Cochleates:

A Formulation and Delivery Platform Technology

BioDelivery Sciences International, Inc.

Overview

- Founded 1995 – University Research
- Publicly traded since June 2002 (NASDAQ: BDSI)
- Patented nanocrystal technology – Formulation and Delivery
- Broad based, unique, powerful enabling platform technology
- Dominant, worldwide, proprietary intellectual property position

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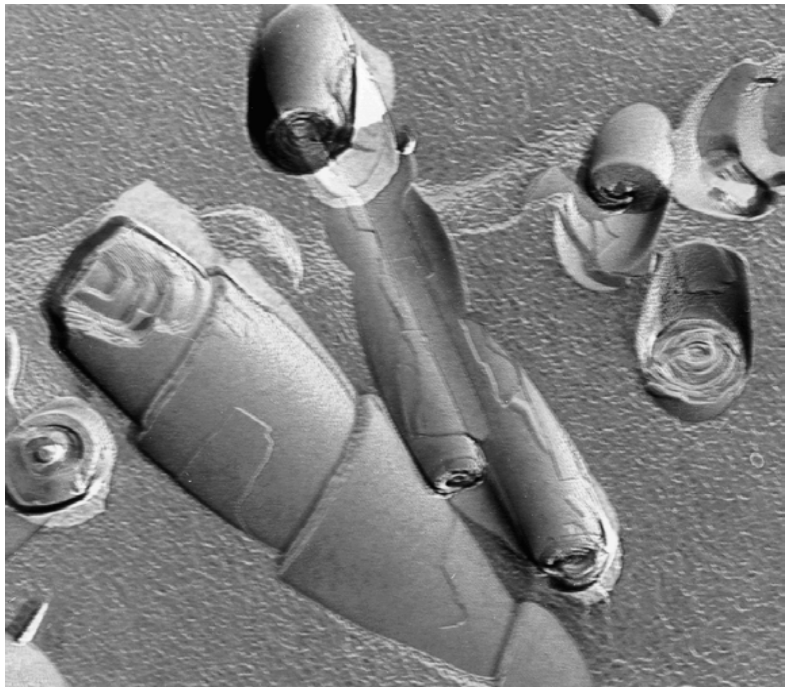
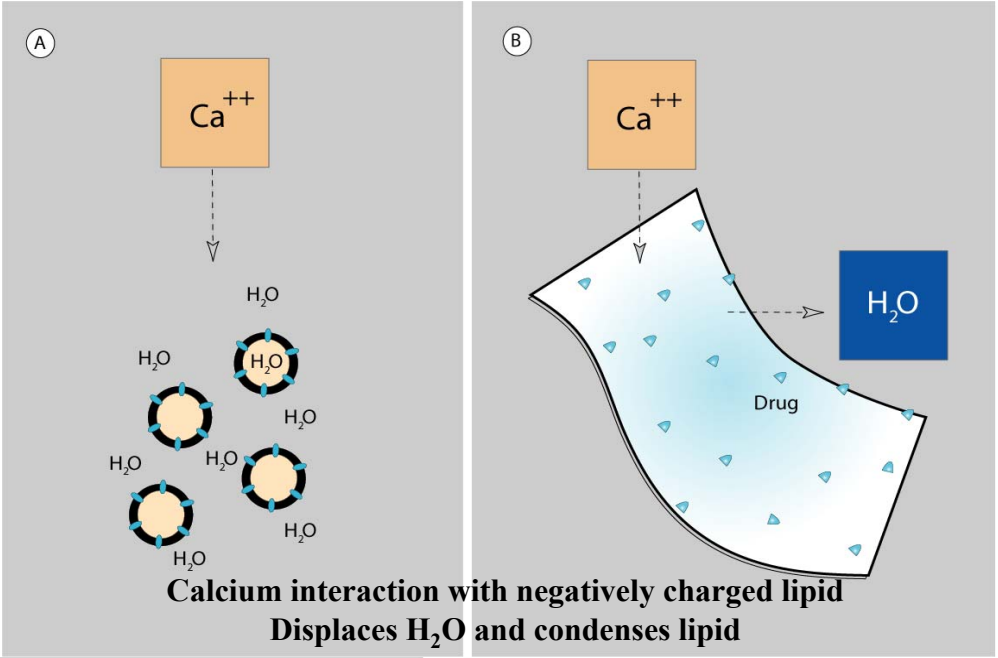
Enabling Platform Technology – Cochleate Delivery Vehicles



