Epidermal Powder Immunization

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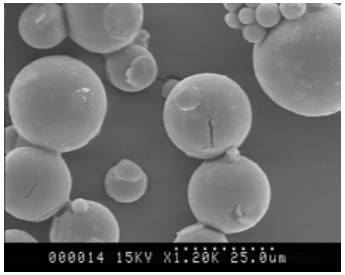
December 17, 2003

Innovative Administration Systems for Vaccines

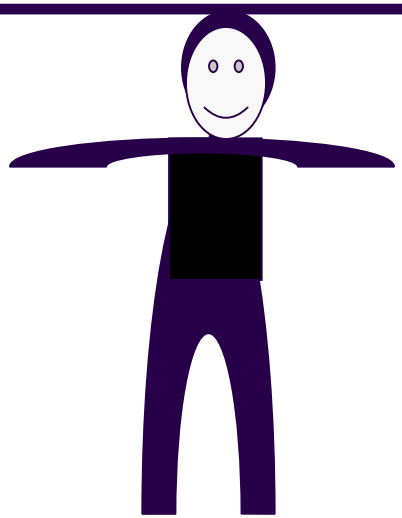
Epidermal Powder Immunization

Devices

Particle Formulation



Immunology



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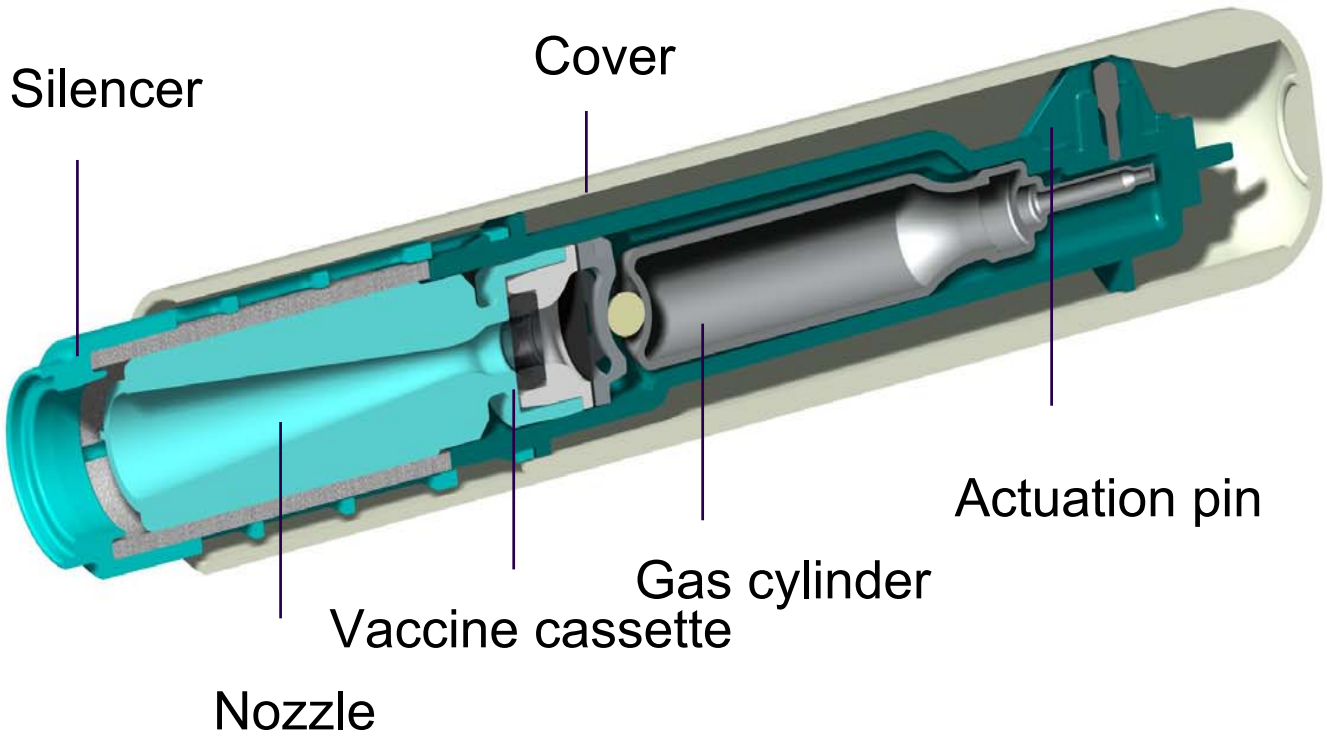
Single Use Device



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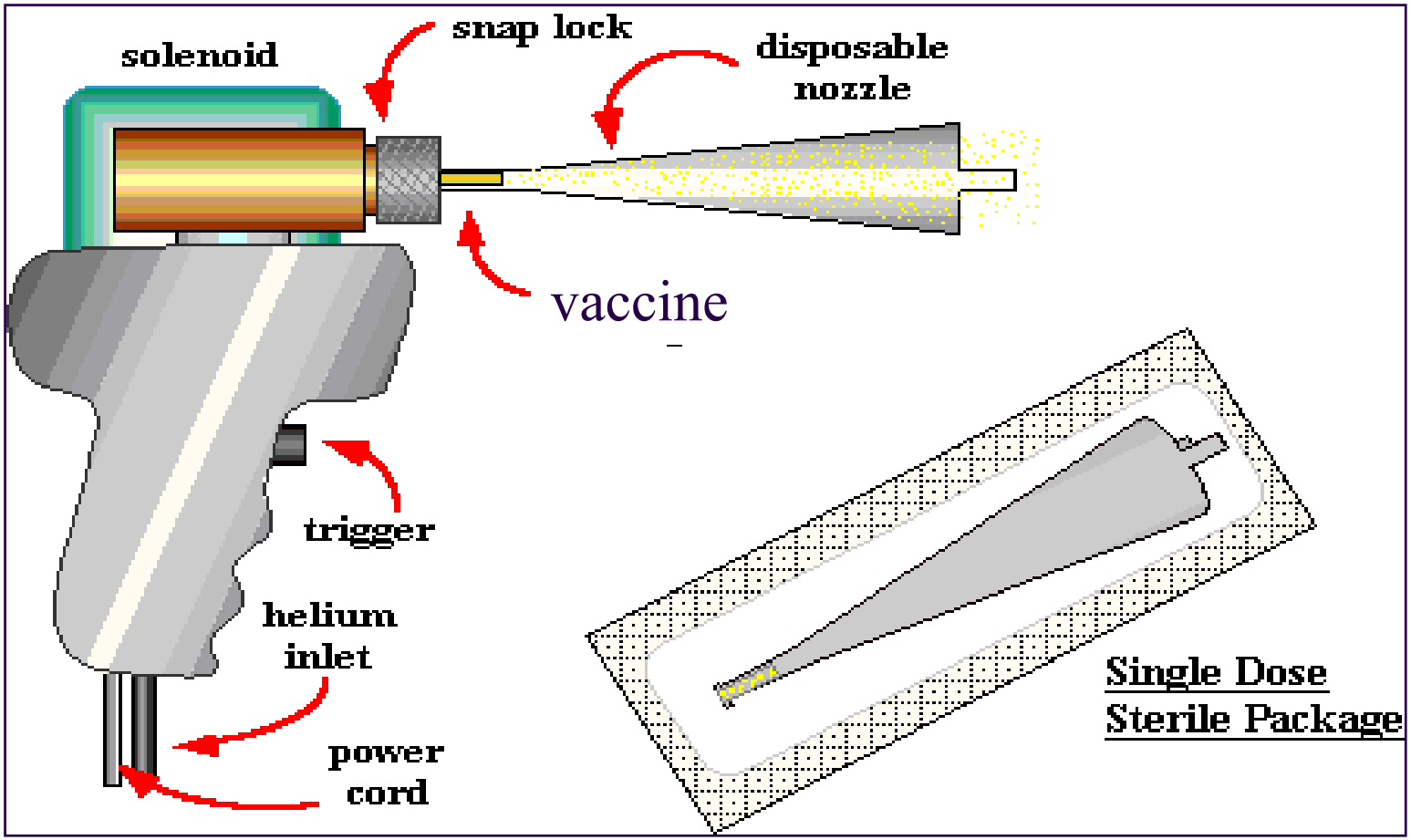
Reusable Device



