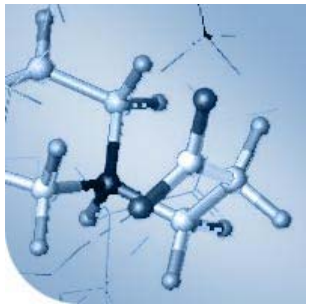
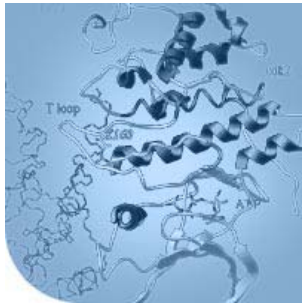
Antiviral Drug Development for Biothreat Agents

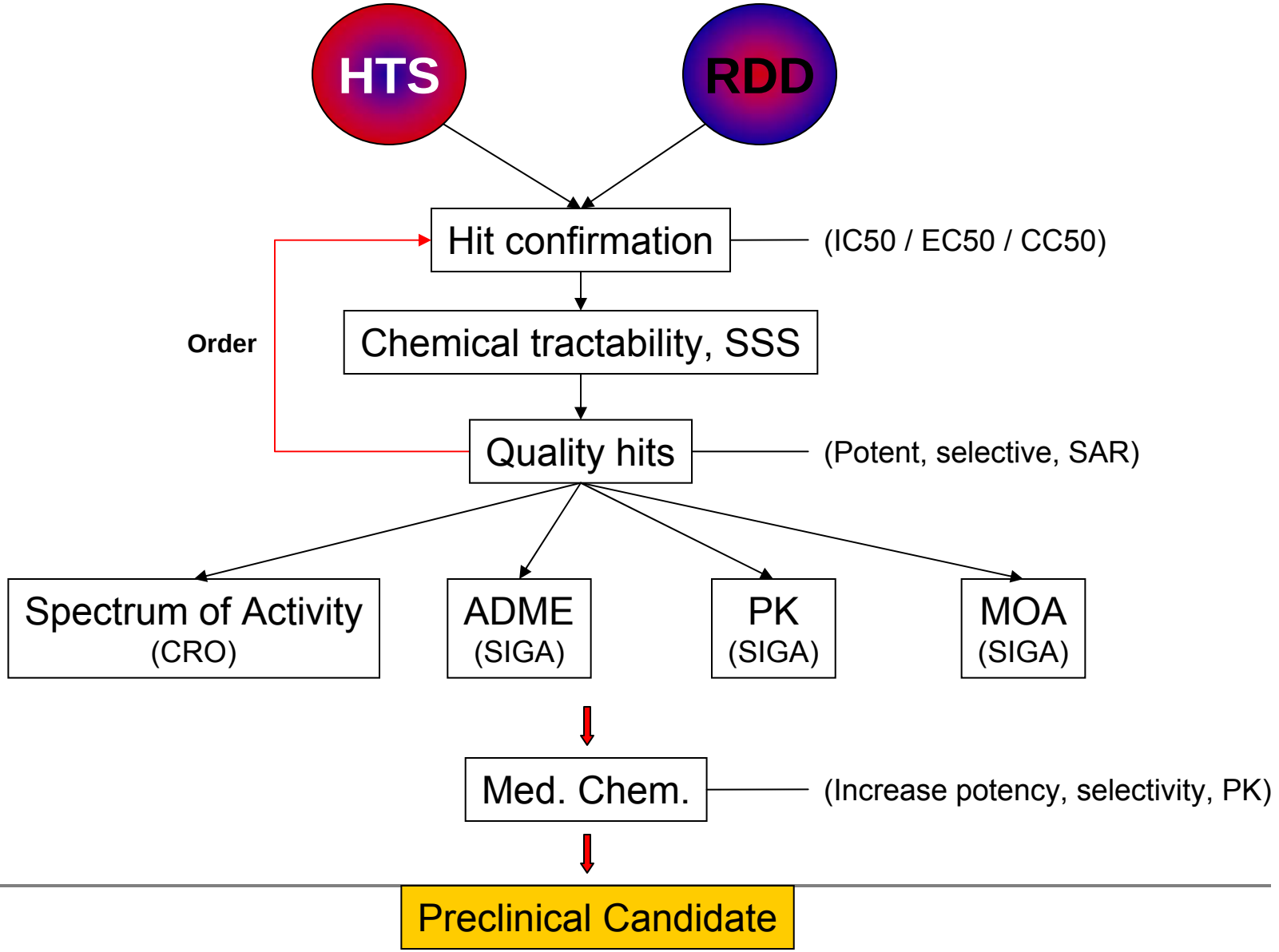




Tove Bolken

SIGA Technologies, Inc

Screening Paradigm – Biology Driven



Hemorrhagic Fever Viruses

Flavivirus	**Filovirus**	**Bunyavirus**	**Arenavirus**
Dengue	Ebola	Rift Valley Fever	Lassa
	Marburg	Crimean-Congo	Junín
		Hantavirus	Machupo
			Guanarito
			Sabià