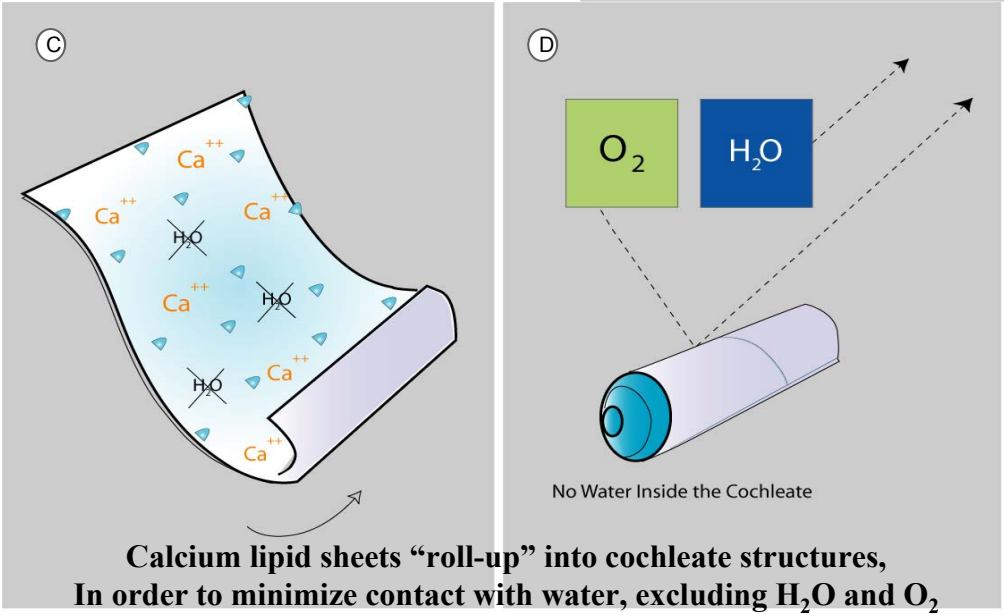
- Stable, phospholipid-calcium precipitates
- Self-assembling crystalline units
- Multilayered structure, containing little or no internal aqueous space
- Resistant to degradation in GI tract
- Increases Processing and Shelf Life Stability
- Composed of naturally occurring materials
- Very inexpensive cost of goods and manufacturing
- Delivery vehicle drugs, proteins, peptides and DNA

How Cochleates Nanoencapsulate Drugs

Calcium Interaction with Negatively Charged Lipid



Calcium interaction with negatively charged lipid
Displaces H_2O and condenses lipid



Calcium lipid sheets "roll-up" into cochleate structures,
In order to minimize contact with water, excluding H_2O and O_2

Formation of Stable Drug-Cochleate Nano Crystal

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FDA-Approved Phosphatidylserine Health Claims

The Food and Drug Administration (FDA) has authorized two health claims for phosphatidylserine (PS)

5 million Americans, including a large percentage of the elderly, have some form of cognitive dysfunction or dementia

"Phosphatidylserine (PS) may reduce the risk of cognitive dysfunction in the elderly."

"Phosphatidylserine (PS) may reduce the risk of dementia in the elderly."

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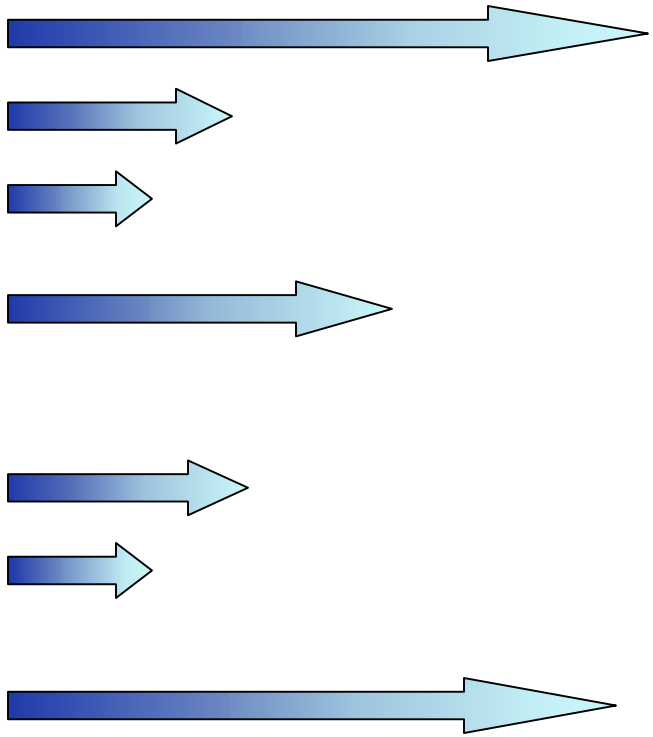
Potential Product Pipeline - Status:

Category	Development	Status			
		Pre-Clinical		Scale-Up/GMP	IND
		In Vitro	*In Vivo*		
Antimicrobials					
Amphoterricin B	*BDSI*				
Antifungal	*Partner/ Evaluation*				
Antibacterial	*BDSI*				
Anti-Inflammatories	*BDSI*				
Anti-Tumors					
Drugs	*Partners/License*				
Therapeutic Oligonucleotides					
Micronutrients	*Partner/ Evaluation*				



COCHLEATES REPRESENT A POWERFUL VACCINE FORMULATION AND DELIVERY SYSTEM

The intrinsic properties of cochleates lead to advantages in the important areas of:

- **Safety: Non-toxic, non-infectious, non-inflammatory, biodegradable**
- **Stability: Proteins, Peptides, DNA; as suspension or powder; No cold chain**
- **Delivery: Accumulated by antigen presenting cells**
- **Efficacy: Neutralizing antibody, Th1 and Th2 help, Cytotoxic T cells, protection from mucosal and parenteral challenge.**

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The intrinsic properties of cochleates lead to advantages in the important areas of:

- **Immune response targeting: specific antigens and adjuvants**
- **Multicomponent vaccines: : mix proteins, peptides and DNA, from multiple infectious agents**
- **Routes of administration: injection or mucosal (oral and intranasal)**
- **Generation of mucosal immunity: Antibody and Cellular**

