Phase I trial of systemic administration of Edmonston strain of measles virus, genetically engineered to express NIS, with or without cyclophosphamide, in patients with recurrent or refractrory multiple myeloma

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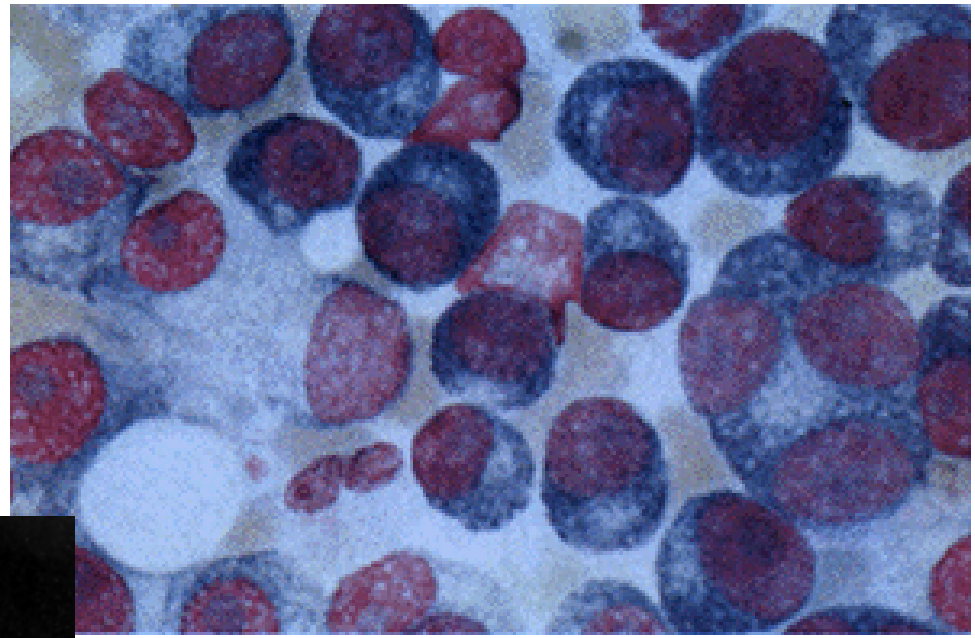
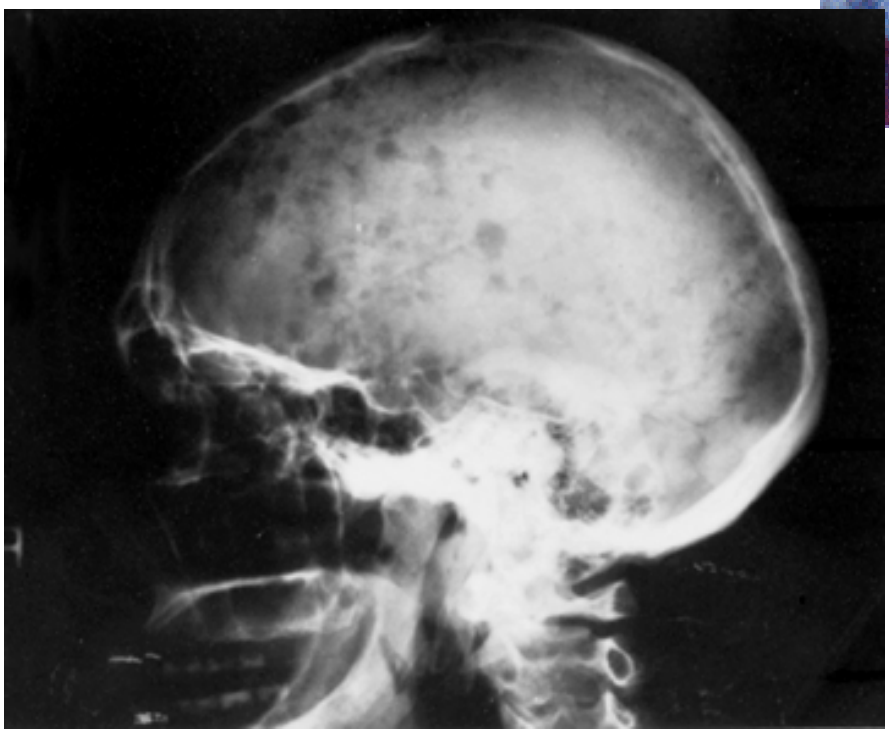
Manufacture

Steve Russell
Sponsor

Multiple myeloma

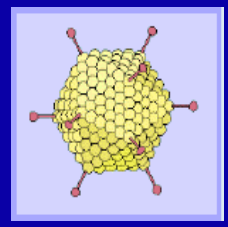
Plasma cell malignancy
Paraproteinaemia
Bone destruction
Hypogammaglobulinaemia





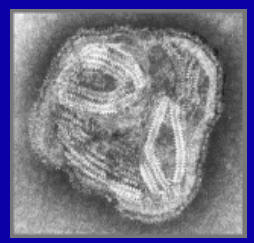
Currently incurable
11,000 deaths per year (USA)
Disseminated from outset
Survival ~ 4yrs

