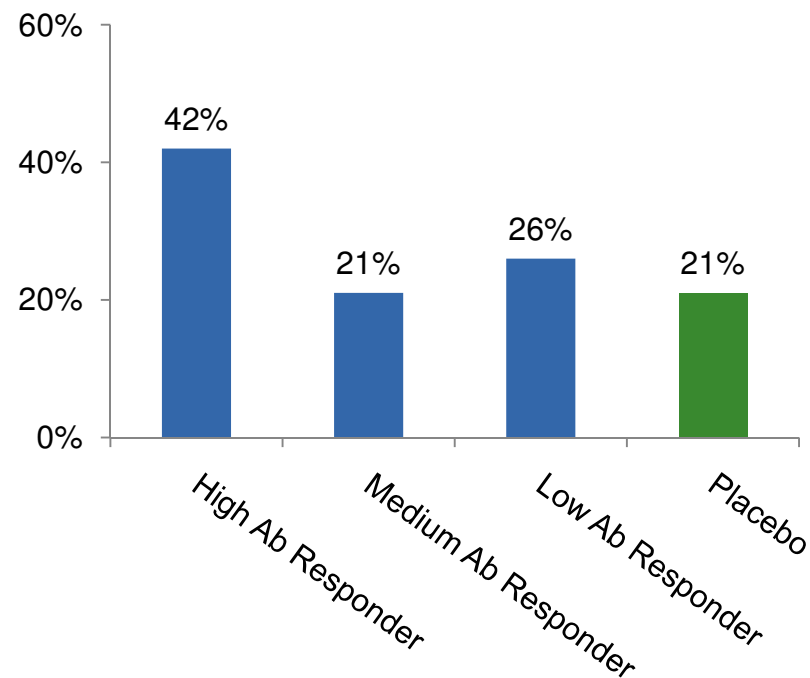


# Prior Clinical Studies Validate the Vaccine Approach to Smoking Cessation



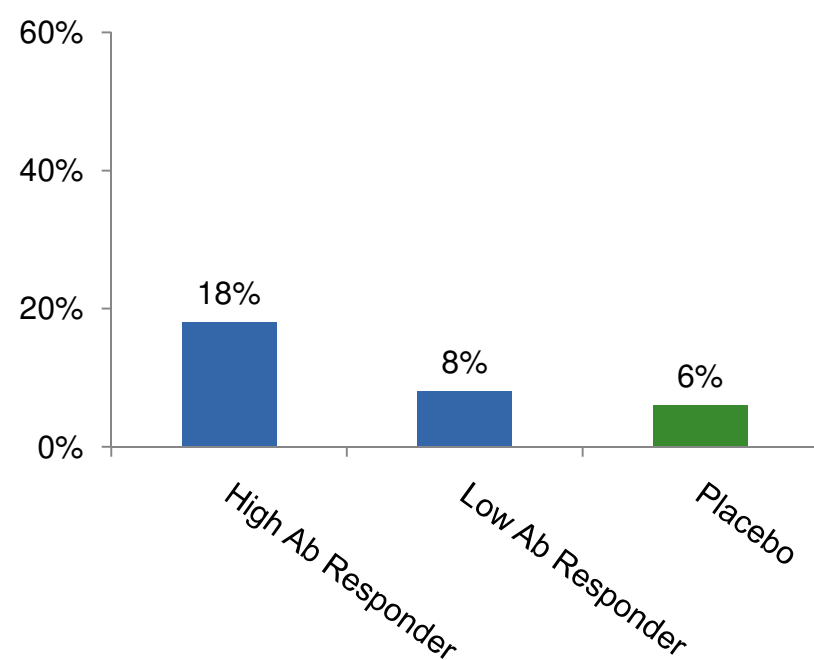
## Nic002 – Cytos (Phase 2)\*

% continuous abstinence (week 8-52)