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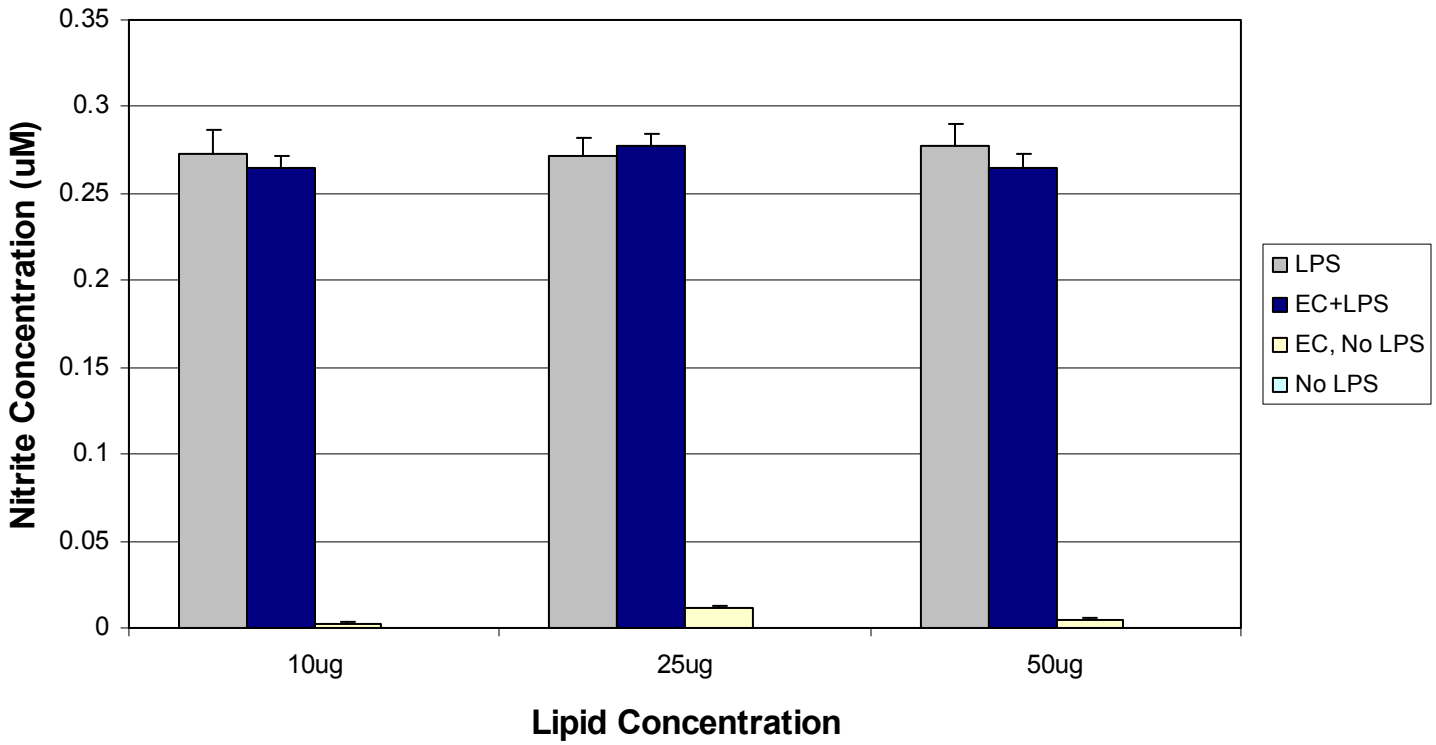
Cochleates are Immunologically Inert:

They Neither Activate Nor Inhibit Macrophage Activation.



Activation State of J774A.1 Macrophages

After Administration of Empty Cochleates

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Protein Cochleates

Influenza Glycoproteins

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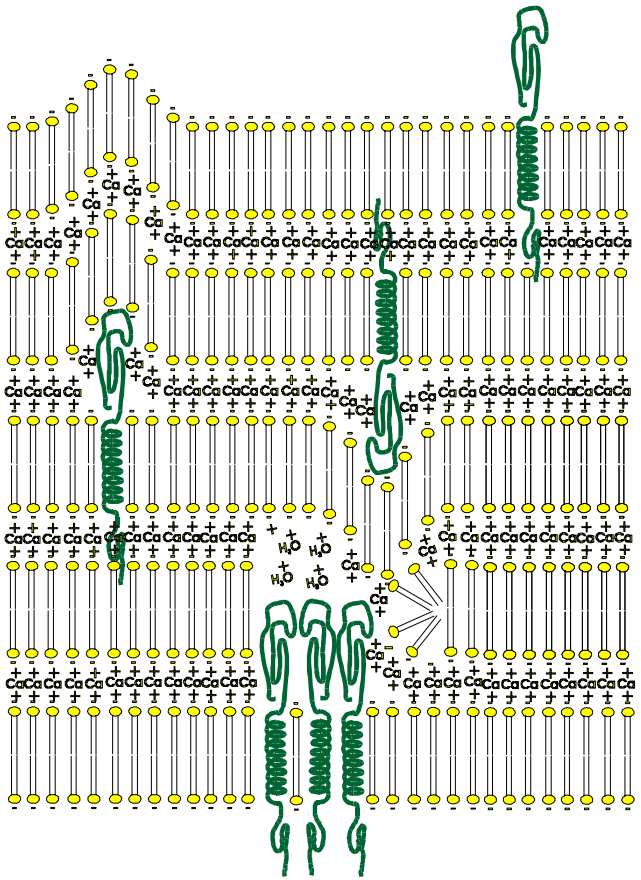
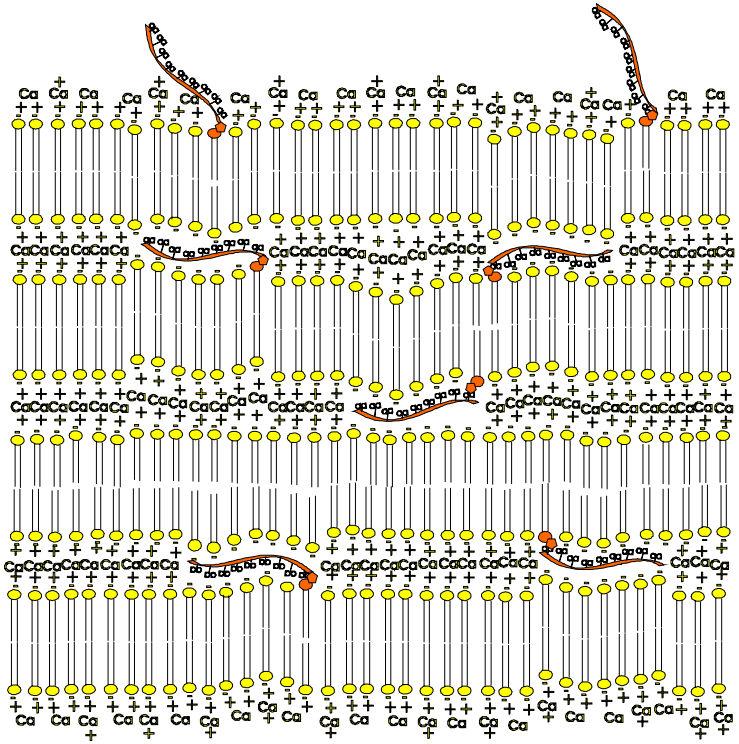
Protein and Peptide Cochleates



