A Phase I Dose-Escalation Trial of vvDD-CDSR (Double-Deleted Vaccinia Virus Plus CD/SMR) Administered by Intratumoral Injection in Patients with Superficial Injectable Tumors

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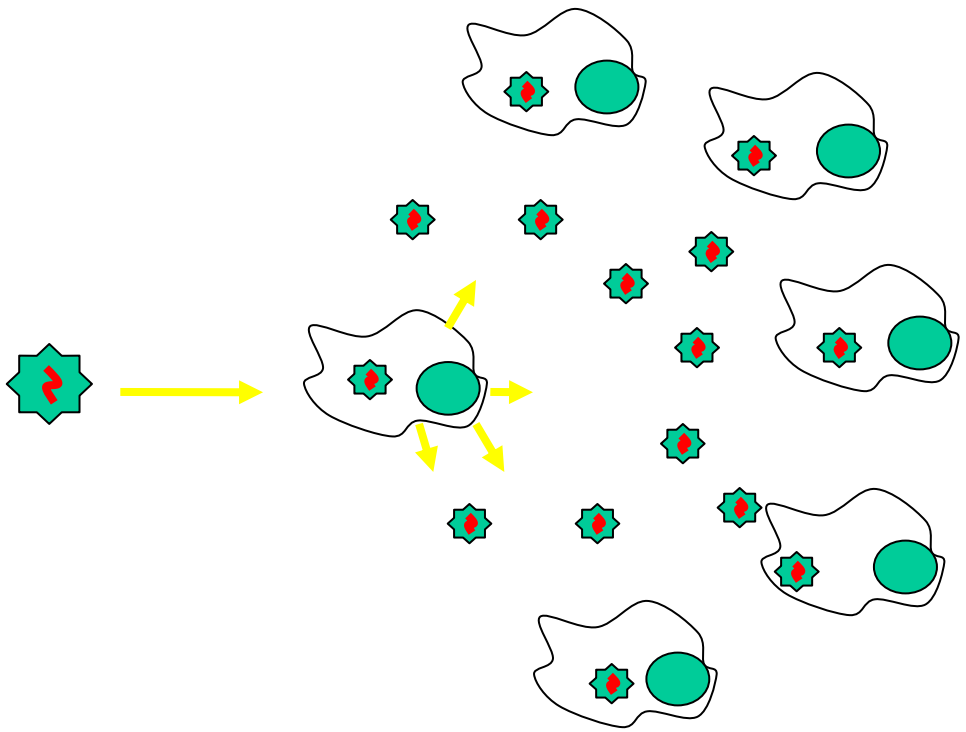
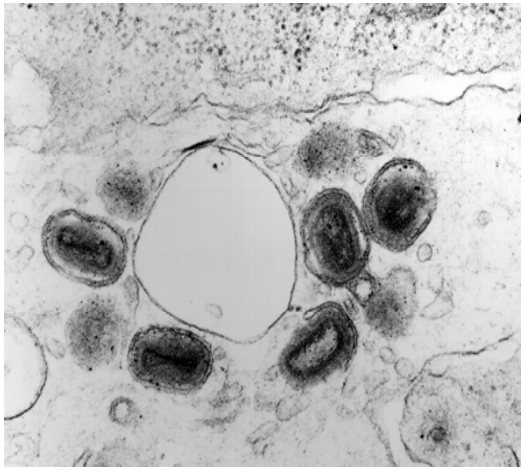
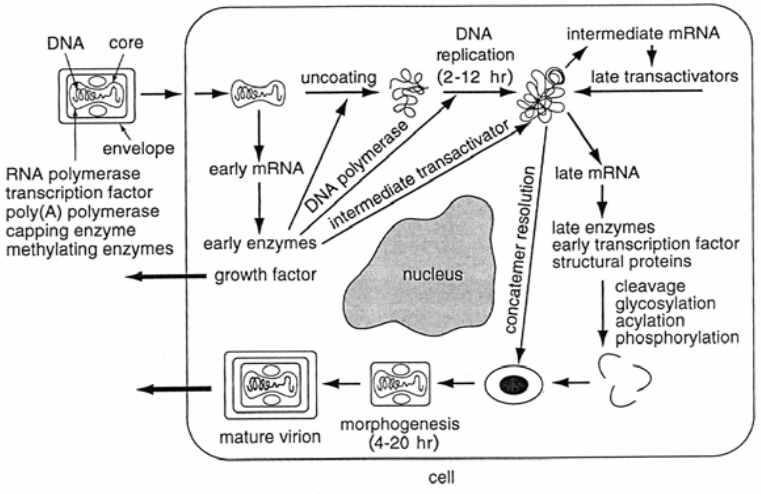
Tumor Specific Replicating Viruses



- Adenovirus
- Herpes
- Autonomous Parvovirus
- Newcastle Disease Virus
- Reovirus
- Measles Virus

