USAMRIID

# Immunizations, registries and anti-bioterrorism efforts

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## Category A Agents

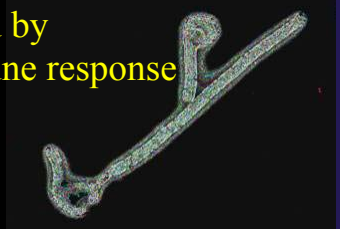
- The U.S. public health system and primary healthcare providers must be prepared to address various biological agents, including pathogens that are rarely seen in the United States. High-priority agents include organisms that pose a risk to national security because they
  - can be easily disseminated or transmitted from person to person;
  - result in high mortality rates and have the potential for major public health impact;
  - might cause public panic and social disruption; and
  - require special action for public health preparedness.

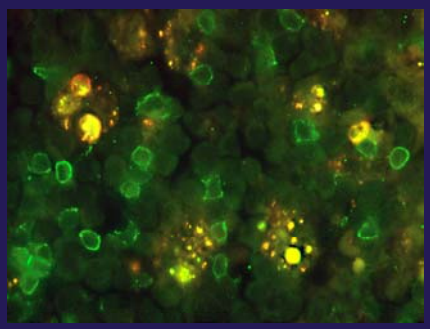
# **Category A** Agents

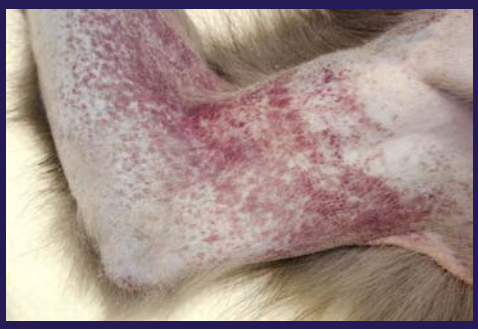
»Anthrax (*Bacillus anthracis*)
»Botulism (*Clostridium botulinum* toxin)
»Plague (*Yersinia pestis*)
»Smallpox (variola major)
»Tularemia (*Francisella tularensis*)
»Viral hemorrhagic fevers (filoviruses [e.g., Ebola, Marburg] and arenaviruses [e.g., Lassa, Machupo])

## Background

- EBOV infections characterized by dysregulation of the host immune response
  - bystander lymphocyte apoptosis
  - proinflammatory cytokines
  - coagulation abnormalities (DIC)