Bunyavirus **– Screening in progress, Hits identified**

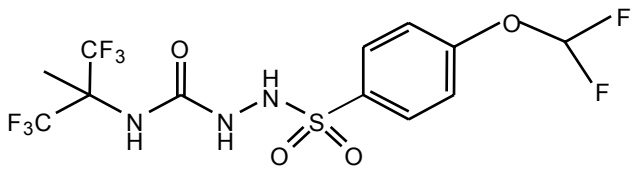
Flavivirus **– Screening in progress, Hits identified**

Filovirus **– Lead series identified**

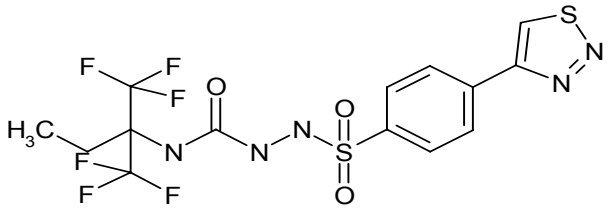
OW Arenavirus **– Preclinical drug candidates**

NW Arenavirus **– Preclinical candidate (SIGA-294)**

Anti-NWA Compound Series ST-294



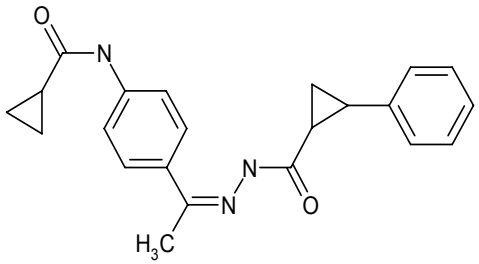
ST-294



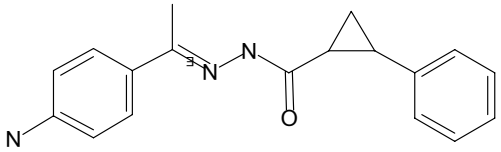
ST-379

			vs. Tacaribe CPE (μM)		EC_{50} vs. Junin (μM)	Cytotoxicity (CC_{50} in μM)				
Compound	MW	cLogP	EC_{50} (μM)	S.I.		293T	Vero	MRC-5	BSC-40	L-929
ST-294	445.3	4.9	0.12	416	0.80	> 50	> 50	> 50	> 50	> 50
ST-379	477.4	4.2	0.08	625	n.d	> 50	> 50	n.d.	n.d.	n.d.

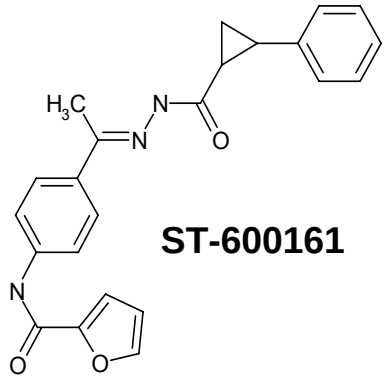
Anti-OWA Compound Series ST-306



VP-408306



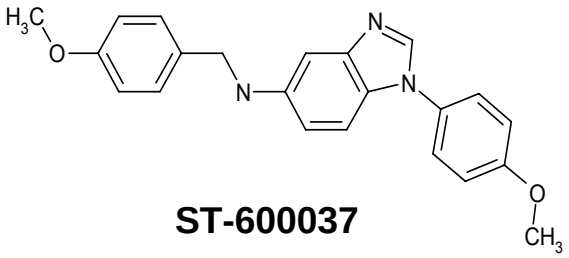
ST-600100



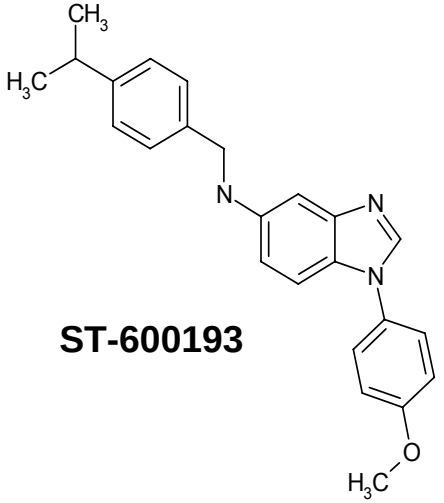
ST-600161

			vs. HIV(Lassa GP) pseudotypes		EC_{50} vs. LFV (μM)	Cytotoxicity (CC_{50} in μM)				
Compound	MW	cLogP	EC_{50} (μM)	S.I.		293T	Vero	MRC-5	BSC-40	L-929
408306	293.4	2.3	0.025	> 2000	0.5	> 100	> 50	n.d.	n.d.	n.d.
600100	361.4	3.2	0.0021	> 23,000	< 0.02	50	n.d.	44	18	> 50
600161	387.4	3.8	0.00035	> 140,000	< 0.02	> 50	> 50	n.d.	n.d.	n.d.