Advantages of Vaccinia as an Oncolytic Virus



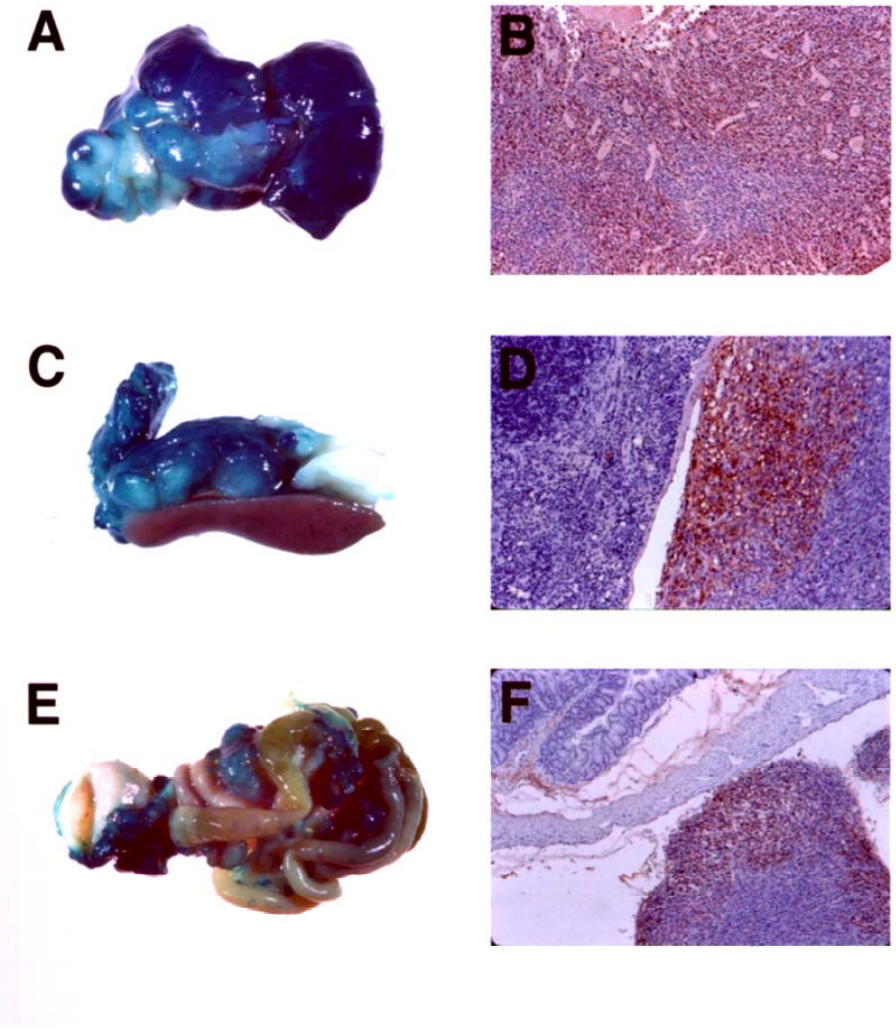


- High Efficiency: Rapid replication and destruction of cancer cells
- Tumor targeting: Systemic delivery of virus leads to high tumor uptake
- Large complex virus with ability to insert genes and delete genes to enhance tumor selectivity
- Safety profile known as a result of smallpox vaccination programs
- Cytoplasmic virus: no chance for integration into genome
- Anecdotal reports of anti-tumor response in patients given Vaccinia Virus

Tumor Selectivity

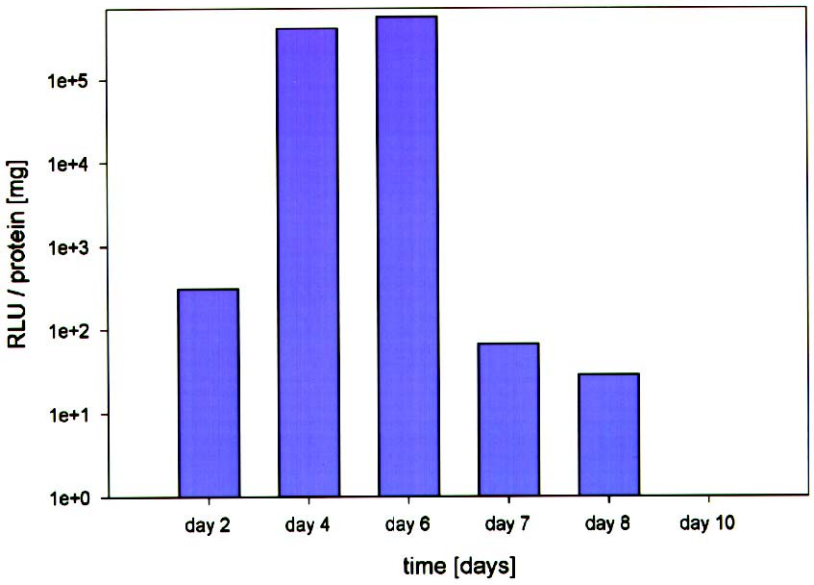
- Natural selectivity
- Deletion of Thymidine kinase
  - Tumor Cells have increased mRNA for Thymidine Kinase
  - Delete Viral Thymidine Kinase Gene (required for DNA Synthesis)
  - Efficient Replication only in Tumor Cells

