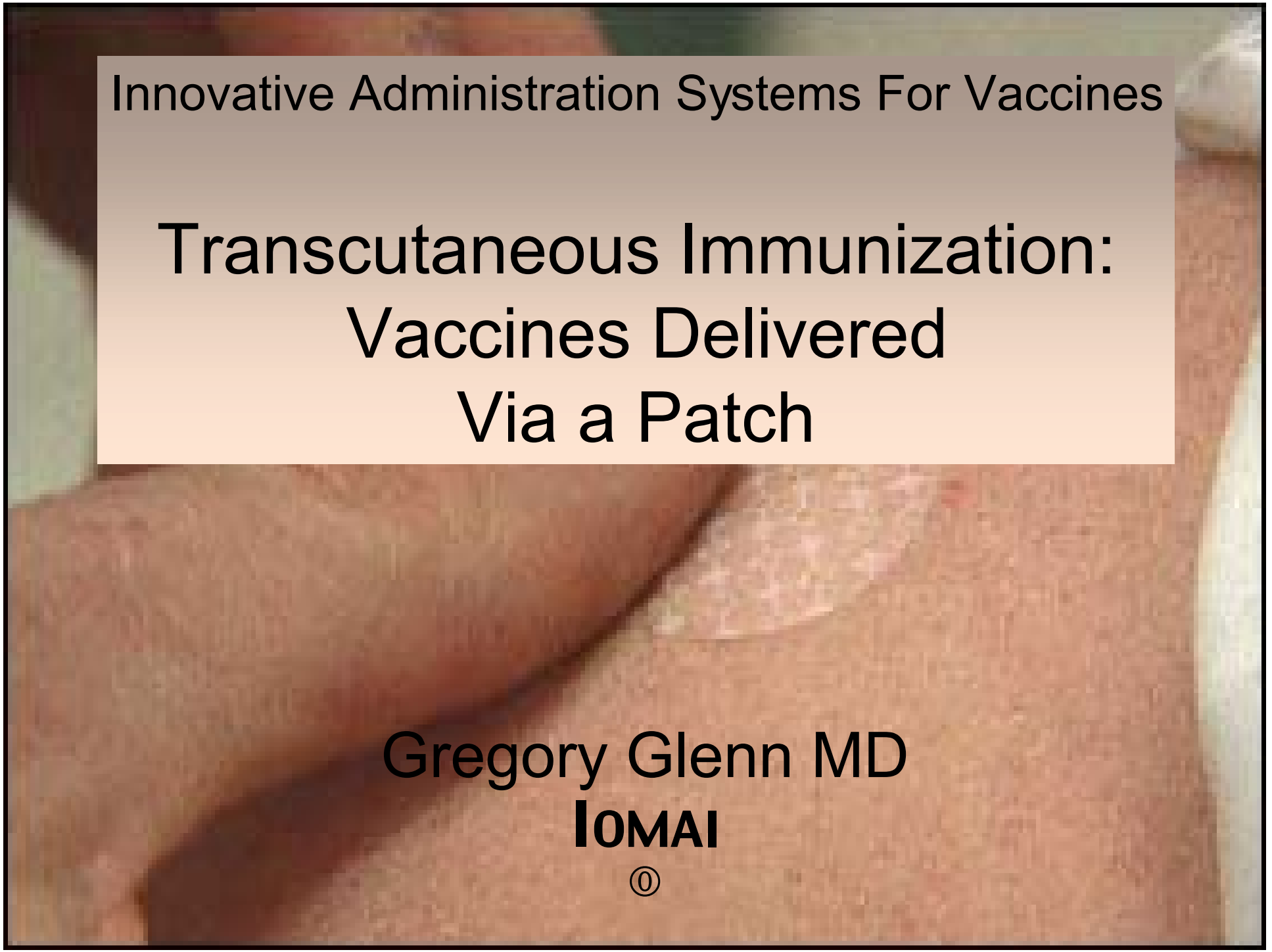


Innovative Administration Systems For Vaccines

Transcutaneous Immunization: Vaccines Delivered Via a Patch

Gregory Glenn MD
IOMAI
©

IOMAI

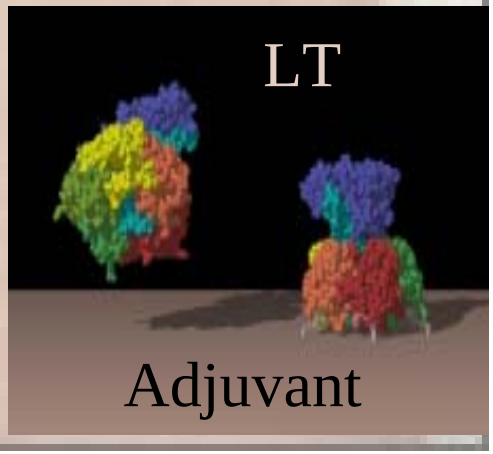
- Focus: delivery of vaccines to the skin
- In Gaithersburg, 53 employees
  - Experienced management team
  - Preclinical, formulation, patch manufacture
  - Clinical testing, (2000 active patches placed)

Vaccination via a Skin Patch

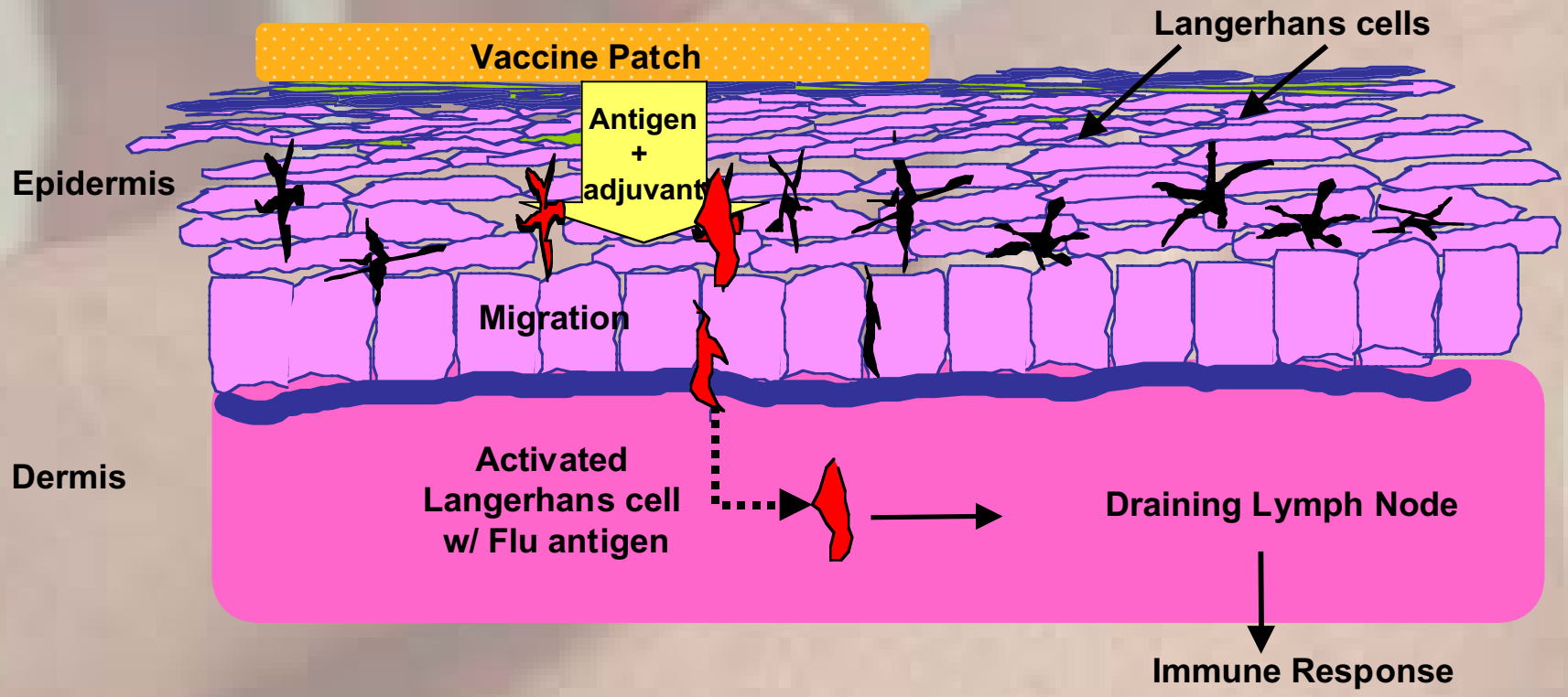
- Scientific Rationale
- Human proof of concept
- Development strategy
- Patch technology
- Biodefense application

Fundamental Observation

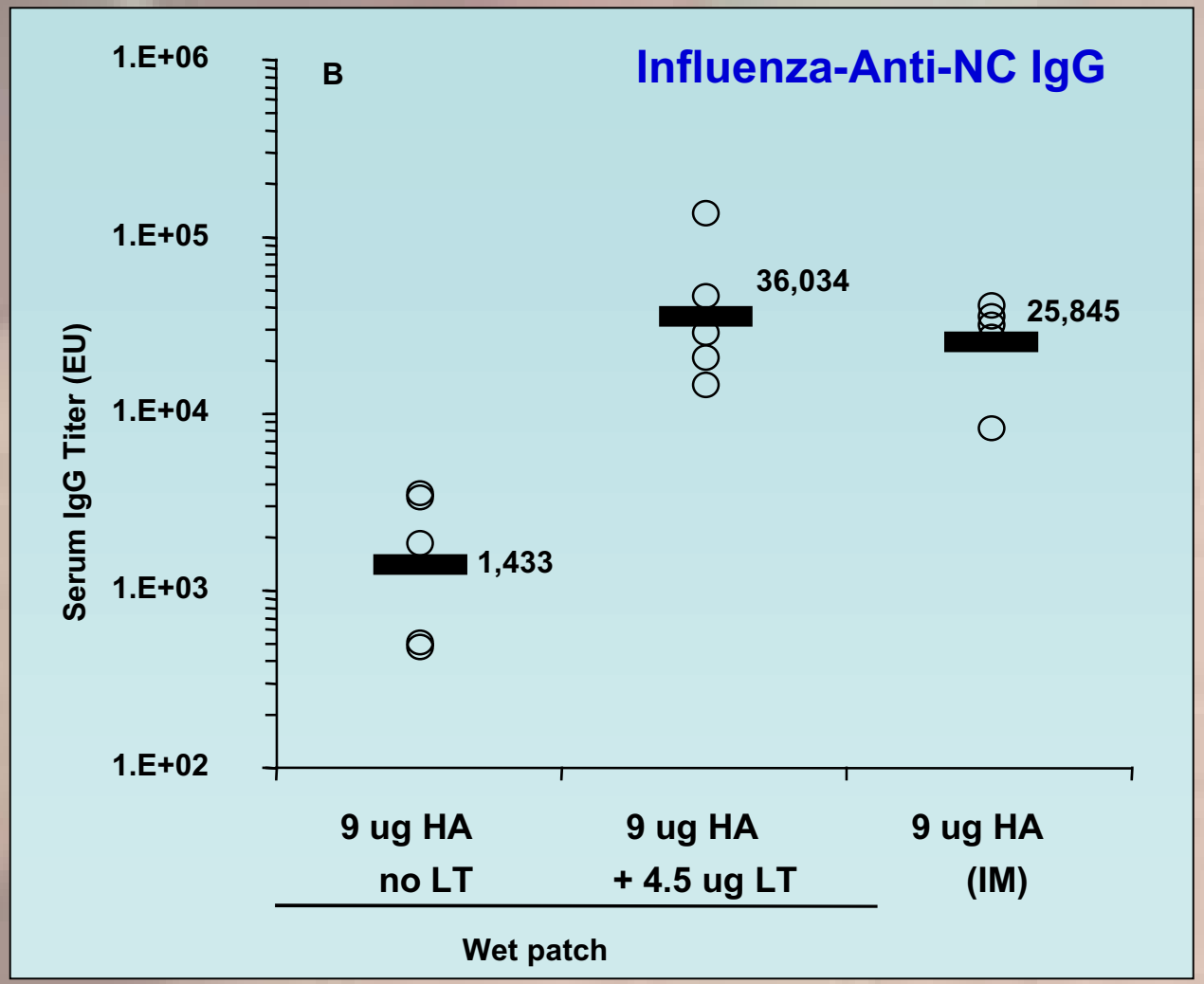
- Adjuvants activate skin immune cells, enhance immune responses to vaccines
- Potent adjuvants can be safely delivered via the skin
- Antigens and adjuvants are readily delivered into the skin