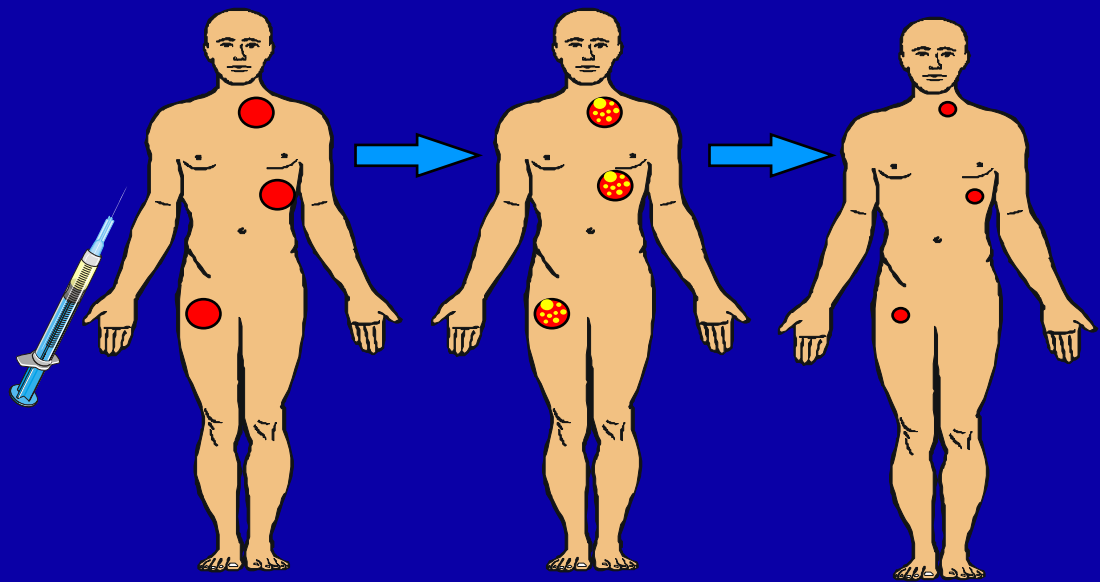
Virotherapy



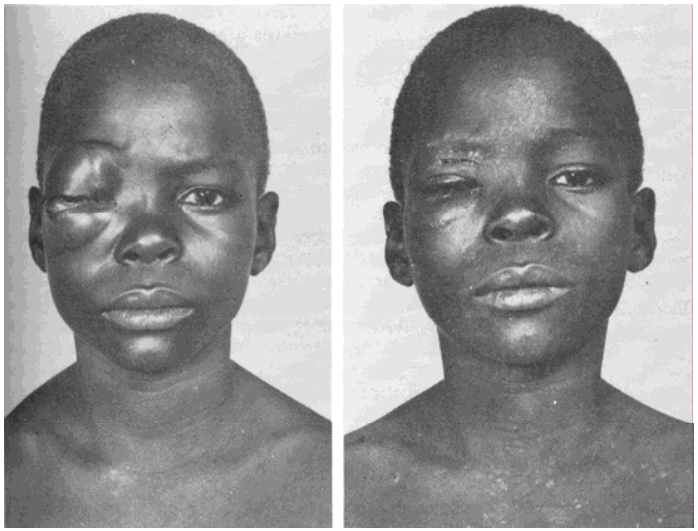
Viruses destroy tissue

Maybe this destructive power could be Harnessed for cancer therapy

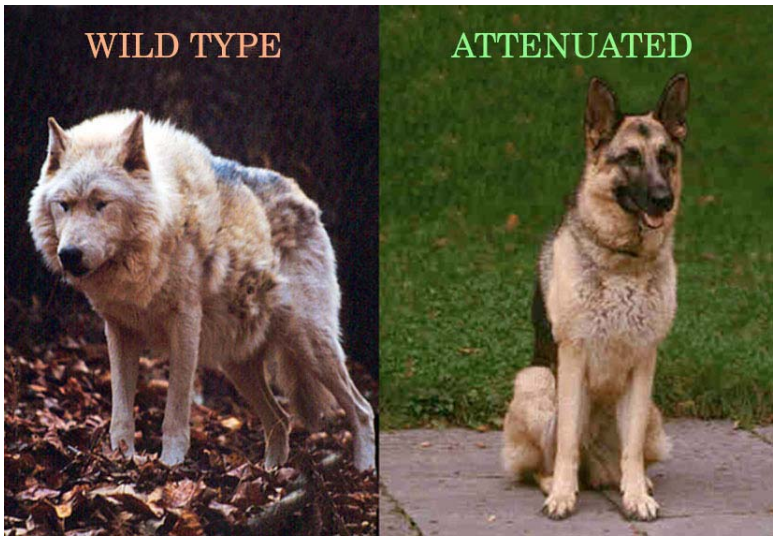




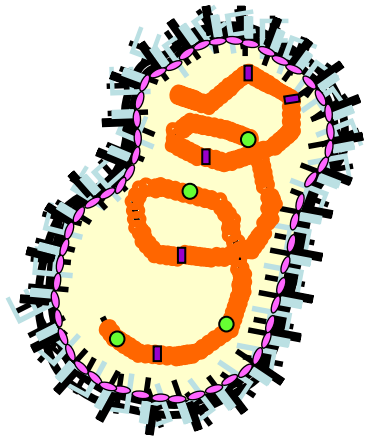
Measles as an oncolytic agent



Bluming and Ziegler (1971) Lancet ii, 105-106



SLAM only SLAM + CD46



-Efficiently infects and kills human myeloma cells (via CD46)

-Selectively kills myeloma cells, spares normal cells

-Has potent antitumor activity against xenograft models of human multiple myeloma

-Can be engineered to express additional genes; recombinants are extremely stable

Edmonston Vaccine Lineage

(Rota et al. 1994, Virus Res., 31:317)

Edmonston

HK/7
Vero/6

Edmonston "Wild Type"