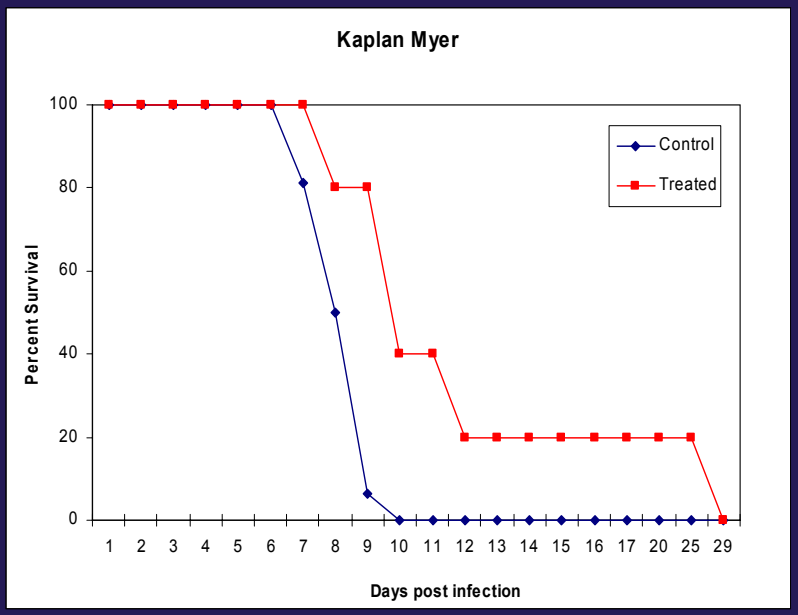
| Vaccine | Gene Product | Survivors / Total Challenged | | | Reference |
|---|---|---|---|---|---|
| | | *Animal Model* | | | |
| | | *Mouse* | *Guinea Pig* | *Macaque* | |
| Vaccinia | GP | NT | 3/5 | 0/3 | Gilligan '97, Geisbert '02 |
| Vaccinia | sGP | NT | 0/5 | NT | Gilligan '97 |
| Vaccinia | VP24 | NT | 0/30 | NT | Chepurnov '97 |
| Vaccinia | VP35 | NT | 0/5 | NT | Gilligan '97 |
| Vaccinia | VP40 | NT | 0/5 | NT | Gilligan '97 |
| VEE Replicon | GP | 18/20 | 8/10(5/5) | 0/3 | Pushko '00, Geisbert '02 |
| VEE Replicon | NP | 20/20 | 1/10 | 0/3 | Pushko, Wilson, Geisbert |
| VEE Replicon | GP+NP | 20/20 | 5/5 | 0/3 | Pushko '00, Geisbert '02 |
| VEE Replicon | VP24 | 37/60 | NT | NT | Wilson '01 |
| VEE Replicon | VP30 | 30/60 | NT | NT | Wilson '01 |
| VEE Replicon | VP35 | 23/59 | NT | NT | Wilson '01 |
| VEE Replicon | VP40 | 32/60 | NT | NT | Wilson '01 |
| Baculovirus | GP | NT | 3/6 | NT | Mellq.-Riem. '03 |
| Baculovirus | GPΔ | NT | 1/6 | NT | Mellq.-Riem. '03 |
| DNA | GP | 50-100% | 14/21 | NT | Vanderz., Xu, Sullivan |
| DNA | sGP | NT | 8/11 | NT | Xu '98 |
| DNA | NP | 70-80% | 5/8 | NT | Vanderzanden '98, Xu '98 |
| DNA | GP+NP | NT | 8/8 | NT | Sullivan '00 |
| DNA + Ad 5 | GP+NP | NT | NT | 4/4 | Sullivan '00 |
| DNA + Baculo | GP | NT | 0/6 | NT | Mellq.-Riem. '03 |
| DNA + Baculo | GPΔ | NT | 2/6 | NT | Mellq.-Riem. '03 |
| Ad5 | GP+NP | NT | NT | 8/8 | Sullivan '03 |
| Ad5 + Ad5 | GP+NP | NT | NT | 8/8 | Sullivan '03 |
| Inactivated Virus | Whole virus | | | 4/5 (baboons) | Mikhailov et al |
| Inactivated Virus | Whole virus | | | 0/5 NHPs | Geisbert et al. |

# Ebola Virus - Therapeutics

| Compound / Drug | Mouse | G.Pig | Nonhuman Primate | Human |
|---|---|---|---|---|
| Ribavirin | NT | No | No | NT |
| S-adenosylhomocysteine | Yes | NT | No | NT |
| rIFN-α | Yes | No | No | NT |
| Equine IgG | Partial | Yes | No | ? |
| Convalescent blood | NT | NT | 0/4 | 7/8 |
| rHuman monoclonal ab | NT | Yes | No | NT |