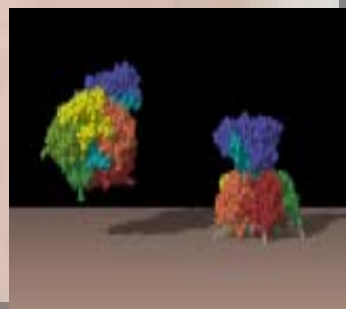


Transcutaneous Immunization: Antigen and Adjuvant Delivery via a Patch



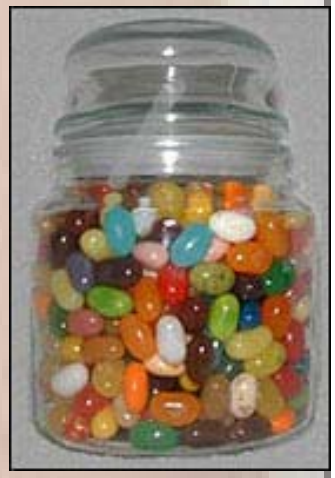
Adjuvants Enhance Immunity in the Context of the Skin: Universal Finding





Transcutaneous Immunization: Delivery of Different Types of Vaccines and Antigens

- **Multivalent subunit vaccines**
  - **Trivalent split-virus influenza**
  - **ETEC colonization factors & toxin (CFA1, CS3, CS6, LT)**
  - **Conjugated multivalent polysaccharides, Hib**
  - **HIV**
  - **Anthrax (rPA)**
- **Toxoid vaccines**
  - **Tetanus and diphtheria toxoids**
- **Toxins - CT, LT, Exo A**
- **Particles**
  - **Virosomal vaccines**
  - **Virus-like particles- human papilloma virus**
- **Inactivated bacterial whole cells - *H. pylori,* ETEC**
- **Live Viruses**
- **DNA**



ESTABLISHED SCIENTIFIC PARADIGM

Published by the American Society of Microbiology

Infection and Immunity

Transcutaneous Immunization with Bacterial ADP-Ribosylating Exotoxins, Subunits, and Unrelated Adjuvants
Infect Immun 2000;68:5306

nature

INTERNATIONAL WEEKLY JOURNAL OF SCIENCE

Skin immunization made possible by cholera toxin

Nature 1998;391:651

Journal of Virology

AMERICAN SOCIETY FOR MICROBIOLOGY

Immunostimulant patch containing heat labile enterotoxin from E. coli enhances immune responses to injeccted influenza vaccine through activation of skin dendritic cells.

J Virol 2003;77:5218

Vaccine

Transcutaneous immunization: T-cell responses and boosting of existing immunity

Vaccine 2001;19:2701

advanced drug deliver reviews

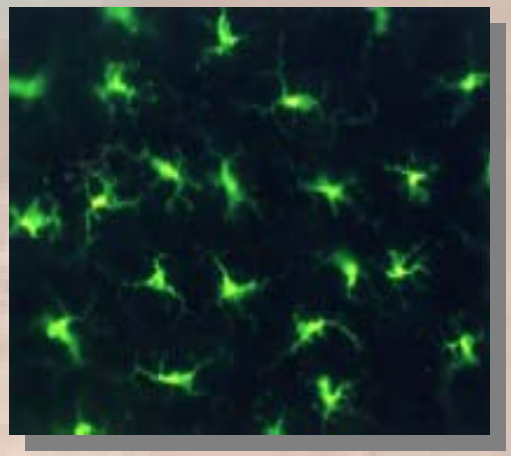
Transcutaneous immunization of domestic anim opportunities and challenges
ADDR 2000;43:45

nature medicine

Transcutaneous immunization: A human delivery strategy using a patch

Langerhans Cells

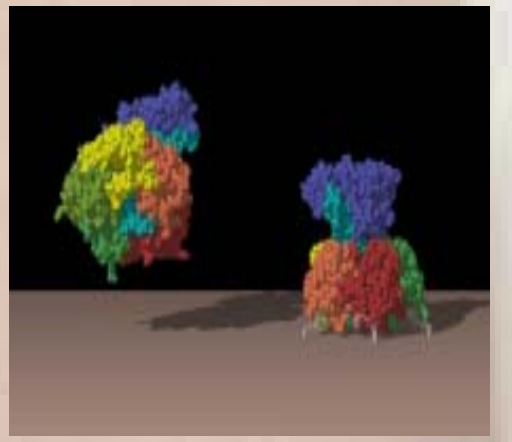
- Network of barrier immune cells
  - Immune surveillance
  - Orchestrates immune response
- High levels of co-stimulatory molecules/cytokine
- Antigen presentation results in T and B cell activation
- Cover 25% of human skin surface area, highly superficial
- Ideal targets for immune manipulation
- Activated by adjuvants delivered to the skin



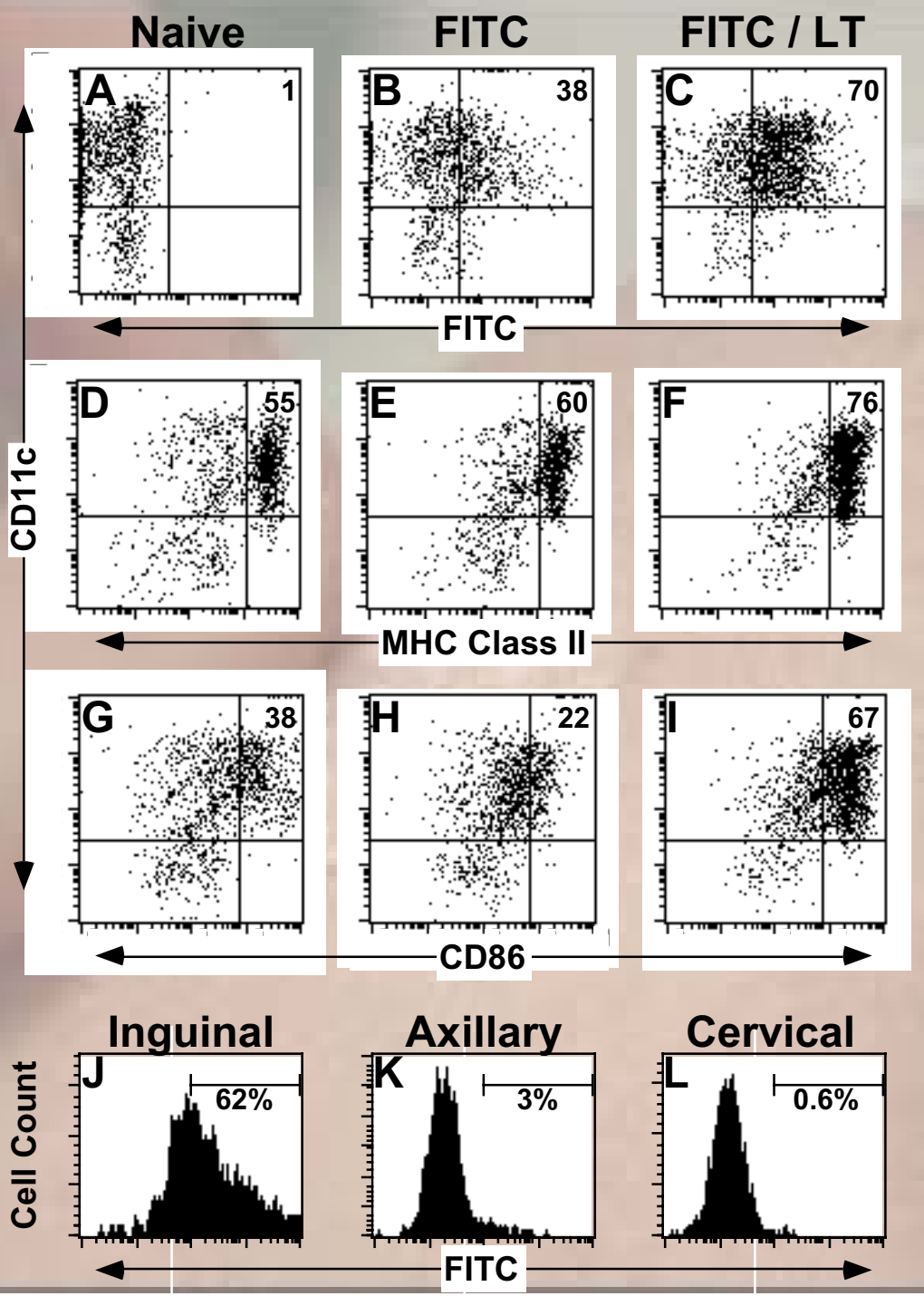
Human LC, 400x

LT as Adjuvant

- LT (heat labile enterotoxin from *E. coli*)
- Readily produced at commercial scale
- Natural product/natural human exposure
- Long history of experimental use as adjuvant
- Demonstrated clinical activity as adjuvant on the skin
- Potent
- Safely used on the skin-P2DBPC
- Stable/stable in formulation