Intraperitoneal Vaccinia -- Peritoneal Carcinomatosis



Puhlmann et al, Cancer Gene Therapy, 1999

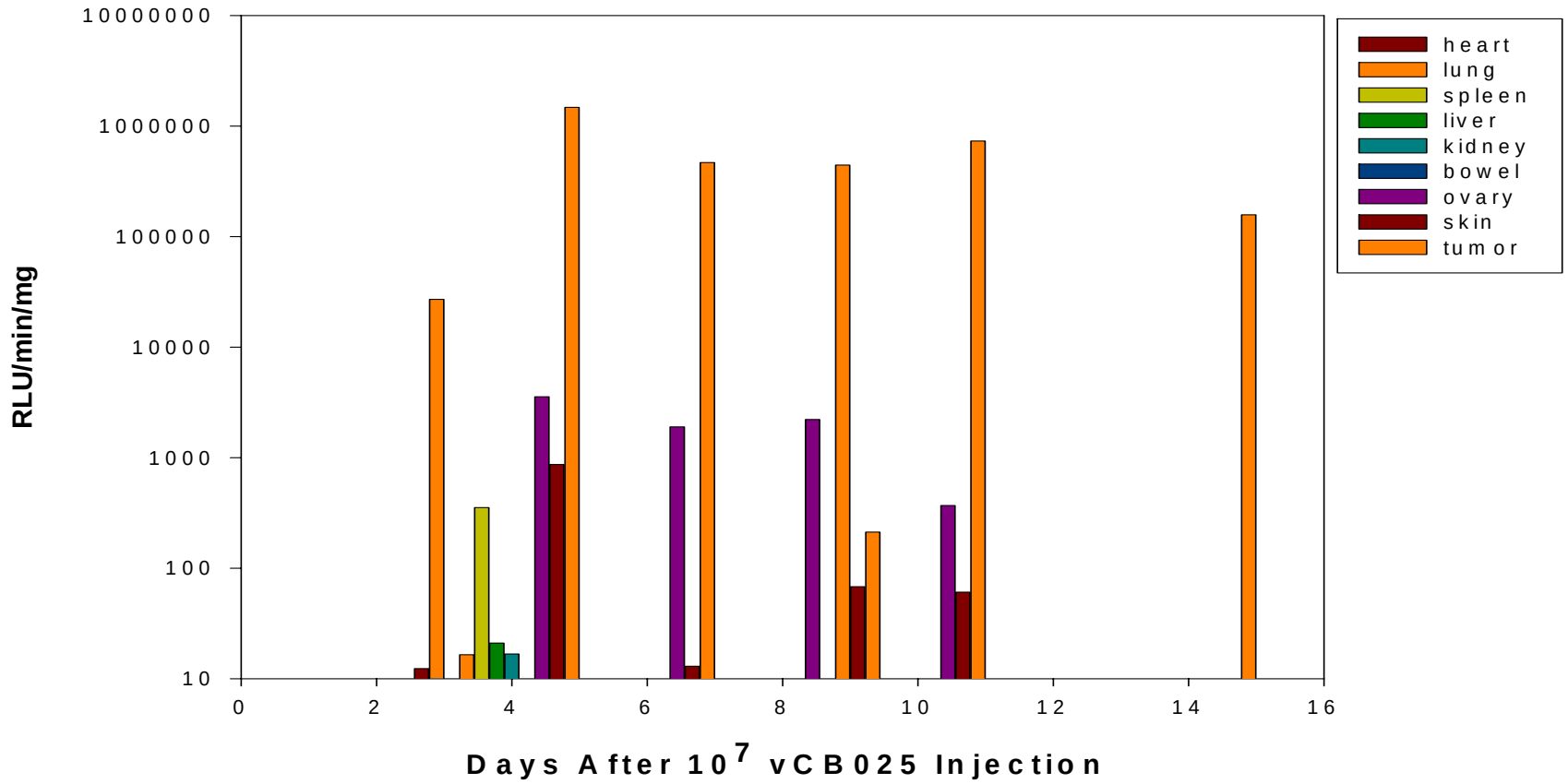
Intraperitoneal Vaccinia - Luciferase Activity



Tissue	RLU/mg protein
Tumor	**174990**
Liver	**8**
Spleen	**64**
Kidney	**9**
Ovaries	**694**
Peritoneum	**43**
Lungs	**11**
Heart	**260**
Muscle	**0**

Puhlmann et al,Cancer Gene Therapy,1999

Intravenous Vaccinia to Subcutaneous Tumors (MC-38) in Nude Mice



McCart et al, Gene Therapy, 2000

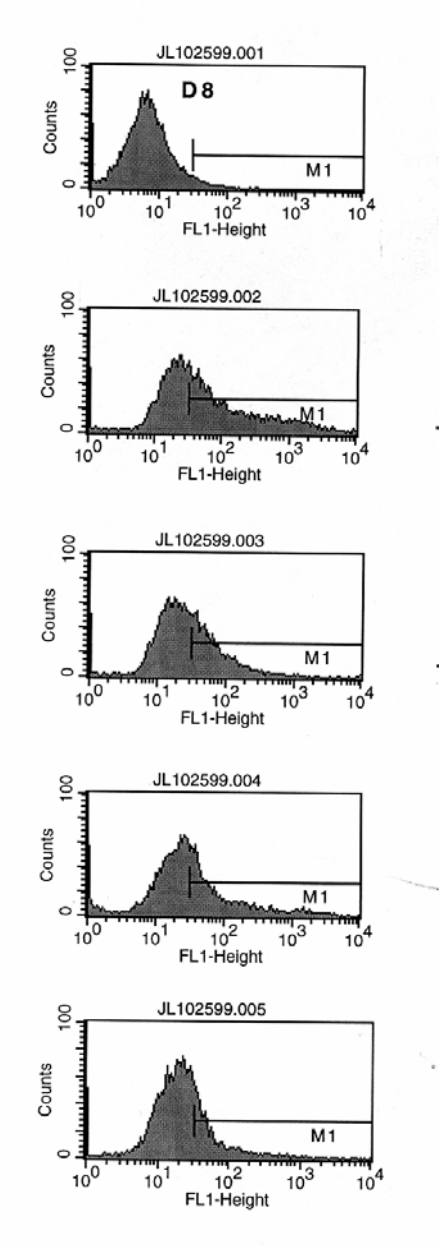
Tissue Luciferase Activity (RLU/mg protein) after Intravenous Delivery of 10^6 Vaccinia-Luciferase

Tumor Model	*Tumor*	*Ovary*	*Liver*	*Lung*
Adenocarcinoma Liver Metastases in Immunocompetent Mice	4,600,000	1450	-----	600
Subcutaneous sarcoma in rat	4337	.74	.023	.056
VX-2 Liver metastases in Rabbit	2103	132	9	7
Human melanoma in athymic mice	558000	78000	215	963