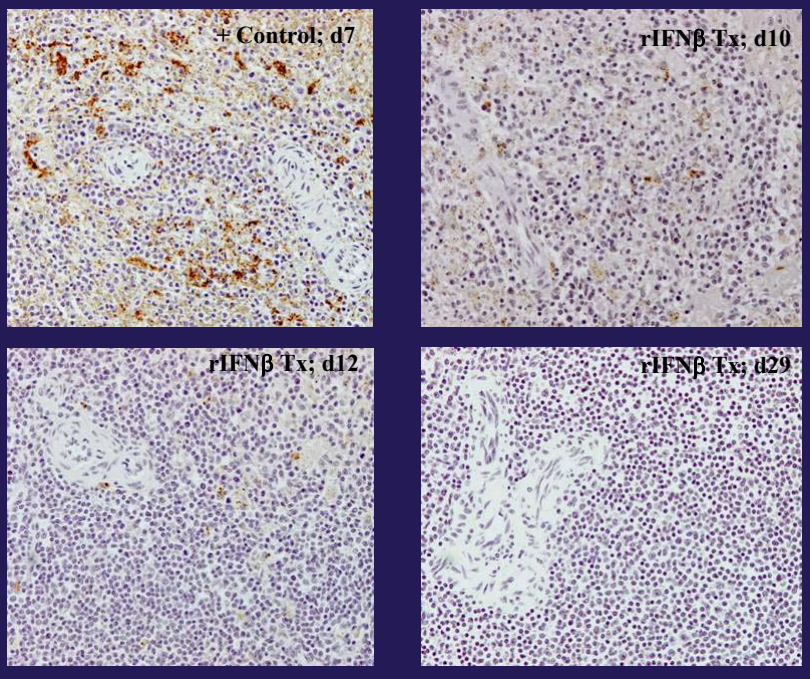
# Treatment of NHP's with IFN-β

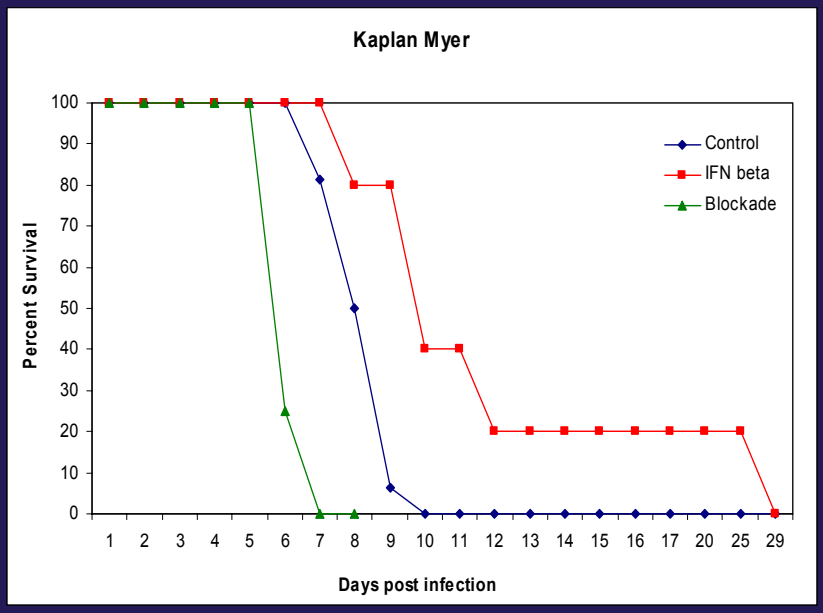
- Infected Ebola-Zaire'95 IM
- First treatment 18 hrs post-infection
- Treated every other day with 10.5 ug/kg ($2.8 \times 10^6$ IU / kg
- Treatment discontinued after Day 9



| Monkey | Day of Death | Viremia D3 | Viremia D6 | Viremia D8 | Viremia D13 |
|---|---|---|---|---|---|
| CH64* | 7 | 0 | 7.1 | | |
| DDF | 8 | 1.8 | 3.9 | 6.1 | |
| CH74 | 10 | 3.1 | 5.9 | | |
| CBT | 10 | 1.7 | 5.7 | | |
| FXA | 12 | 0 | 4.9 | | |
| HBX | 29 | 0 | 4.2 | | 2.4 |

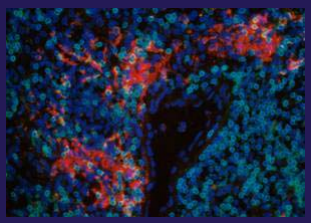
Mean day of death untreated Rhesus NHPs infected with EBOZ: 8.37 + 0.89 days

