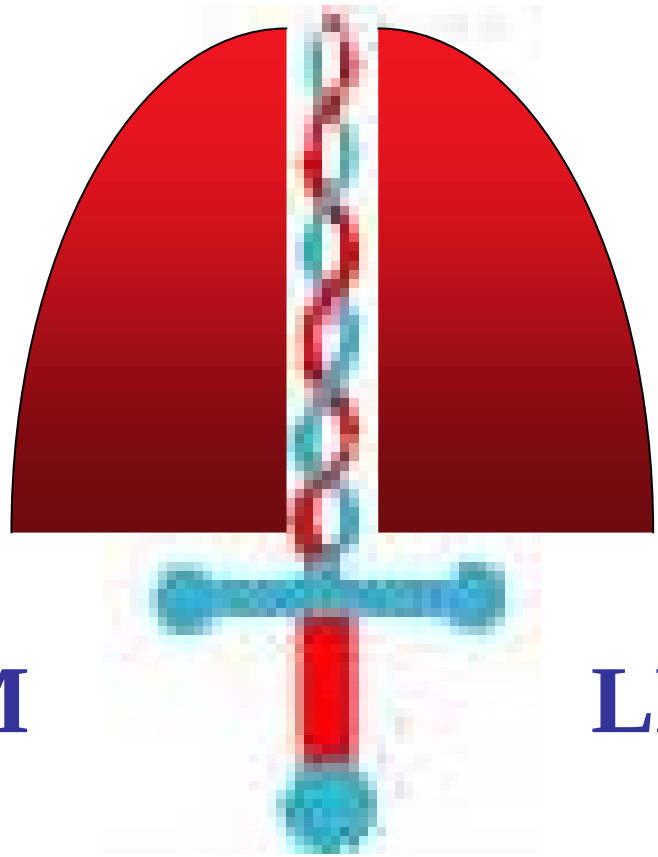
Lung Biodefense



UNM LRRI

UNM Aerobiology Program

Animal Infection Model Development Center

Rick Lyons, University of New Mexico-Health Sciences Center

Albuquerque, NM

Bacteria:

BW relevance

- ***Bacillus anthracis***
- ***Salmonella typhimurium***
- ***Yersinia pestis***
- ***Francisella tularensis***

Clinical relevance

- ***Staphylococcus aureus***
- ***Streptococcus pneumonia***

Viruses:

BW relevance

- **Cowpox**
- **Influenza**

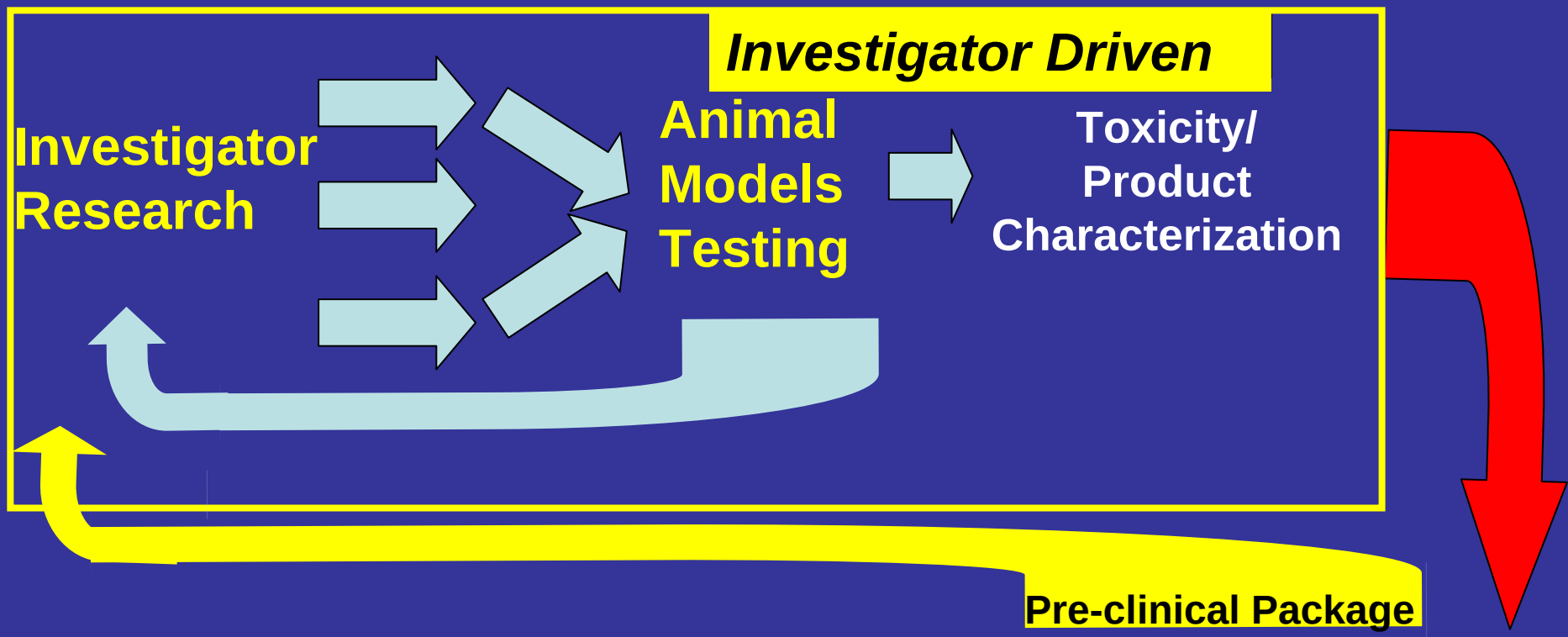
BW & Clinical relevance

- **Herpes Simplex Virus I**
- **Respiratory Syncytial Virus**

Challenges of Biothreat Animal Models

- Very little information regarding lung interactions
- Models not well characterized
- Molecular before the model ??
- Emphasis on model extrapolation and primates