Anti-Arena Compound Series ST-37



ST-600037



ST-600193

			vs. HIV(Lassa GP) Pseudotypes		EC_{50} vs. LFV (μM)	Cytotoxicity (CC_{50} in μM)				
Compound	MW	cLogP	EC_{50} (μM)	S.I.		293T	Vero	MRC-5	BSC-40	L-929
600037	359.4	4.9	0.014	1030	0.04	> 50	> 50	> 50	> 50	> 50
600193	371.5	6.6	0.0013	11,400	0.02	48	46	n.d.	n.d.	n.d.

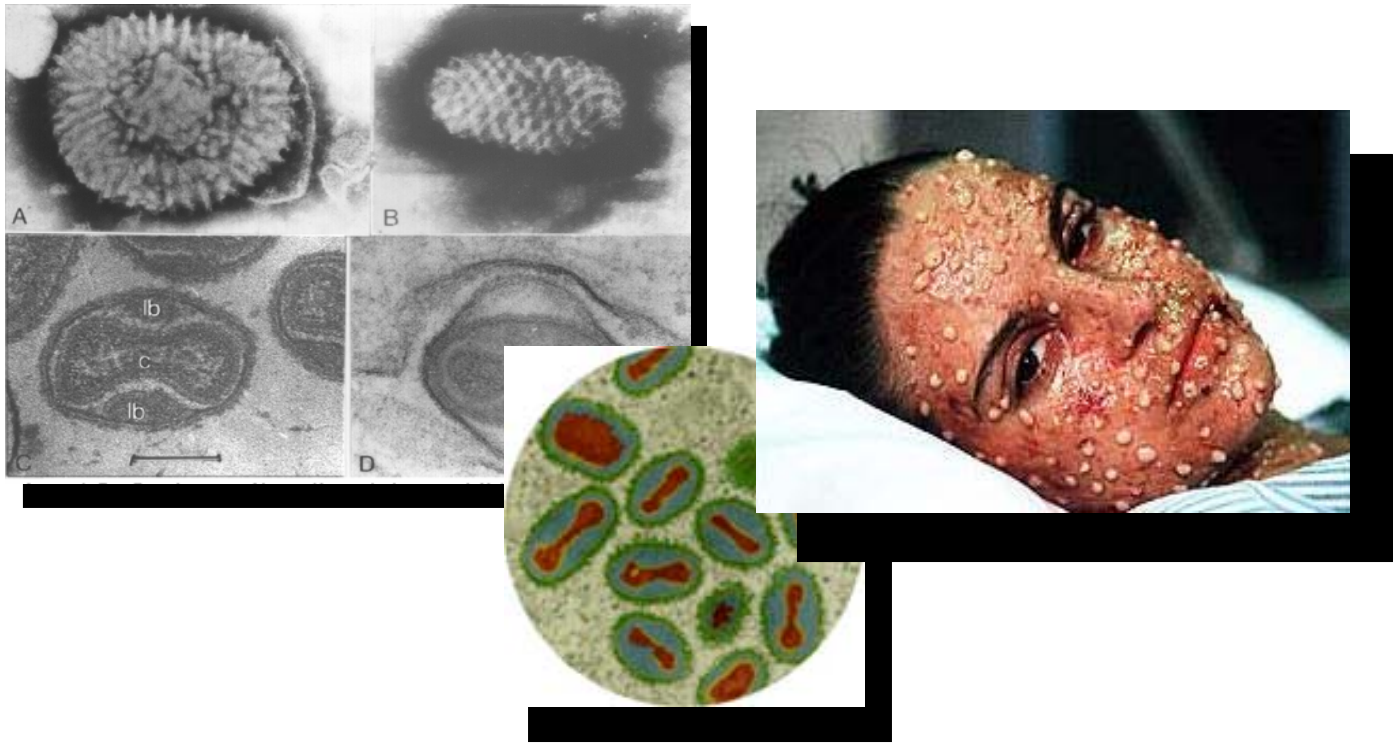
HFV Antiviral Development Plans

- Tolerability and multi-dose PK study in guinea pigs
- Animal efficacy studies in guinea pig model