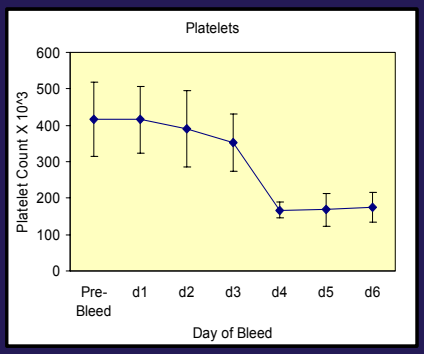


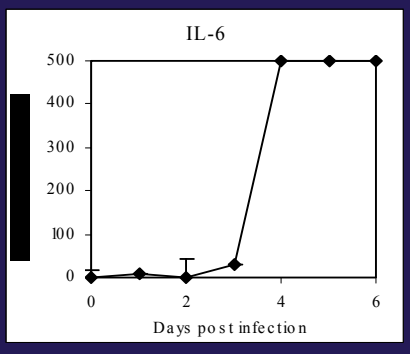


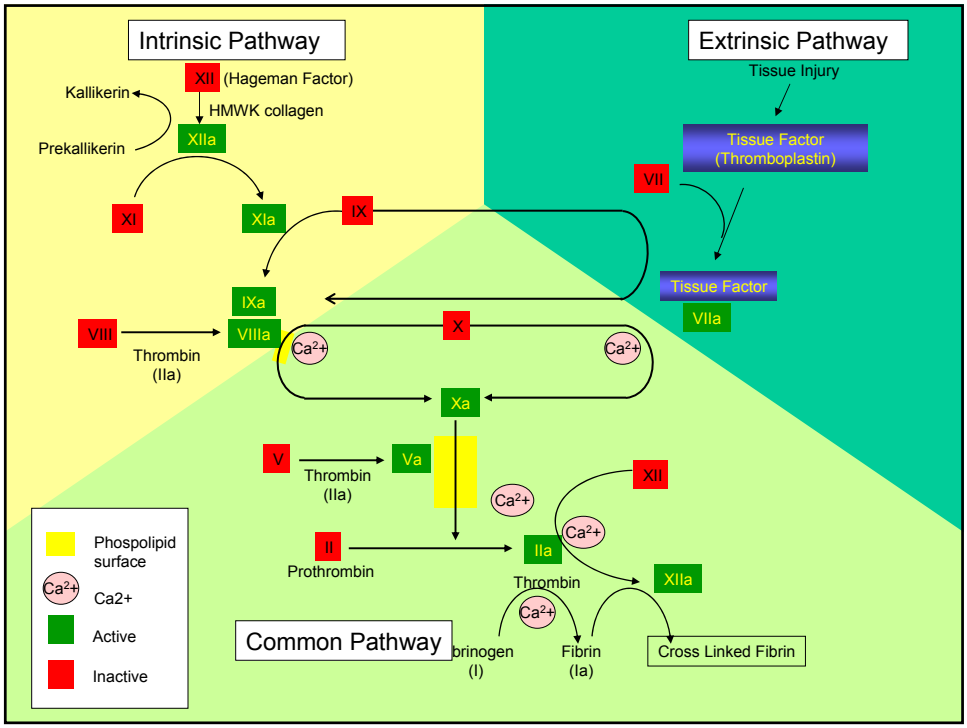

▲ Blockade performed with an antibody to the IFN-a receptor

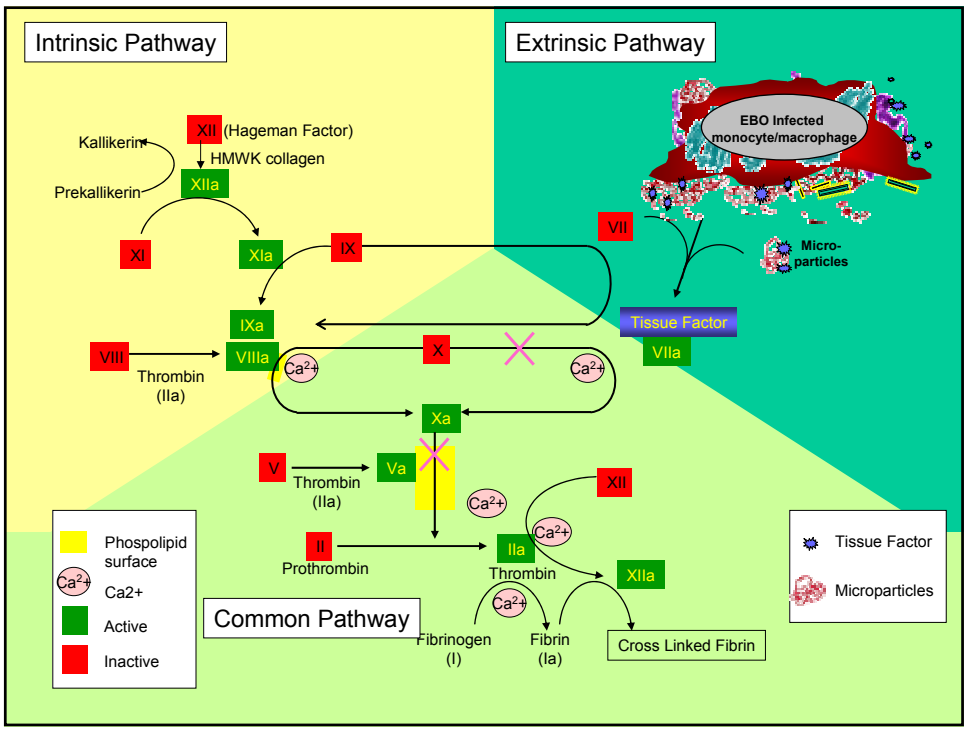
## Cytokine production and Coagulation in ZEBOV-infected NHPs