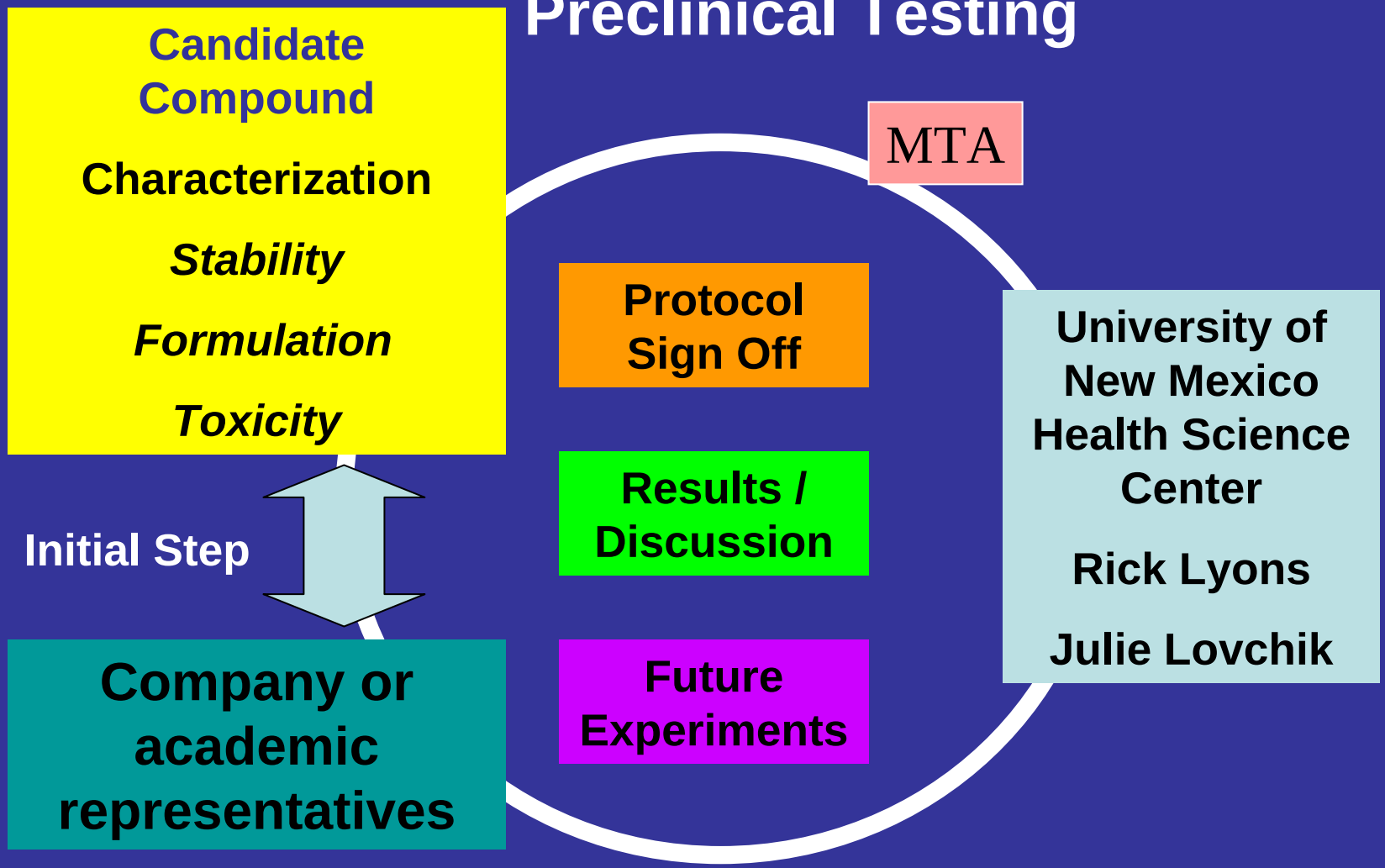
Goal: Comparable Data Sets



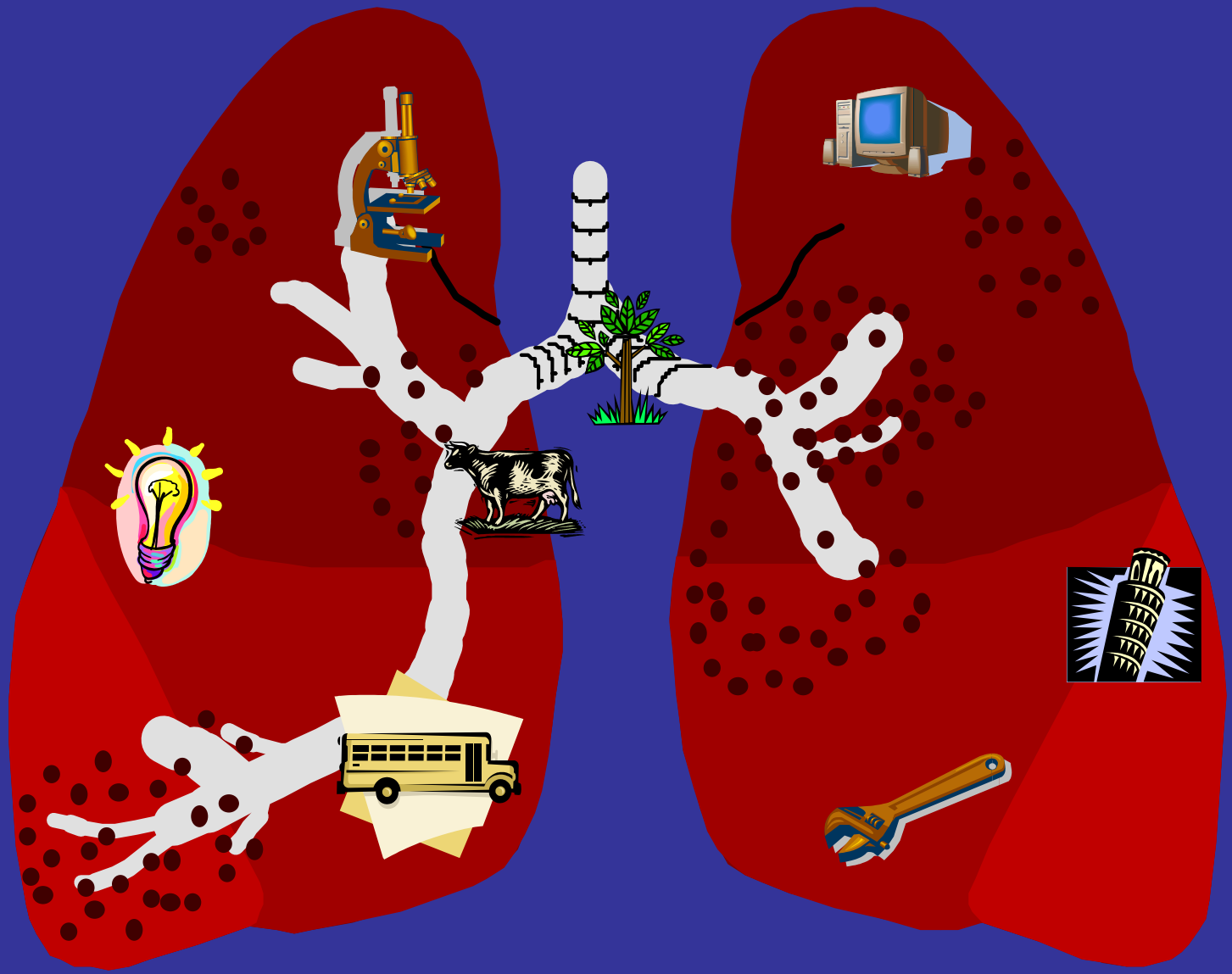
DECISION ANALYSIS

CDS TESTING IN STANDARDIZED MODELS
UNMHSC

Flow Chart for Entering Compound for Preclinical Testing

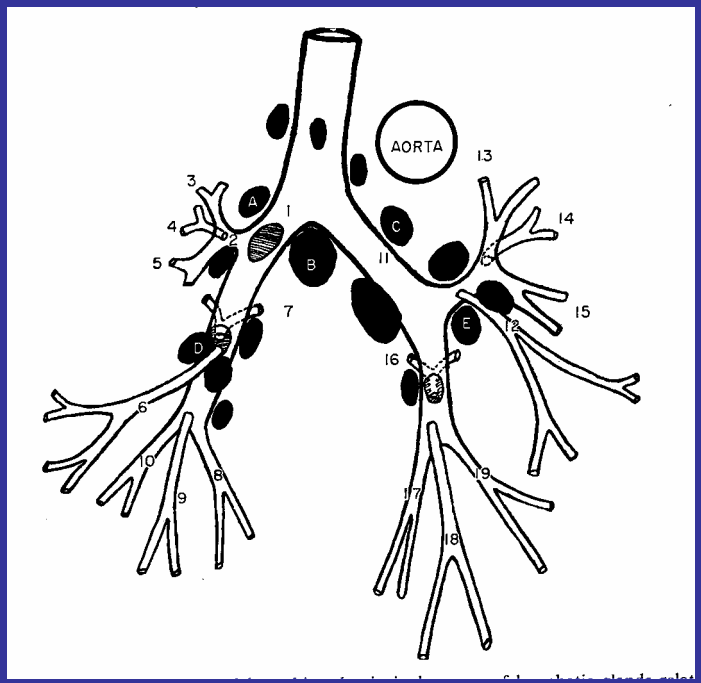


Getting Things into Lungs



Human versus Murine Pulmonary Architecture

Mouse lung a good model for the terminal bronchioles of humans



The cells lining the majority of mouse airways are similar to cells lining terminal bronchioles of humans