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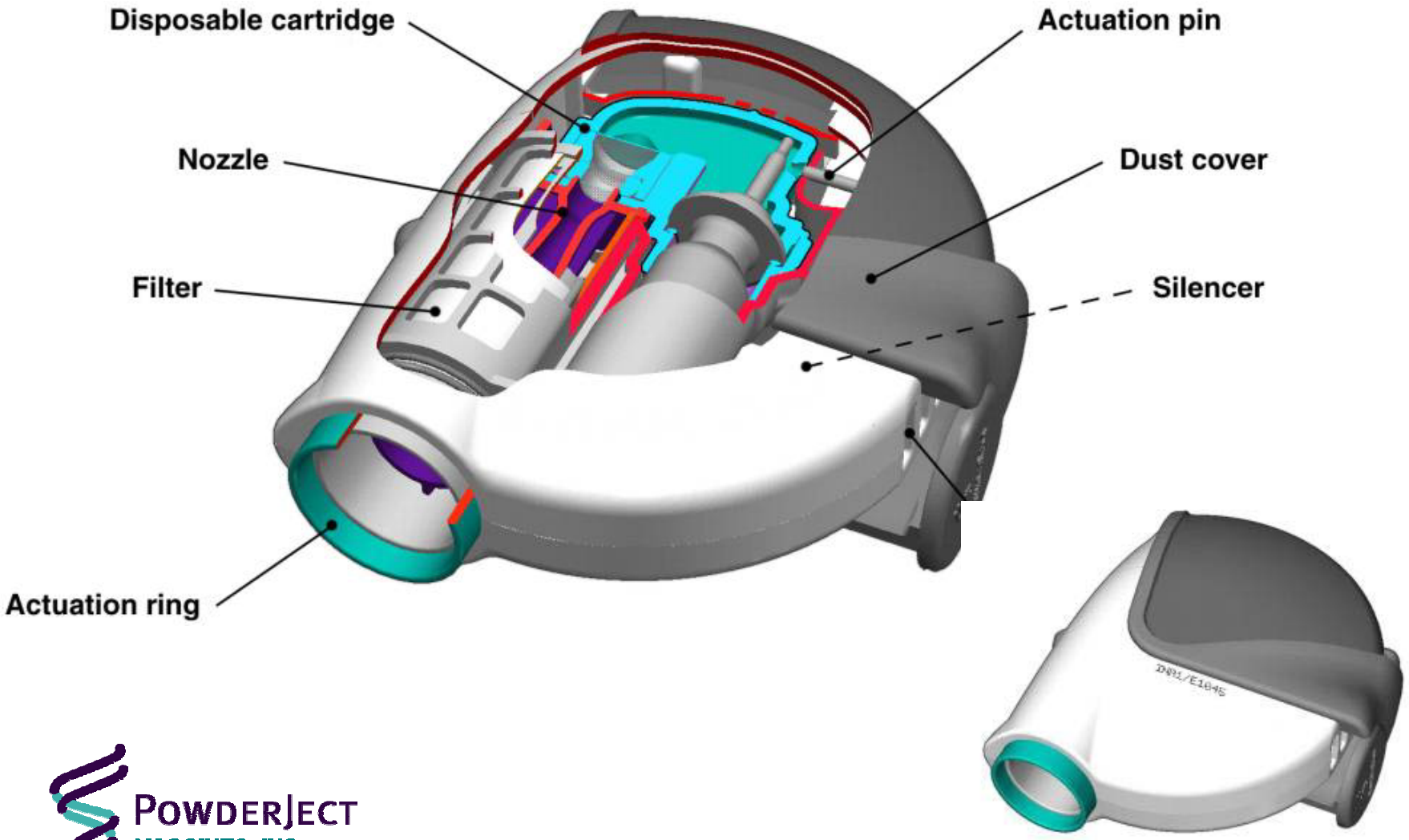
Multi-use Dermal PowderJect NR System



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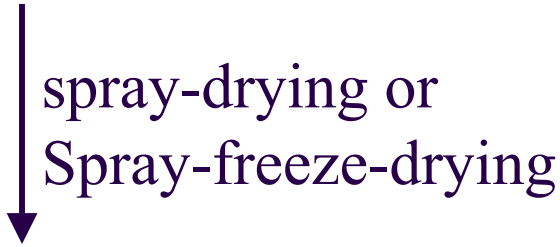
Particle Formulations

Liquid vaccines + excipients (sugars, stabilizers)



Particles suitable for EPI
- Size: 20-50μm
- Density: 0.5-1.0g/ml
- Moisture: 2-3%