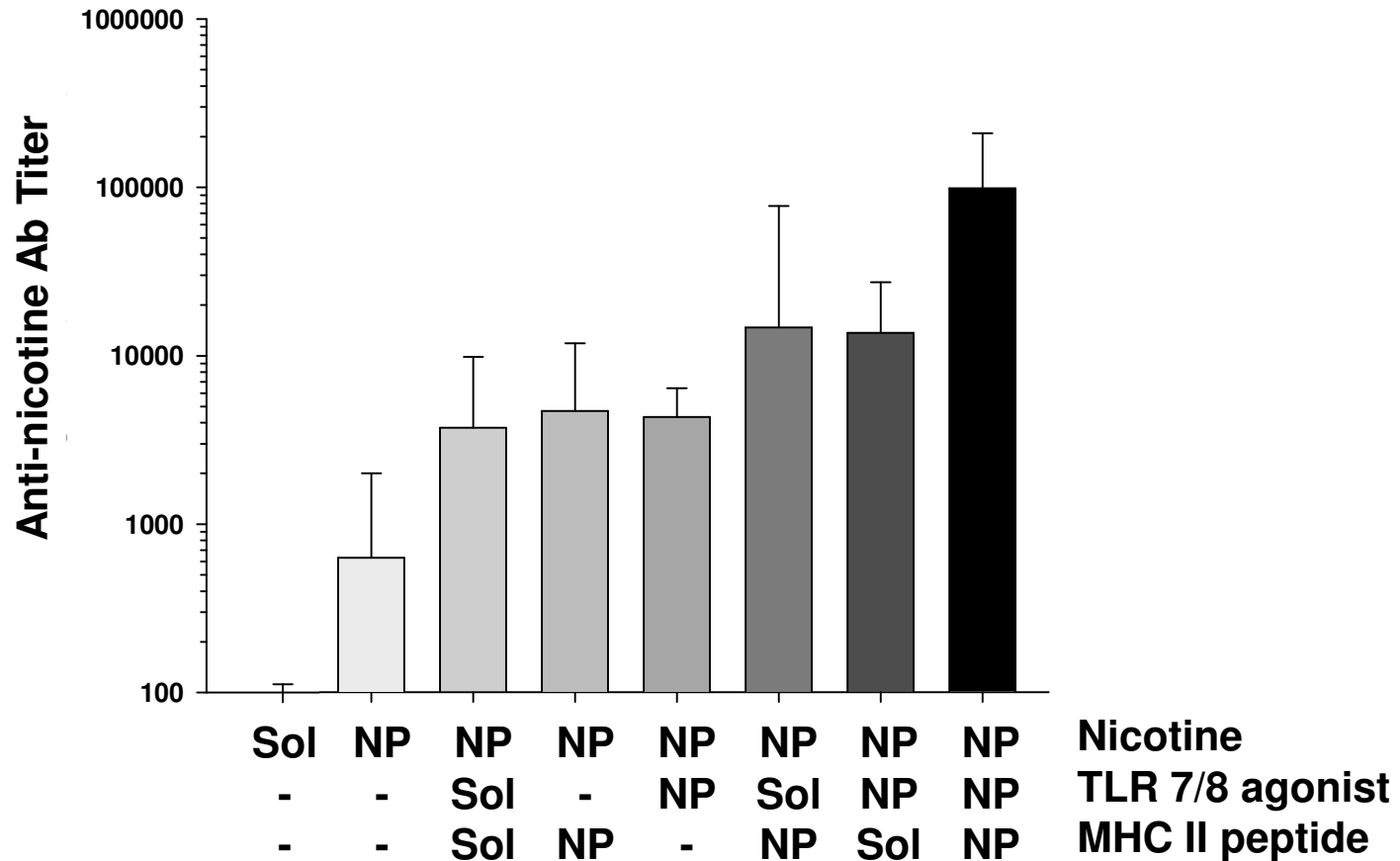
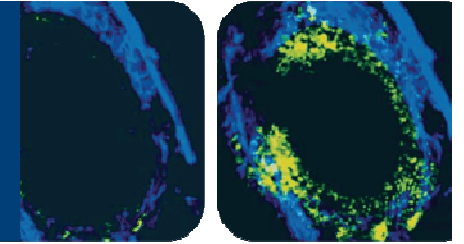
## NicVax - Nabi (Phase 2)\*\*