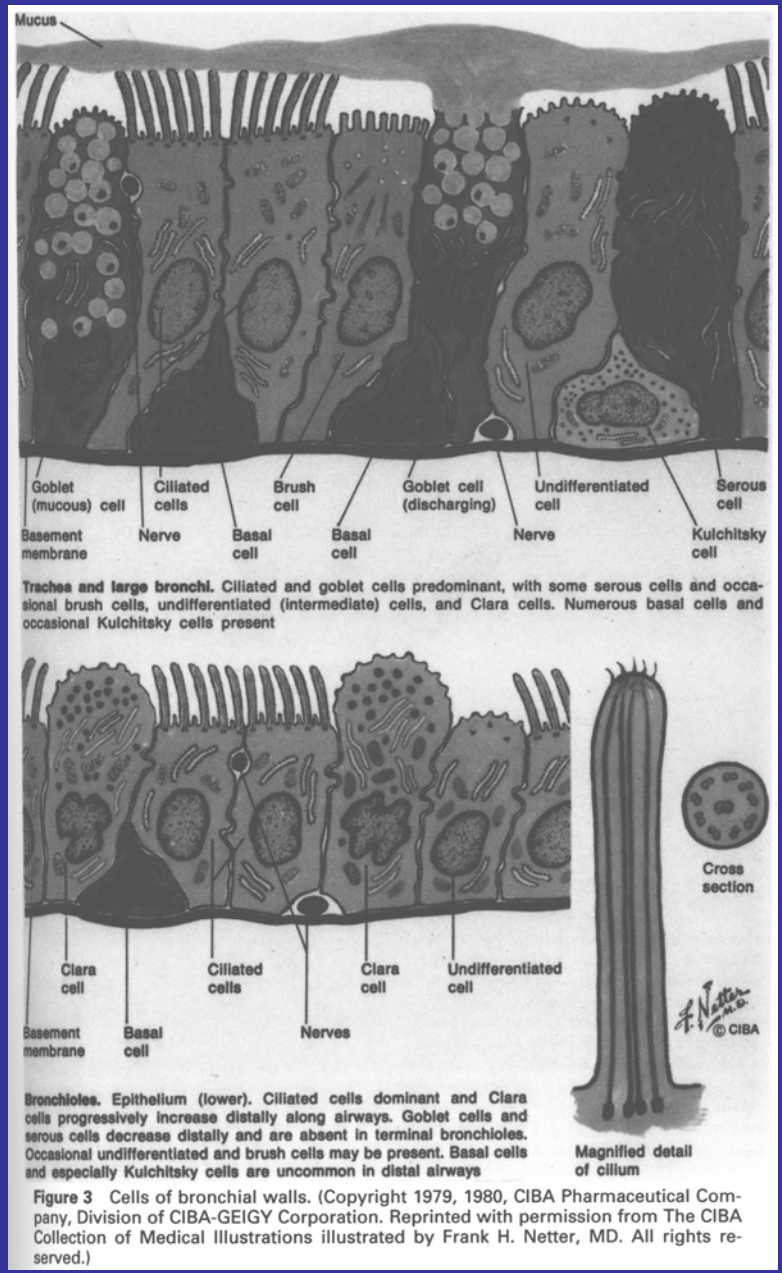


Figure 3 Cells of bronchial walls. (Copyright 1979, 1980, CIBA Pharmaceutical Company, Division of CIBA-GEIGY Corporation. Reprinted with permission from The CIBA Collection of Medical Illustrations illustrated by Frank H. Netter, MD. All rights reserved.)

Taken from : *Concepts in Inhalation toxicology, McClellen & Henderson*

Internal Particle deposition mechanisms

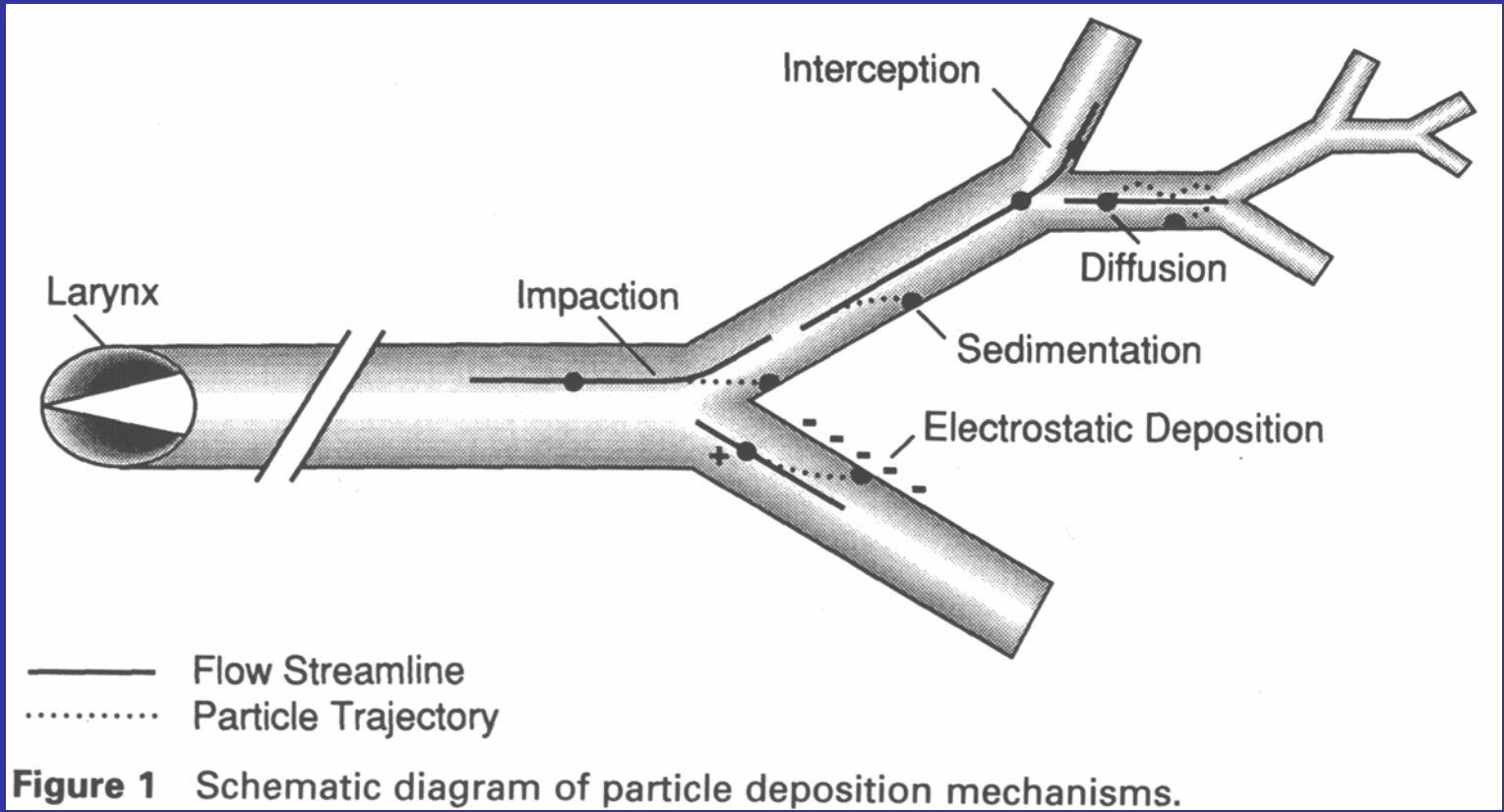
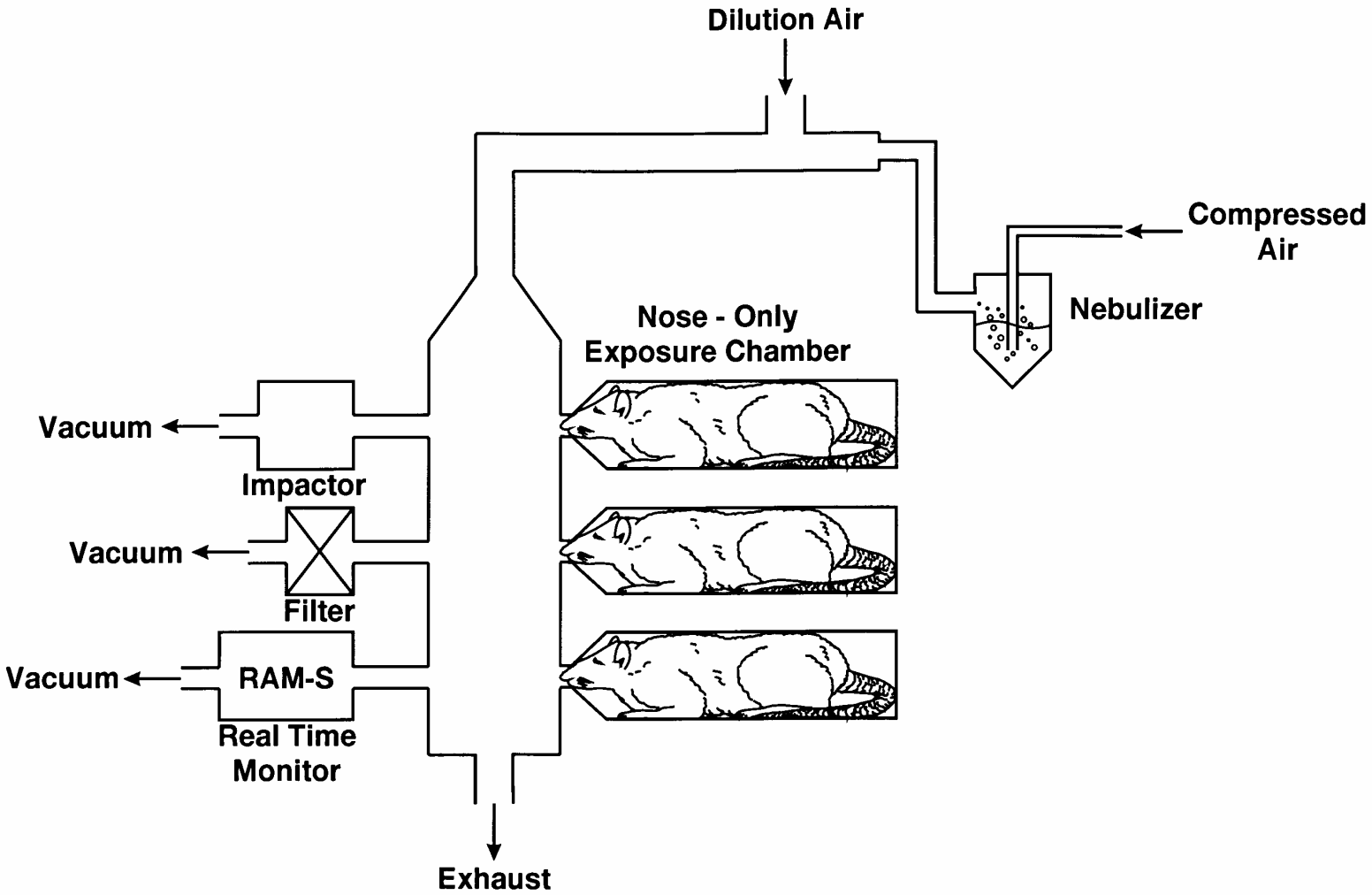