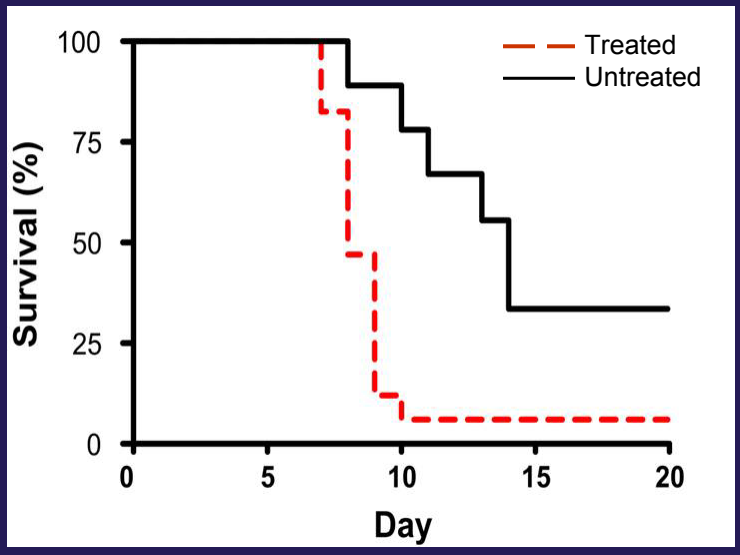





Intrinsic Pathway
Extrinsic Pathway
Tissue Injury
XII (Hageman Factor)
Kallikerin
HMWK collagen
Prekallikerin
XIIa
XI
XIa
IX
Tissue Factor (Thromboplastin)
VII
Tissue Factor
VIIa
IXa
VIII
VIIIa
Thrombin (IIa)
Ca2+
X
Xa
V
Va
Thrombin (IIa)
XII
II
Prothrombin
IIa
Thrombin
XIIa
Fibrinogen (I)
Fibrin (Ia)
Cross Linked Fibrin
Common Pathway
Phospolipid surface
Ca2+
Active
Inactive

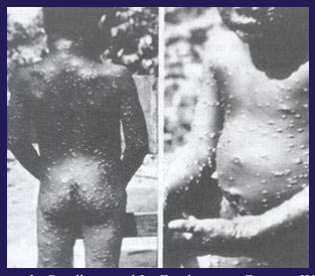

Intrinsic Pathway
Extrinsic Pathway
EBO Infected monocyte/macrophage
Micro-particles
XII (Hageman Factor)
Kallikerin
HMWK collagen
Prekallikerin
XIIa
XI
XIa
IX
VII
Tissue Factor
VIIa
IXa
VIII
VIIIa
Thrombin (IIa)
Ca2+
X
Xa
V
Va
Thrombin (IIa)
XII
II
Prothrombin
IIa
Thrombin
XIIa
Fibrinogen (I)
Fibrin (Ia)
Cross Linked Fibrin
Common Pathway
Phospolipid surface
Ca2+
Active
Inactive
Tissue Factor
Microparticles