Membrane Proteins



Lipid-Linked Peptides

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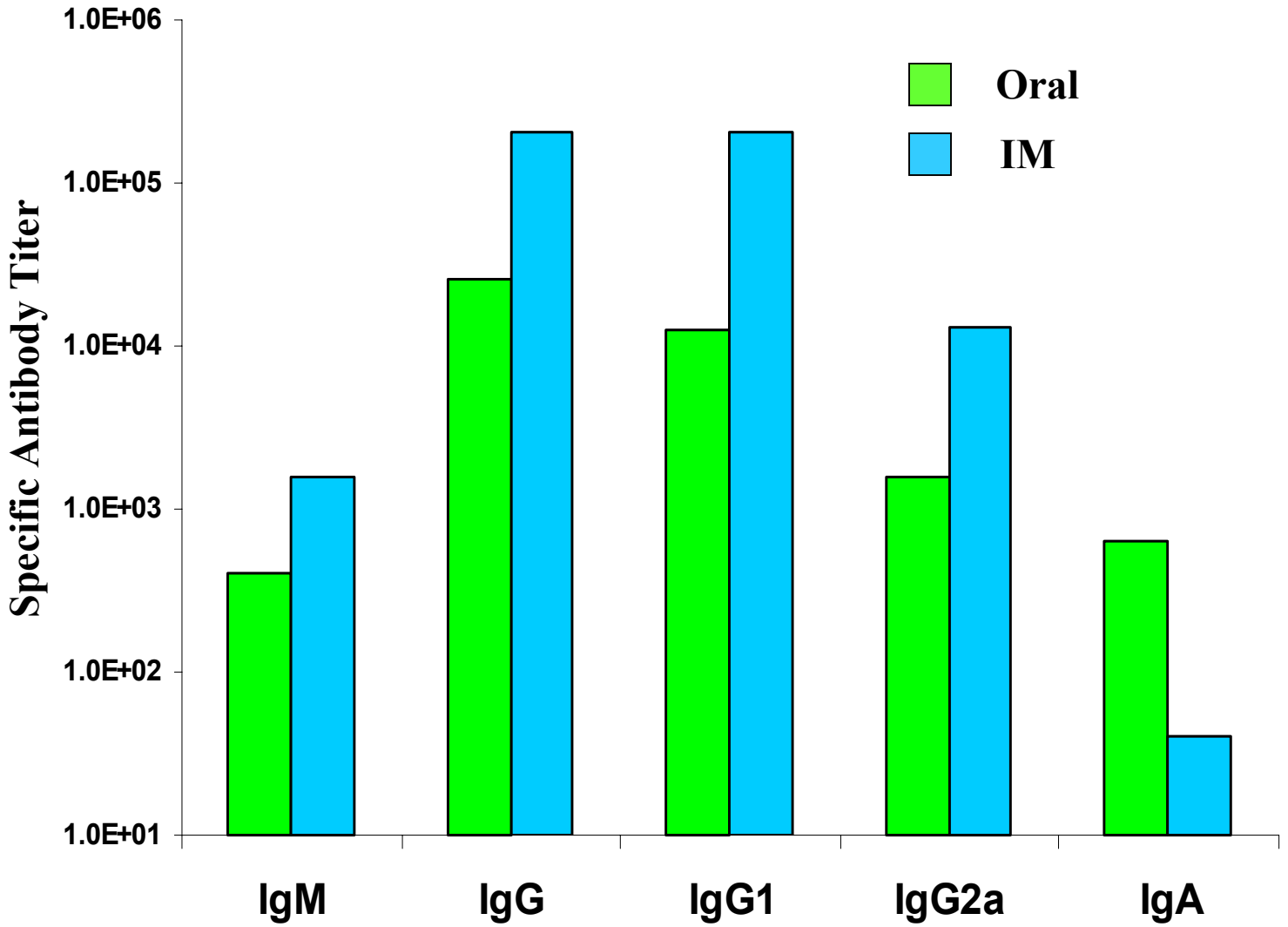
Influenza Specific Antibody: Oral vs Intramuscular