Figure 1 Schematic diagram of particle deposition mechanisms.

Taken from : *Concepts in Inhalation toxicology, McClellen & Henderson*

Typical Nose Only set up



Aerosol

Advantages

Mimic particulates

Even distribution

Disadvantages

Technical challenging

Large portion to nares, upper respiratory tract and gut

Large quantity of viruses or bacteria needed

Depositions dependent on multiple factors

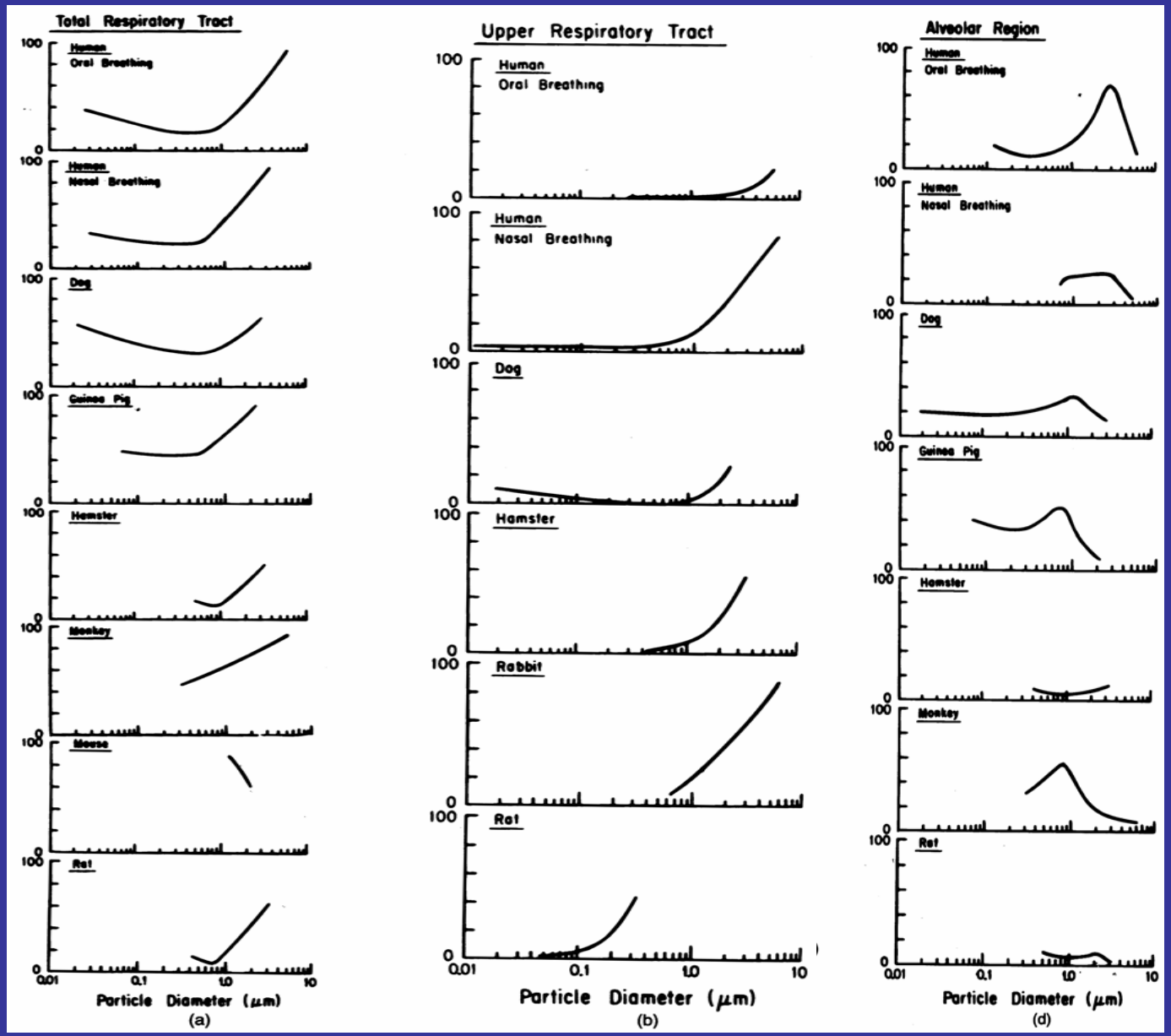
- **Rate of breathing**
- **Environmental**

Efficiency to pulmonary region very poor in rodents

Special situations difficult to adapt

Difficult to transfer between institutions

Efficiency of Depositions among different Species



Taken from : *Concepts in Inhalation toxicology, McClellen & Henderson*

Complex turbinate structure of rodents impede optimal aerosolization

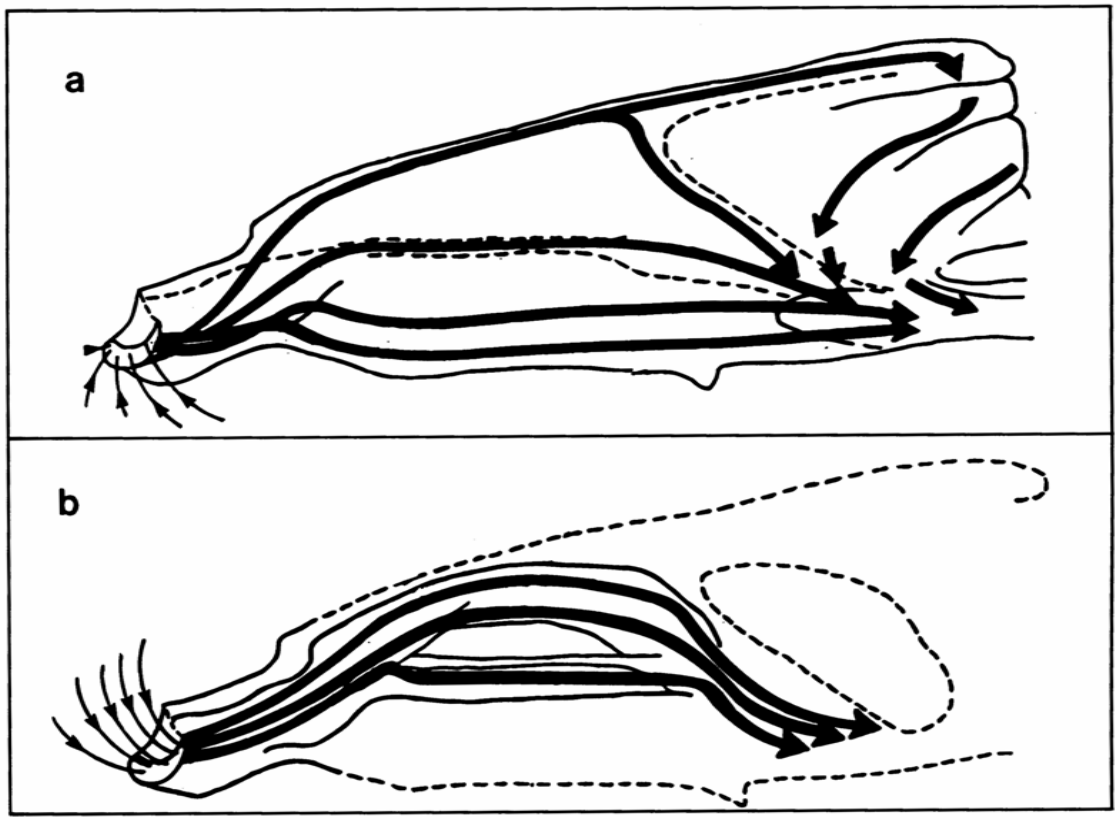


Figure 2 Diagrammatic representations of inspiratory airflow streams in the nose of the F344 rat. Panel (a) shows major medial streams, while panel (b) shows major lateral streams. Adapted from Morgan et al. (1991).