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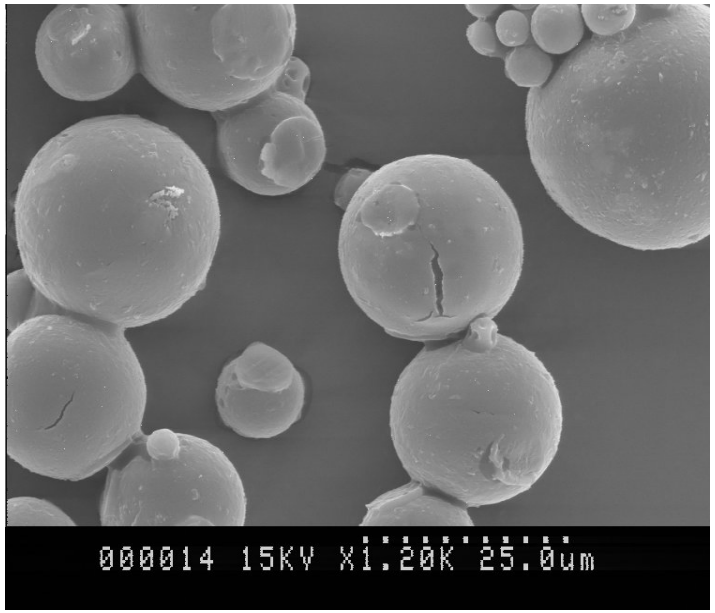
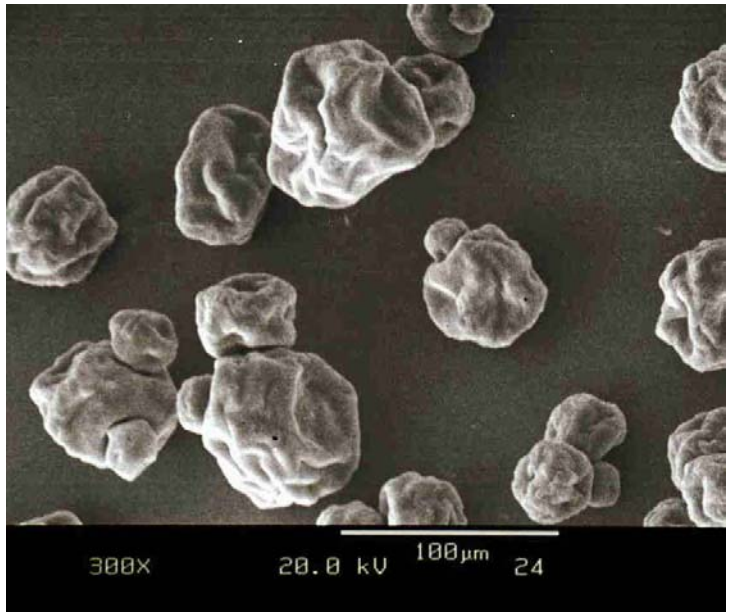
SEM Images of Particles



Spray-dried



Spray-freeze-dried

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Stability of SFD Influenza Vaccine

- After storage for 12 weeks at 40ºC:
  - Physical stability of particles
  - Biochemical stability of vaccine antigen
  - Retaining of immunogenicity
- May not need cold chain for storage and transportation

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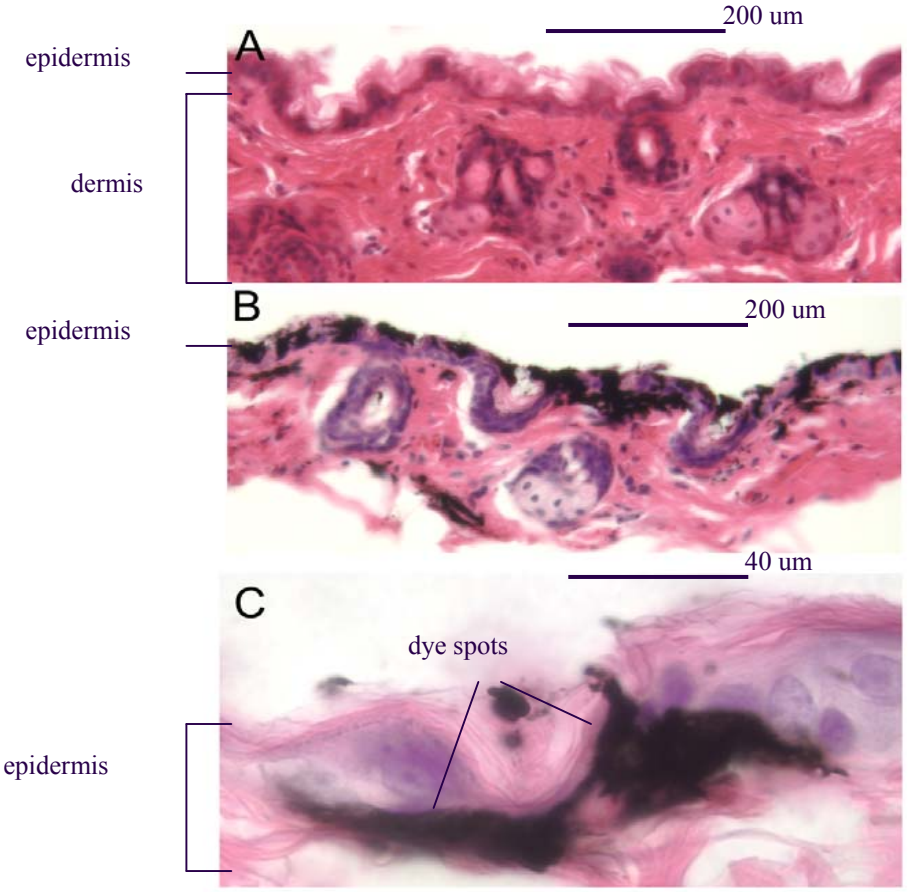
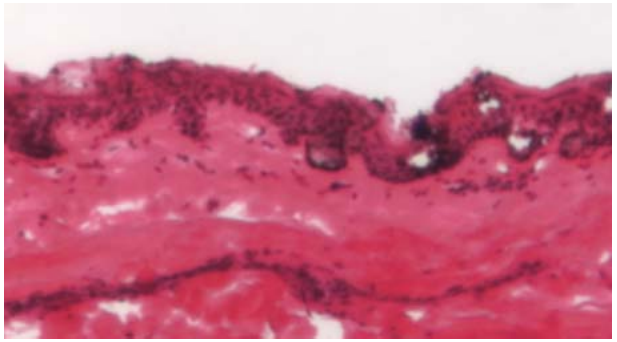
Particle Penetration