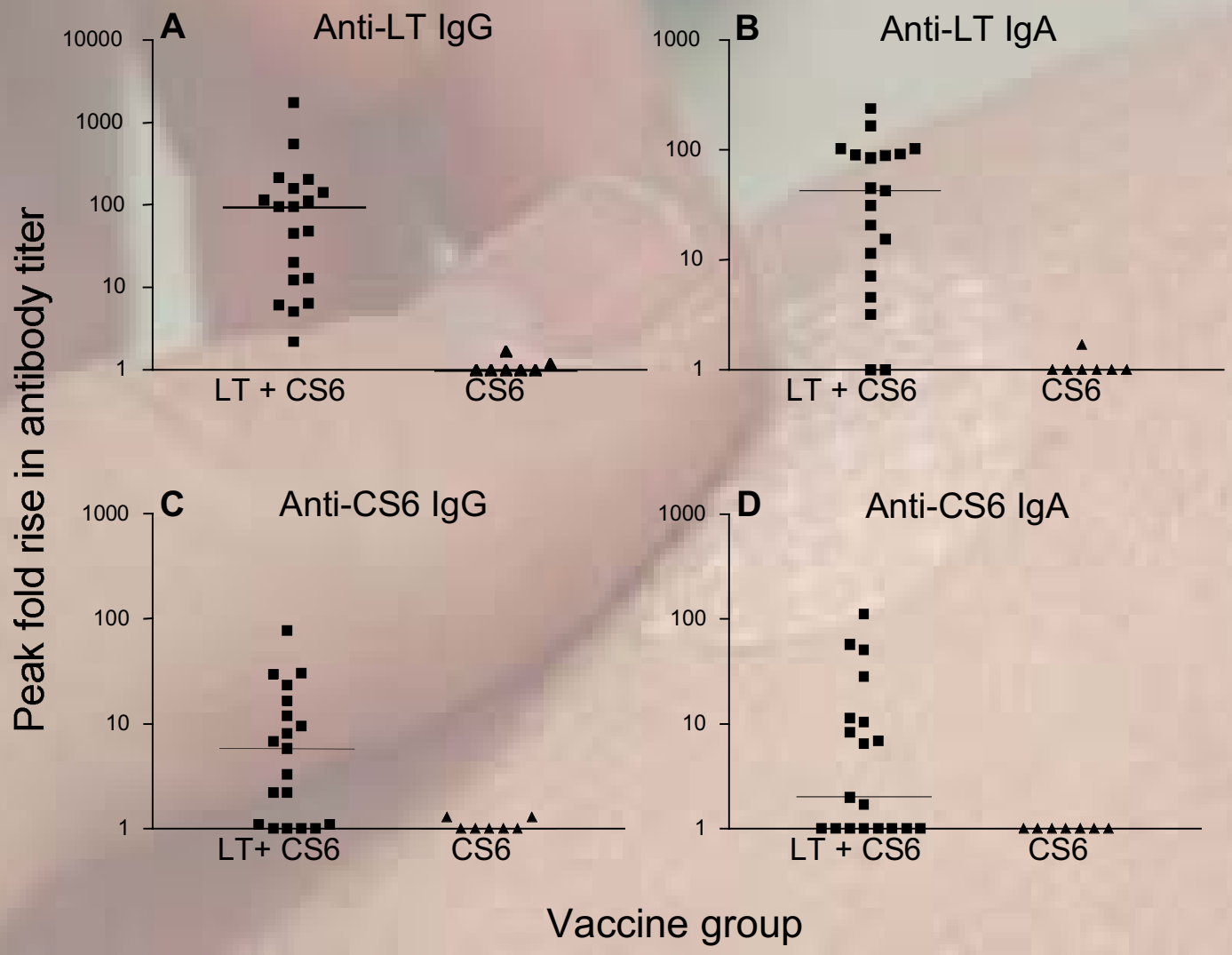
The Adjuvant LT Increases the Number and Activation State of Migrating LCs in the Lymph Node



Clinical Proof of Principle

- Safe
- Adjuvant effect
- Delivery of large proteins possible
  - Transcutaneous vs transdermal
- Relevance of preclinical animal data?

Human Antibody Responses to Colonization Factor (rCS6) and LT: Critical role of the adjuvant, delivery of large molecules



Safety and immunogenicity of a prototype enterotoxigenic Escherichia coli vaccine administered transcutaneously.
Guerena-Burgueno F, Hall ER, Taylor DN, Cassels FJ, Scott DA, Wolf MK, Roberts ZJ, Nesterova GV, Alving CR, Glenn GM.
Infect Immun 2002 Apr;70(4):1874-8

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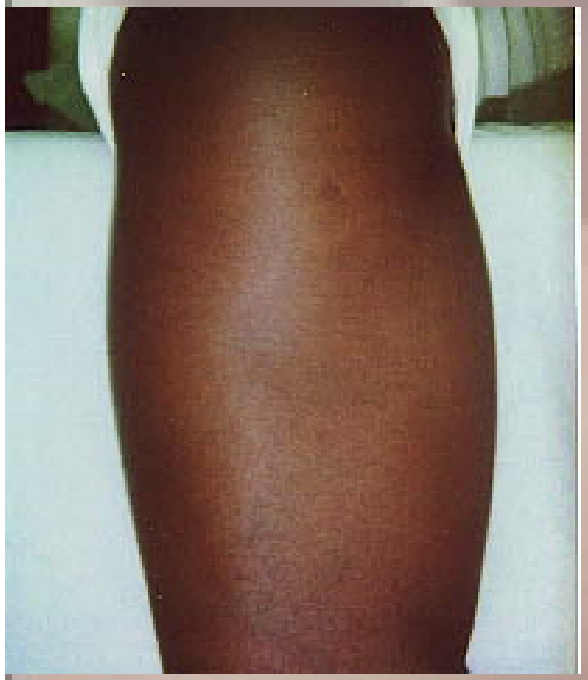
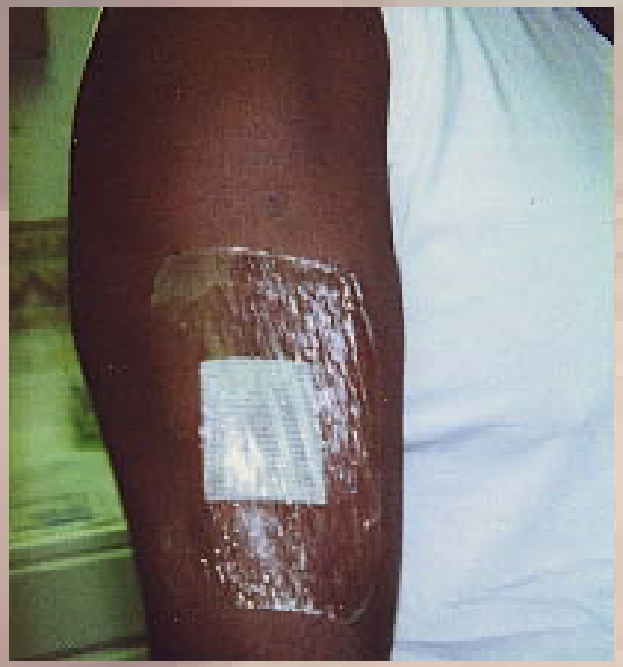
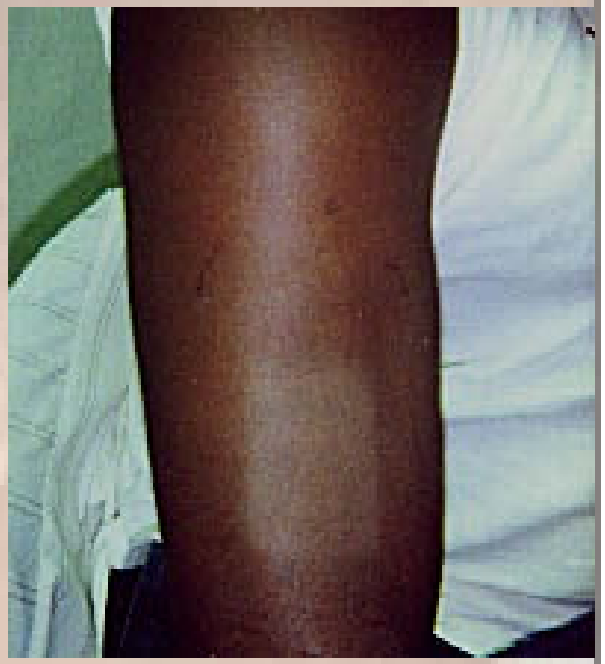
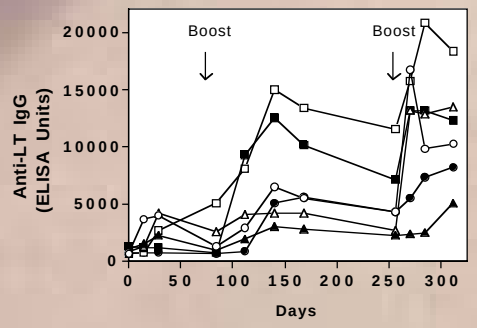
Gauze/Tegaderm “Wet” Patches