Taken from : *Concepts in Inhalation toxicology, McClellen & Henderson*

Intranasal & intratracheal delivery

Advantages

Technology is easily transferred among labs

Dosing reproducible

Most of dose delivered to lung

Adaptable to modifications

Disadvantages

Liquid introduced

Distribution multi-focal but not evenly distributed

GLP Challenges

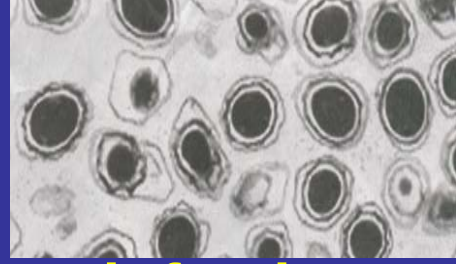
Basically measuring several bell shaped curves for each experiment no matter what method of delivery

- Dosing
- Depositions

Standardize as much as possible

- Protocol for production of inoculums
- QC equipment and personnel

Anthrax- Pathogenesis

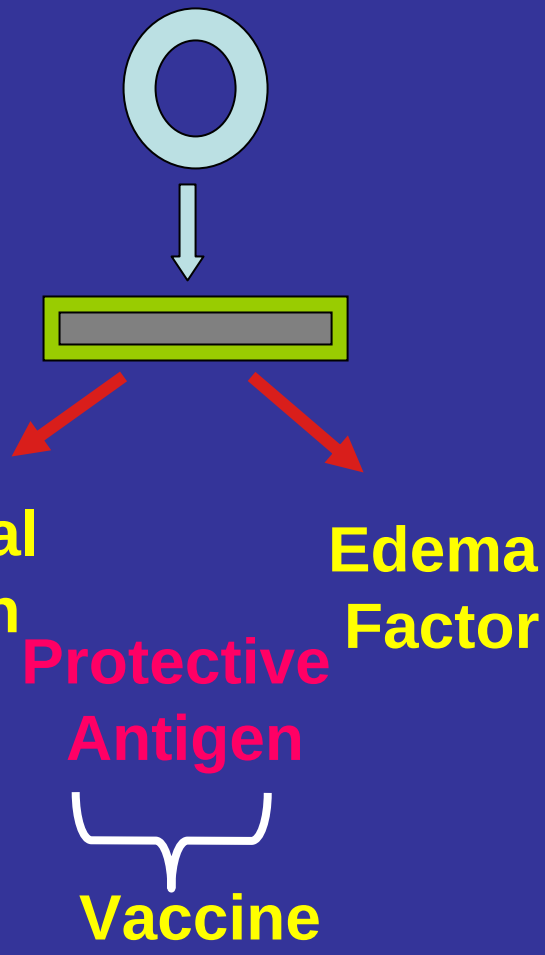


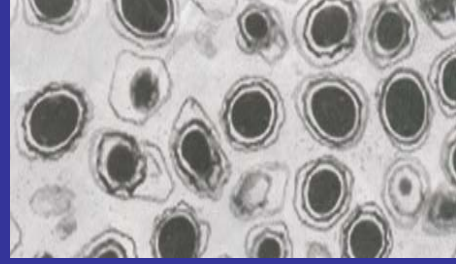
Anthrax has at least three factors to establish an infection

1. **Capsule**
   (Large influence in murine model)

2. **Lethal toxin**

3. **Edema factor**





Anthrax Models

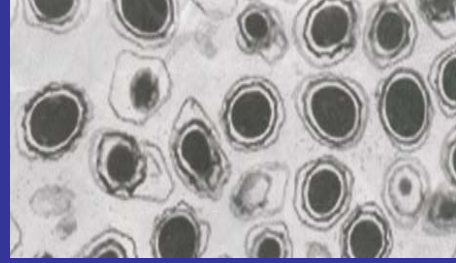
B. anthracis, Ames strain

Subcutaneous:

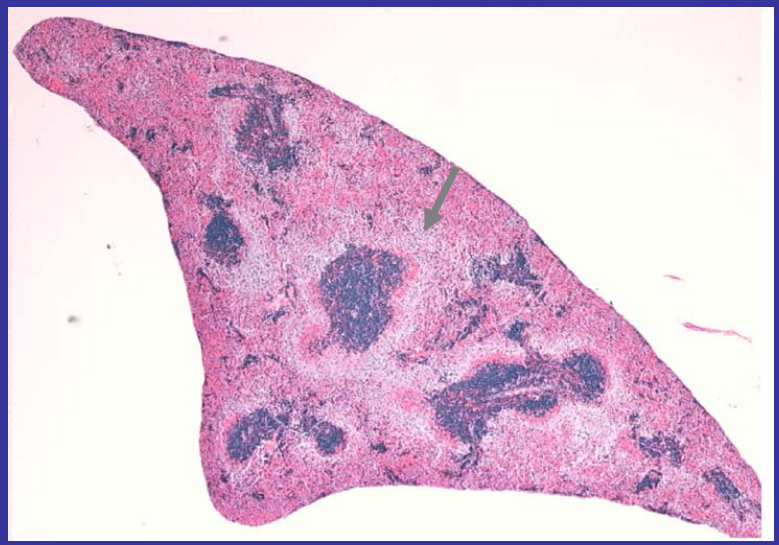
Administration of 10LD_{50} spores
Dissemination to spleen ~ 3-4 days
Death in ~ 4-5 days

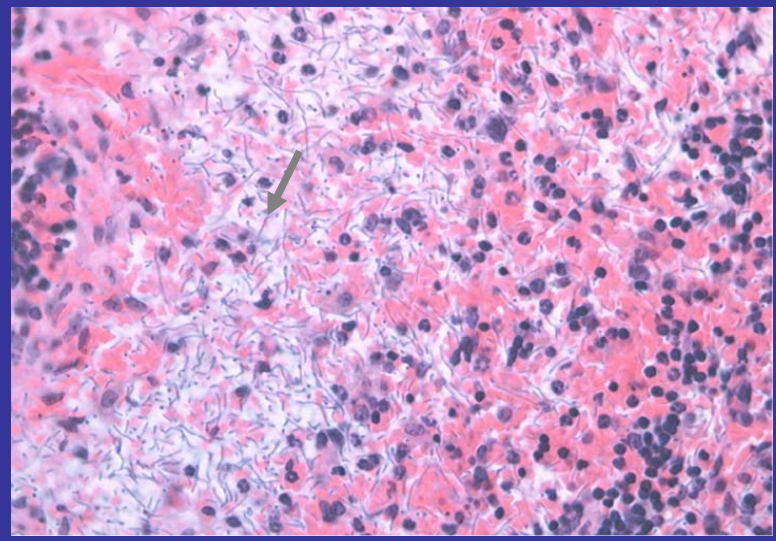
Pulmonary:

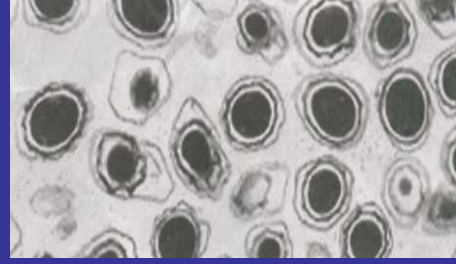
Intratracheal administration of spores
Dissemination to spleen ~ 1-2 days
Death in ~ 2-3 days
More reproducible endpoints than intranasal
Pathology identical to intranasal