Go/No-Go →

- Formulation, CMC, scale-up
- IND enabling toxicology, PK & ADME
- Definitive animal efficacy study in guinea pigs
- Animal efficacy study in non-human primates

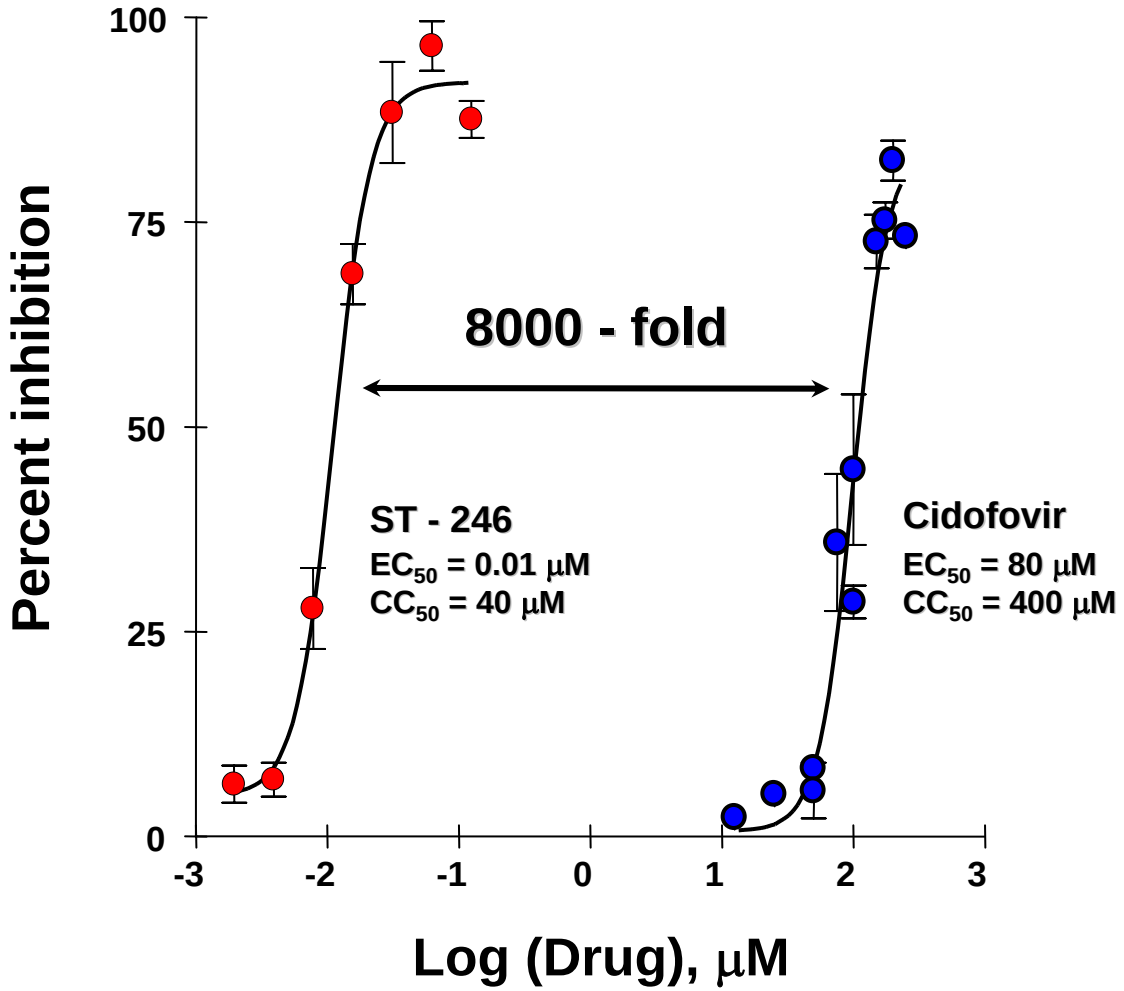
Development of a Poxvirus Antiviral: ST-246



ST-246 Progress to Date

- ST-246 is a potent, non-toxic and specific inhibitor of orthopoxvirus replication
- ST-246 is effective in multiple rodent challenge models against orthopoxvirus induced pathogenesis and/or disease
- ST-246 is orally bioavailable with excellent PK parameters
- ST-246 pre-clinical development is complete
- ST-246 IND approved, Fast-Track status granted
- Orphan Drug Designation for prevention and treatment of smallpox approved
- Human clinical studies with ST-246 are underway
- Emergency Use Authorization application planned Q107