Glenn et al
Nature Medicine,
Dec 2000

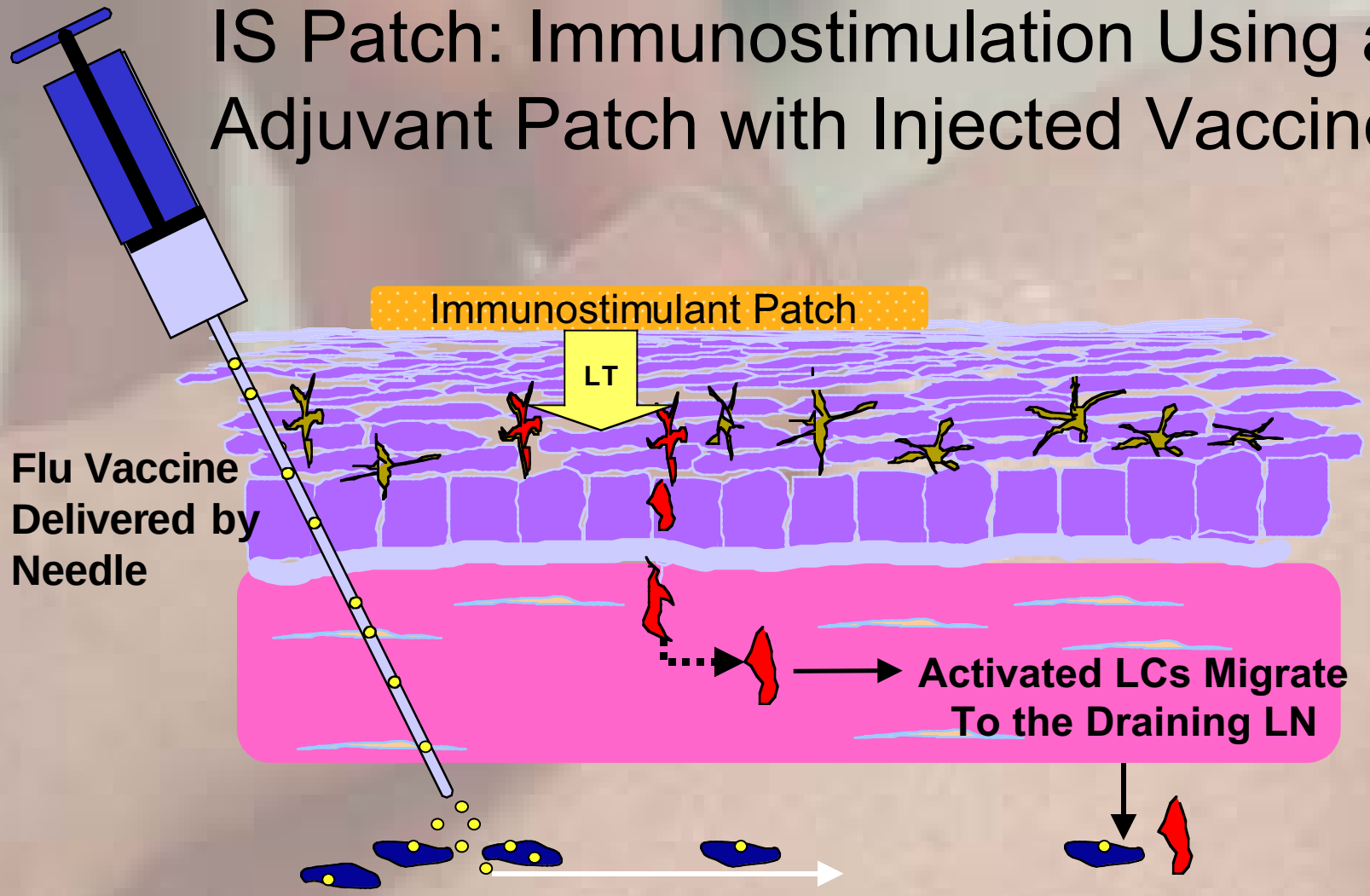
Conclusions

- Large molecules readily delivered in context of human skin
  - LT 86kD
  - CS6 1,500 kD
  - Transdermals<0.5kD
- Adjuvant plays critical role for immunogenicity
- Responses robust-equivalent to natural immunity generated by ETEC infection

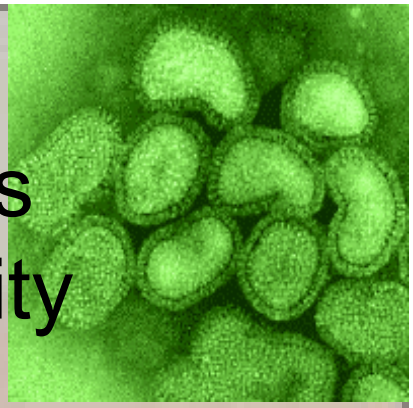
Second Major Application

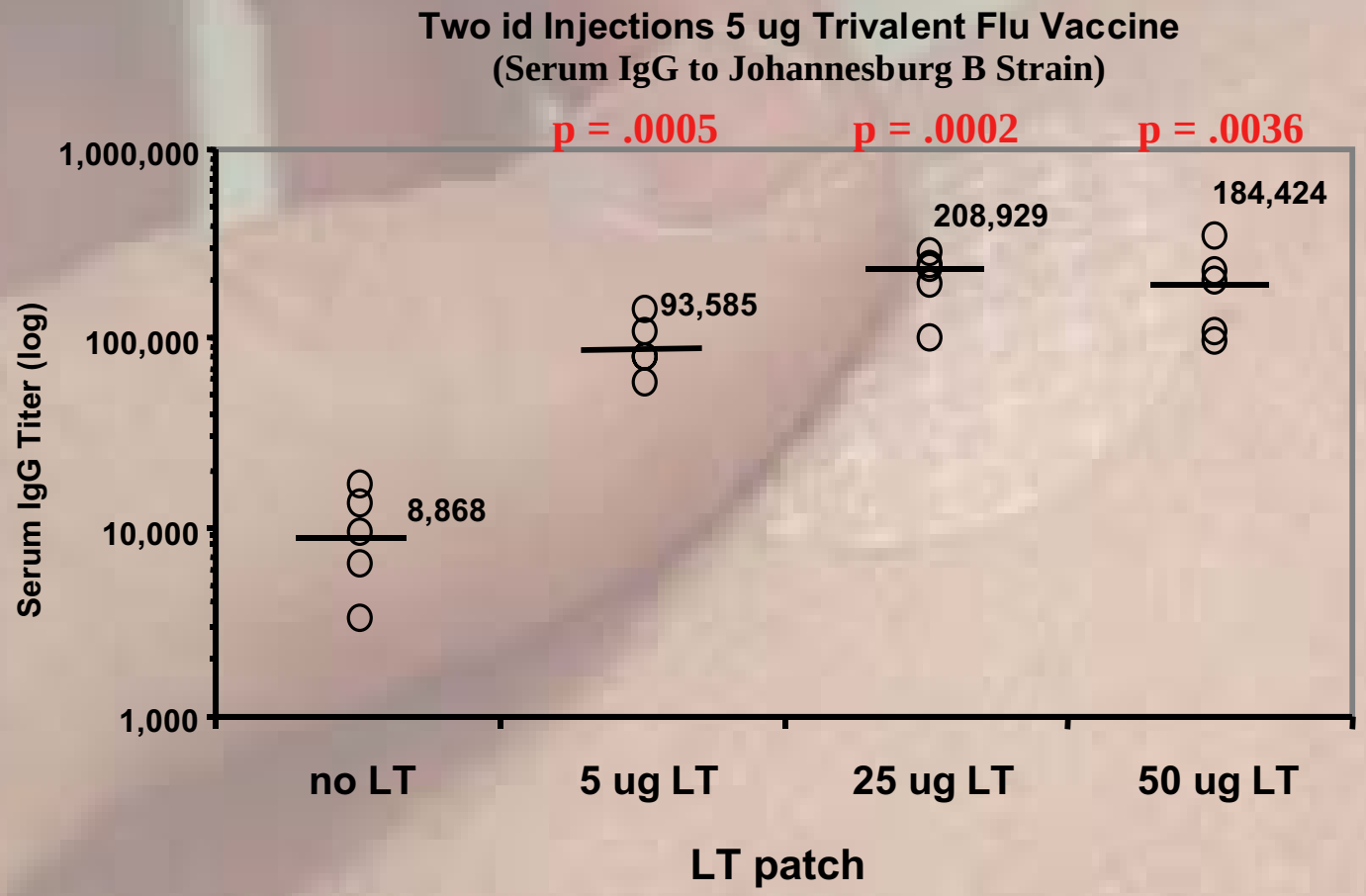
- Transcutaneous immunization (TCI)
  - Adjuvant and antigen delivered together
- Immunostimulant patch-(LT IS Patch)
  - LT alone in conjunction with injected vaccine

IS Patch: Immunostimulation Using an Adjuvant Patch with Injected Vaccine



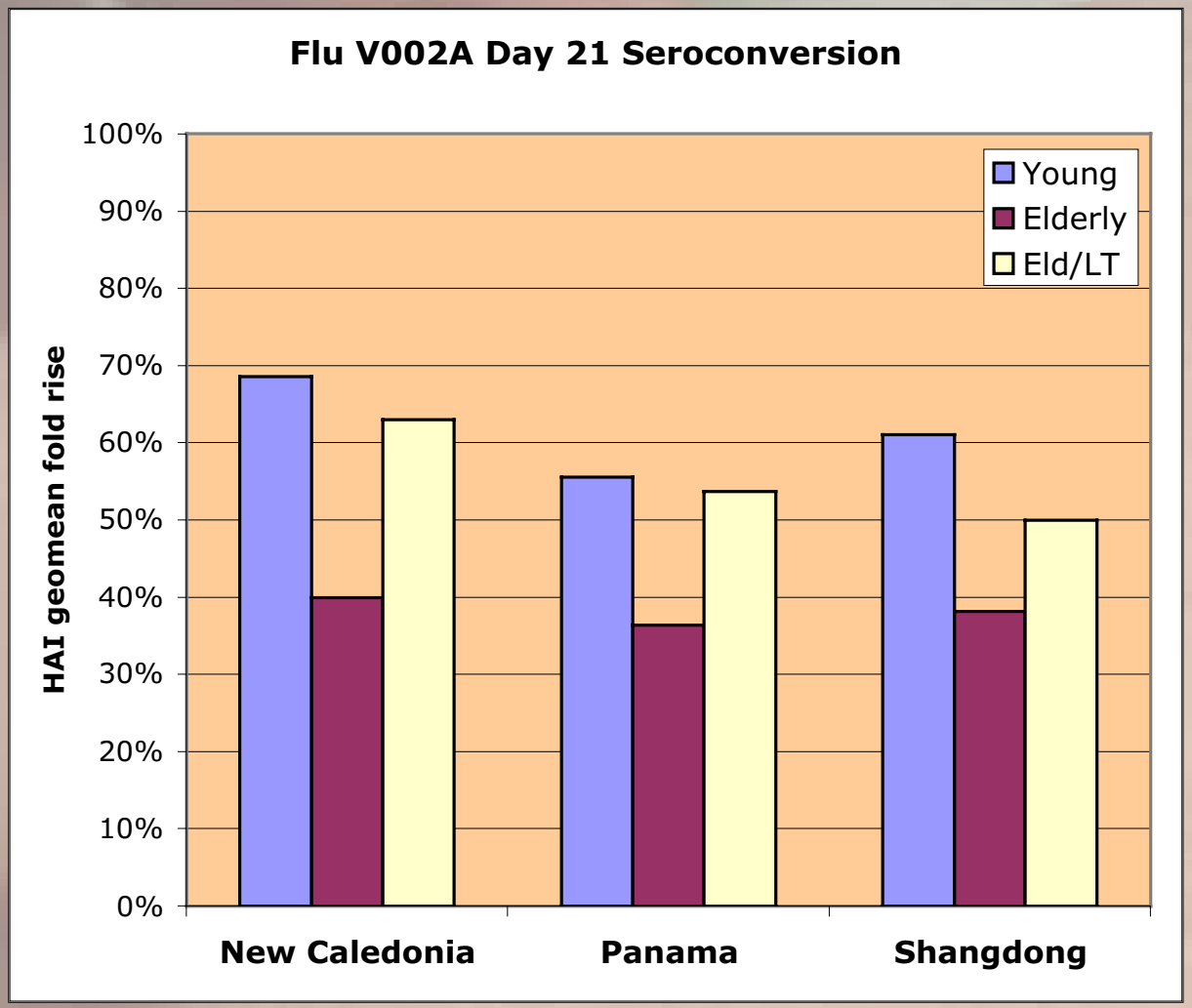
LT IS Patch for Influenza Split Virus Vaccine: Enhanced Immunnogenicity