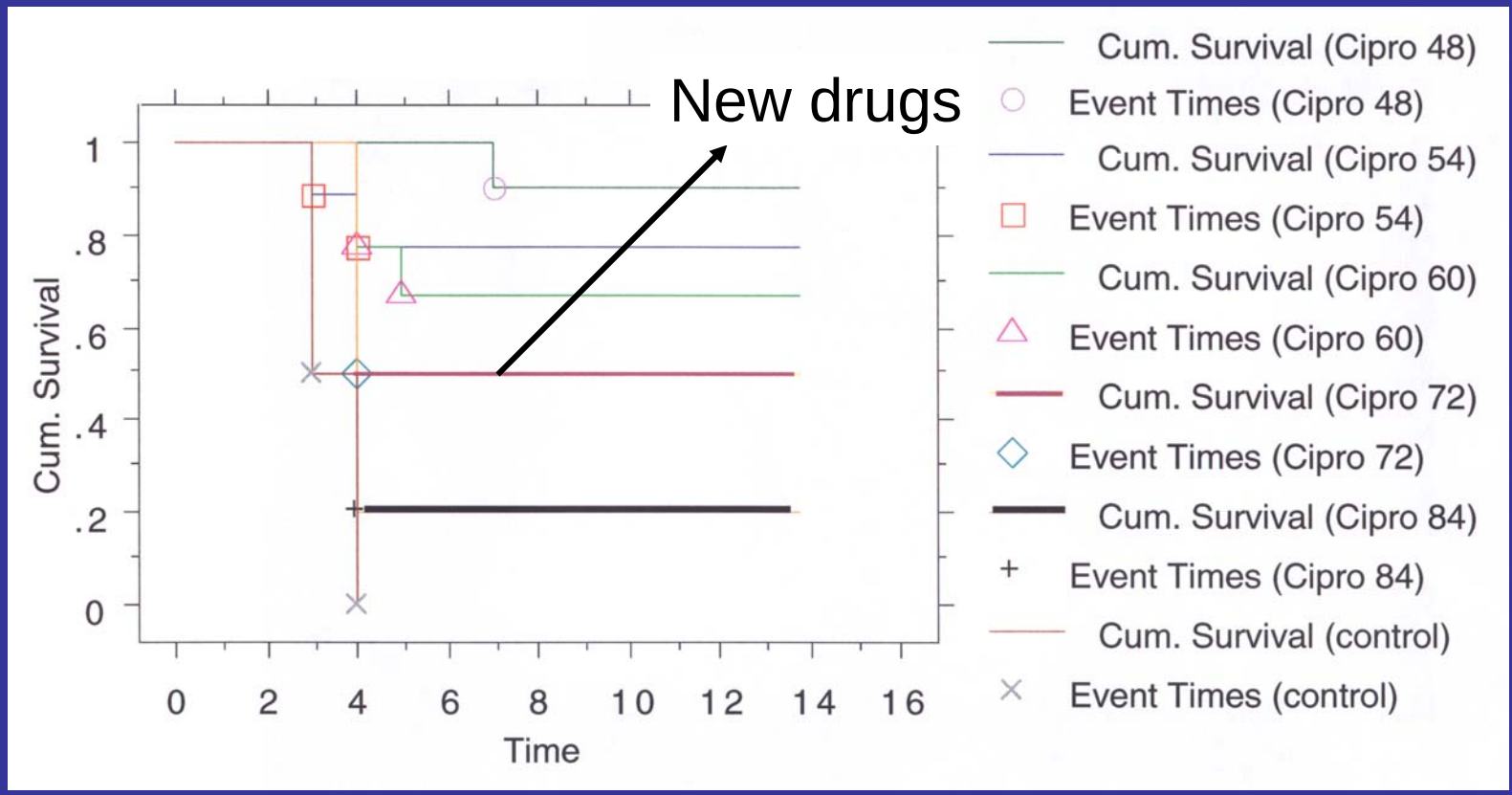
Anthrax Induced Splenic Lesions BALB/c Mice-Day2



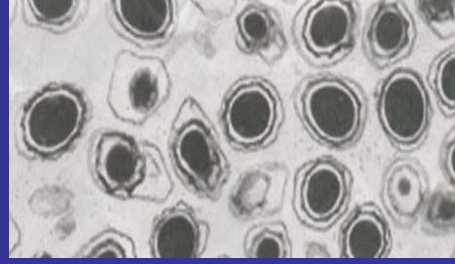


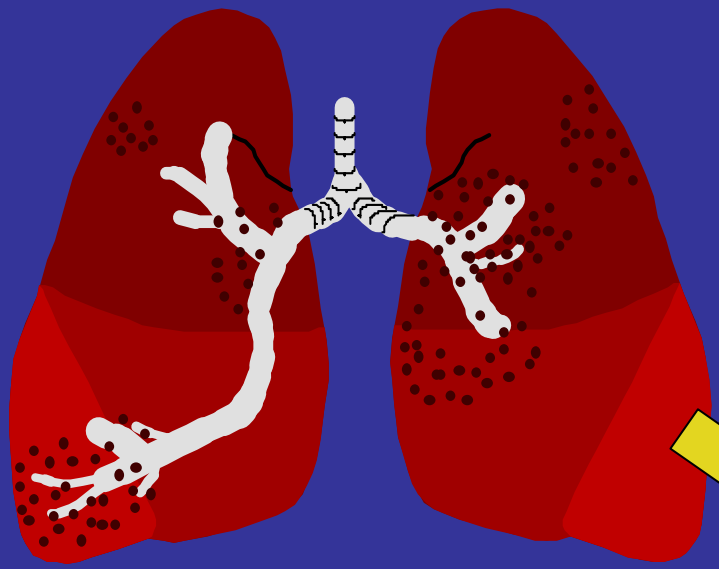


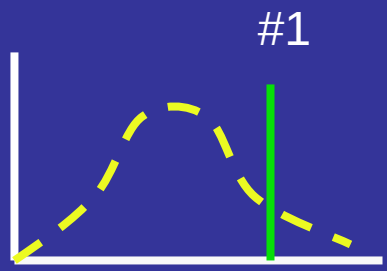
Rescue of Anthrax Infection with Ciprofloxacin