HK/24
HA/28

Edmonston-Enders

HA/12
SK (33°C)/17*
CEF (33°C)/22*

AIK-C

HK/24
HA/28

Edmonston Seed A

CE (am)/22
DK/15
WI-38/19*

Zagreb

CE(am)/6
CEF/3

CEF/5
CEF (32°C)/85

Schwarz

Edmonston Seed B

CEF(36°C)/3

Edmonston B
Rubeovax

CEF(36°C)/8
CEF(32°C)40

Moraten

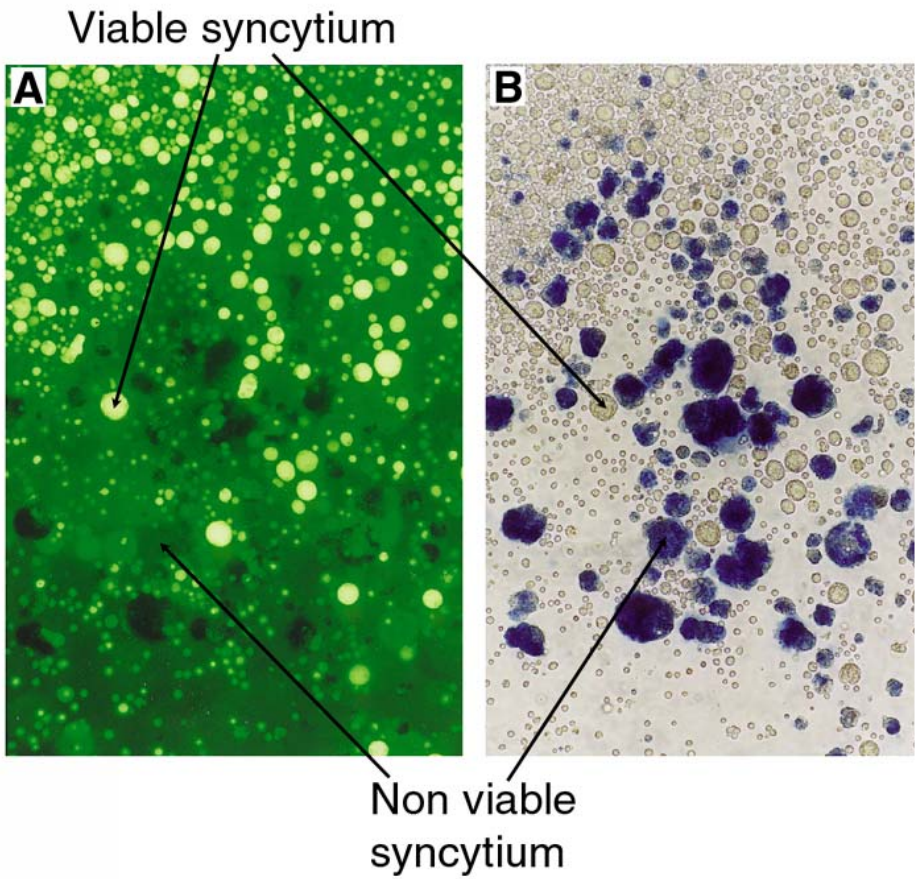
HeLa

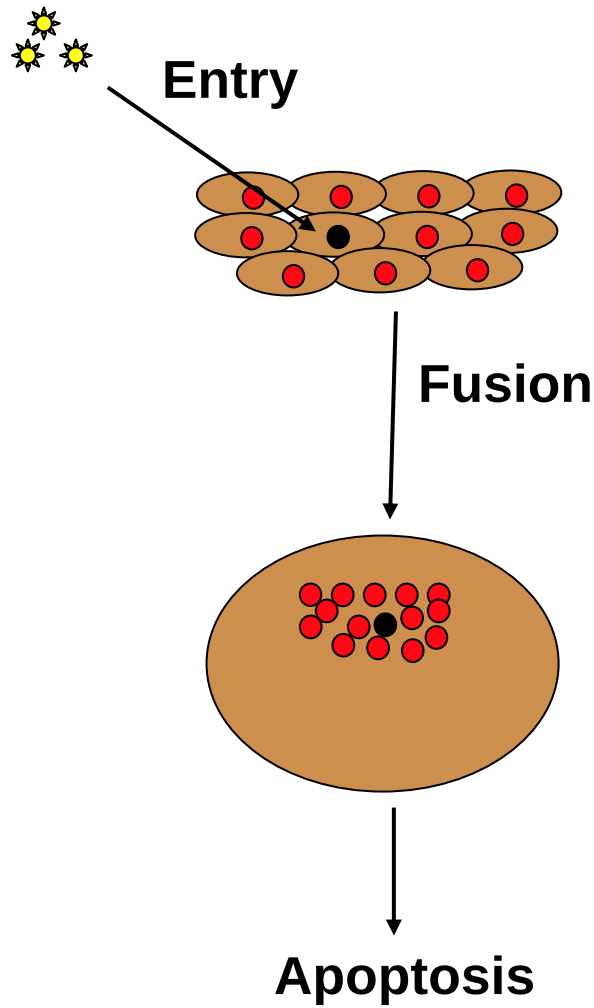
MV-SPUD

Infectious clone

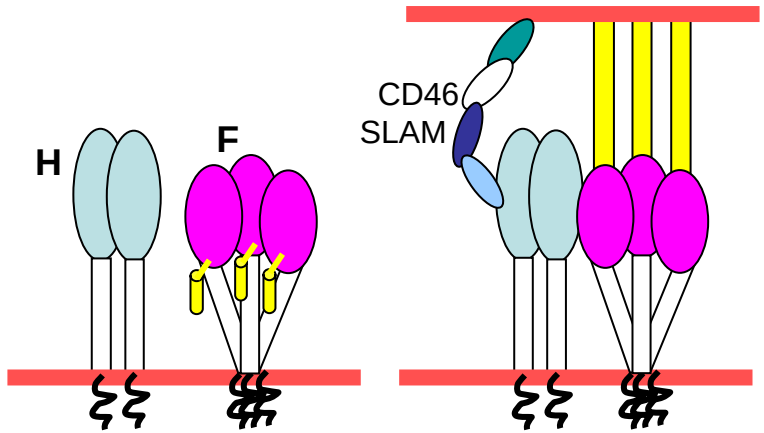
(Radecke et al., 1995 EMBO J, V14, p5773)

Measles virus cytopathic effect (cell fusion)





Fusogenic proteins: measles F and H



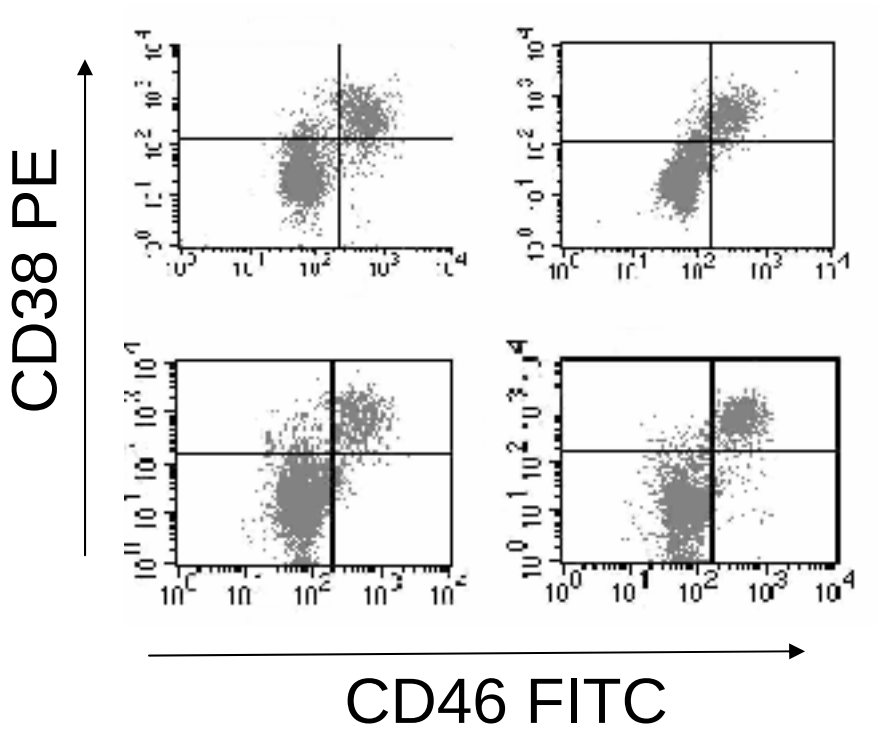
H binds to CD46 or SLAM
F triggers fusion

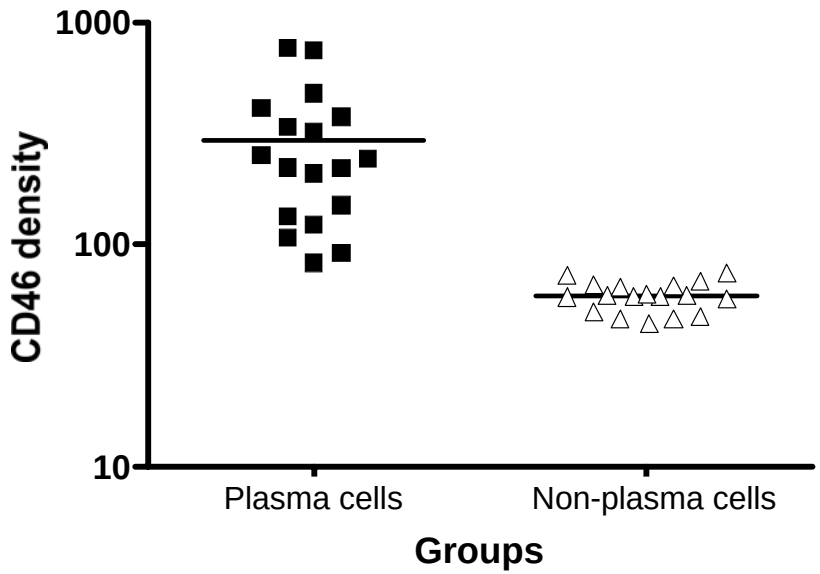
SLAM is expressed only on activated immune cells.
CD46 is ubiquitous
CD46 is overexpressed on human myeloma cells…..

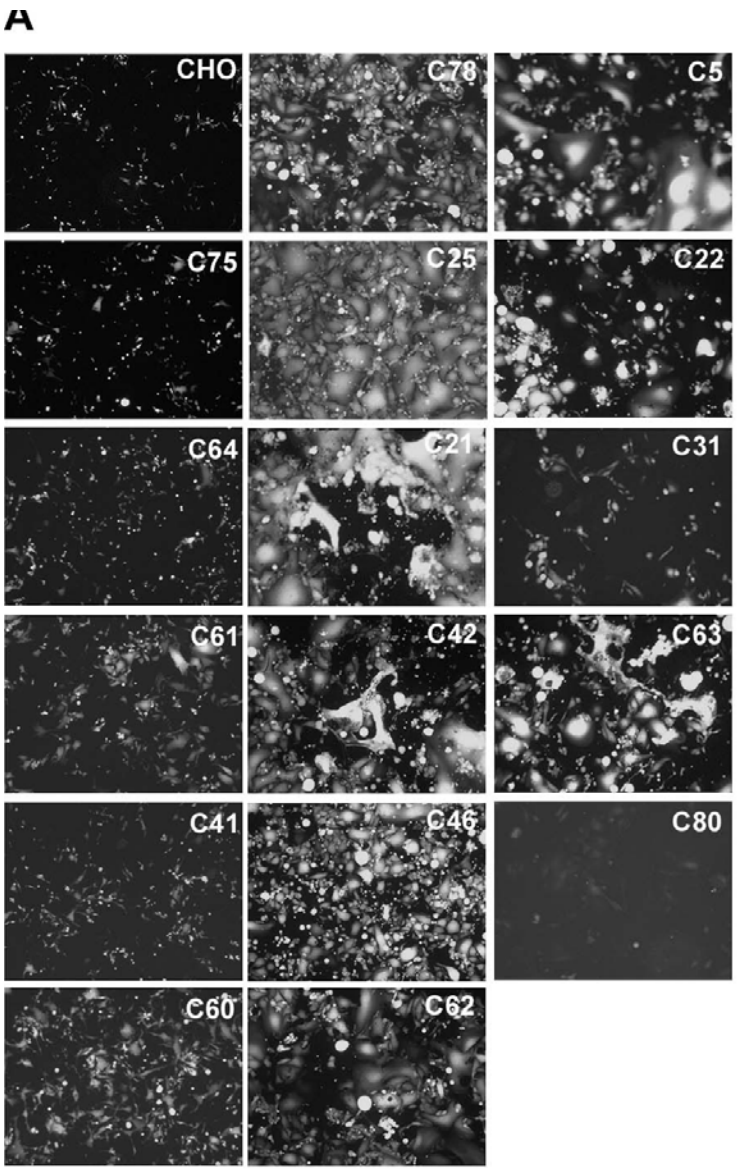
High CD46 expression in multiple myeloma