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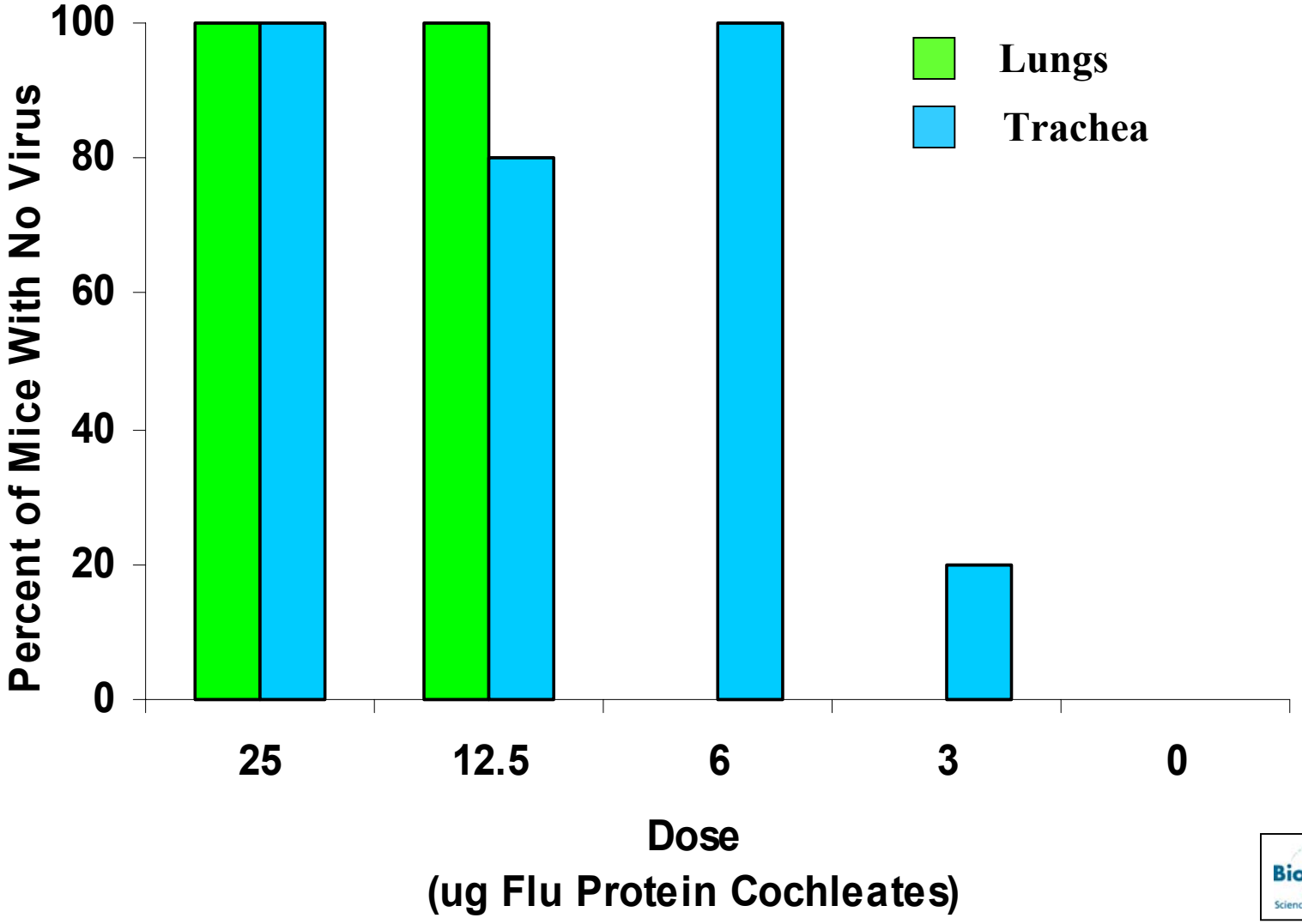
Protection from Influenza Virus Challenge By Oral Administration of Protein Cochleate Vaccine



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Protein Cochleates

Commercial Influenza Vaccine

Vs.