% continuous abstinence (week 8-52)

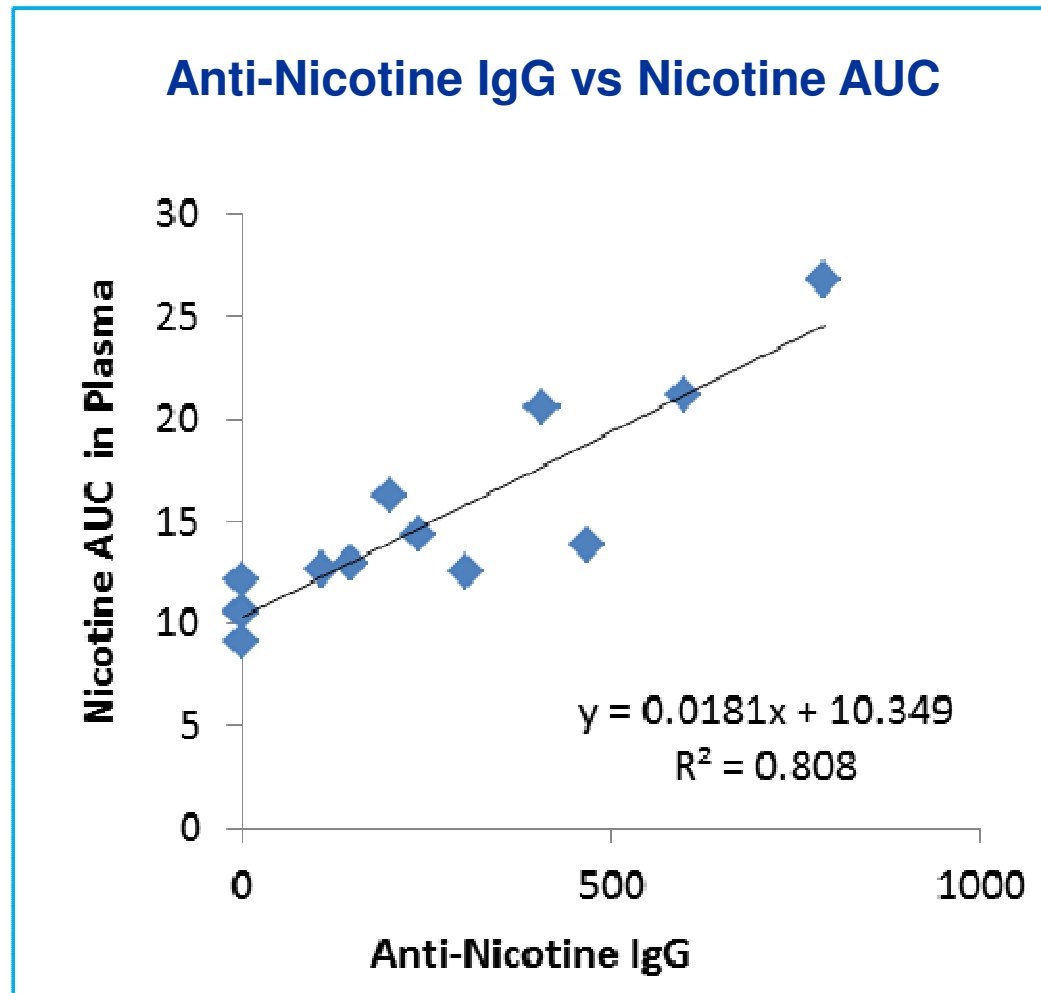
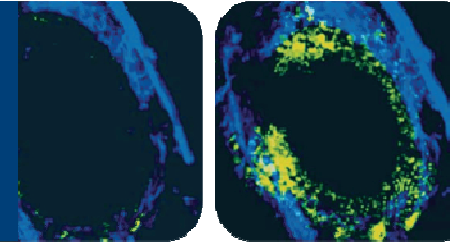