Mouse



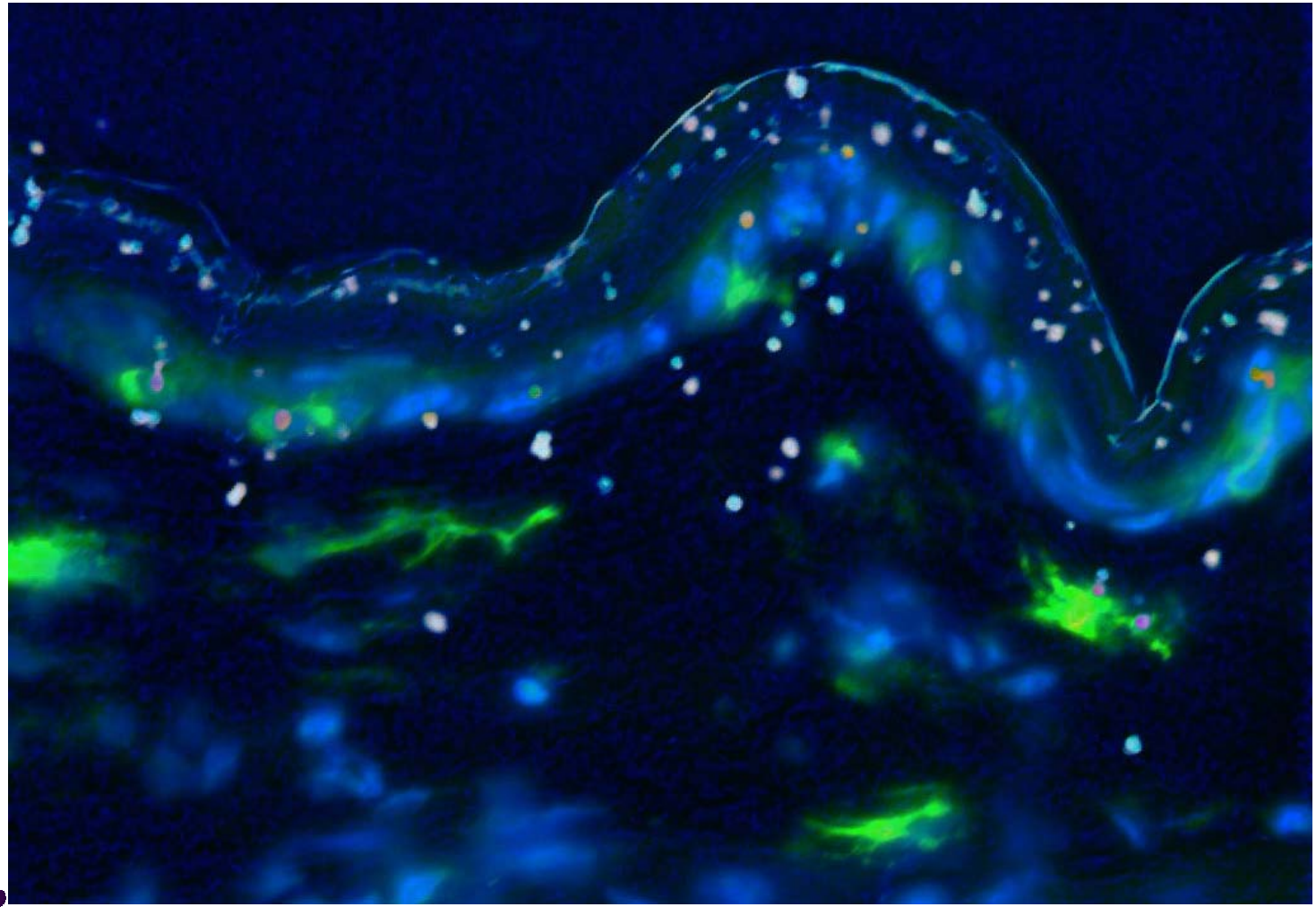
Human



Pig skin model:

Epidermis: 70-80%
Dermis: 20-30%

Mouse Skin



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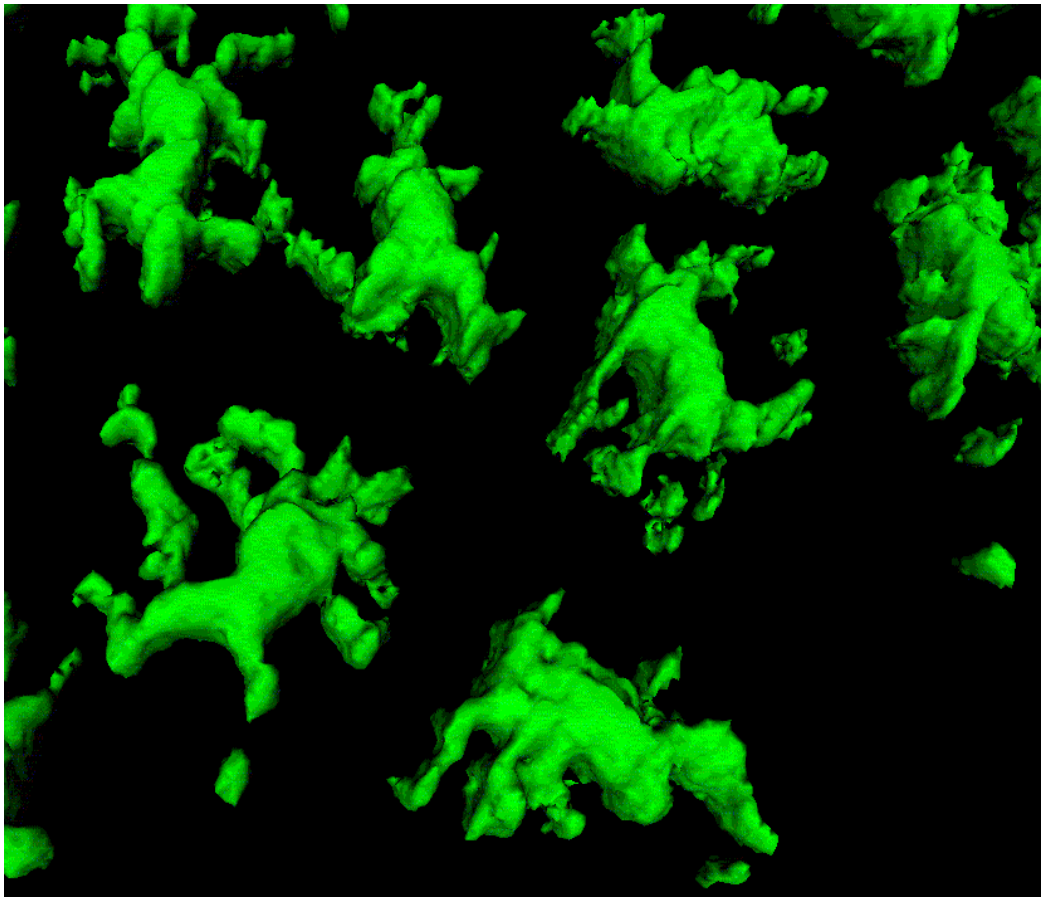
MPLSM Image of Mouse LCs