Puhlmann et al,Cancer Gene Therapy,1999

Vaccinia-GFP, In Vivo Transduction Efficiency

10^8 PFU IP in Nude Mice



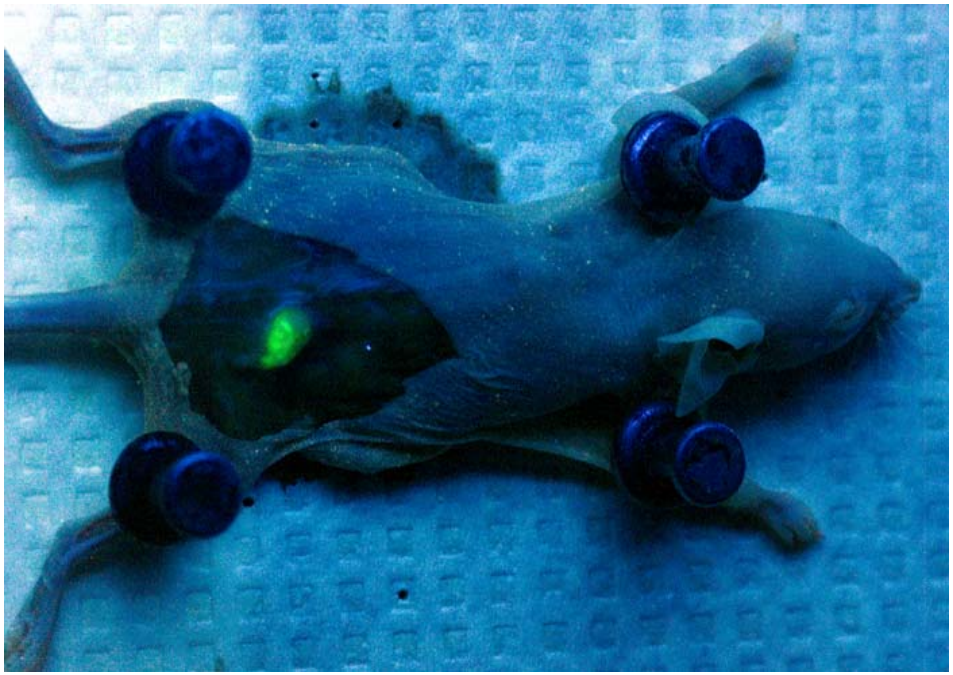
2%

49%

35%

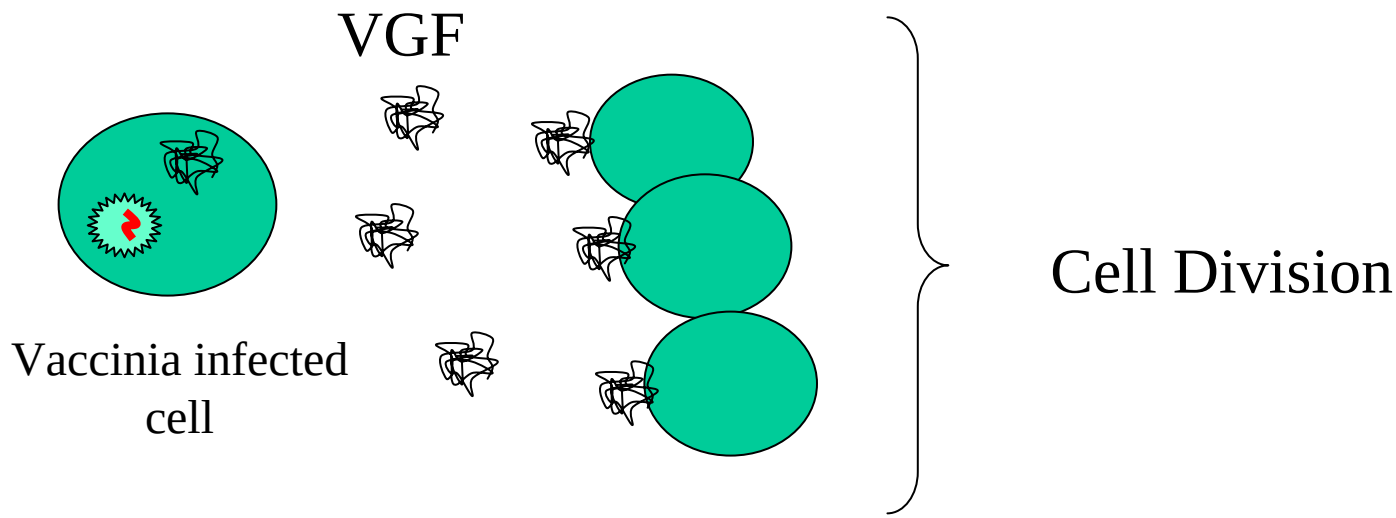
35%

24%



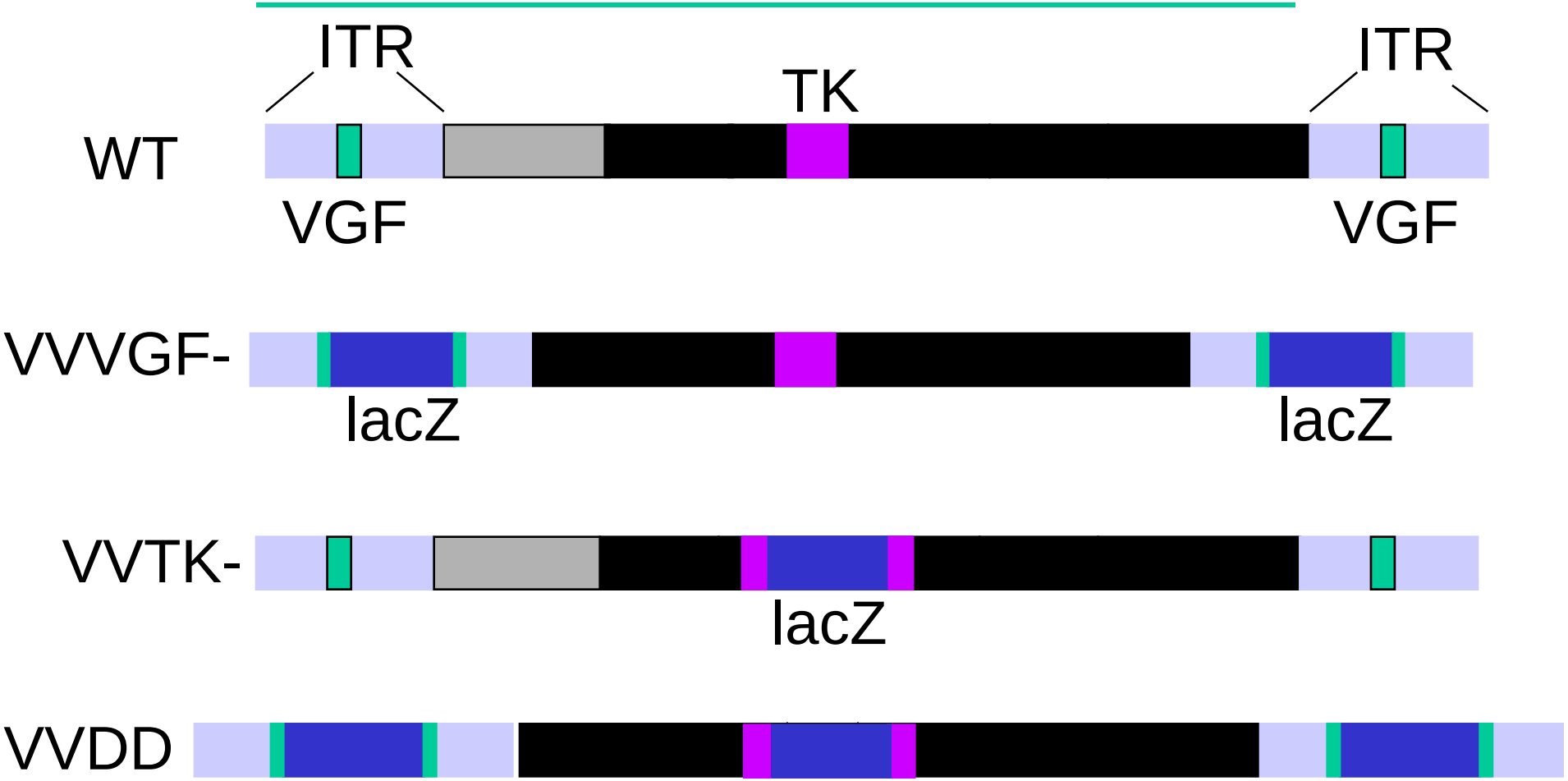
Improve Selectivity/Safety

- Delete other vaccinia genes essential for replication in non-dividing cells
  - Vaccinia Growth Factor