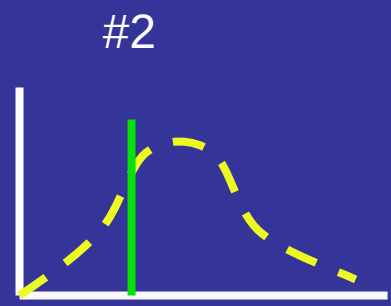


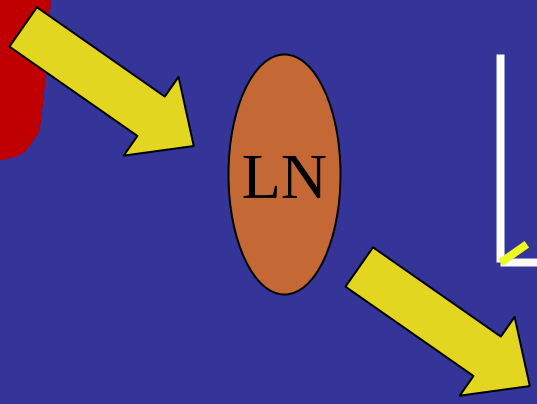
Anthrax models are not in Synch

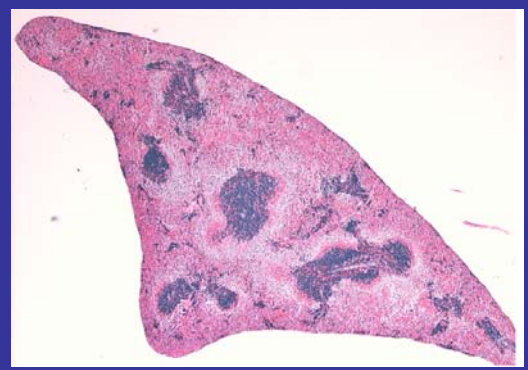


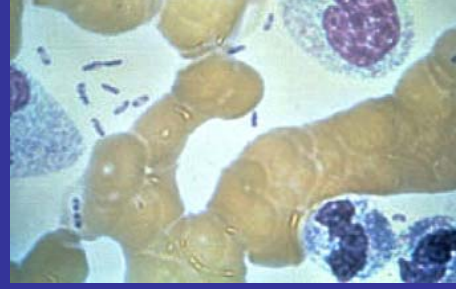












Plague Model

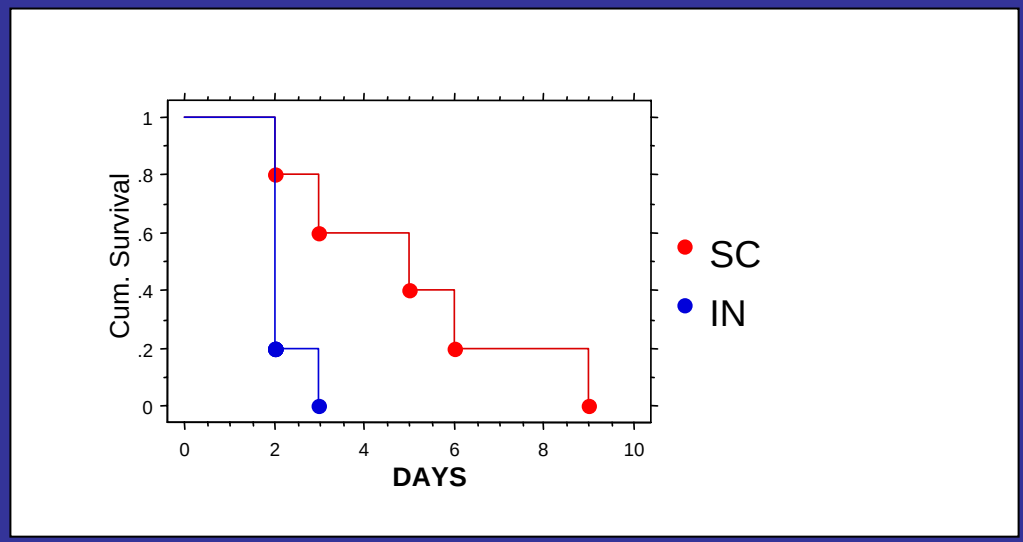
Y. pestis

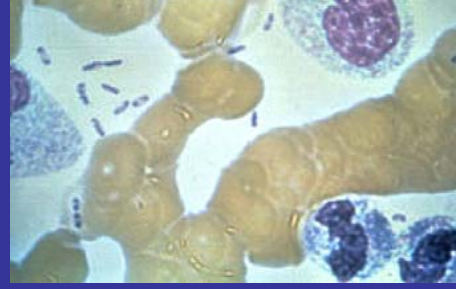
Pulmonary Model

- Infect BALB/c mice intranasally with organisms in 50 μl of PBS
- Mice typically die on Day 3 post-infection.

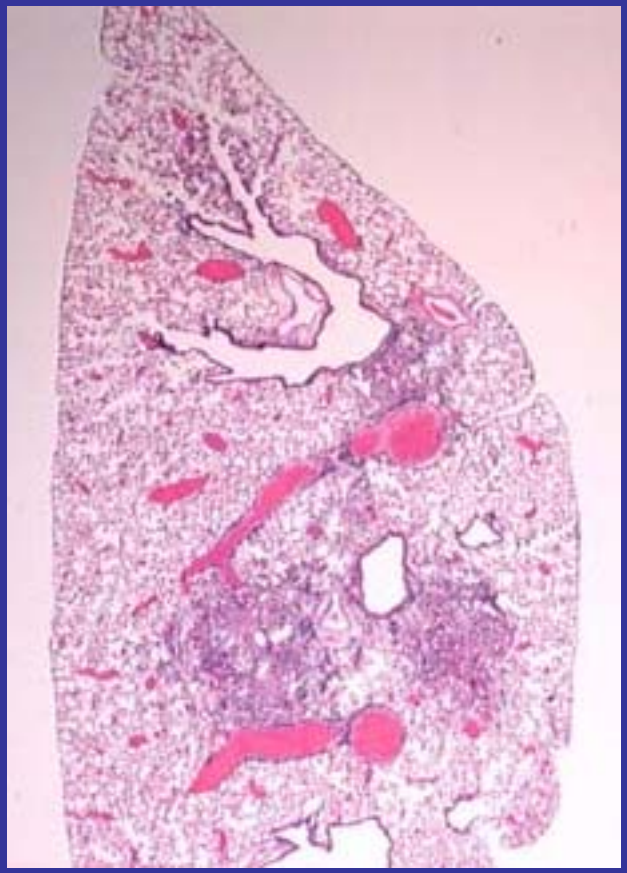
SC Model –

- Infect in 200 μl of PBS
- Mice typically die on Day 8-10 post-infection.