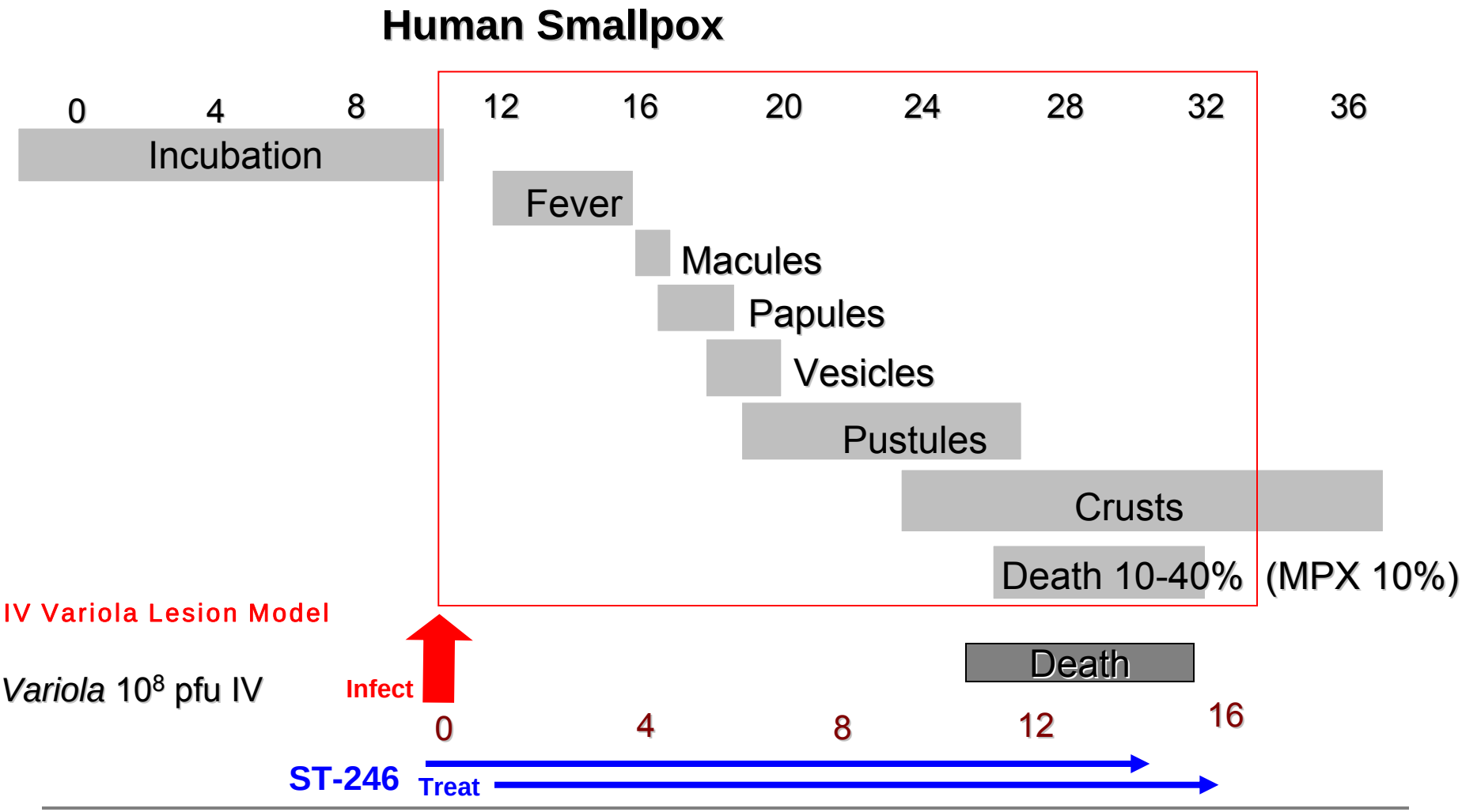
Antiviral Activity vs. Vaccinia Virus



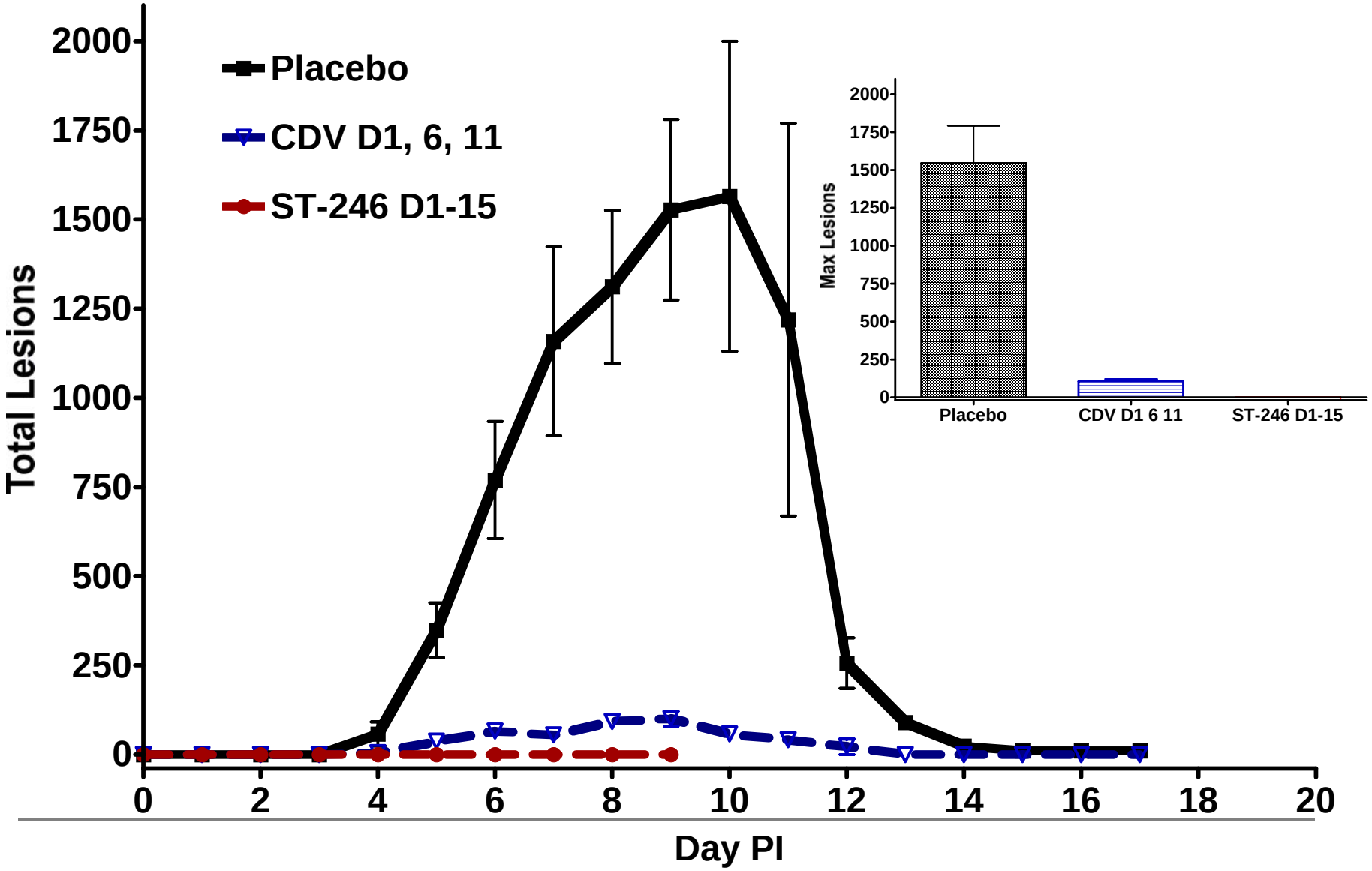
Animal Efficacy Highlights

- ST-246 protects animals from all orthopoxvirus pathogens tested (VV, CPX, **ECTV**, RPV, **MPX, VaV**)
- Addition of ST-246 up to 72h post infection protects animals from disease & death
- ST-246 reduces viral replication in lung by 6 logs
- ST-246/cidofovir protect mice from ECTV/IL4 recombinant