U. Tirlapur, W. Mulholland, E. Arbuthnott, M. Kendall 19 May 2003.

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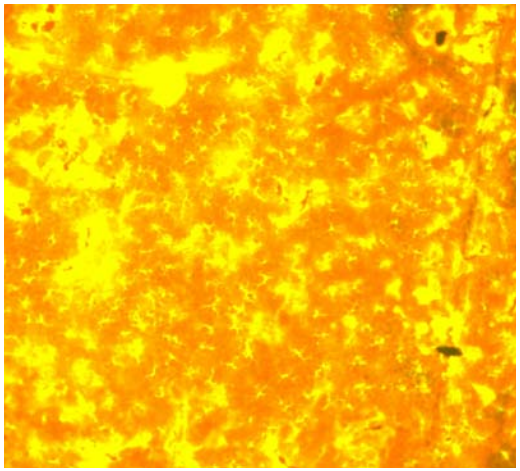
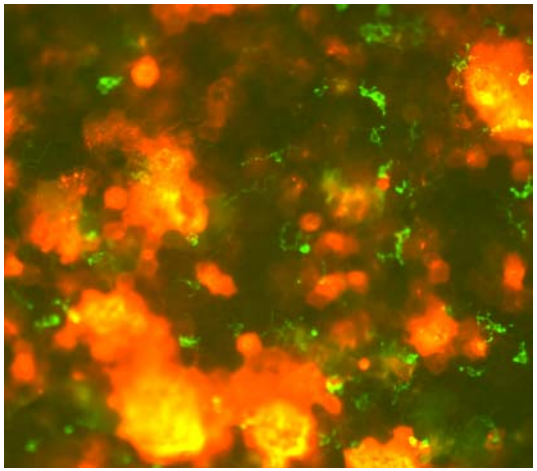
EPI Delivers Vaccines to Langerhans Cells

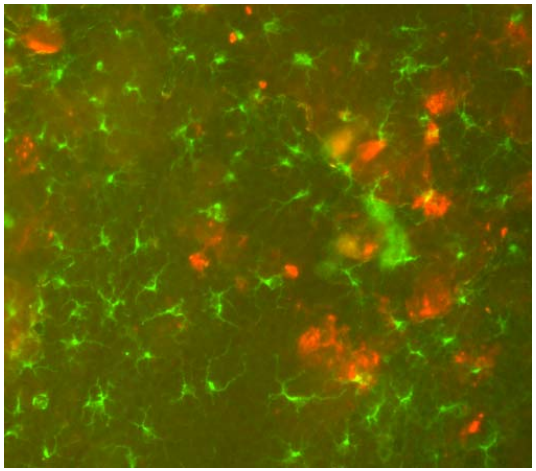
4 hr



2 days



5 days



There are 10^5 LCs at each EPI site

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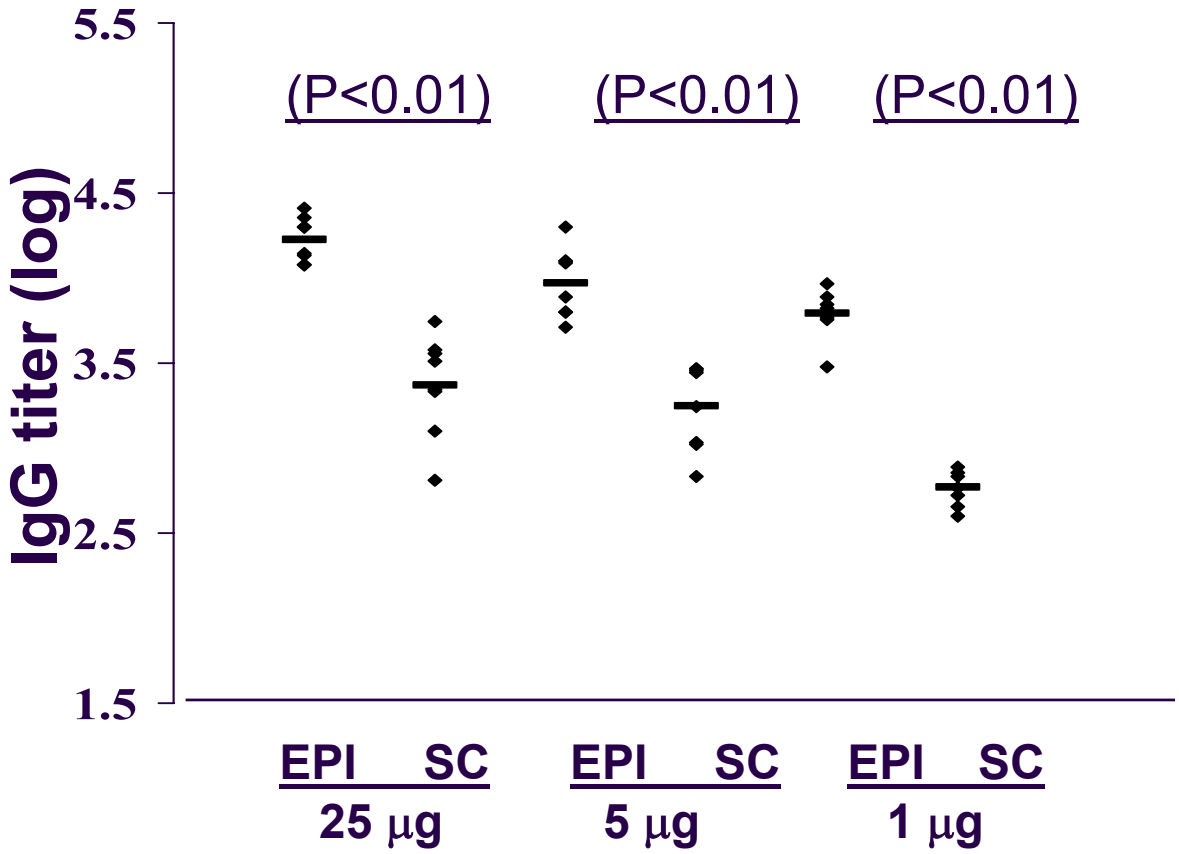
Role of LCs in Immune Responses

- Antigen-carrying LCs migrate to lymph node
- Local depletion of LCs prior to EPI resulted in lower antibody response
- Increased production of cytokine and chemokines by epidermal cells (LCs and keratinocytes): MCP-1, IL-12, TNF-α, IL-6 etc.
- Adoptive transfer of migrating LCs induce immune responses in animals