**Two independent studies indicate that an effective vaccine for smoking cessation can be achieved if antibody titers can be increased across a greater percentage of the population**

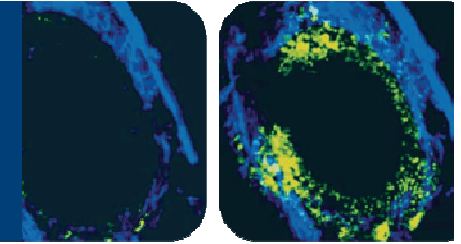
# Optimization of an Anti-Nicotine Nanoparticle



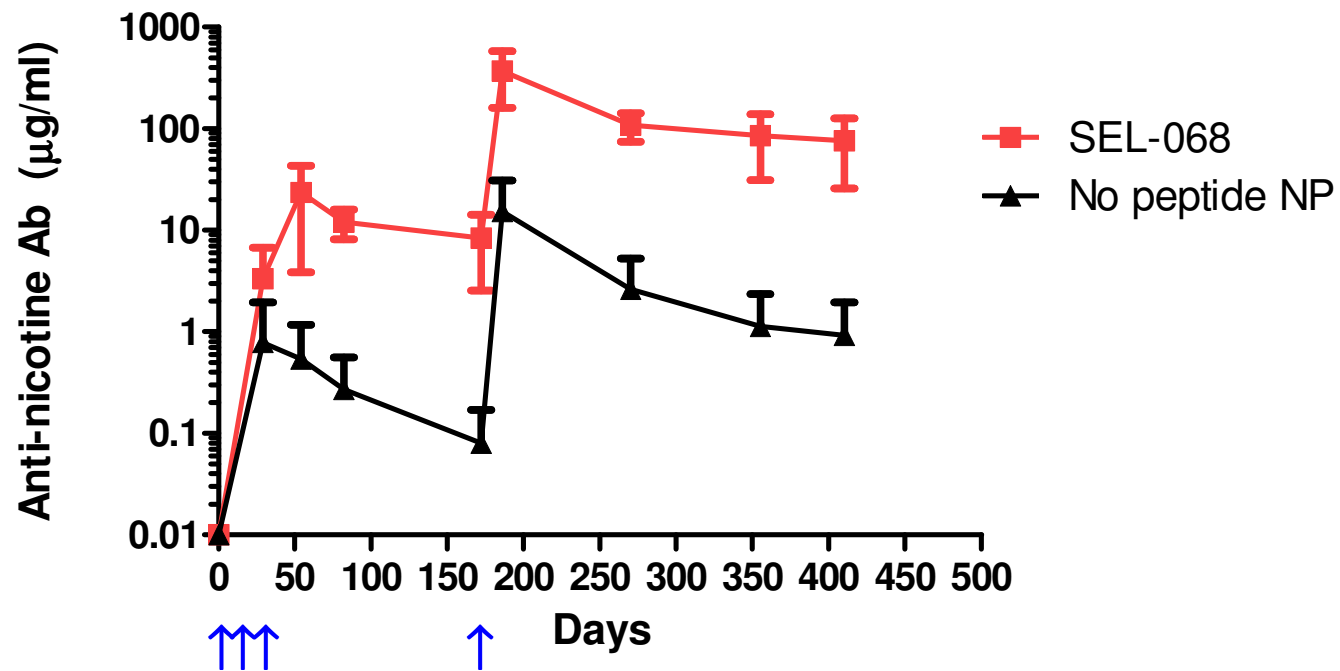
# Anti-Nicotine Antibody vs Nicotine AUC