- Expressed at higher density on myeloma cells
- NOT myeloma specific
- Therapy should specifically attack high density

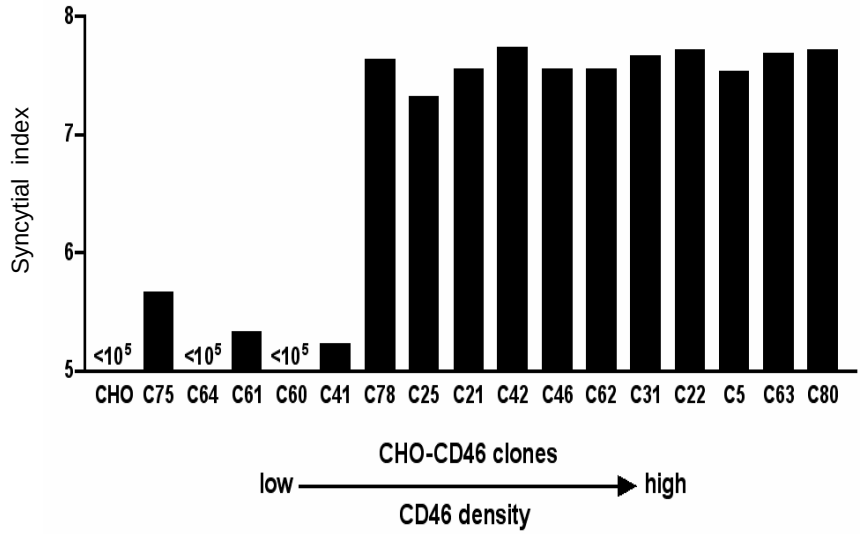
Unsorted bone marrow aspirated from patients with multiple myeloma



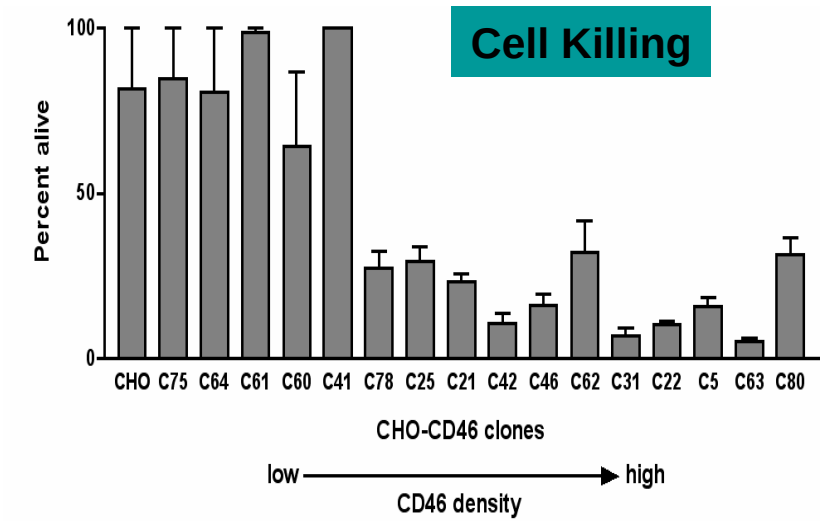




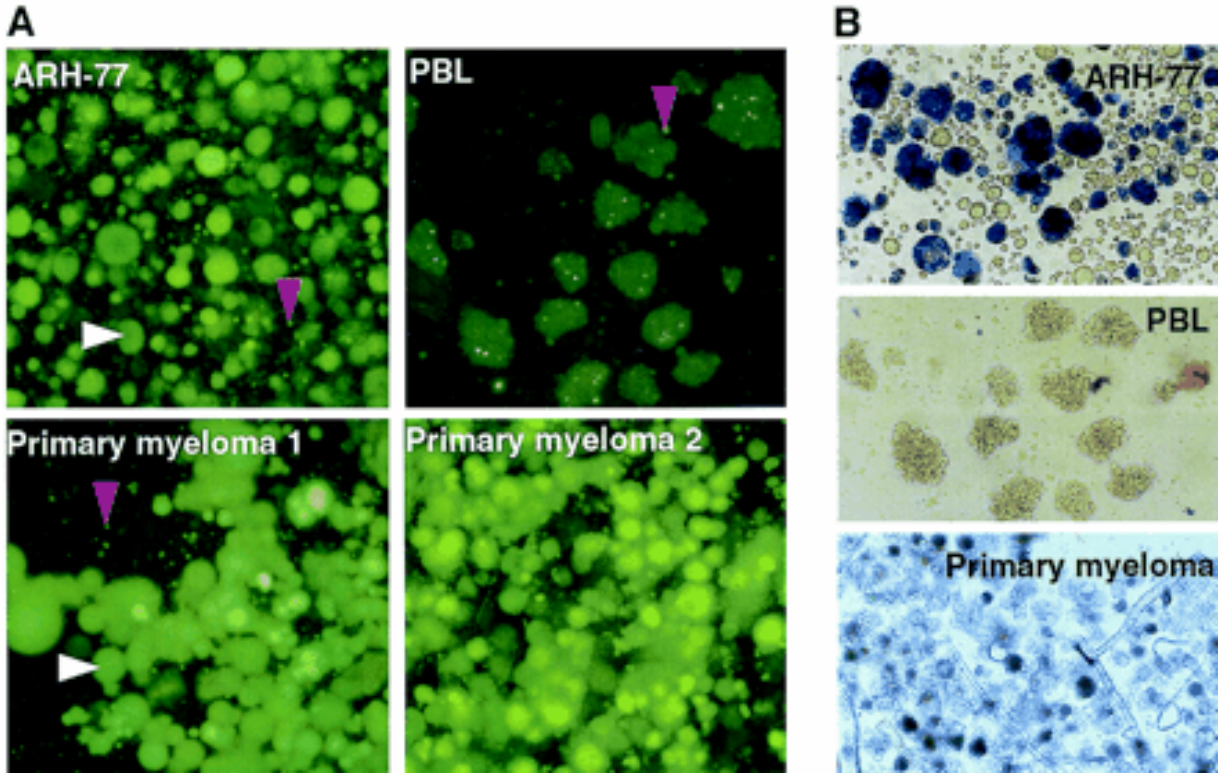
Syncytial Index

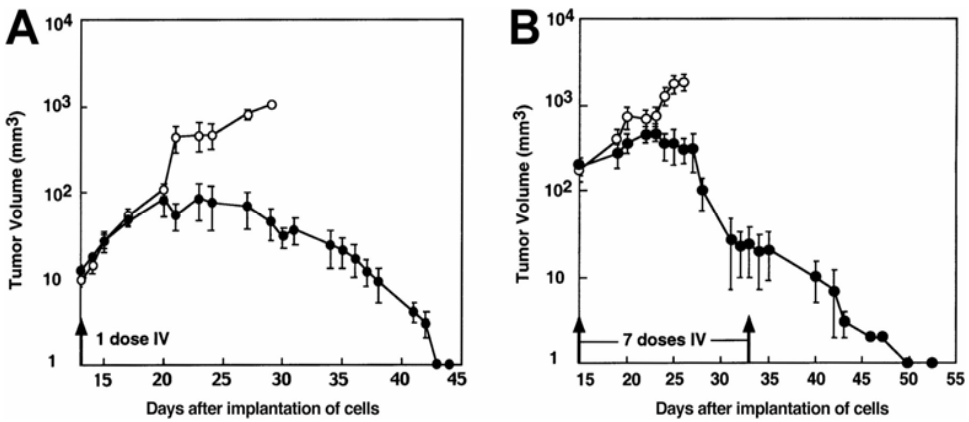


Cell Killing



MV-Edm oncolytic activity in myeloma





Peng et al., Blood, 98, p. 2002-7 (2001).