EPI of Mice with Aichi/68 Virus: Antibody Response After Prime



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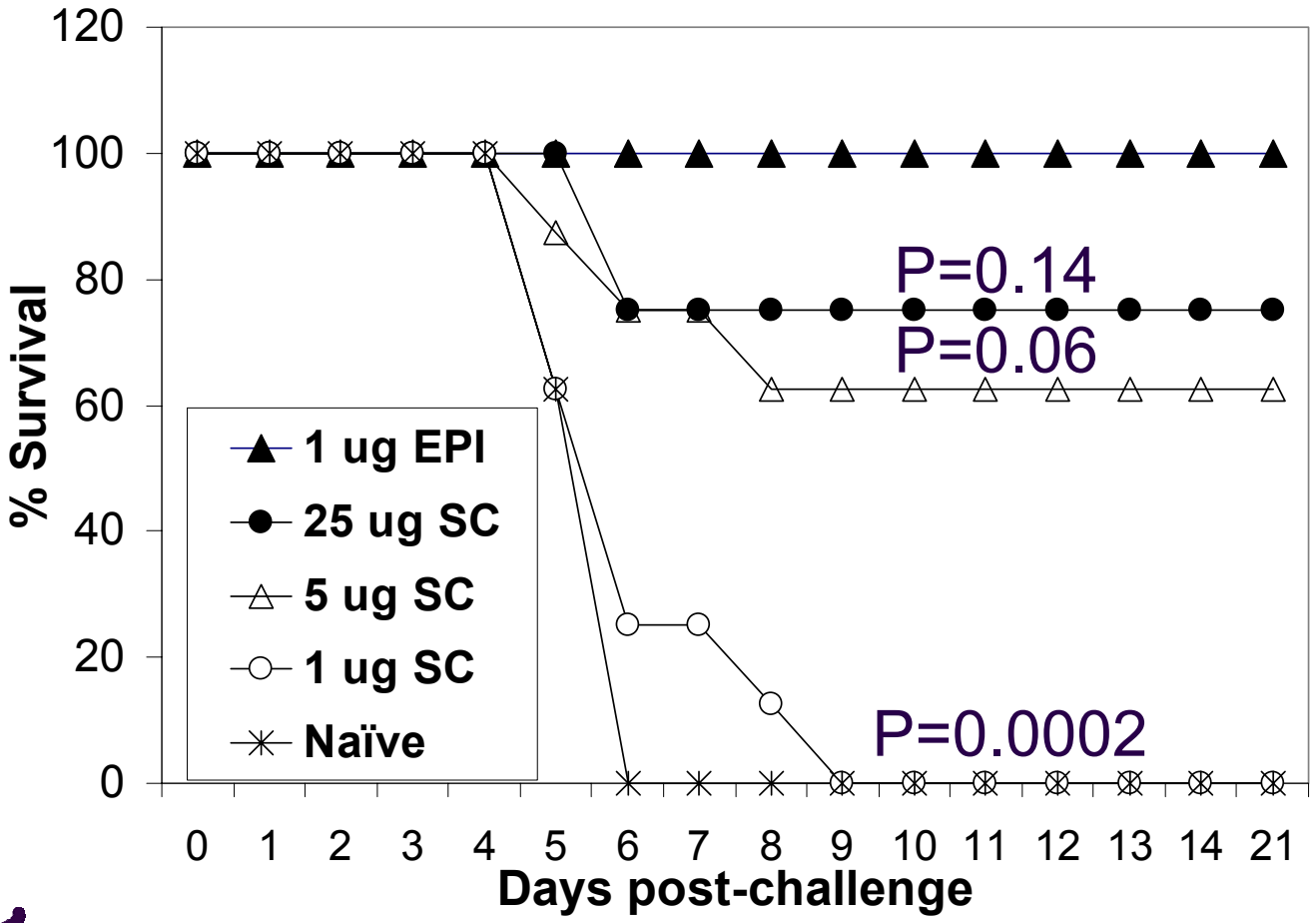
Protection against 10X LD50 Challenge



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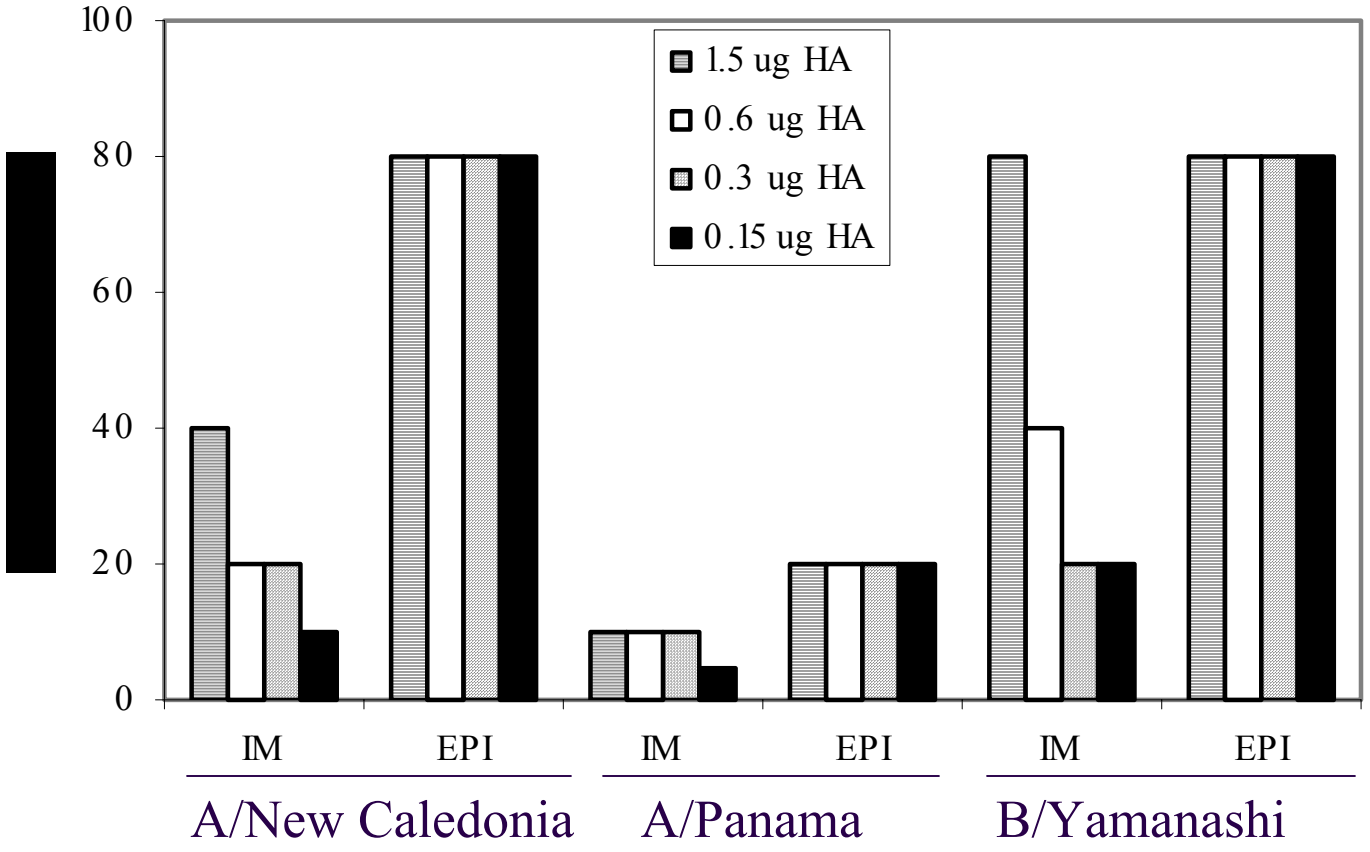
EPI of Mice with a Trivalent Influenza Vaccine: Post-Prime HI Titers