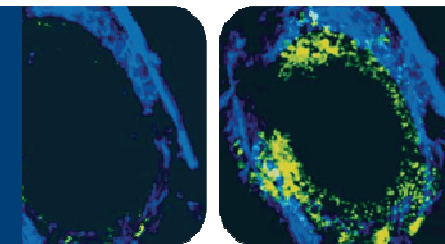
# Persistence of Anti-Nicotine Antibodies



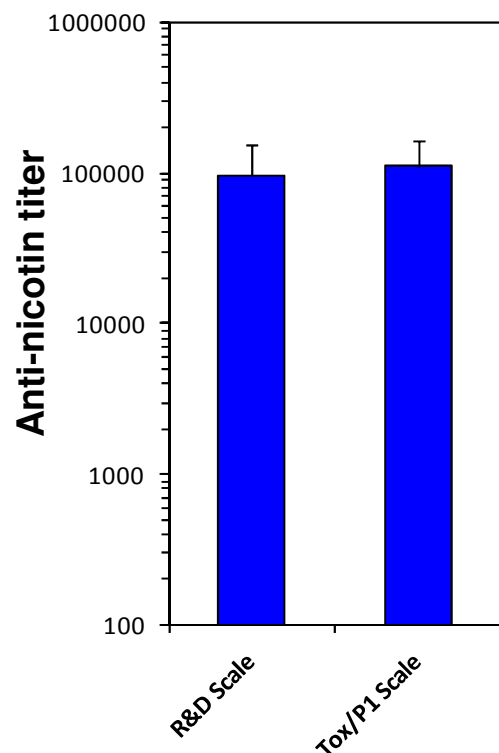
Mice immunized on Days 0, 14, 28, and 180



# SEL-068: High Antibody Titers Across Mice and Non-Human Primates

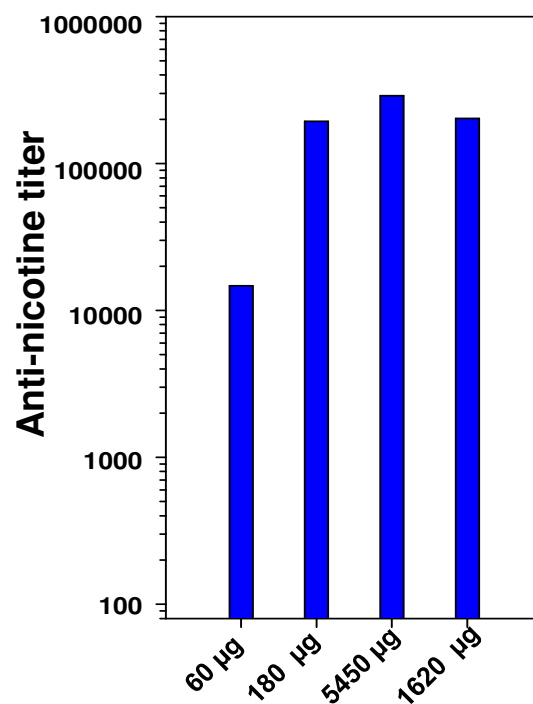


**Mice**  
(n=5 per group)



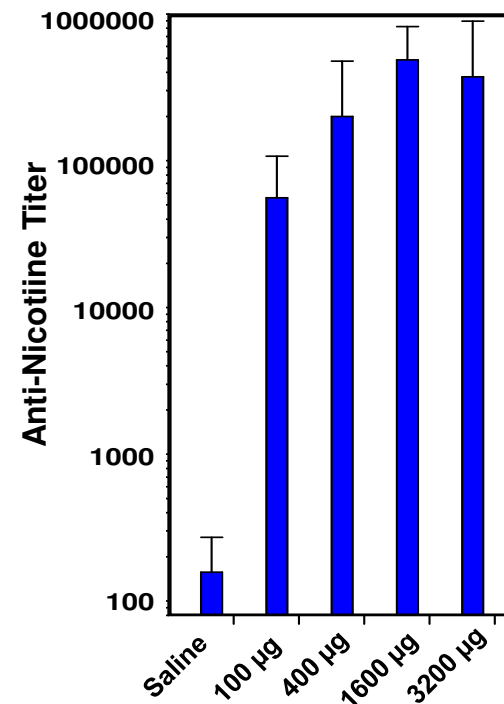
- R&D and Tox Scale
- d0, d14, d28
- Antibody titers at d40