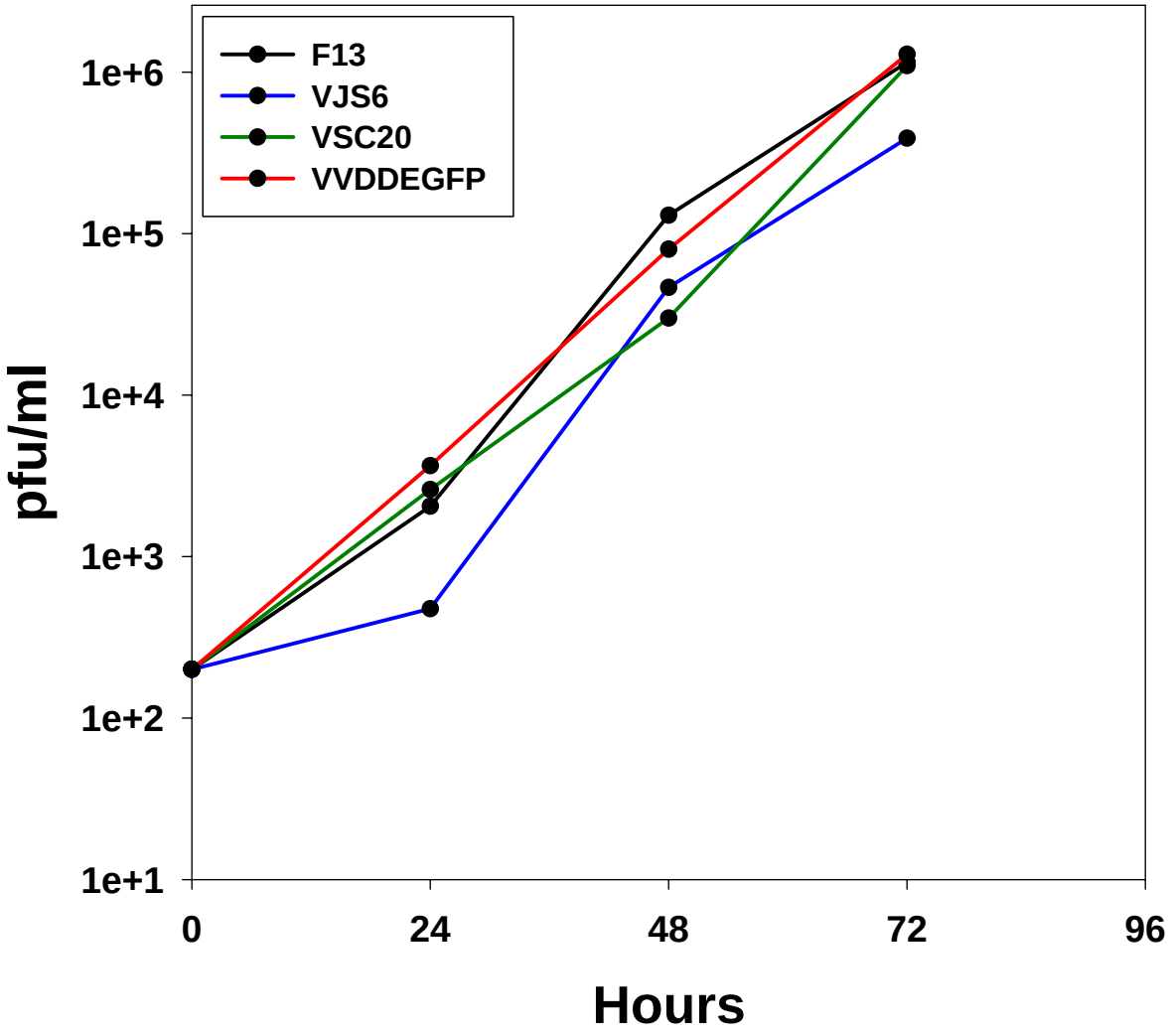


Buller et al (J Virol 62(3), 1988)