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Phase I Clinical Study

- 3 groups of 12 subjects
  - Group 1: Fluvirin
  - Group 2: PJ Fluvirin
  - Group 3 PJ Fluvirin double dose
- Single immunization only
- Antibody responses at days 0, 14, 21, 28
- Safety, reactogenicity

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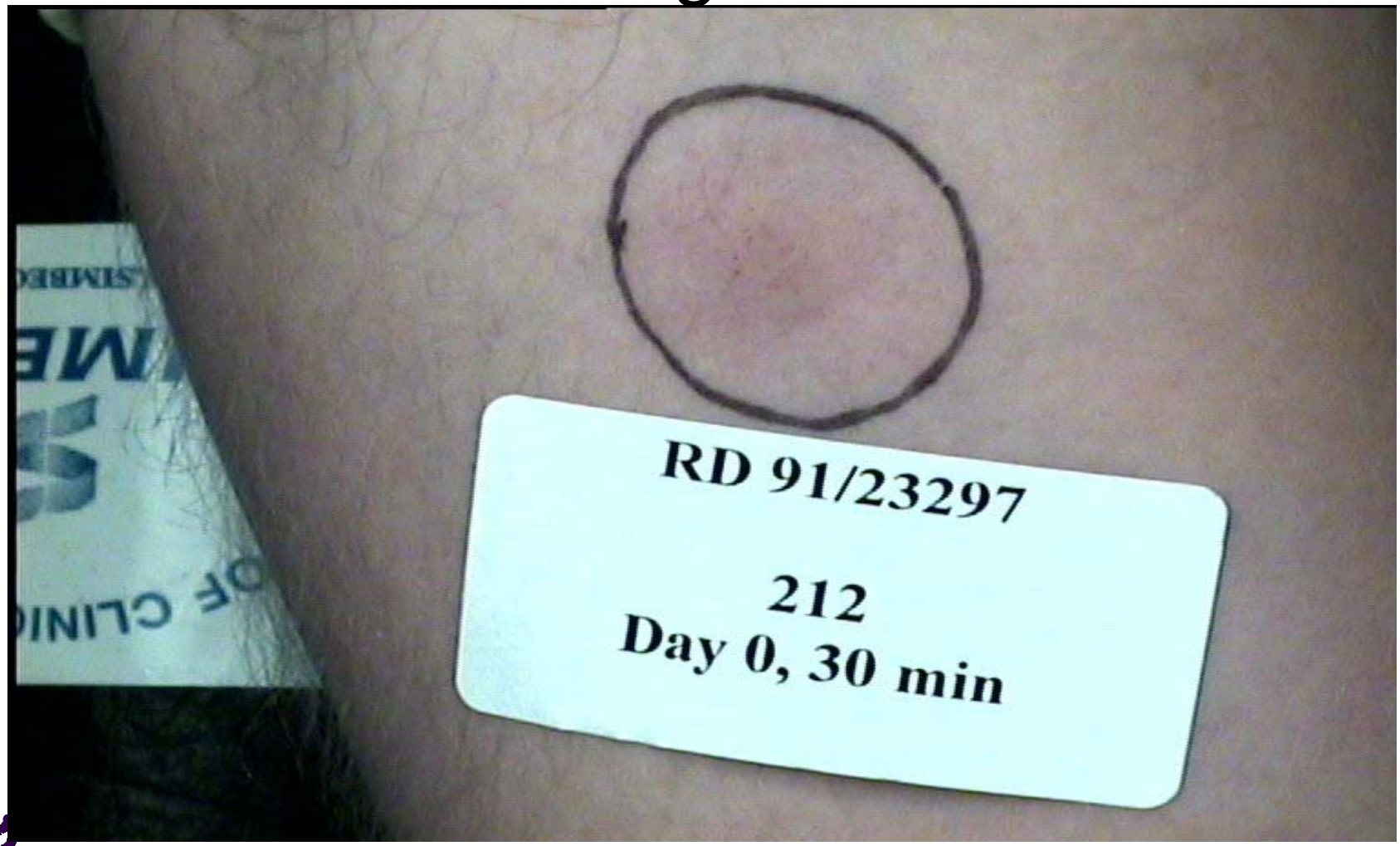
Local Reactogenicity: Day 0, 30 Minutes Post-dosing



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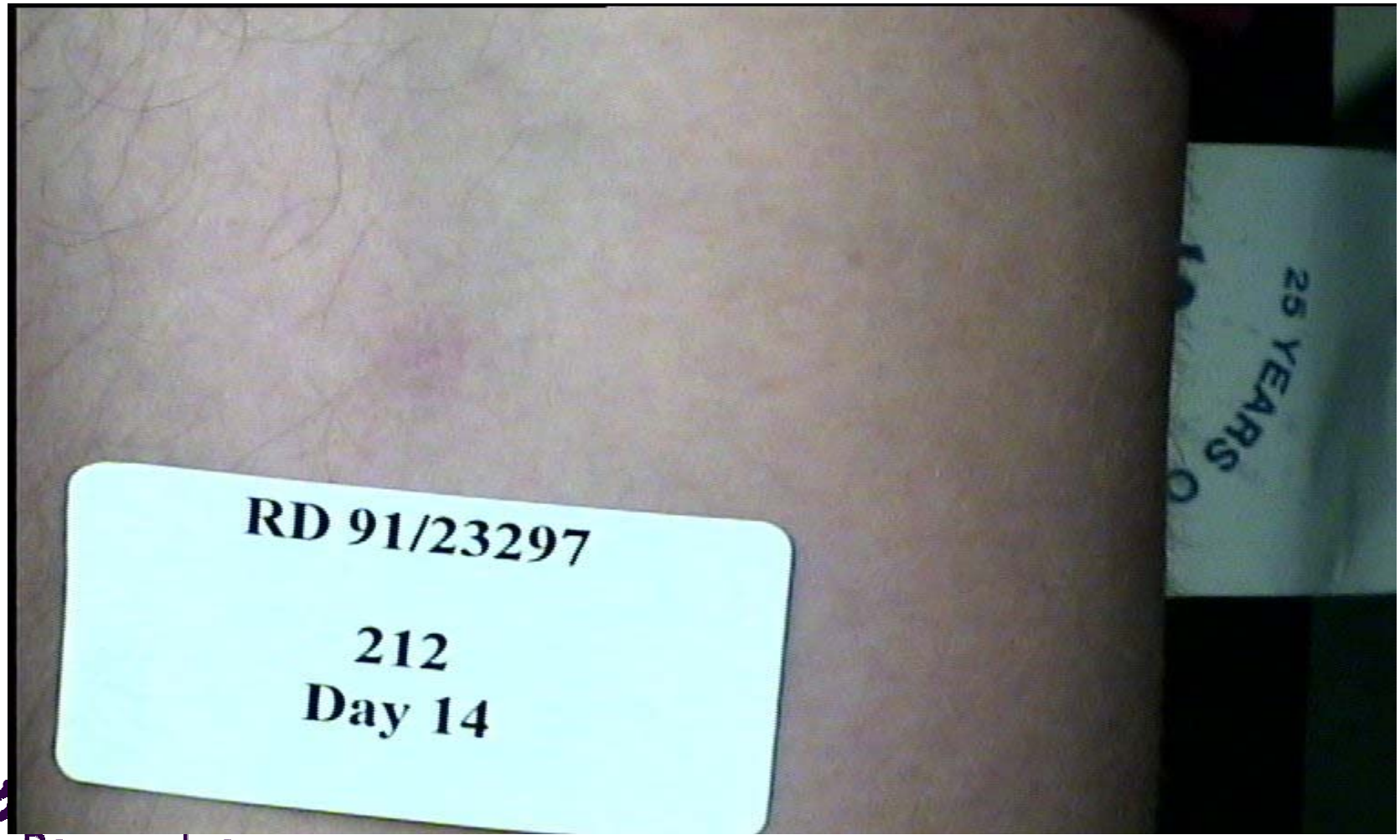
Local Reactogenicity: Day 14