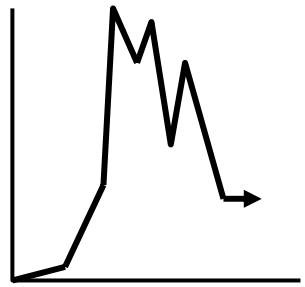
Measles virotherapy for myeloma: Problems with MV-Edm.

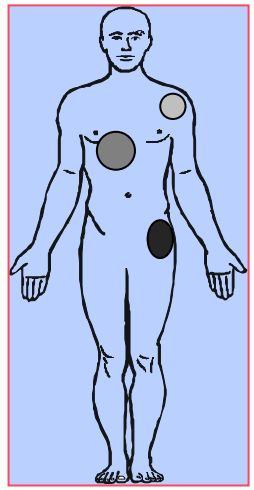
1. **Inability to monitor spread**

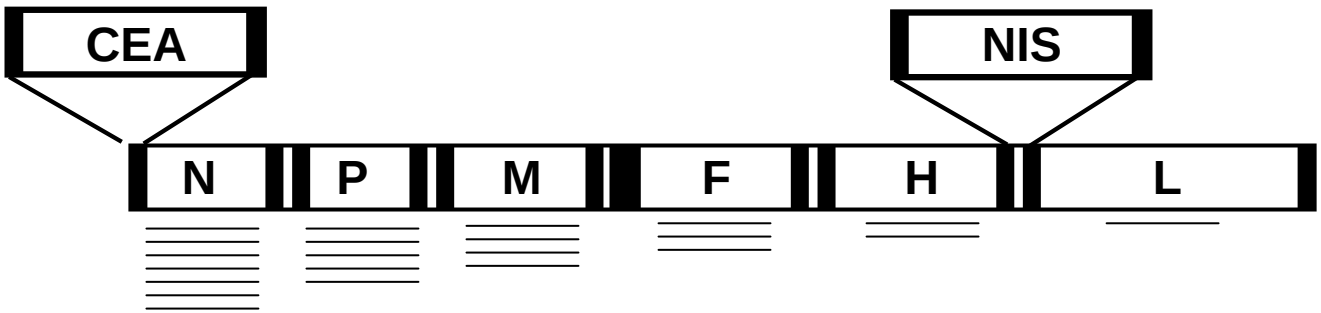
2. **Anti-measles antibodies may block vascular delivery**

3. **Anti-measles cytotoxic T lymphocytes may prevent intratumoral spread**

Recombinant measles viruses







MV-CEA: IP
ovarian cancer

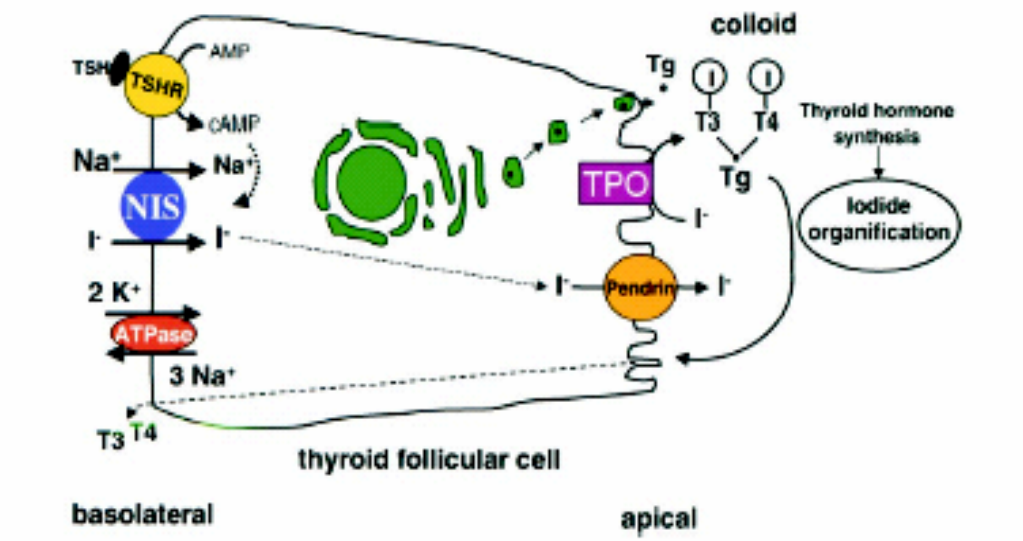
MV-NIS: IV
multiple myeloma

MV-CEA Clinical Protocol

- Advanced ovarian cancer
- IP administration of MV-CEA in 500 ml saline
- Repeated every four weeks x 6
- Dose escalation (10^3 to 10^8)
- CEA monitoring to guide dose escalation

- No manufacturing problems
- Six patients treated (three at 10^3, three at 10^4)
- No dose-limiting toxicities
- Transient viremia in two patients
- No CEA elevations yet……

The thyroidal sodium iodide symporter (NIS)

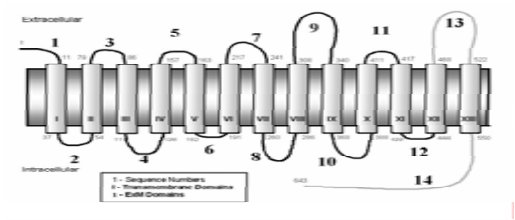


Radioiodine

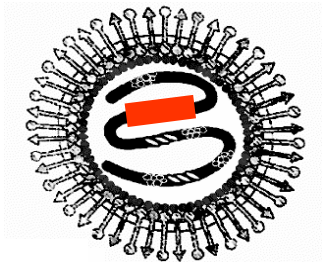
I-123	gamma	0.5 days	
I-124	positron	4 days	
I-125	gamma	60 days	
I-131	beta + gamma	8 days	
Tc99m	gamma	0.2 days	

Imaging virus spread (MV-NIS)

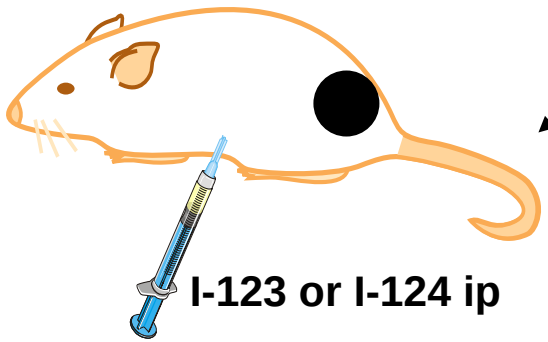
NIS protein



NIS gene



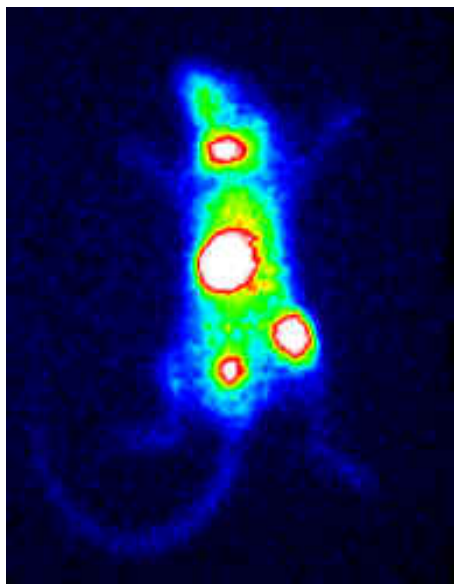
QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.



