WHO Monkeypox Research Priorities

Animal Models of Monkeypox Infection

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National Institute of Allergy and Infectious Diseases

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NIAID

Monkeypox Animal Model Development

- Purpose in early 2000s was to license next-generation smallpox vaccine under FDA's Animal Efficacy Rule
- Therefore, trying to model human smallpox disease using monkeypox as workhorse BSL3 model
- Existing NHP models used intravenous route of inoculation of virus
- NIAID sought a respiratory inoculation route, comparing intravenous to aerosol, intranasal, intratracheal

Monkeypox Animal Model Development

- Selected Zaire 79 (V79-I-005) as strain
  - Extensive experience with the strain
  - Preference for a lethal model or at least severe disease
- Prepared a stock that was sequenced (GenBank: DQ011155) and used by all labs for challenge
- Significant effort on PRNT assays

Cynomolgus Macaque Studies

- Challenge route comparison
  - Dose ranging
  - Serial pathogenesis
- Vaccine efficacy
- Antiviral efficacy
- Combination studies

Dose Resulting in Severe Disease in 90% of animals

- Any of the following defines Severe Disease
  - Death
  - Moribund sacrifice
  - Overall poor clinical assessment
  - Severe rash - greater than 100 total body pox lesions
  - 50% or greater change in pulse and/or respiration rates

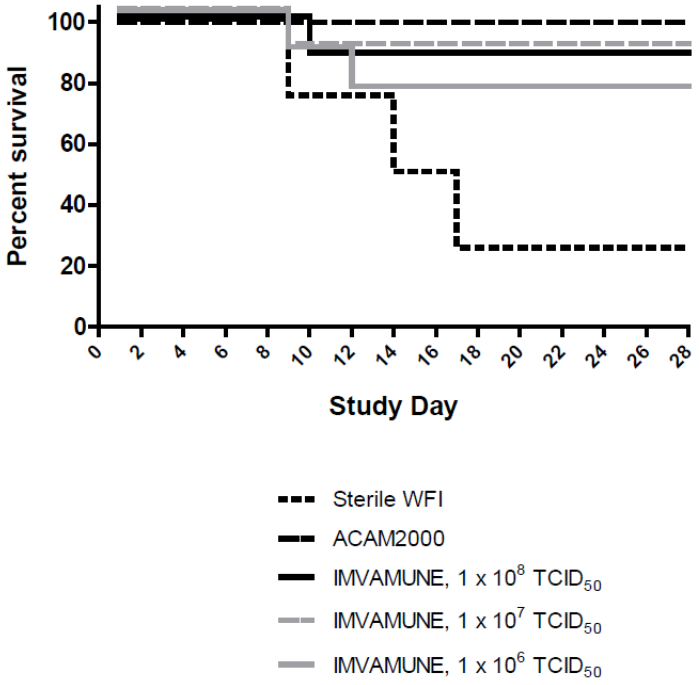
IV	IN	IT	Aerosol
$2x10^6$ pfu/ml	$1.1x10^6$ pfu/ml	$1.7x10^9$ pfu/ml*	$1x10^5$ pfu/ml

Pathology Summary

- Following challenge by all respiratory routes:
  - Disease severity is challenge dose dependent
  - The number of skin lesions is not challenge dose dependent – high doses >> few lesions
  - Symptoms of respiratory distress observed, development of bronchopneumonia
  - Virus widely disseminated