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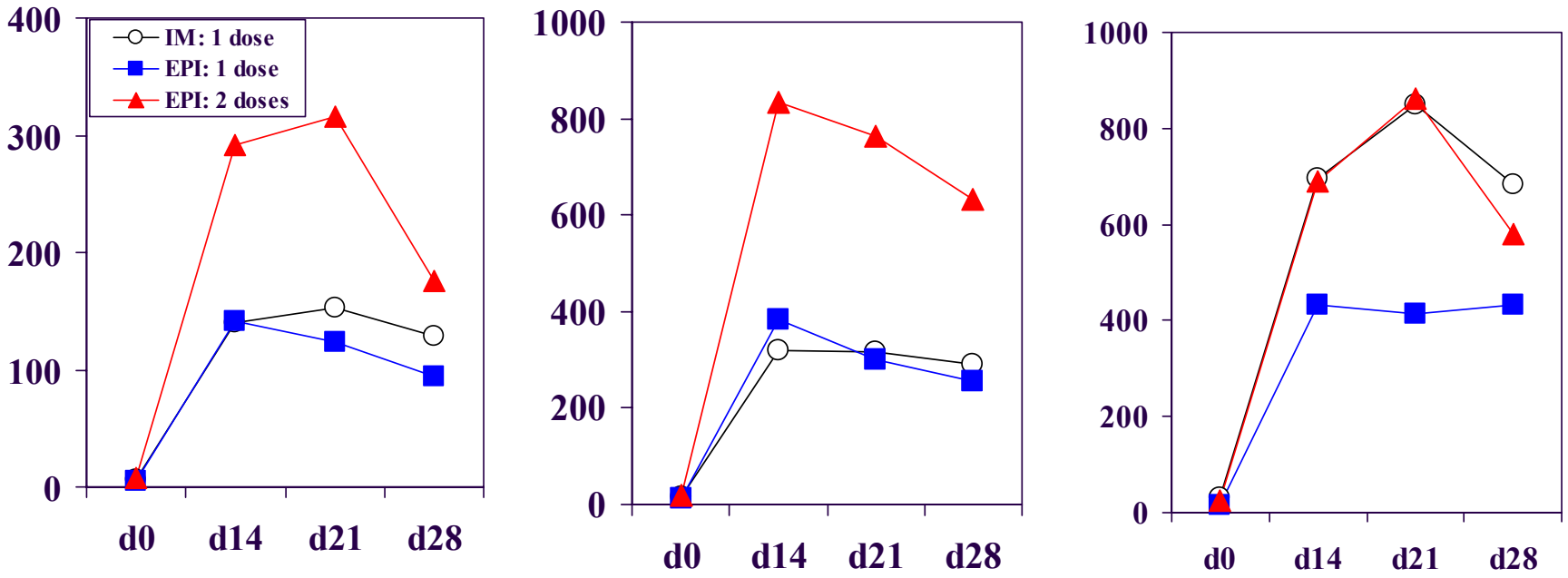
EPI of Humans with a Trivalent Influenza Vaccine



A/New Caledonia A/Moscow B/Sichuan

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Vaccines and Animal Models Evaluated

- Inactivated vaccines:
  - Influenza, HSV-1 equine herpes virus-1, rabies
- Subunit vaccines:
  - Hep B, HIV-gp120, diphtheria-tetanus toxoid, pneumococcal polysaccharide and conjugate, *H. influenzae* b polysaccharide and conjugate
- Live attenuated virus
  - Vaccinia
- Animals: mice, guinea pigs, pigs, monkeys, humans.

Immunogenicity in Animals and Humans

Species	Influenza vaccine
mouse	EPI>IM
Guinea pigs	EPI=IM
Pigs	EPI<<IM
Rhesus macaques	EPI<IM
Human	EPI≥IM

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EPI with Adjuvants

- Many adjuvants were successfully formulated and delivered.
  - Alum salts, CpG DNA, QS-21, MPL, Polymers, lipid-based adjuvants.
- Some adjuvants (CpG DNA, LT/CT-derivatives) are more potent in the skin, thus smaller dose may work
- Some adjuvants appear to be safer due to skin sloughing, limited systemic distribution, lower dose requirement

Projected Regulatory Time Line and Issues

- The pre-clinical and phase I results support developing a Flu vaccine.
- May be suitable for administering biodefense vaccines (e.g. small pox and anthrax vaccine)

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Additional Information

- Formulations are prepared using protein stabilizers (sugars) which can be found in other human products
- The powder processes are well-developed and have been used to produce other pharmaceutical drugs.
- The single-use device is suitable for self-administration
- The reusable device can be used by non-medical staff with limited training.
- Devices are being developed for DNA vaccine products at PowderJect Vaccines.

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Acknowledgements

- PowderJect Vaccines (Madison, WI): Research,pre-clinical safety, project management
- PowderJect Technologies (Fremont, CA): Formulation and process development
- PowderJect Pharmaceuticals (Oxford, UK): Device, clinical, and regulatory
- Evans Vaccines (Speke, UK): Powder manufacturing
- Simbec Research Limited (Merthyr Tydfil, UK): Phase I study center

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