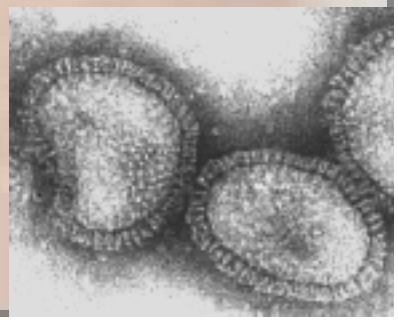


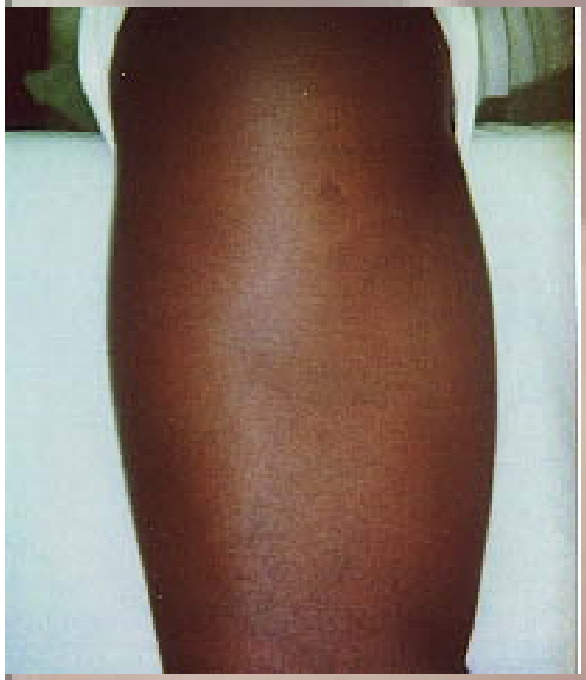
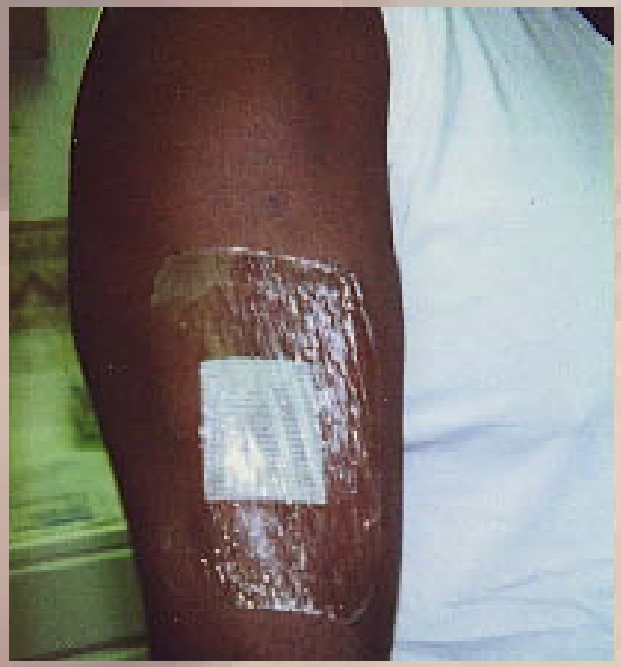
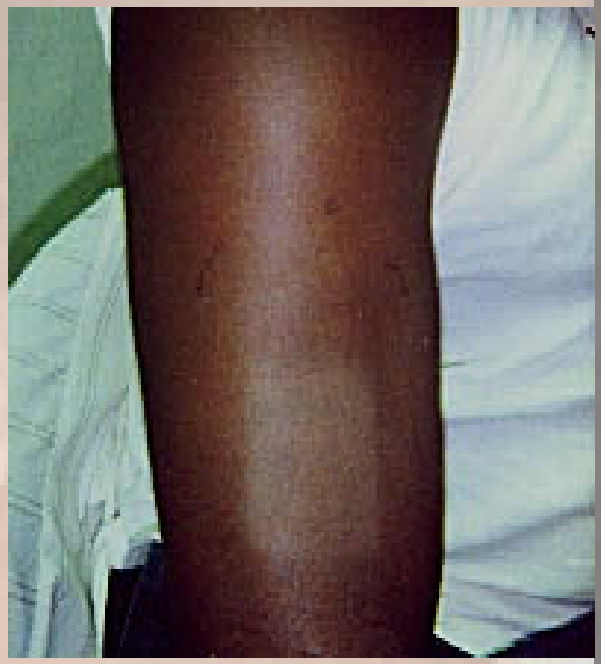


Published in: Xabier et al, J. Virol, May 03

Phase IIa LT IS Patch in the Elderly-Enhanced Immunogenicity





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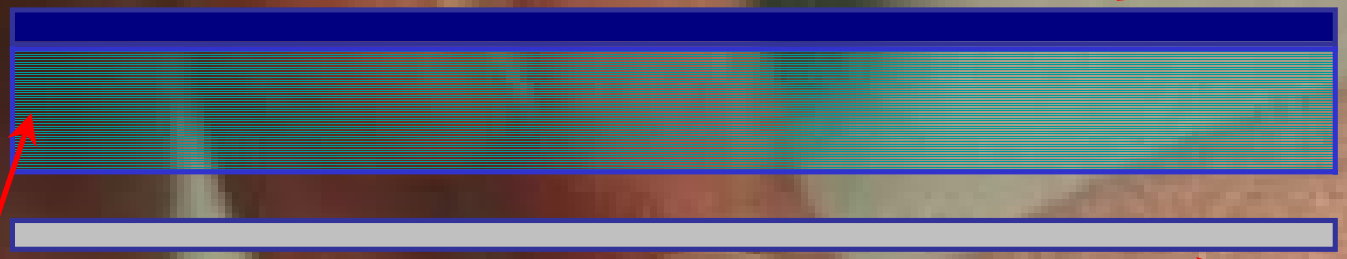
Making Products

LT Alone as Strategic Focus for Development of Skin Patches

- Delivery,Safety, Stability
- LT alone applications
  - IS Patch using LT alone with flu
  - LT ETEC immunogen, anti-toxin immunity
- Formulate manufacturable LT patches
- Optimize using LT immune response readout
- Leading to Patches with LT and 2nd antigen)
  - LT+Anthrax
  - LT+Flu
  - 

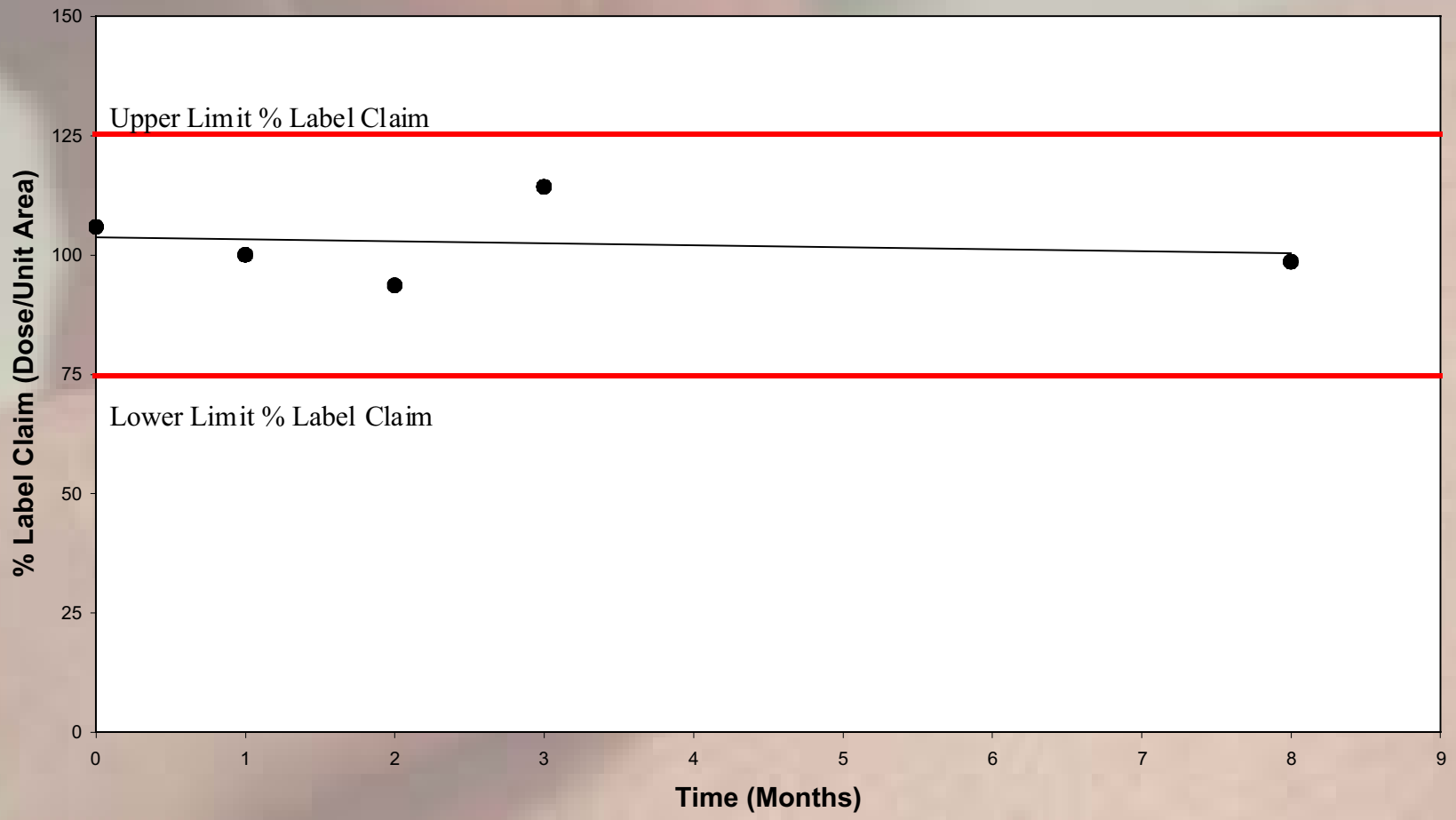
Protein in Adhesive Patch



IOMAI Patch Systems are:

- Small and Thin
- Comfortable To Wear
- Readily Manufactured

Protein in adhesive Patches Stabilize LT: Results for % Label Claim for PIA Patch



Patches were stored at 5 °C and sampled according a written stability protocol. SE-HPLC analysis was performed at the indicated time points. Patches were extracted with 200 mM NaPi for 1.5 hours. Supernatants were then analyzed for LT and aggregate content with G2000 SWxl size exclusion column on a Agilent 1100 HPLC System with a DAD detector set to 220 nm. The mobile phase was 200 mM NaPi with a flow rate of 1.0 mL/min. No notable degradation was detected at 8 months.