Cochleate Formulation of commercial vaccine

Intranasal Application

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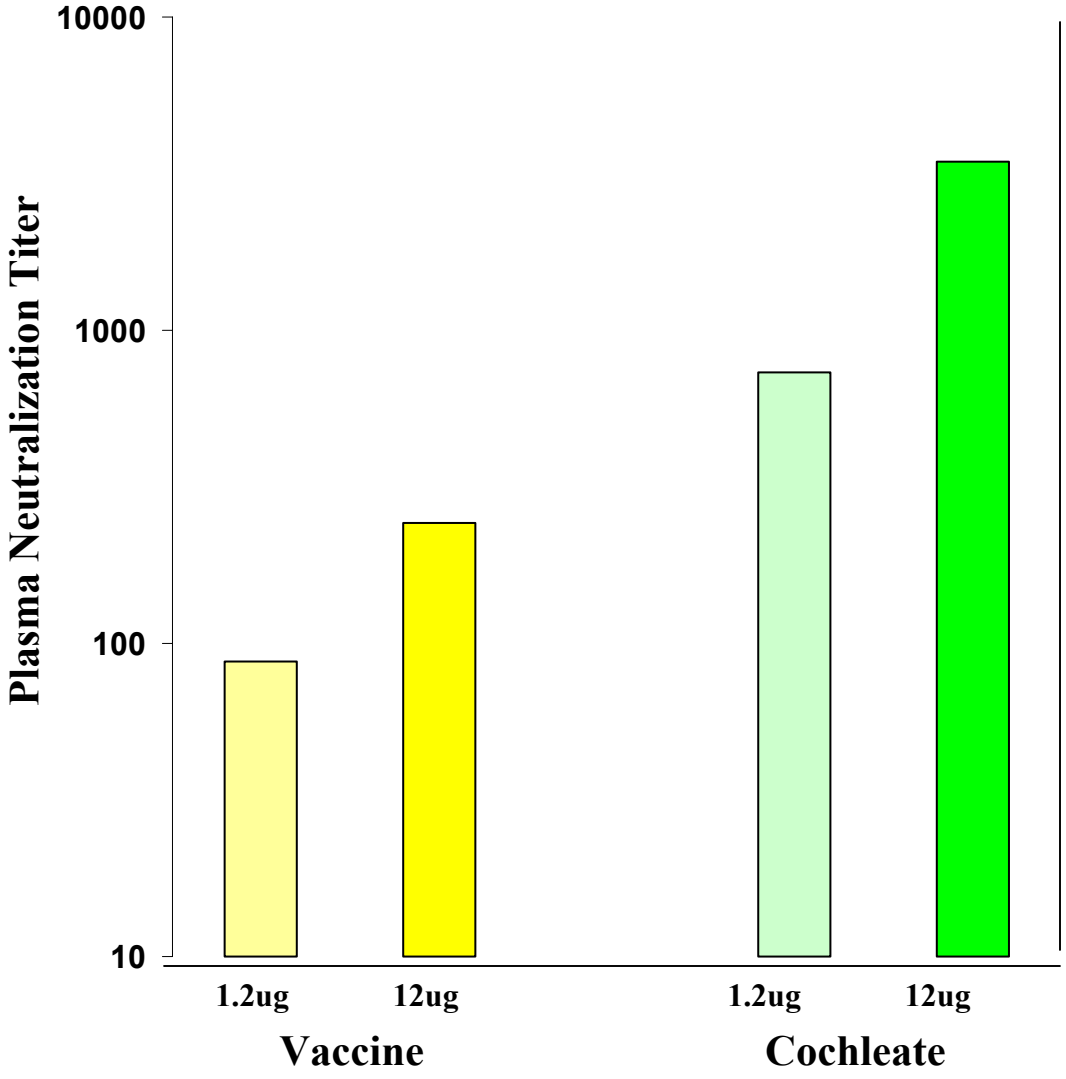
Cochleate Formulations of Influenza Proteins

Comparison of Commercial Vaccine to Cochleate Formulation- Intranasal Neutralization Titers- Day 144



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DNA Cochleate Vaccines

Biologically active DNA capable of expressing antigenic foreign gene products is effectively delivered when DNA cochleates are given by oral, intranasal and intramuscular routes.

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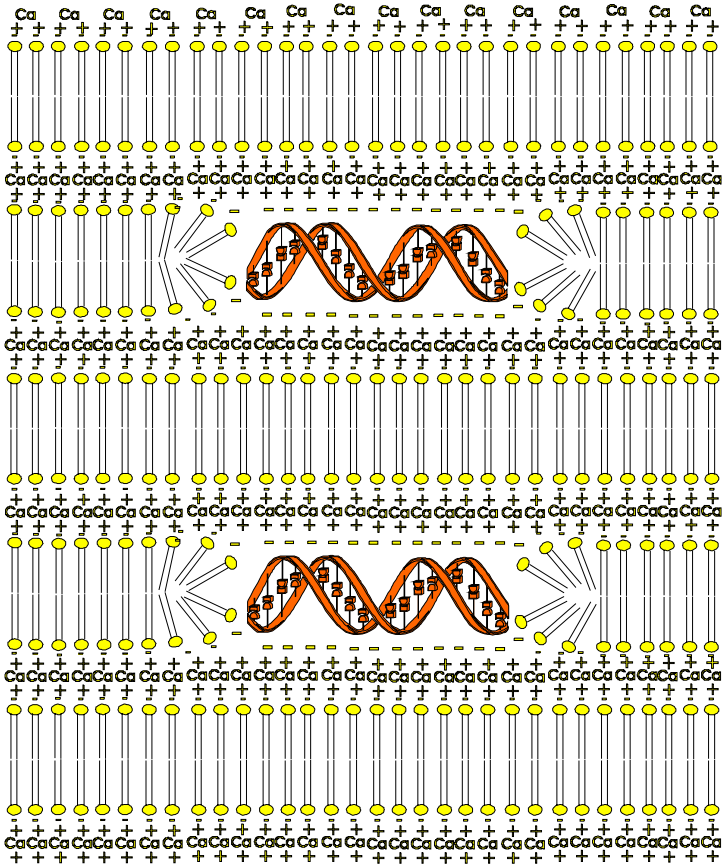
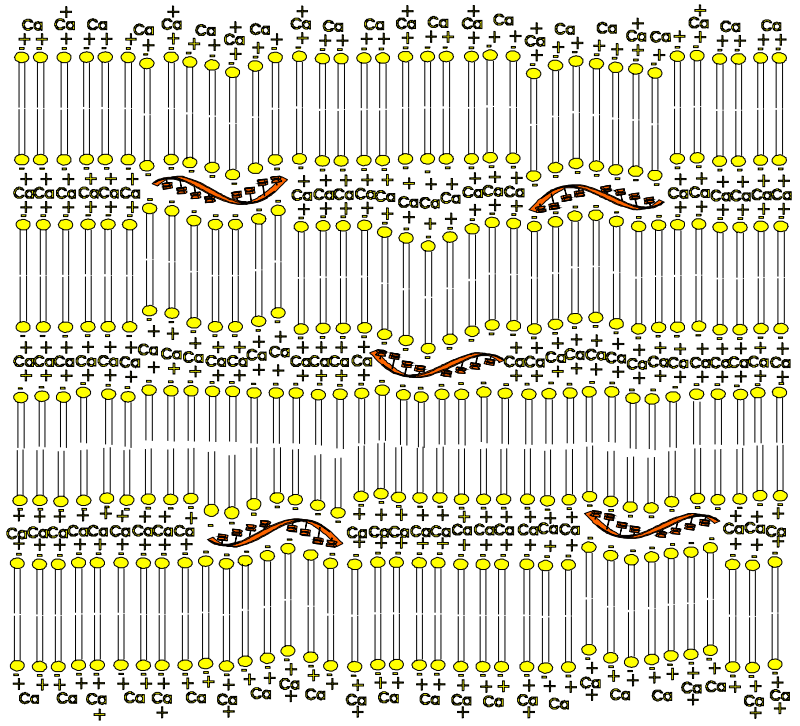
NUCLEIC ACID COCHLEATES