•Significant increase in survival after treatment ($P$ = 0.023)

## Smallpox overview

- Incubation period 7-19 days – no clinical symptoms but intense viral replication
- Sudden onset of high fever; then general lethargy, severe headache, backache, and vomiting
- Fever begins to fall after 2-3 days and a rash appears on tongue and face
- Macular rash spreads to trunk and extremities
- Rash progresses to vesicles, pustules and then scabs over – deep scars remain after scabs heal



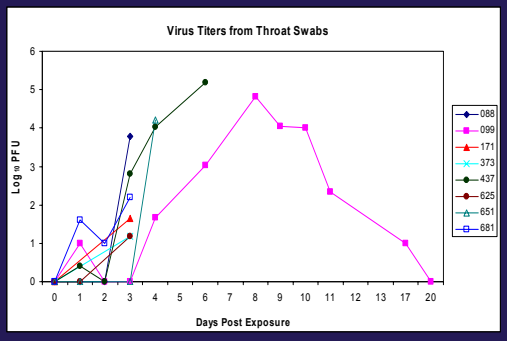
Fenner, F. et al., *Smallpox and Its Eradication*. Geneva: WHO, 1988

# Smallpox Vaccine

- Current vaccine:
  - Who should get the vaccine?
  - What are the side-effects?
  - Does the risk side effects = the need for the vaccine?
  - How long is the vaccine good for?
  - Who can take the vaccine?
  - What about those individuals who cannot get the vaccine

# Ring Vaccination

- Ring vaccination was very effective in Africa but will it work here?
  - Early detection / diagnostics
  - Identifying contacts
  - Transmissibility
  - Infrastructure to handle a multi-center release?
  - What about the individuals that cannot or will not take the vaccine?



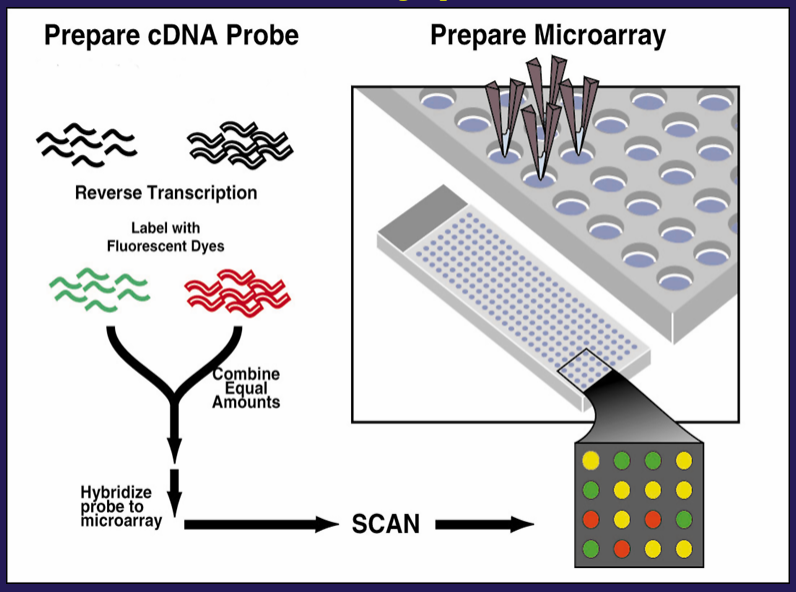
## Weaponized or Modified viruses

- Genetic manipulation of virus
  - Pox viruses are uniquely suited to the introduction of new genes including immune-modulation or lethality factors (e.g. IL-4 and mouse pox)
- Weaponization of virus
  - Release of the virus at Arlask: Was the virus hotter? Was there vaccine breakthrough?