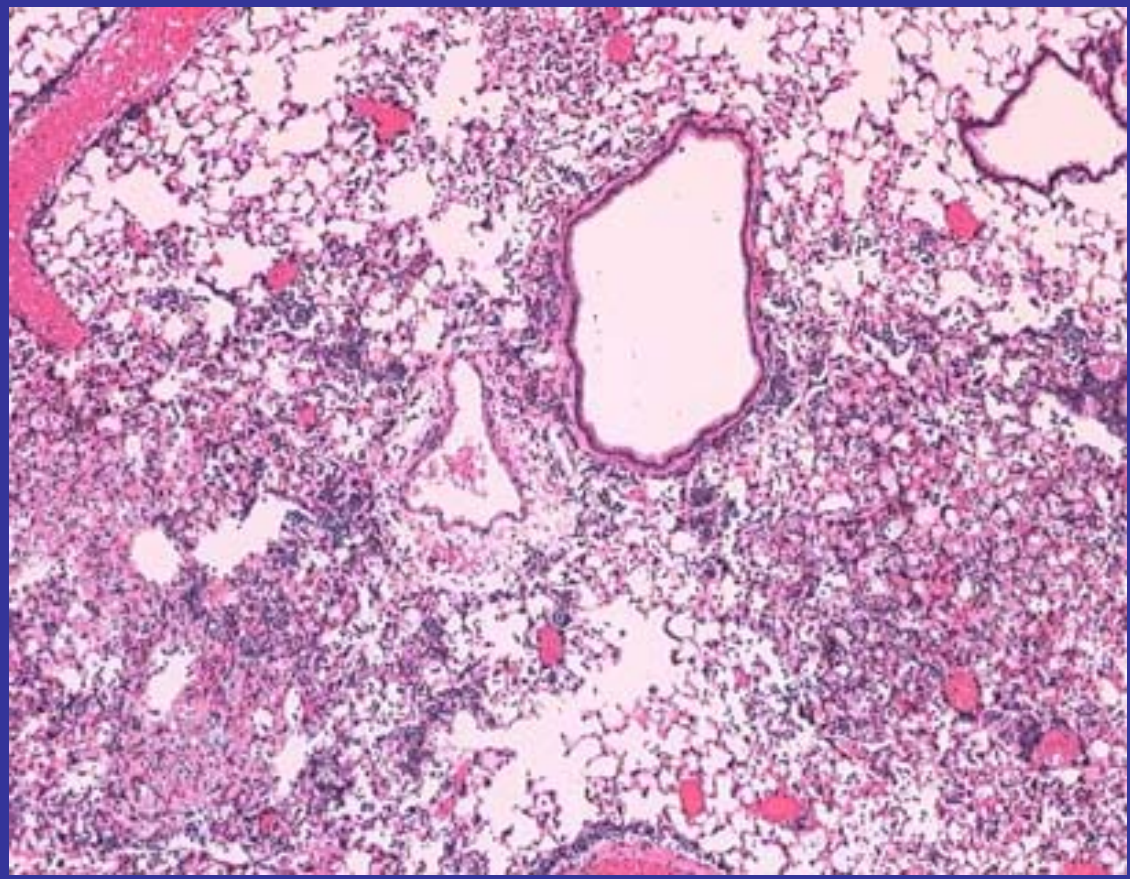


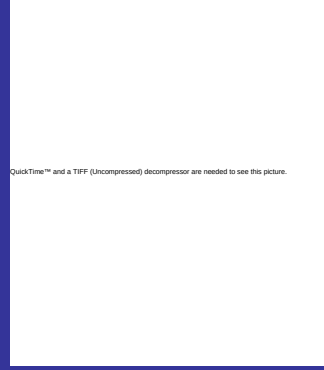


Lung D2 2x



Lung D2 10x





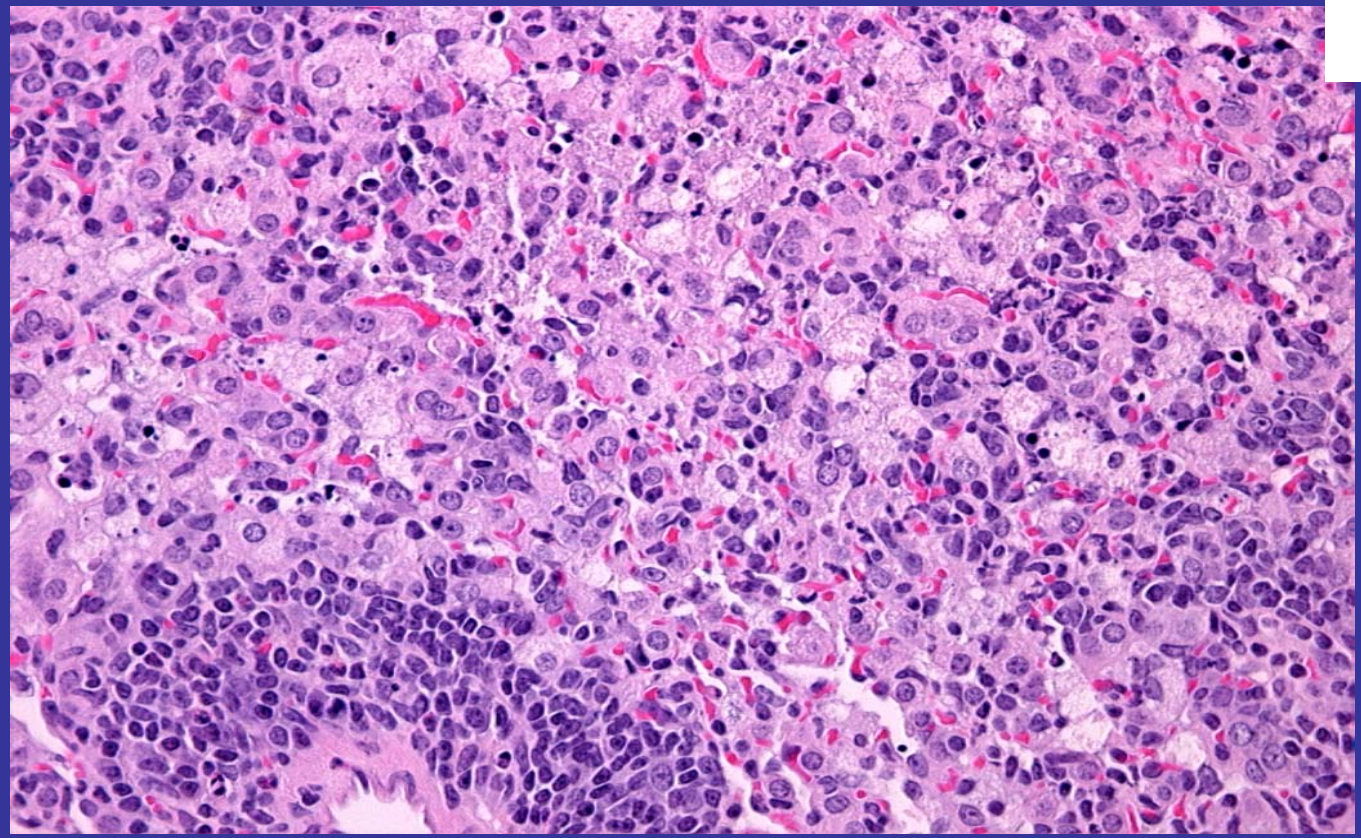
Cowpox Model

Pulmonary Model:

Mice infected intratracheally with virus in 50 μl of PBS
Mice typically die on Day 10-12 post-infection.

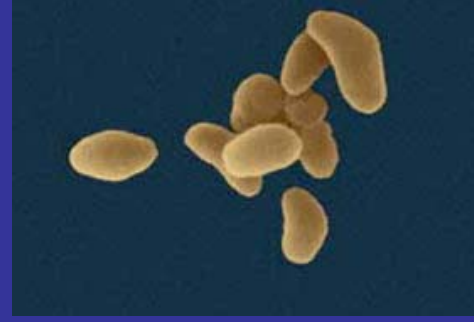
BALB/C MOUSE: 15 DAYS POST COWPOX INFECTION

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.



Lymphoplasmacytic and histiocytic peribronchovascular inflammation.
Type II alveolar epithelial proliferation and degeneration (some with viral inclusions).

Tularemia
Pulmonary Model



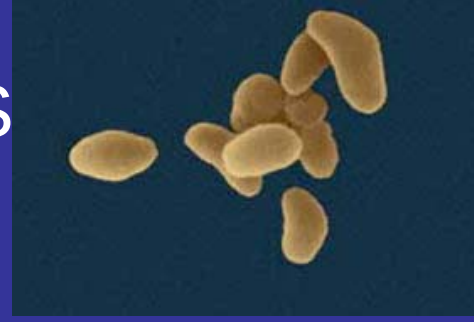
Virulent *F. tularensis:* (Biovar type A)

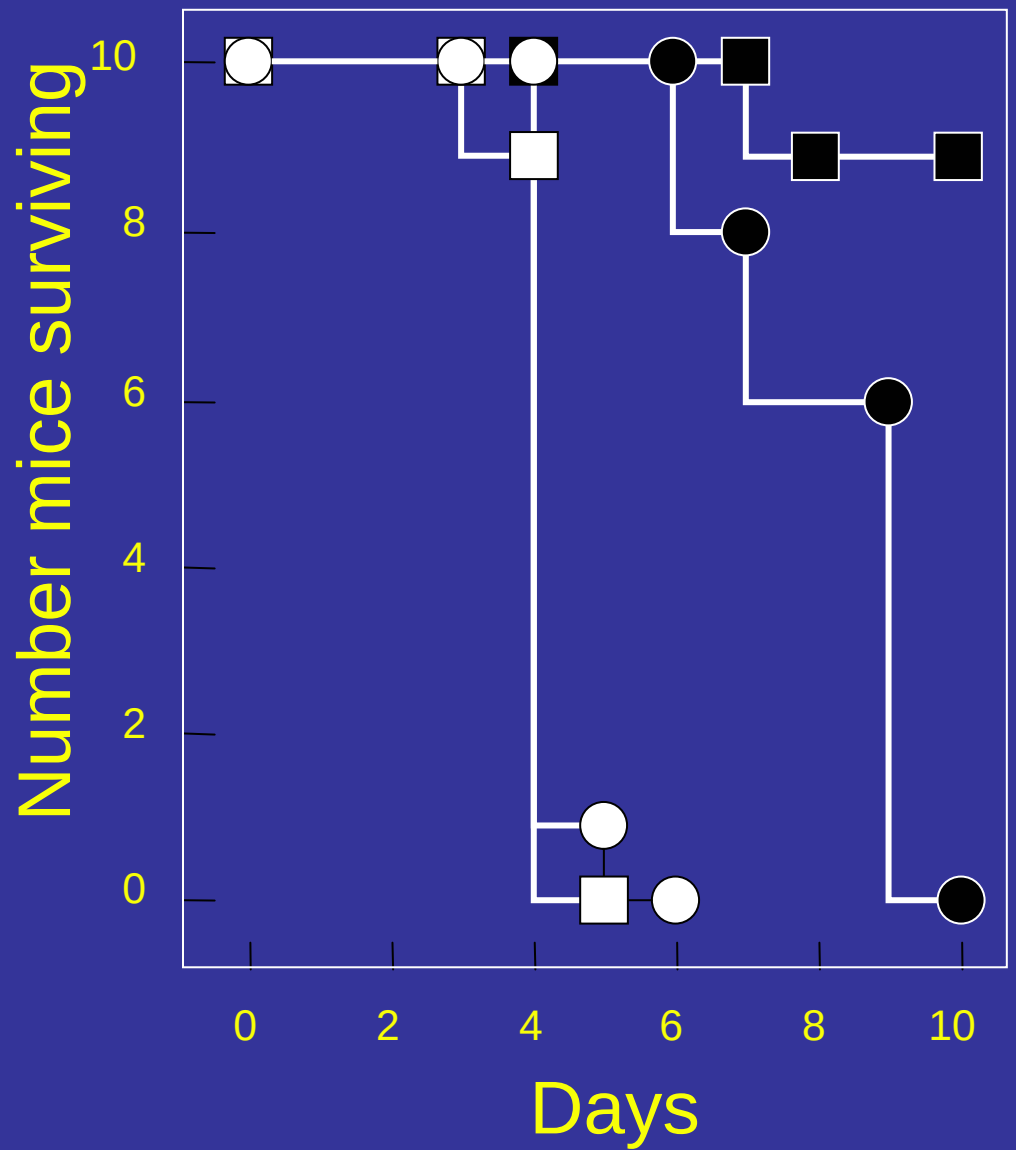
- BALB/c mice are infected intranasally with organisms

LVS strain: (Type B)

- BALB/c mice are infected intranasally with organisms

FT-NM 1 kills mice faster than LVS

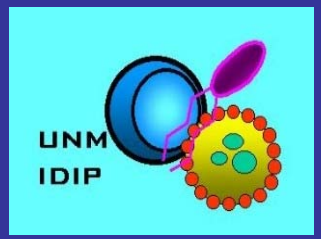




LVS
■ 1 x 10^3
● 5 x 10^4

FT NM1
□ 1 x 10^3
○ 5 x 10^4

Funding



Graduate students and Postdocs funded by Infectious Disease and Inflammation Training Program 2 T32 AI007538-06