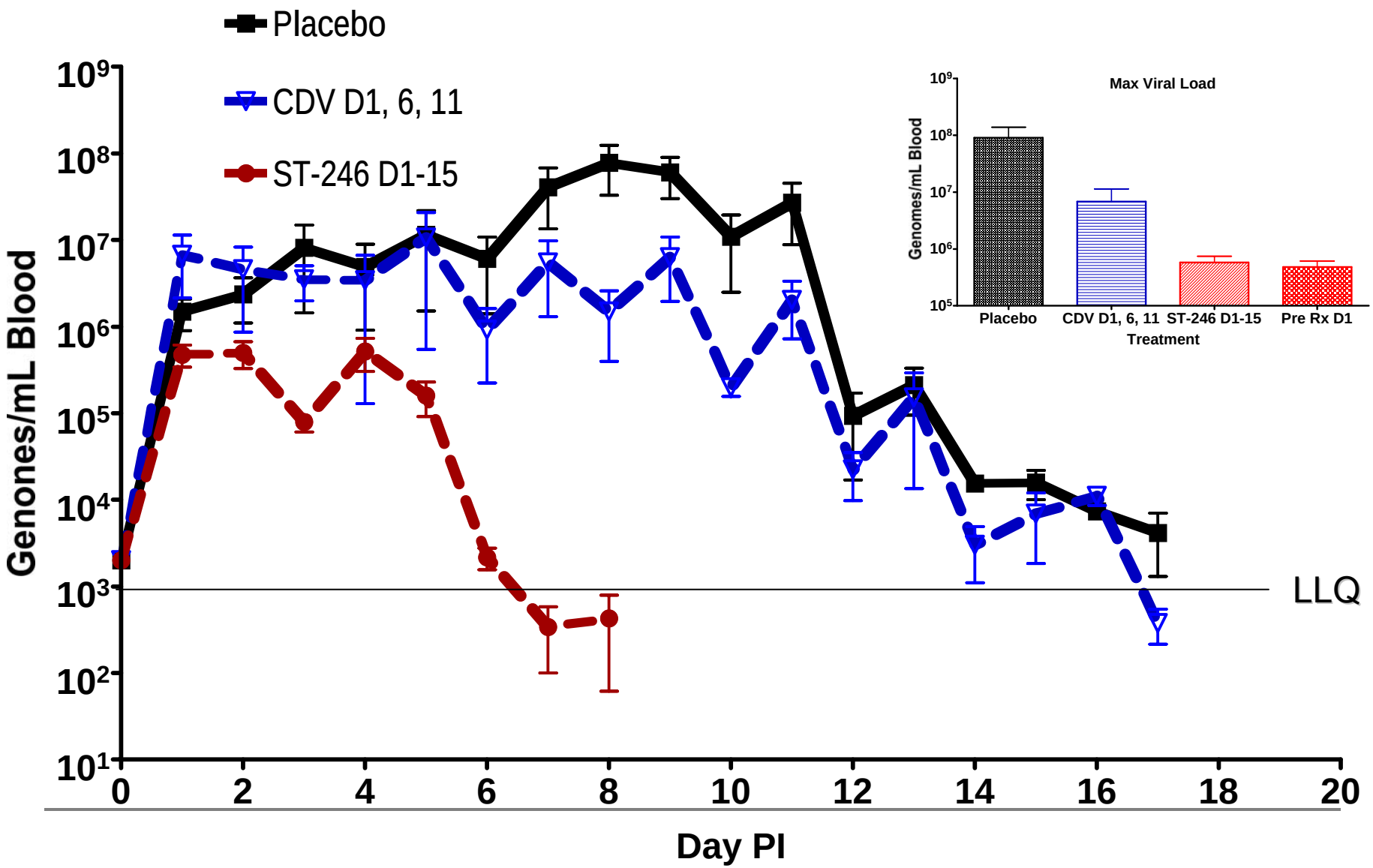
Comparison of the Clinical Course of Smallpox in Humans and Infected Nonhuman Primates