## Directions

- Development of new vaccines
  - DNA vaccines
- Development of anti-virals
- Development of alternative therapeutics
- Development of better diagnostics (CDC & USAMRIID)
- Development of animal models (USAMRIID & CDC)
- Application of new technologies

# cDNA microarray procedures-1



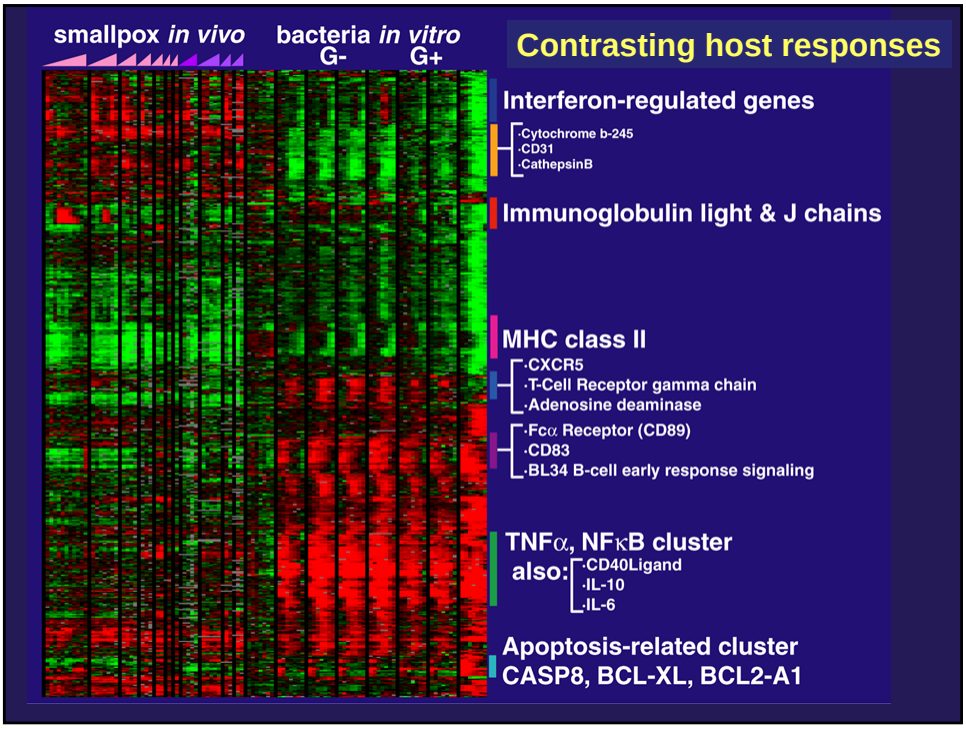

## Desired expression signatures from variola virus-infected hosts

Signatures that indicate or provide…

- early identification: variola virus-specific, orthopoxvirus-generic
- prognosis for variola-infected host: favorable, unfavorable
- early favorable response to therapy (interrupted infection)
- early markers for protective response to vaccine
- analogous signatures for monkeypox infection

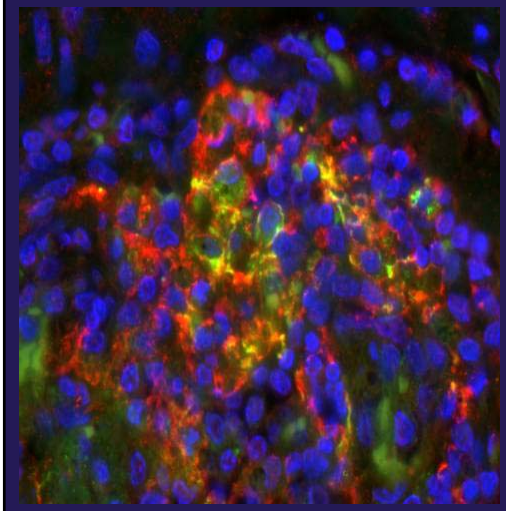
## Host genome-wide expression profiling: potential benefits

- Diagnosis
  - early detection of infected individuals
  - recognition of variant agents
  - prognostic markers
- Mechanisms of virulence and disease
  - novel strategies for therapy, prophylaxis
- Prevention
  - early signatures of a protective immune response to vaccination



# We've come a long way

- Continued development and testing of new vaccines (new platforms, short – term vaccination strategies, multi-valent vaccines)
- Screening of anti-virals
- Development of animal models and continued pathogenesis studies
- Development of immune-modulating therapies or therapeutic strategies that target or interrupt the clinical disease course
- Development of improved diagnostic and diagnostic indicators.




## Contributors:

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