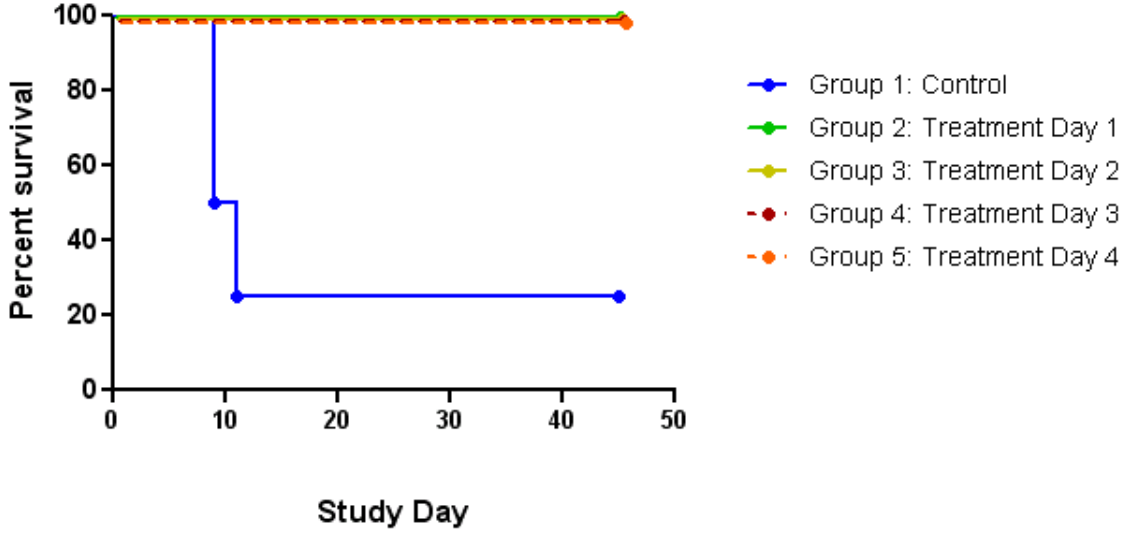
Vaccine Efficacy

- ACAM2000, Day -39
- Imvamune, Days -67 & -39
- Aerosol challenge, D0, $1.1x10^5$ pfu



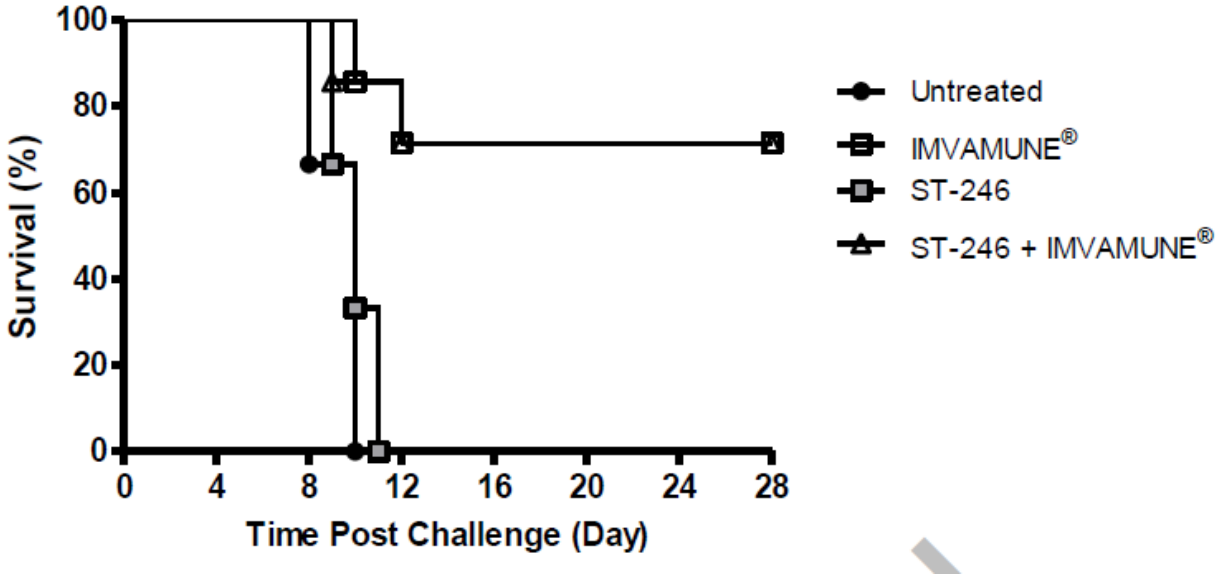
Antiviral Efficacy

- 10 mg/kg TPOXX administered at varying days post-challenge with 1 x 10^5 pfu via aerosol



Antiviral + Vaccine Combination Studies

- TPOXX, Days 0-13
- Vaccine, Day 0
- Challenge, $5x10^7$ pfu, IV, Day 45



Conclusions

- None of the challenge routes fully mimic human smallpox disease.
- For medical countermeasure efficacy studies, we aimed for a severe model of disease.
- All of the countermeasures (vaccines, antivirals, combinations) presented demonstrated efficacy even in severe disease models, no interference of antiviral with vaccine immune response.

Thank you!