DNA Plasmids



Anti-Sense DNA

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DNA Cochleates

Human Immunodeficiency Virus Type 1

plasmid pCMVHIV-1, expresses env, rev, tat

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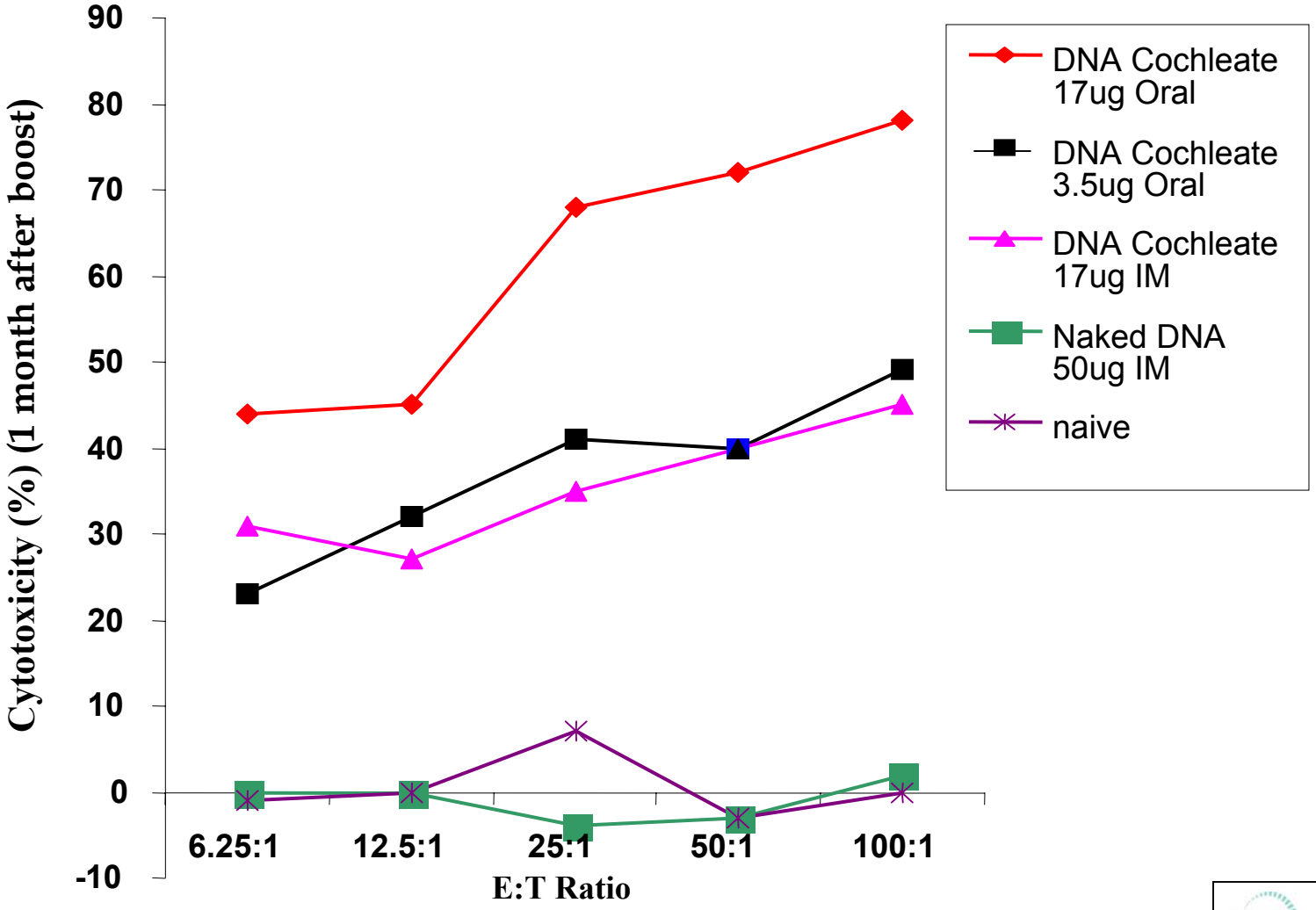
Antigen Specific Cytotoxic T Cells Induced By Oral Immunization with Encochleated DNA Complexes