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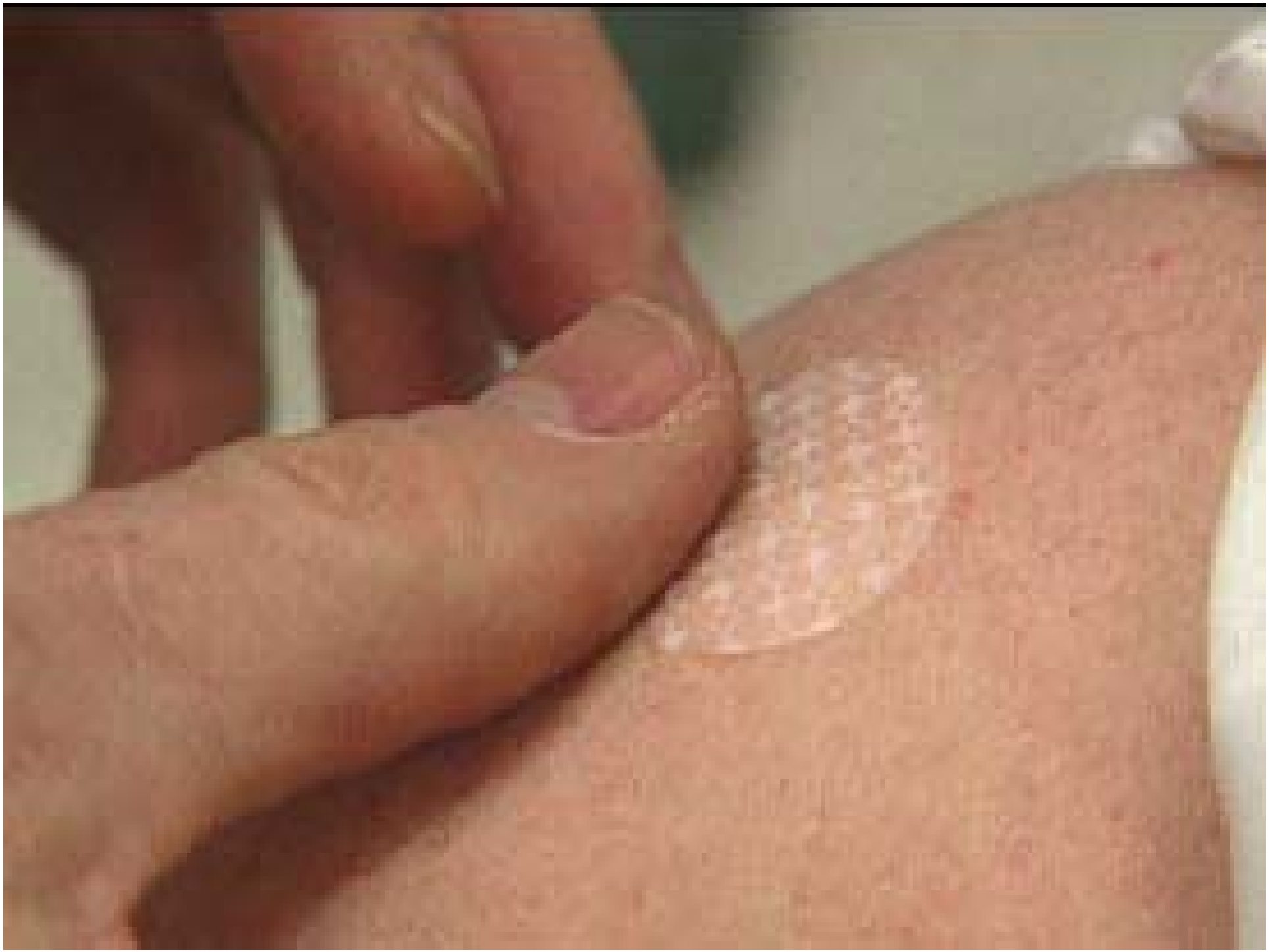
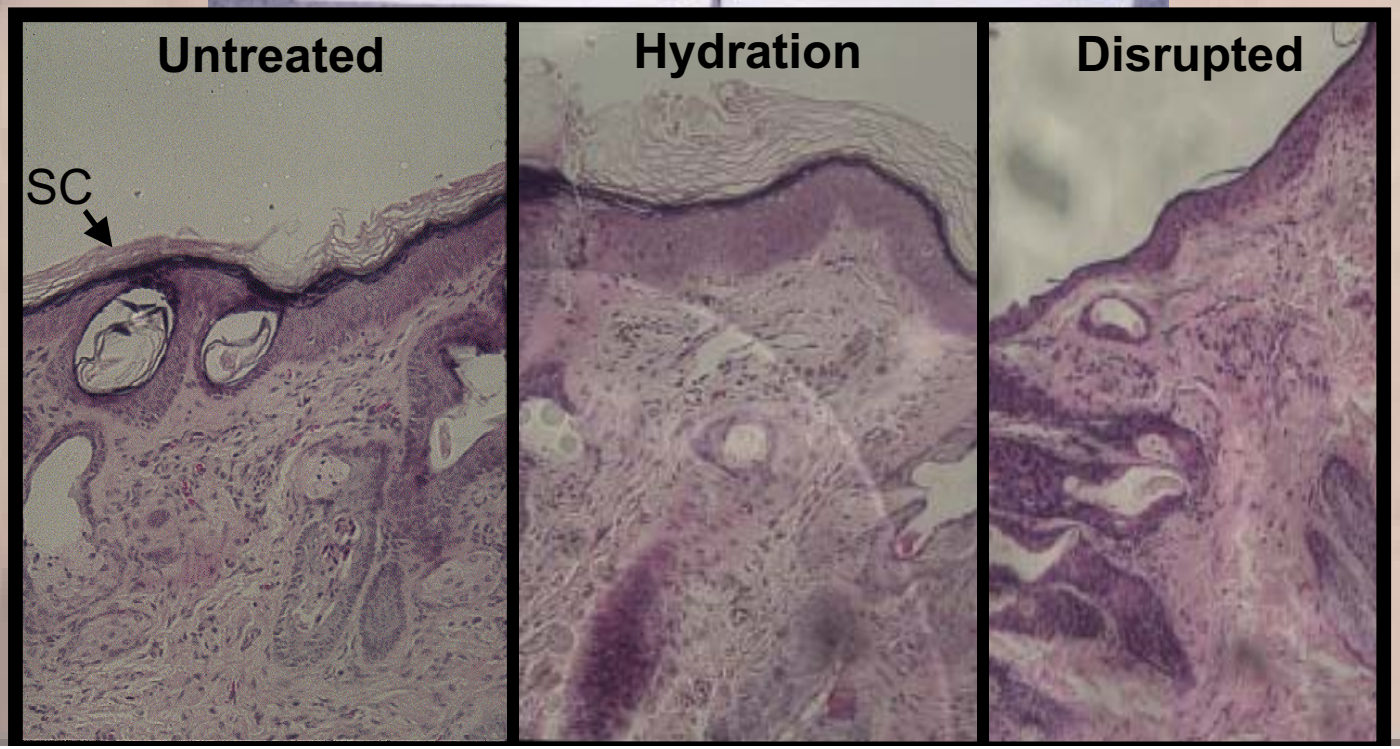


Step 1-Hydration and SC Disruption



Effect of Human Stratum Corneum Disruption: Using LT Patches-anti-LT IgG as readout

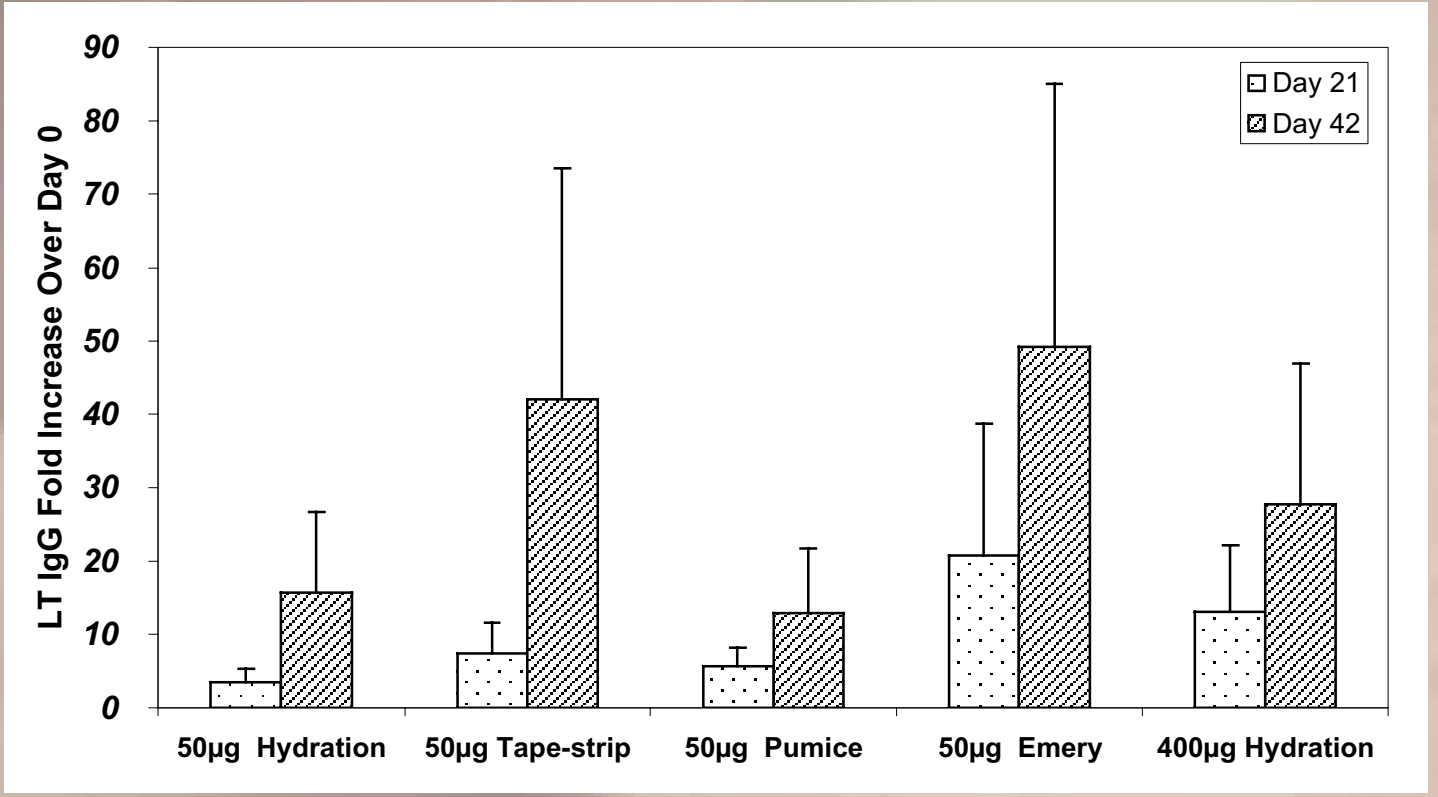


Figure 1: LT IgG response after one and two doses in NLT105 – Eight subjects per group were pretreated with the indicated methods as described, then vaccinated with 50µg or 400µg LT on Day 0 and Day 21. LT IgG ELISA was run on sera from Day 0, 21, and 42, reported as fold increase of relative ELISA units.