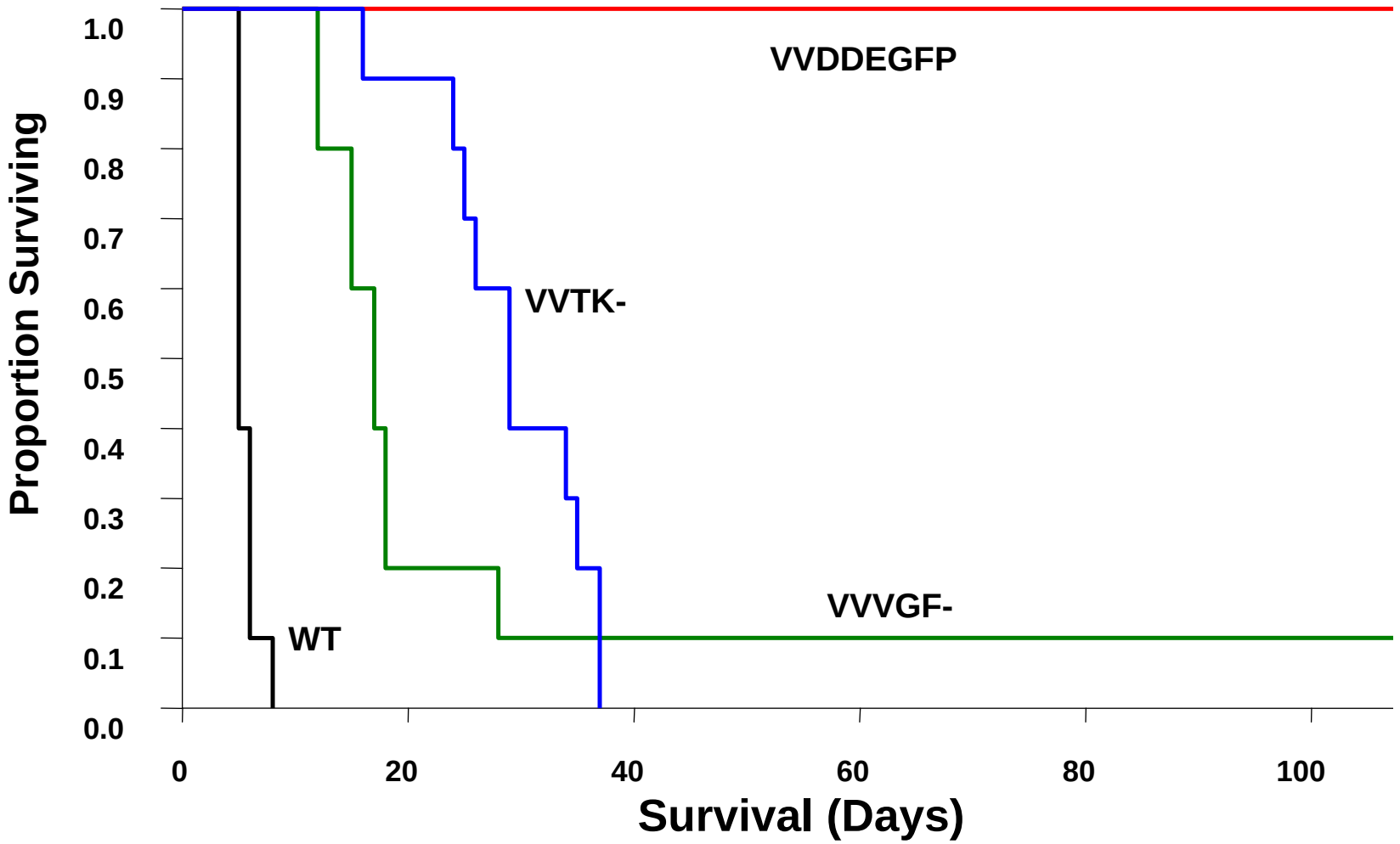
VGF and TK Deleted Vaccinia



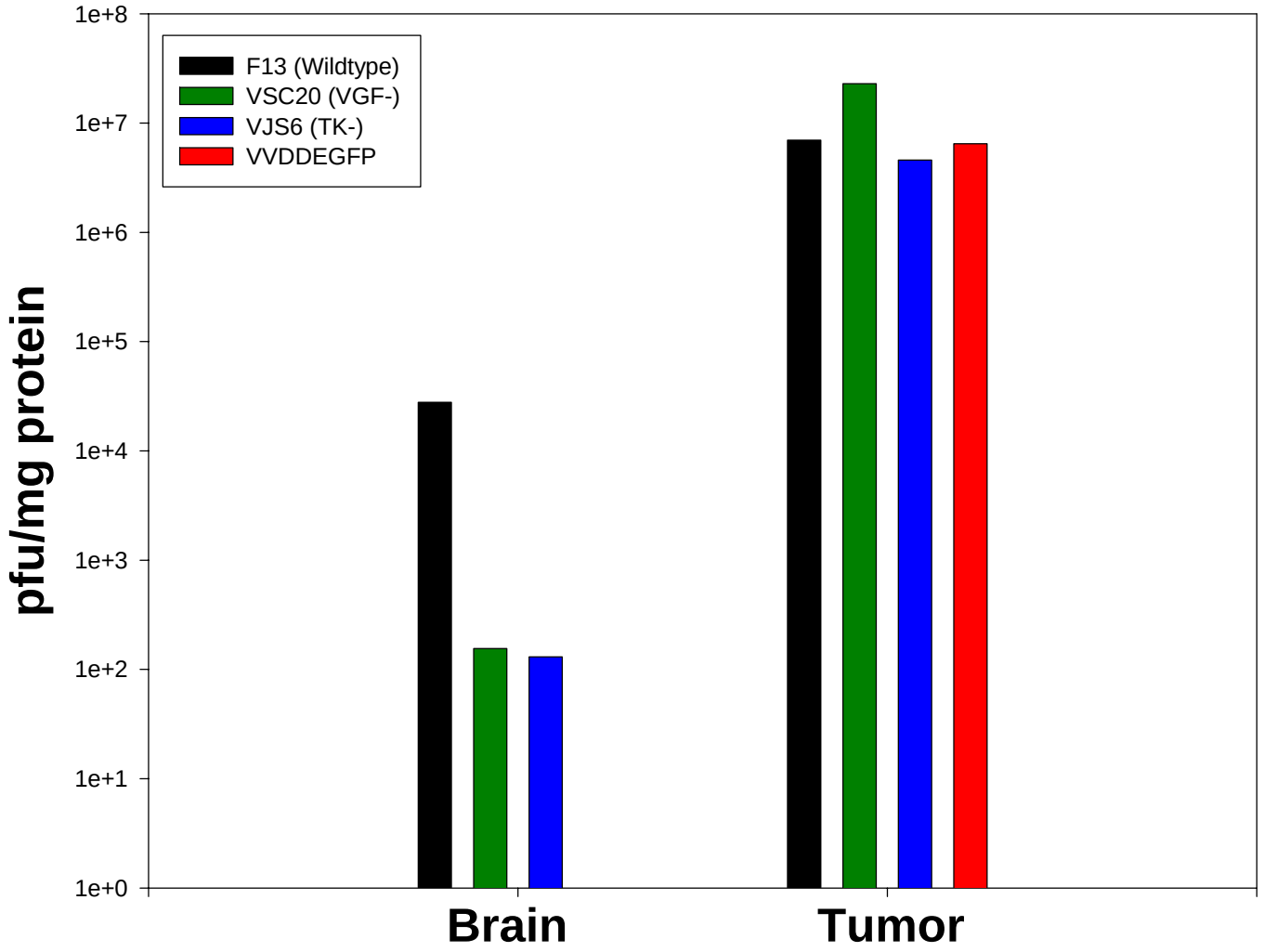