MV-NIS iv

I-123 or I-124 ip

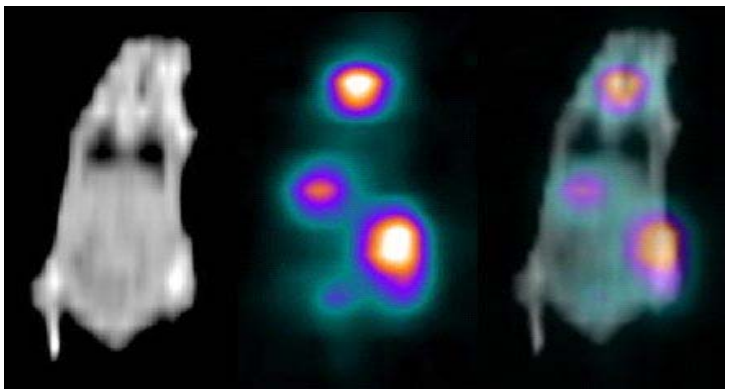
Gamma camera



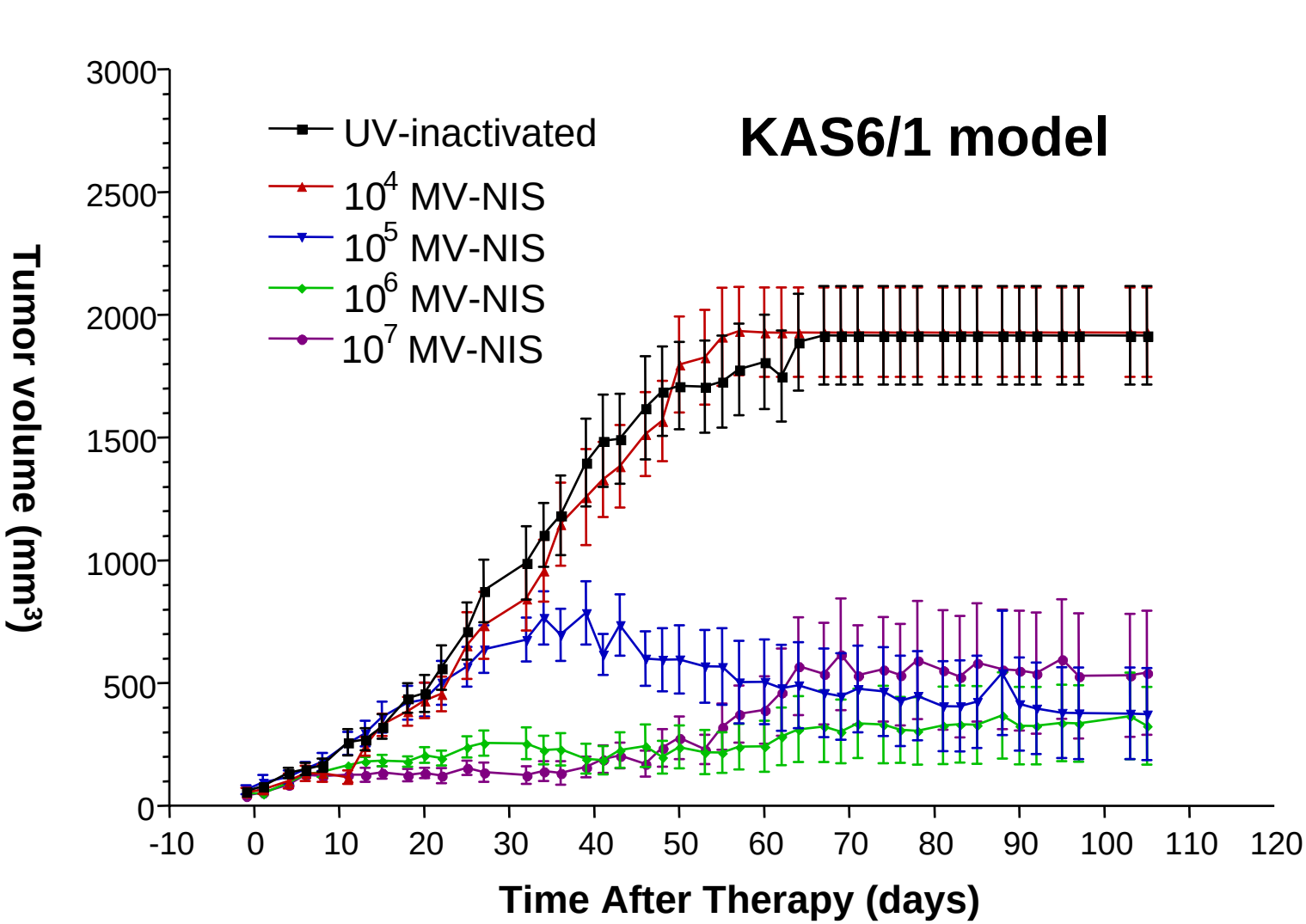
SPECT/CT

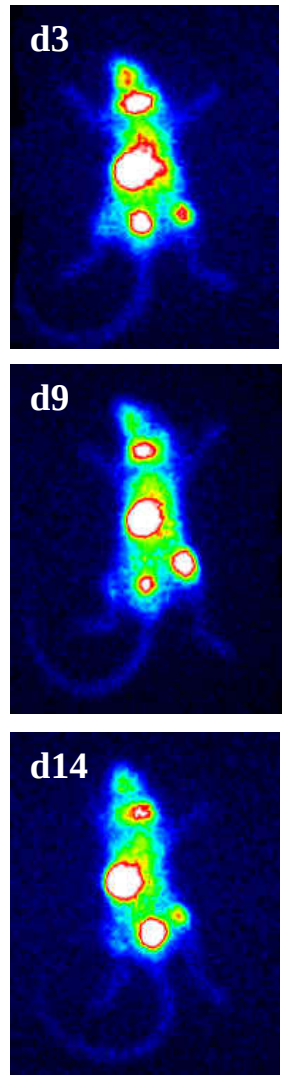
QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.