Variola: Total Suppression of Lesions by ST-246



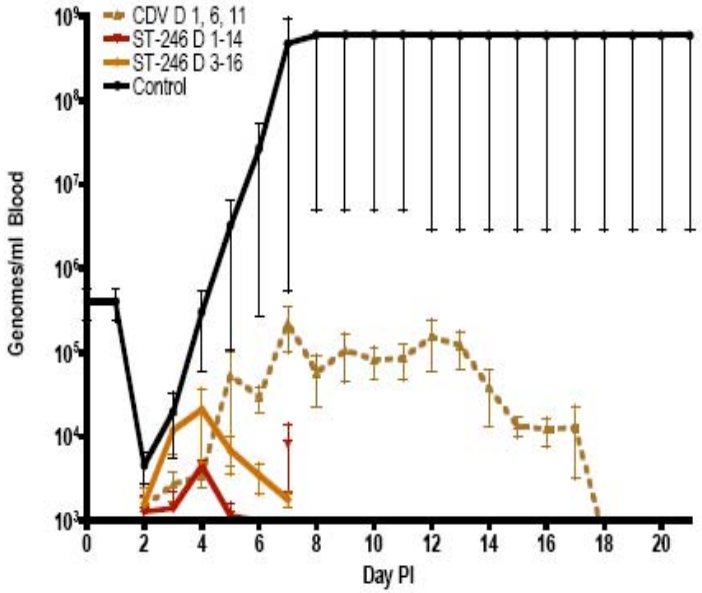
Viral Load – CDV vs. ST-246

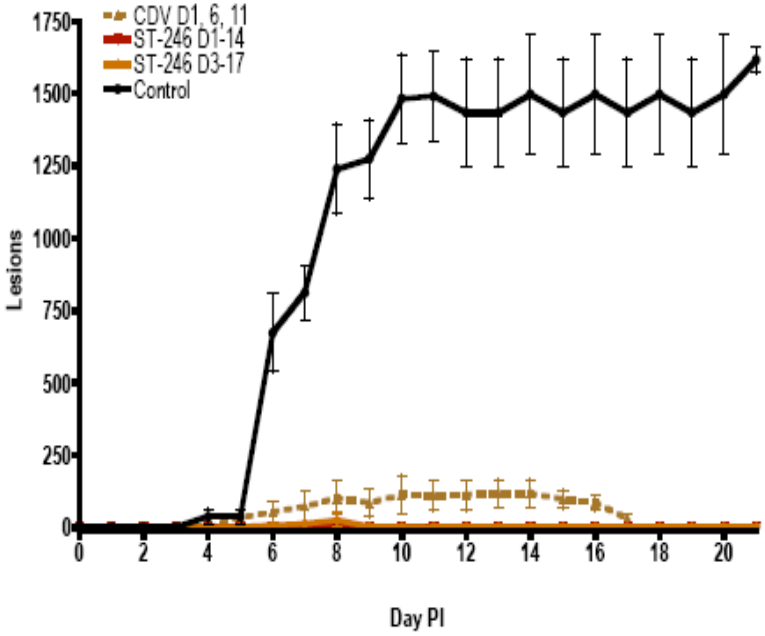


Monkeypox-NHP Challenge at USAMRIID

- 5 x 10^7 IV MPX Challenge
- 100% Mortality
- Multi-organ disease with high titers of virus
- End Points: Death, lesion count, viral load
- ST-246 dosed at 300 mg/kg starting 1 day or 3 days post infection
- Day 3 represents therapeutic intervention
- CDV dosed IV on day 1, 6, & 11

Monkeypox-NHP Efficacy (USAMRIID)





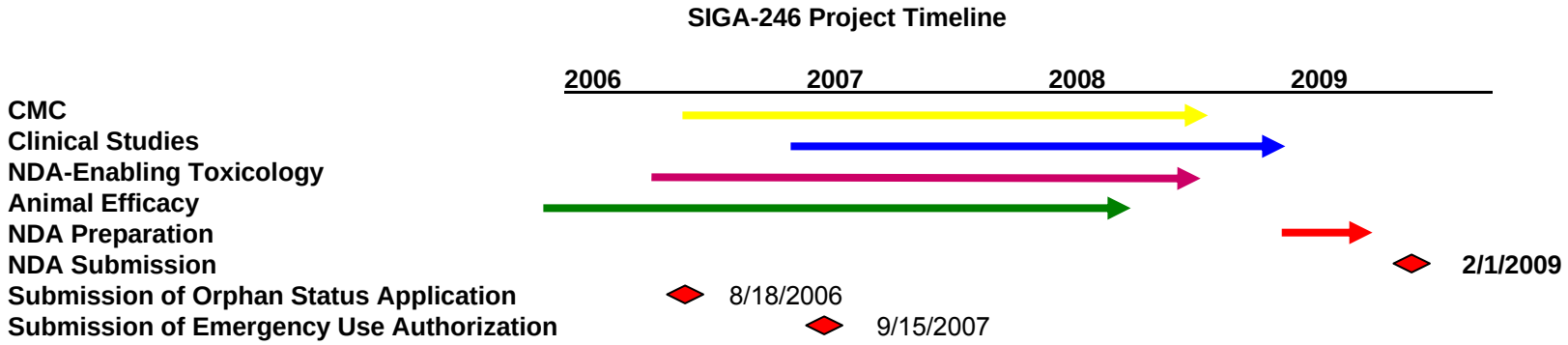
In this model, clinical symptoms are evident by 2 days and the temperature begins to spike between 2-3 days post infection

Uses for the ST-246 Smallpox Antiviral

- Prophylaxis - Prevent disease in non-vaccinated individuals
- Post-exposure Prophylaxis - Treat non-symptomatic individuals previously exposed to smallpox
- Therapeutic – Treat individuals exhibiting smallpox disease symptoms
- Adjuvant to Vaccination
  - Use in combination with vaccines to prevent smallpox disease
  - Prevent vaccine-related complications
  - Prevent disease in those populations unable to be vaccinated

ST-246 Development Timeline

- IND-enabling activities
  - CMC completed
  - ADME completed
  - Toxicology completed
- FDA pre-IND Meeting, Sept. 15th 2005
- IND Approved 12/08/05, Fast Track Status
- Human Safety Trials, Q206
- NHP Efficacy Trials, Q306
- NDA Enabling PK, Toxicology, CMC ongoing
- GLP Animal Efficacy Trials in 2007
- Complete NDA Filing Q109



Important Corporate/Federal Partners

- United States Air Force
- United States Army
- Advanced Biologics
- TransTech Pharma
- Molsoft
- National Institutes of Health
- Office of Biodefense Research
- DTRA/DOD
- USAMRIID
- UTMB
- SFBR

Long Term Goals