Viral Titers on Nonconfluent NIH3T3 Cells



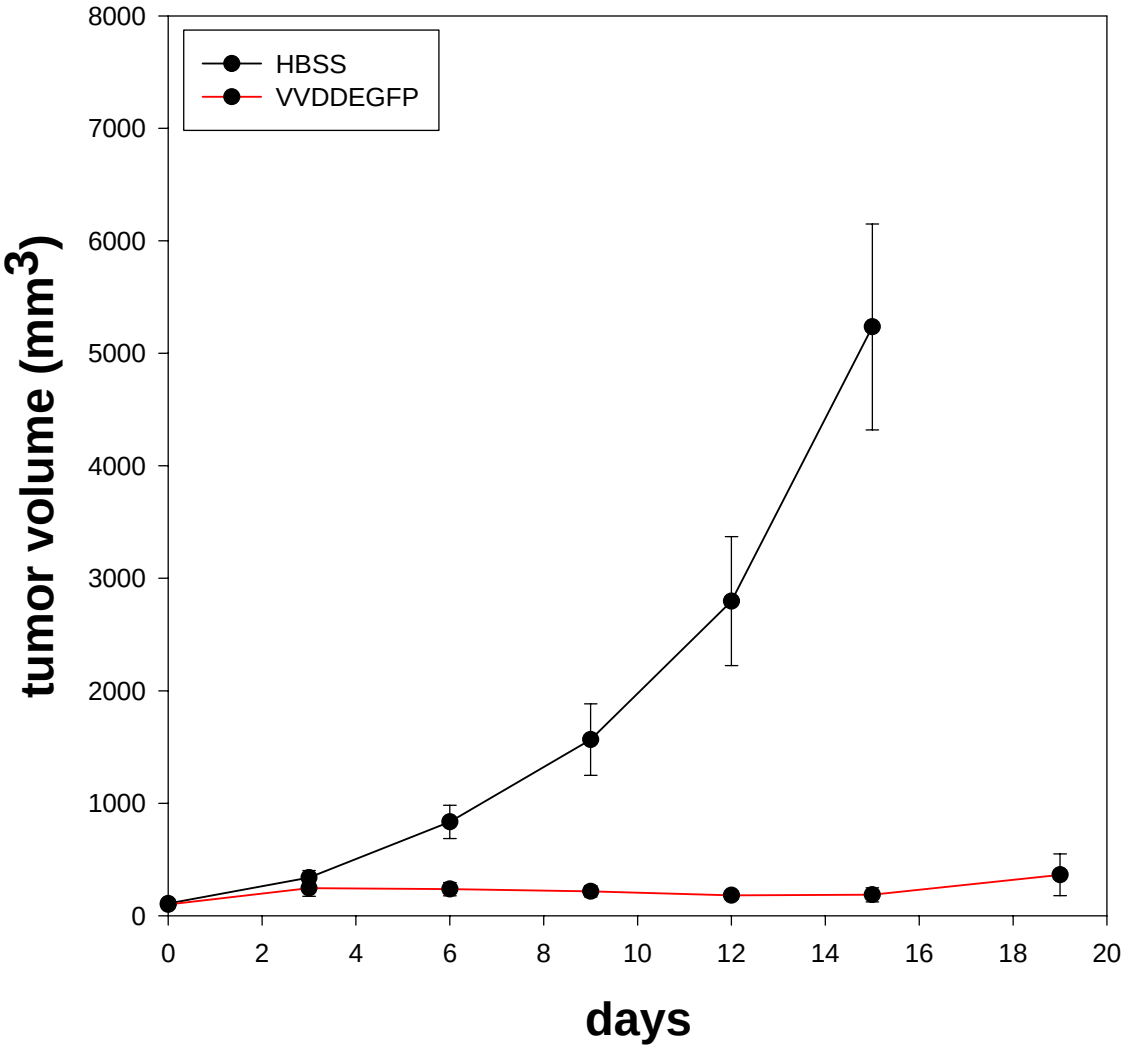
Viral Pathogenesis in Nude Mice (10^8 pfu delivered IP)