PET/CT



MV-NIS (intravenous) is a potent anti-myeloma agent





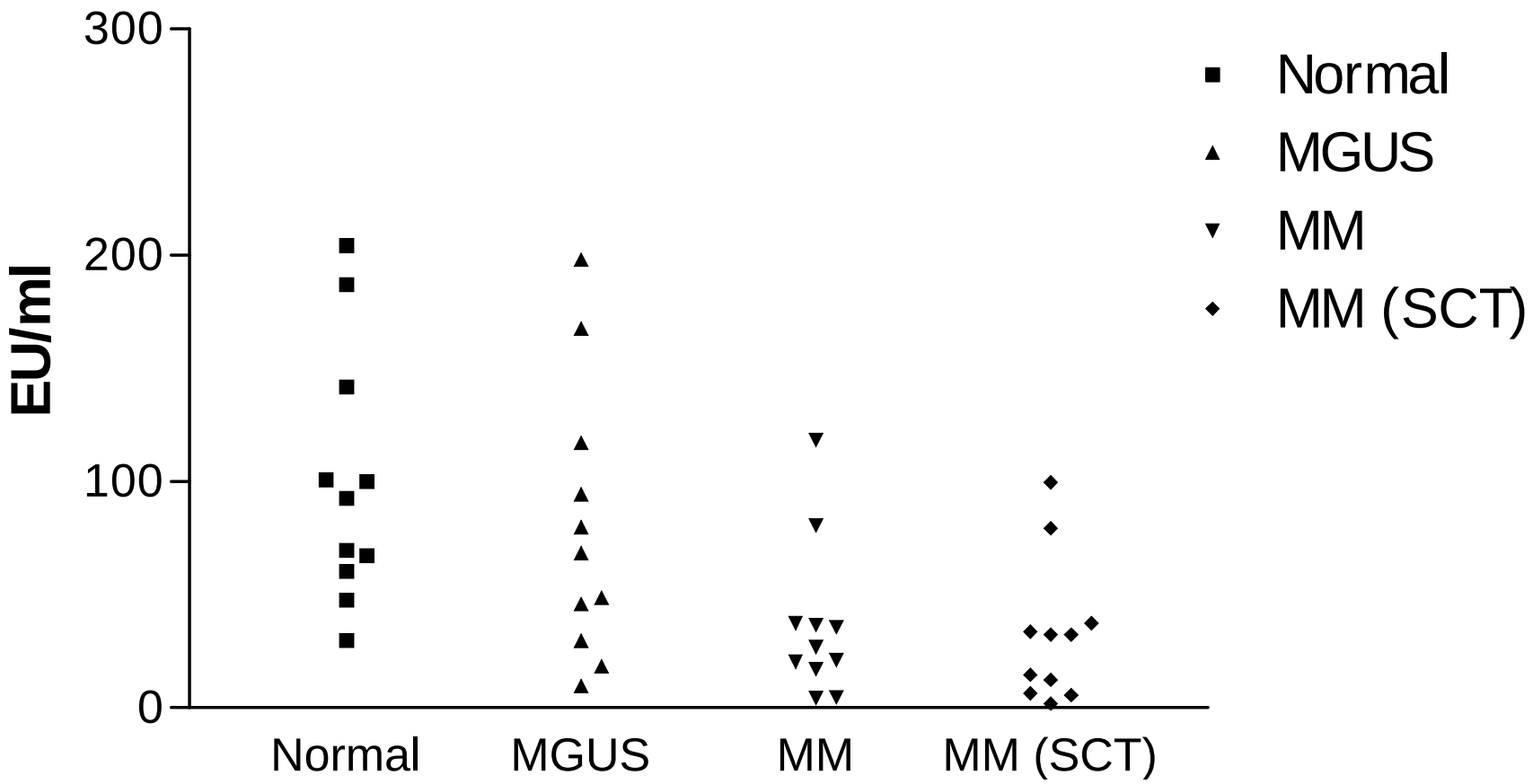
Measles virotherapy for myeloma: Problems with MV-Edm.

1. Inability to monitor spread

2. Anti-measles antibodies may block vascular delivery

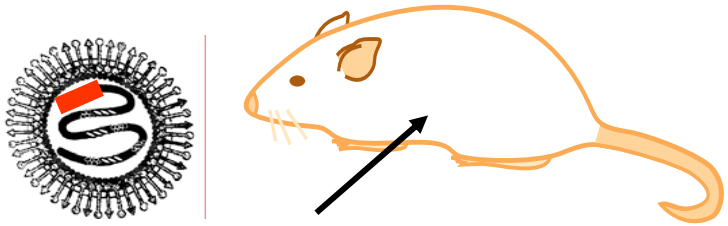
3. Anti-measles cytotoxic T lymphocytes may prevent intratumoral spread

Low Anti-Measles Antibody Titers in Myeloma Patients



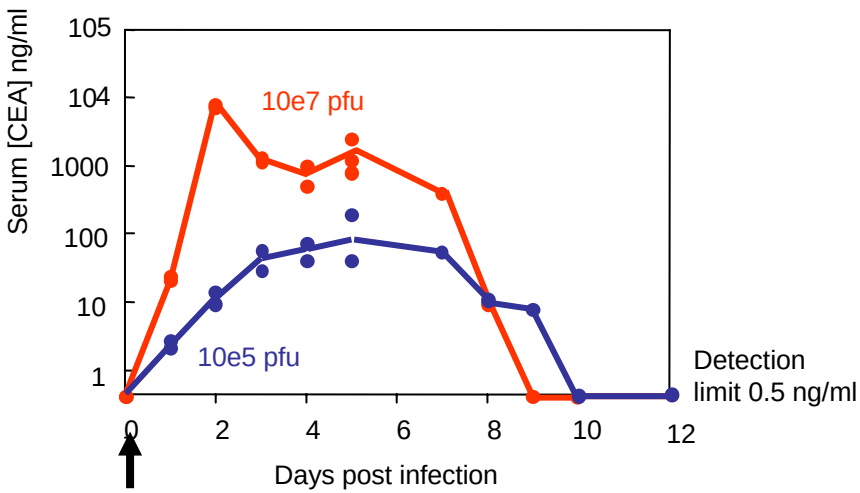
Cyclophosphamide suppresses immune response to MV