From: Expert Review of Vaccines 2:253-267, April, 2003

Consistent Responses to Single Application of LT in Protein in Adhesive Patches in the Elderly

Surrogate for Delivery Anti-LT IgG

		n=	Fold Rise	% seroconversion
FLA102	45/Emery	8	4.8	88%
FLA201a	LT 45µg/Emery	100	4.9	76%
	Placebo/Emery	100	1.0	0%
SLA103	45µg/Emery	40	3.3	67%
	45µg/Buffer/IPA	20	3.0	70%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Transcutaneous Skin Pretreatment System
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IOMAI
...Immunity is only skin deep™
Transcutaneous Immunization Patch
IOMAI
...Immunity is only skin deep™
Contains One Transcutaneous Immunization System Consisting Of A Pretreatment Swab And An Immunization Patch.*
*One 5 cm² patch containing no active component.
See patient instructions for application.
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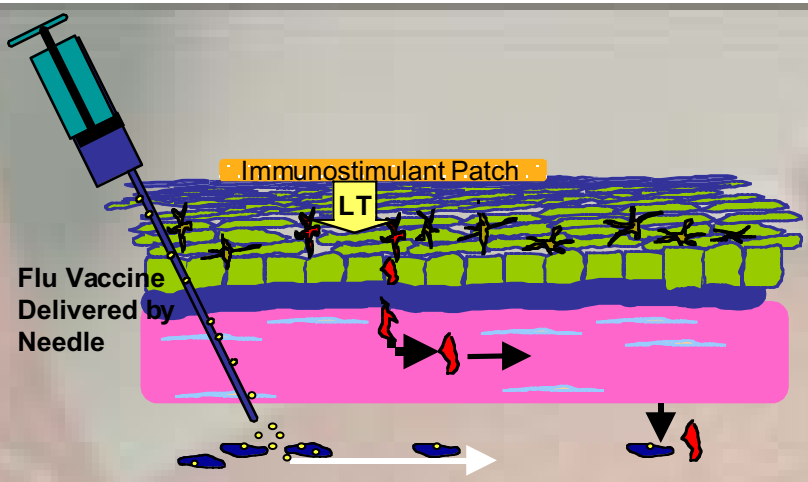
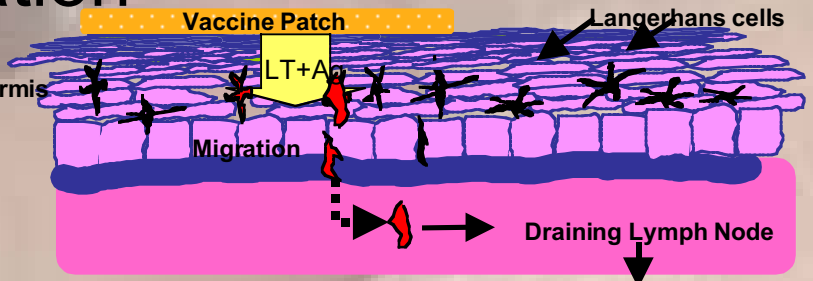
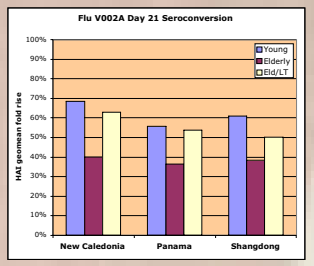
Development Strategy

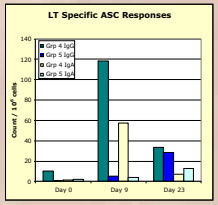
- LT alone applications
  - Phase II evaluation
    - Superflu
    - ETEC
- TCI-adjuvant and antigen
  - Anthrax
  - Flupatch

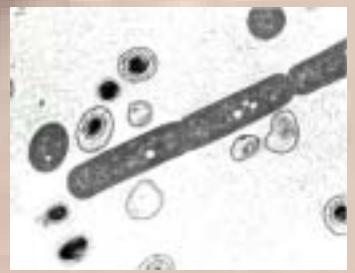


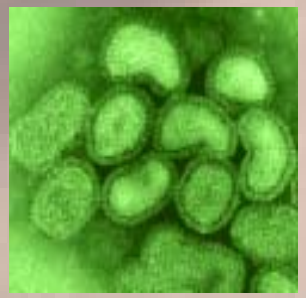


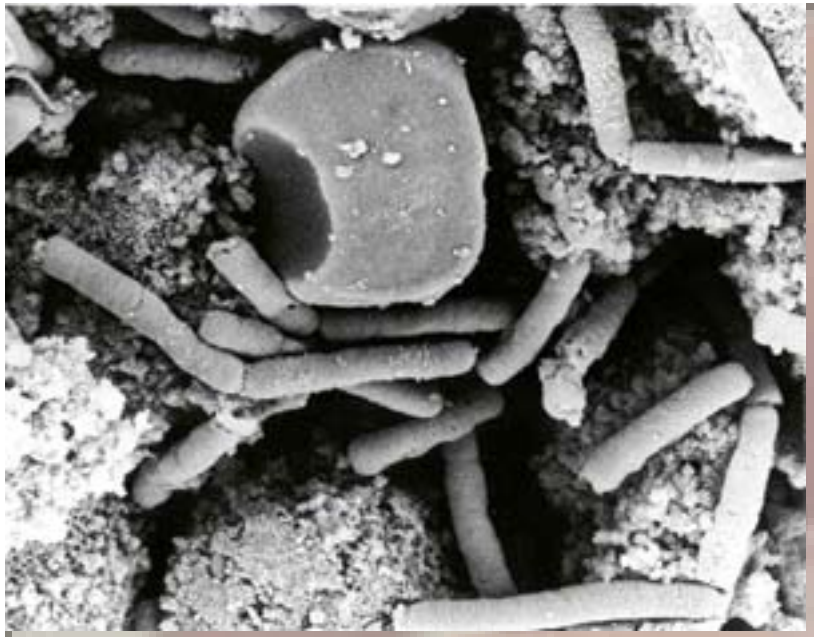


Immune Response





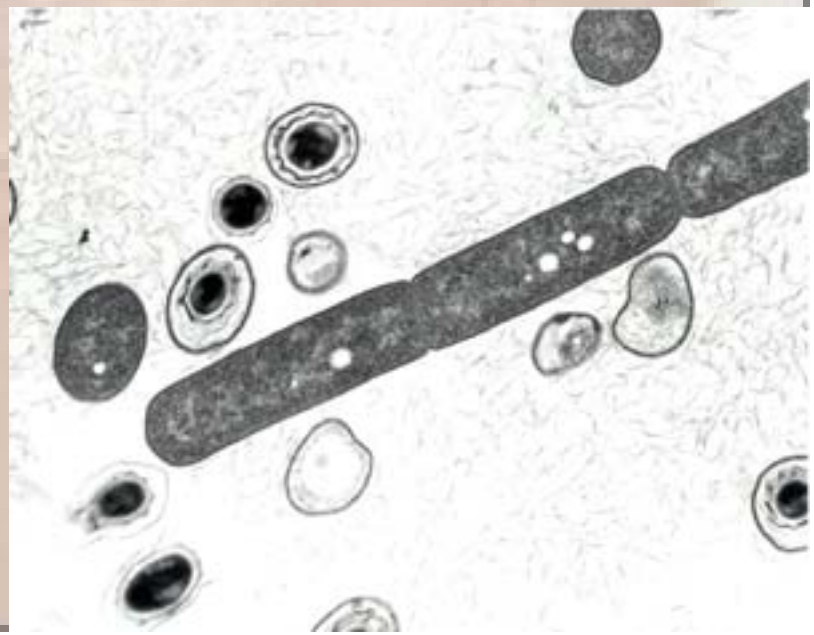




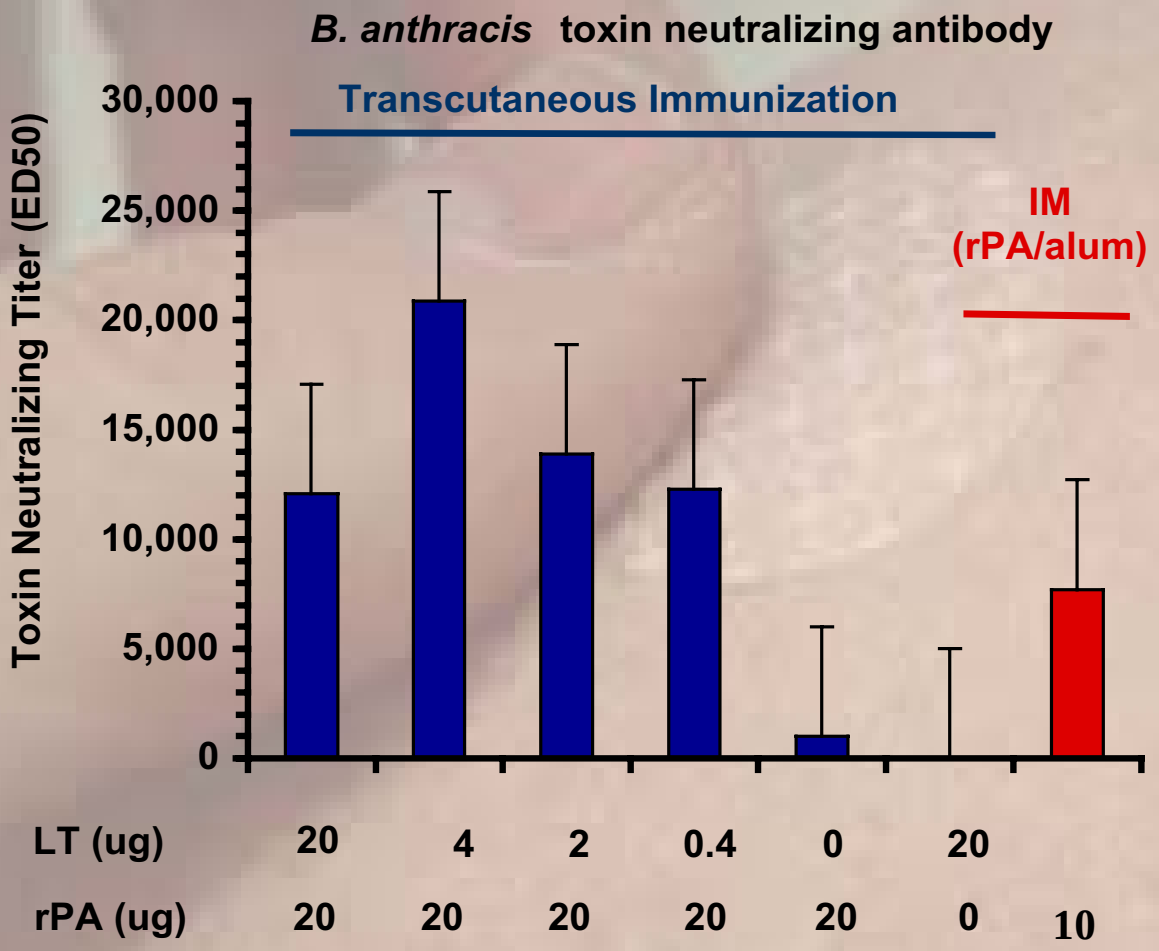
TCI Anthrax Vaccine

- Spore forming, gram+ rod
- Inhalation anthrax 90% fatal
- Toxin-PA component binds
- PA antibodies protective

- Anthrax vaccine by TCI
- rPA as antigen
- LT as adjuvant
- Delivered together



Transcutaneous Immunization with rPA and LT-Adjuvant Elicit Anthrax Toxin Neutralizing Antibodies