**Rhesus Monkeys**  
(n=4, 1 per group)



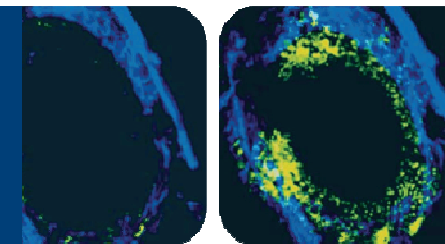
- R&D Scale
- d0, d28, d56
- Antibody titers at d70

**Cynomolgus Monkeys**  
(n=50, 10 per group)



- Tox scale =P1 scale
- d1, d29, d57
- Antibody titers at d85

# High Specificity for Nicotine



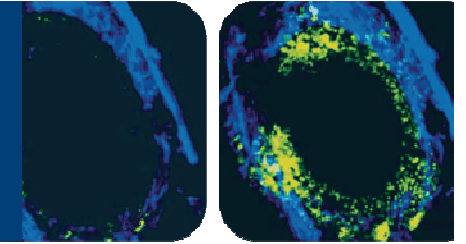
## Preliminary data

Compound	% Cross-reactivity
Nicotine	100
Cotinine	3.7
Nornicotine	7.6
Nicotine-N-Oxide	<1
Norcotinine	<1
Cotinine-N-Oxide	<1
Acetylcholine	<1
Buspirone HCL	<1
Bupropion HCl	<1

Compound	% Cross-reactivity
Cytisine	<1
Iproniazid phosphate	<1
Mecamylamine	<1
Acetylcholine	<1
Choline	<1
Niacin	<1
Serotonin	<1
Dopamine	<1
$\gamma$ -Aminobutyric acid (GABA)	<1

- Specificity determined by competition ELISA to immobilized poly L-lysine-nicotine
- Percent crossreactivity determined as described in Pentel et al., JPET, 2006, 317: 660-666

# Summary



## **tSVP Platform**

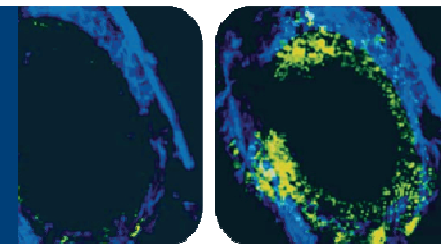
- **Self-assembling, biocompatible nanoparticles**
- **Directed delivery of TLR agonists to lymph node**
- **Universal T cell help peptide**
- **High antibody titers to poorly immunogenic antigens**
- **Efficient in vivo induction of CTL activity**
- **Antigen-specific immune tolerance**

## **SEL-068 Anti-nicotine vaccine**

- **Dose-dependent anti-nicotine response**
- **High titers in mice and two species of non-human primates**
- **Long term persistence of titers**
- **GLP tox study in NHP shows no evidence of systemic toxicities**
- **Successful GMP manufacturing and initiation of Ph 1**



# SEL-068 Product Development Timeline



• Selecta begins operations	Fall, 2008	} Start of program to first subject dosed < 3 years
• Nicotine program initiated	2009	
• >100 formulations made and tested	2009-2010	
• Clinical Candidate selected	Q4 2010	
• GLP toxicology study in NHP initiated	Feb, 2011	
• GLP Tox complete, no systemic findings	Aug, 2011	
• GMP supplies released	Aug, 2011	
• Phase 1 Clinical trial initiated	Nov, 2011	

**Selecta self-assembling, synthetic nanoparticle platform enables rapid iterative optimization of development candidates and scale up to GMP**