Median Viral Titers After 10^7 pfu IP Vaccinia Tumor bearing



Mean Tumor Volume After 10^9 pfu of IP VVDDEGFP



Other Tumor Response Data with TK/VGF Deleted Vaccinia

- Complete intraperitoneal response in human ovarian xenograft model (A2780)
- Potent anti-tumor response in subcutaneous human colon cancer xenograft model (HT-29)
  - Both intraperitoneal and intratumoral delivery effective

Replication in Normal Non-human Primate Skin

TK/VGF Deleted

Area of skin reaction caused by 10^6 pfu replicating vaccinia in the back of Rhesus Macaque. The Wyeth and NYCBOH strains are more commonly used in vaccine trials.

TK/VGF Deleted Vaccinia was Safe as an Intravenous Injection at 10^8 pfu in Non-human Primates

Phase I Clinical Trial

- Mutant Vaccinia Expressing Cytosine Deaminase and Somatostatin Receptor
  - Cytosine deaminase for conversion of 5-FC to 5-FU
  - Somatostatin receptor for in vivo imaging of gene expression
- Patients with cutaneous and/or subcutaneous tumors will receive intratumoral injection of vaccinia
  - Up to 3 tumors will be injected
  - Volume = 25% of tumor volume
  - Dose escalation from 3×10^7 pfu to 3×10^9 pfu in cohorts of 2 to 6 patients
  - Repeat every 3 weeks for a total of 4 cycles
  - Follow toxicity, pharmacokinetics, shedding, viral replication, and response

Future Trials

- If this trial demonstrates efficacy at a safe dose, then we will pursue regional treatment studies:
  - Intraperitoneal treatment of peritoneal carcinomatosis
  - Intra-arterial treatment of liver tumors

Virus	Tumor model	Endpoint	Results
VJS6	Peritoneal carcinomatosis	Biodistribution	Tumor selectivity
Vac-PNP	Liver metastases Immunocompetent	Survival	Survival advantage Depends on 6-mpdr
Vac-PNP	Liver metastases Nude	Survival	Survival advantage Improved compared to immunocompetent
Vac-CD	Liver metastases Immunocompetent	Survival	Survival advantage Depends on 5-FC
Vac-CD	Liver metastases Nude	Survival	Survival advantage Improved compared to immunocompetent
Vac-CD	SQ MC-38 Nude	Tumor response	Significant tumor response Mildly improved with 5-FC
VJS6	Liver metastases	Biodistribution	Tumor selectivity
VJS6	Liver metastases Nude	Biodistribution	Tumor selectivity-- Longer duration compared to immunocompent
Vac-Luc	Liver metastases	Biodistribution	Intra-portal/intraperitoneal/intravenous equivalent
Vac-Luc	Rabbit liver metastases	Biodistribution	Tumor selectivity
Vac-Luc	Rat MCA Sarcoma	Biodistribution	Tumor selectivity
Vac-Luc	SQ MC-38 colon cancer	Biodistribution	Tumor selectivity
Vac-Luc	SQ B16 melanoma	Biodistribution	Tumor Selectivity
Vac-Luc	SQ HT-29 Human colon	Biodistribution	Tumor selectivity
Vac-Luc	SQ MC-38 Immunocompetent	Biodistribution	Hyperthermia improves viral uptake into tumor
Vac-Luc	SQ MC-38 Immunocompetent	Tumor response	Hyperthermia improves anti-tumor response
Vac-Luc	SQ MC-38 Immunocompetent	Tumor response	T-cell depletion improves tumor response
Vac-Luc	SQ MC-38 Immunocompetent	Biodistribution	T-cell depletion prolongs viral replication in tumor
VvDD	SQ MC-38 Immunocompetent/m/f	Biodistribution	Tumor selectivity Non-pathogenic
VvDD	SQ MC-38 Nude	Biodistribution	Tumor selectivity Non-pathogenic
VvDD	SQ MC-38 Nude	Tumor response	Significant tumor response
VvDD	A2780 ovarian nude	Survival	Survival advantage
VvDD	A2780 ovarian nude	Biodistribution	Tumor selectivity
VvDD	Rhesus Macaques	Biodistribution	Non-pathogenic Intravenous, intradermal, limb perfusion