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Protection Against Inhalation Spore Challenge

Group	No. of AJ mice	Vaccination (TCI)		Immunization Route	Challenge results
		LT* (µg)	rPA* (µg)		Protection (%)
1	10	20	50	TCI	100
2	10	4	20	TCI	100
3	2	1	5	TCI	100
4	8	20	0	TCI	0
5	10	0	50	TCI	100
6	10	Alum	5	IM	100
7	10	naïve			0

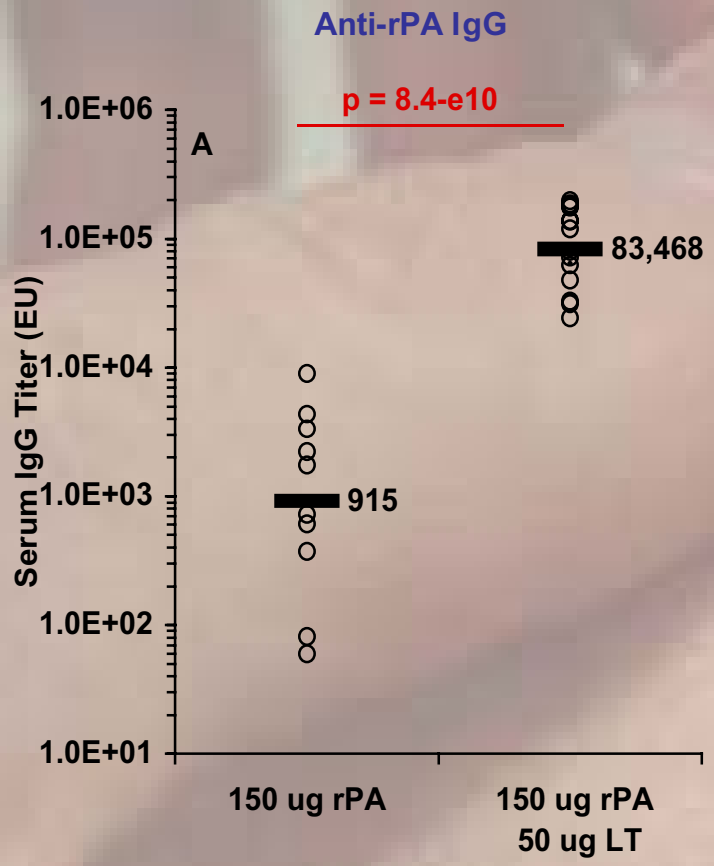
Immunized day 0, 14, and 28, challenged 3 wks after last dose

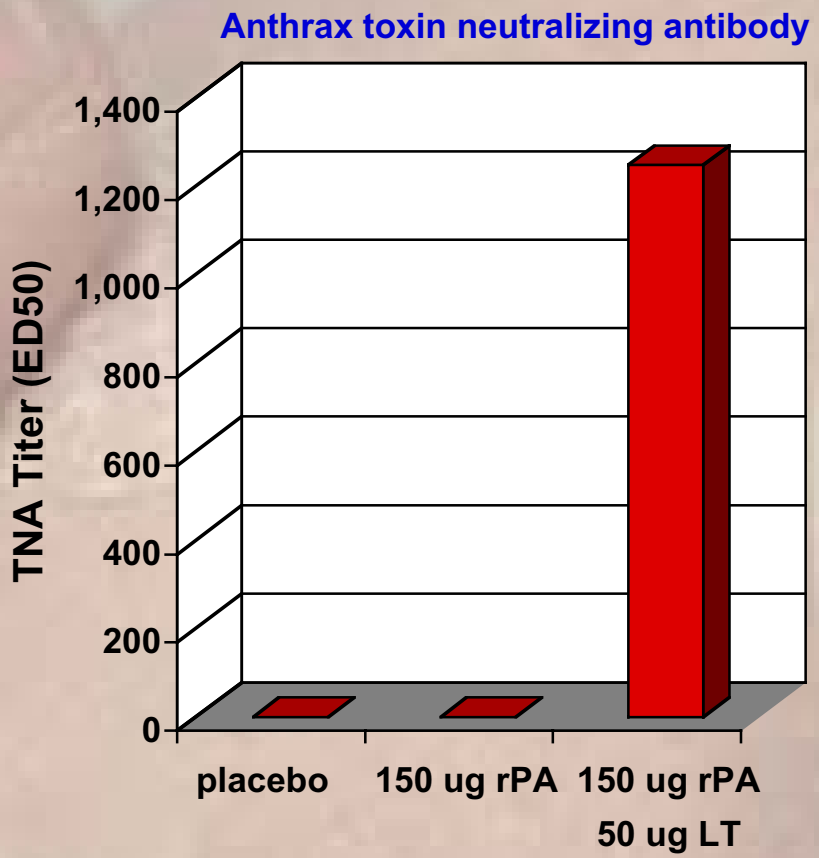
IOMAI/DSTL

Rabbits Immunized with a Protein in Adhesive Patch Containing LT and rPA

3 ds (d 0, 14, 28), TCI

2 wks post immunization





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Protocol 1198-107

Conclusions

- Clinical experience in 16 trials validate the safety and immunogenicity of TCI
- Clinical experience is critical for exposing the viability of vaccine technologies
- Vaccine delivery via a patch is feasible and task is to develop a commercial product


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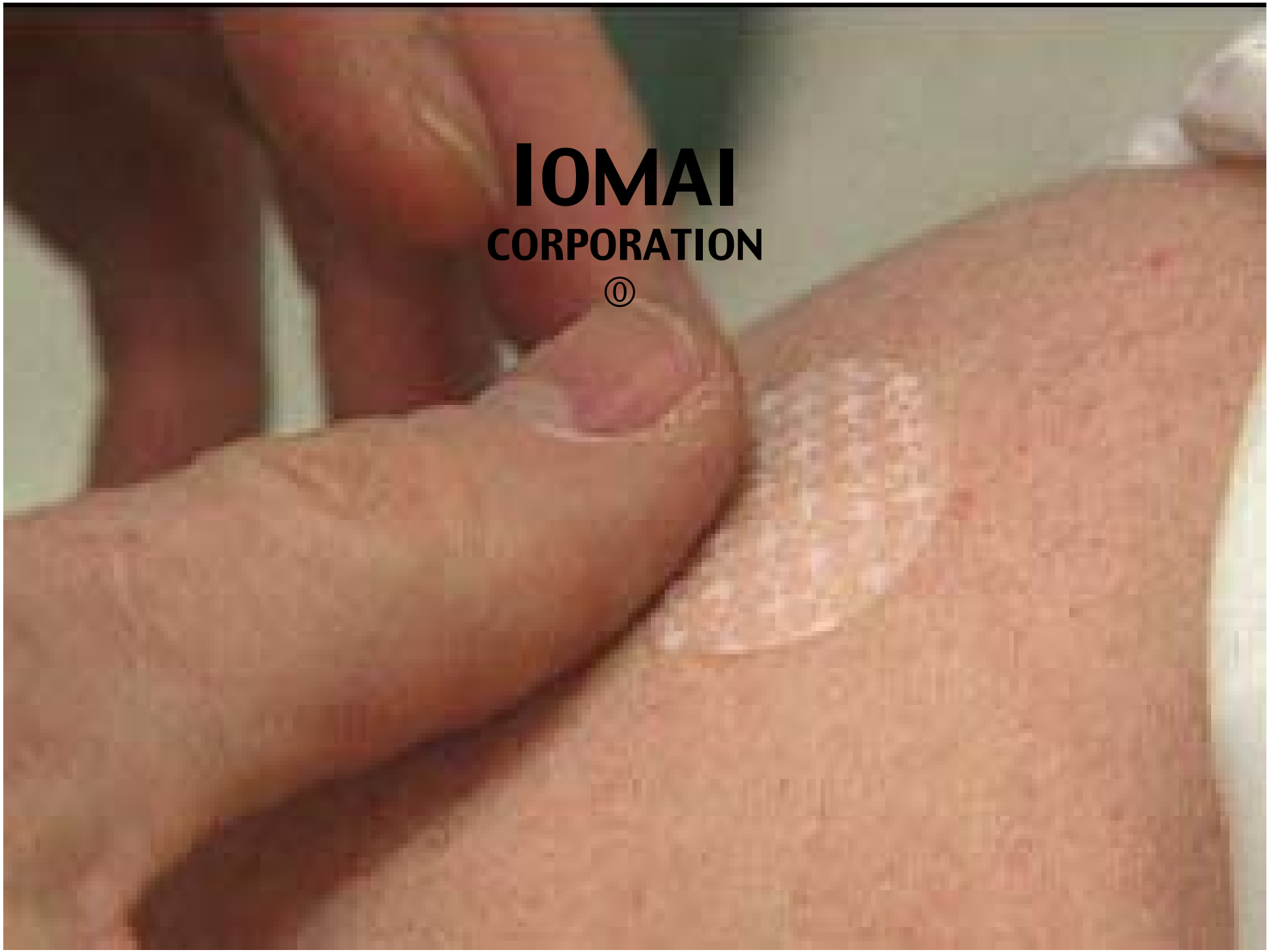
IOMAI
CORPORATION

Selected Publications

Needle-free skin patch vaccination method for anthrax, Matyas et al. **Infect Immun (in press)**

Transcutaneous immunization and immunostimulant strategies, Glenn et al. **Immunol Allergy Clin N.A. (in press)**

Transcutaneous immunization and immunostimulant strategies: capitalizing on the immunocompetence of the skin, Glenn et al. **Expert Rev Vaccines (2003);2:253**

Immunostimulant patch containing heat labile enterotoxin from E. coli enhances immune responses to injected influenza vaccine through activation of skin dendritic cells, Guebre-Xabier et al. **J Virol (2003);77:5218**

Transcutaneous immunization, Glenn et al. **New Generation Vaccines, 3rd Edition (Jan 2004)**

Safety and immunogenicity of a prototype enterotoxigenic Escherichia coli vaccine administered transcutaneously, Guerena-Burgueno et al. **Infect Immun (2002);70:1874**

Transcutaneous immunization using colonization factor and heat labile enterotoxin induces correlates of protective immunity for enterotoxigenic Escherichia coli, Yu et al. **Infect Immun (2002);70:1056**

Transcutaneous immunization: T cell responses and boosting of existing immunity, Hammond et al. **Vaccine (2001);19:2701**

Transcutaneous immunization with bacterial ADP-ribosylating exotoxins, subunits, and unrelated adjuvants.Scharton-Kersten **Infect Immun (2000);68:5306**

Transcutaneous immunization: a human vaccine delivery strategy using a patch, Glenn et al. **Nat Med (2000):6:1403**

Transcutaneous immunization: a new vaccine delivery strategy, Glenn et al. **The Jordan Report 2000: Accelerated Development of Vaccines**, **2000**

Transcutaneous immunization with cholera toxin protects mice against lethal mucosal toxin challenge, Glenn et al. **J Immunol (1998);161:3211**

Skin immunization made possible by cholera toxin, Glenn et al. **Nature (1998);391:851**