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DNA Cochleates

Herpes Simplex Virus 2 plasmid expresses HSV-2 gD

- Cytokine plasmid expresses IL-12

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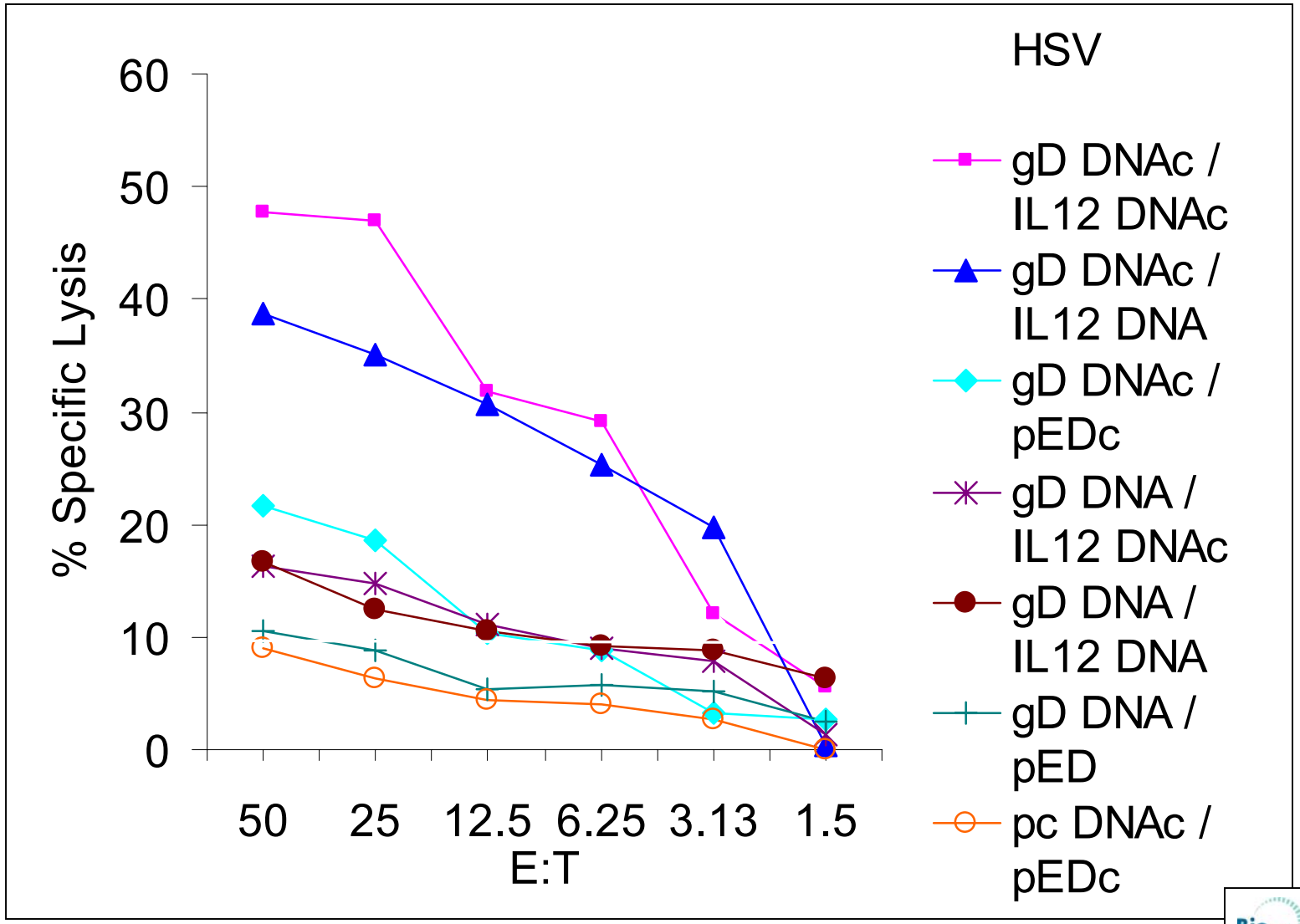
Encochleation of gD and IL12 Plasmids Enhances HSV Specific CTL Responses



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Summary: Cochleate Immunogenicity Studies

Formulations:

Pathogens

- **HIV-1**
- **Influenza A**
- **Parainfluenza**
- **Herpes Simplex type 1**
- **Herpes Simplex type 2**
- **Other viruses**
- **Bacteria**

Antigens

- **Viral Glycoproteins**
- **Bacterial membrane proteins**
- **Peptides**
- **DNA (polynucleotide) vaccines**

Routes of Administration

- ***Mucosal:***
- **Oral, Intranasal, Intraocular**
- ***Parenteral:***
- **Intramuscular, Intradermal, Subcutaneous**

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Summary: Cochleate Immunogenicity Studies

Immune Responses:

Antibody

- Serum
- Saliva
- Bronchial
- Intestinal
- Fecal
- Vaginal

Proliferation

Spleen

- Peyer's patches
- Mesenteric lymph nodes
- Inguinal lymph nodes

Cytotoxicity

Spleen

- Intestinal Intraepithelial lymphocytes (iIELs)

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Summary: Cochleate Immunogenicity Studies

Protection from Virus Challenge

Cochleate vaccine	*Route of Immunization*	*Route of Challenge*	*Protection from:*
Influenza A (protein)	**Intramuscular or oral**	**Intranasal**	**Replication**
Herpes simplex 1 (DNA)	**Intragastric or intramuscular**	**Intravaginal**	**Lethal dose**
Herpes simplex 2 (DNA)	**Intramuscular 1^0, intragastric or intramuscular 2^0**	**footpad**	**Lethal Dose, Neurological symptoms**

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Summary

- ***Safety*** **: non-toxic, noninfectious, nonreplicating**
- ***Stability*** **: Protein and DNA; as suspension or powder**
- ***Efficacy*** **: more effective than unformulated DNA or proteins**
- ***Route of delivery*** **: injection or mucosal (oral and intranasal)**
- ***Combination vaccines*** **: mix proteins, peptides, DNA, adjuvants**

Cochleates represent a potentially powerful subunit vaccine delivery system uniquely suited to meeting the challenges of modern vaccine development.

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