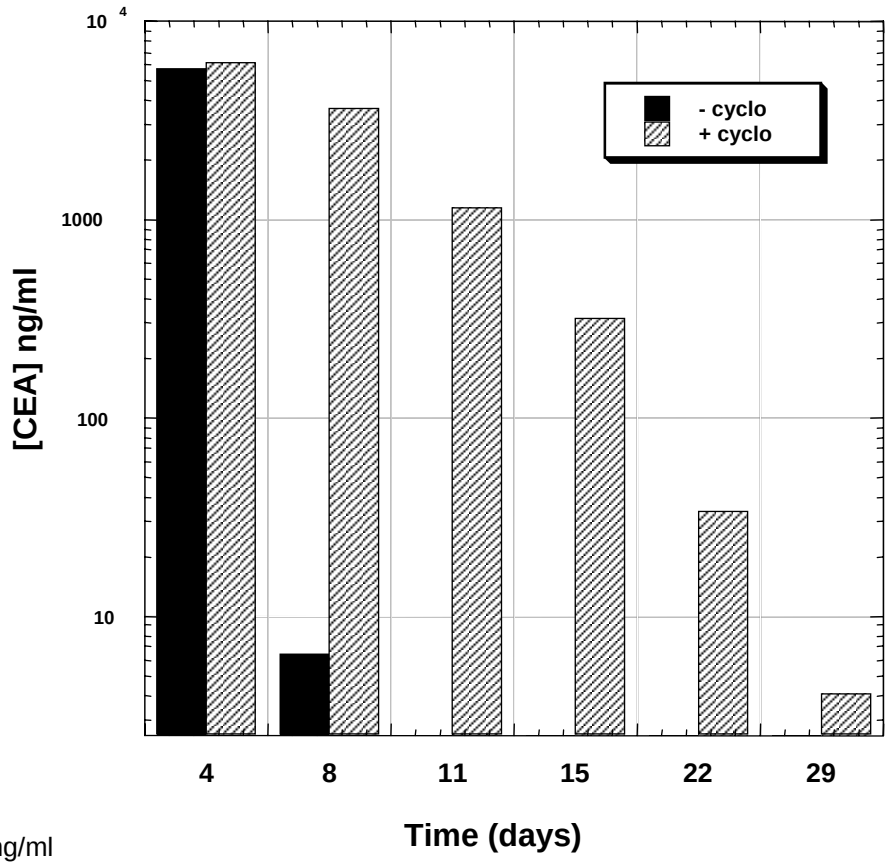
IFNAR Ko CD46 Ge mice



IP injection **MV-CEA**

+/- cyclophosphamide 125 mg/kg



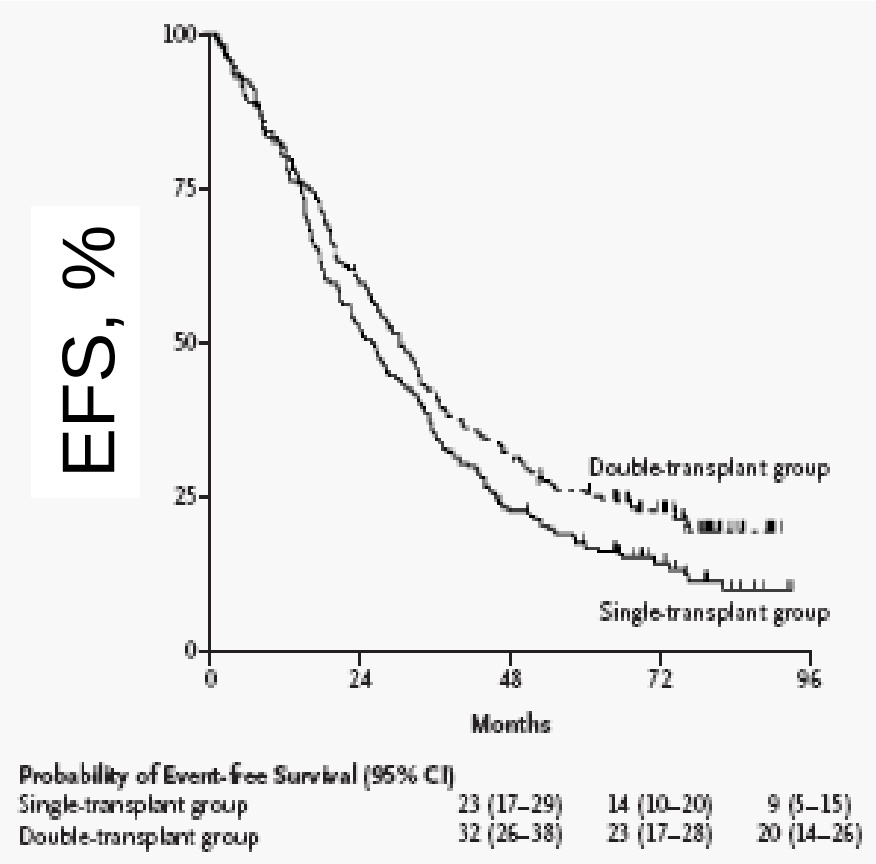


Peng et al, Nature Medicine 2002, 8, 527-531

The Status of Myeloma Therapy

- Progress past decade….
  - Transplantation, thalidomide, lenilidomide, bortezumib
- But patients dying—no cure in sight
  - 11,000 deaths per year; 15,000 new cases
- Innovative therapies are required

No Survival Plateau



Probability of Event-free Survival (95% CI)			
Single-transplant group	23 (17–29)	14 (10–20)	9 (5–15)
Double-transplant group	32 (26–38)	23 (17–28)	20 (14–26)

- Single versus Double Transplant
- *Median EFS < 3 years*

Attal NEJM 349:2495-02

Phase I Trial

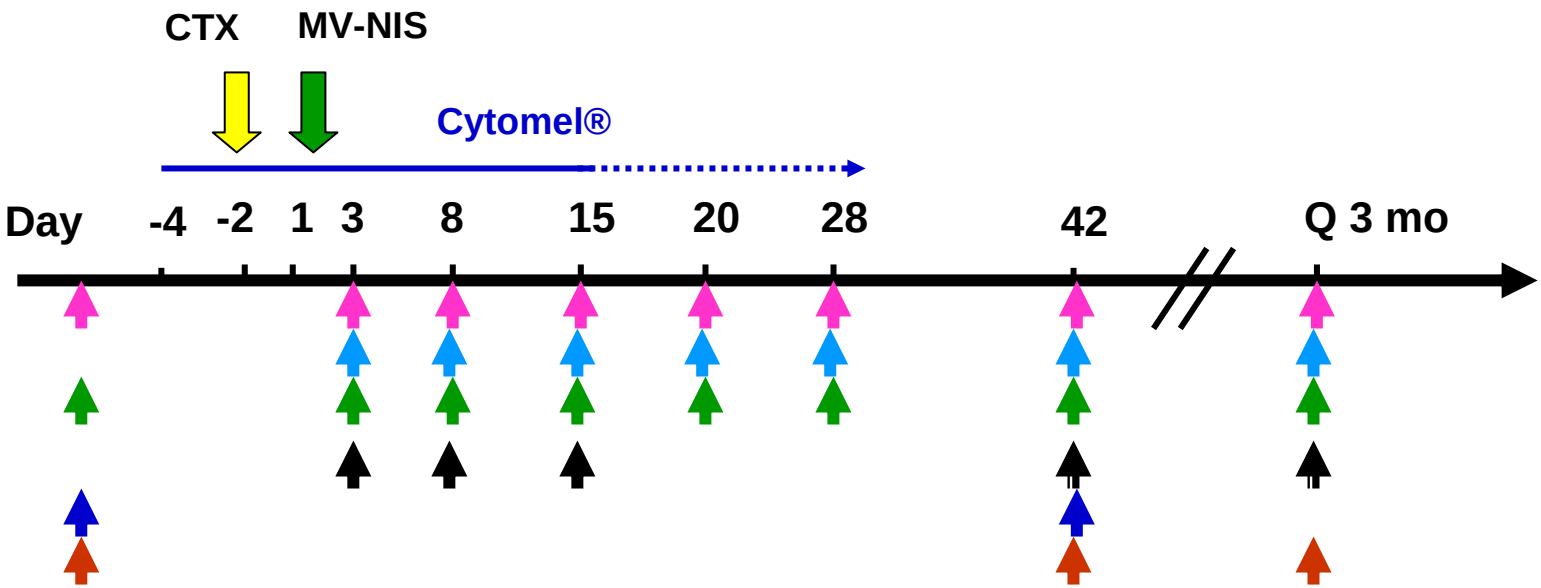
Step 1: MV-NIS alone

Agent	Dose	Route	Day
MV-NIS	*10^6 to 10^9 $TCID_{50}$*	30 min I.V.	1

Step 2: MV-NIS + Cyclophosphamide

Agent	Dose	Route	Day
Cyclo	10 mg/kg	I.V.	-2
MV-NIS	*MTD/100 to 81 x MTD/100)*	*30 min* I.V.	1

Trial Schema



KEY

- Cyclophosphamide
- MV-NIS
- CBC, chemistry, coagulation
- Viral levels, Blood, sputum & urine
- Free light chain
- 123-I gamma camera imaging
- Bone marrow aspirate/biopsy
- Anti-MV antibody and T cell subsets

Potential toxicity & complications

1. **Cytomel: tachycardia, tremor** ← ***Screen for symptomatic CAD and arrhythmia. Reduce dose to 25 mcg bid***
2. **123-I: none**
3. **MV-NIS**
   a. Infusion reaction
   b. Measles-like illness
   c. Virus transmission
4. **Cyclophosphamide**
   a. Immunosuppression: worsening of 2b-c?

Potential toxicities-MV-NIS

Infusion reactions

- ***Allergic → acetaminophen & benadryl***
  - ***Rigors → meperidine hydrochloride***
  - ***Anaphylaxis → cessation of infusion; fluids, benadryl, methylprednisone and epinephrine***

Potential complications-MV-NIS

Measles-like illness

Fever, rash, coryza, transient immune suppression ± otitis media, pneumonia, encephalitis

Possible since myeloma patients are immunocompromised, but should be self-limited because….

Potential complications-MV-NIS

Measles-like illness

…. because measles vaccine….

- **…..strains are extremely safe after *billions* of doses administered**
- **…..is recommended for**
  - **HIV-infected children**
  - **Immunosuppressed patients following HSCT**

    Dykewicz CA. Summary of the Guidelines for Preventing Opportunistic Infections among HSCT Recipients. Clin Infect Dis. 2001;33(2):139-44
  - **We routinely give MMR post HSCT to MM patients**

Potential complications-MV-NIS

Measles-like illness

Contingency plan

- **Measles immunoglobulin**
- **Ribavirin**

  Clin Infect Dis 1994; 19(3):454-62

  Antivir Chem Chemother 2004; 15(3):111-9

Potential complications-MV-NIS

Safety of Starting Dose?

- **10^6 $TCID_{50}$**
  - **HIV^+ & HIV^- infants**

    Am J Dis Child 1992; 146(5):550-5; Pediatr Infect Dis J 1991; 10(4):303-11; Vaccine 1995; 13(3):276-80.
  - **Edmonston IV to monkeys**

    NEJM 1960; 263(4):153-9.
  - **Upcoming primate studies**
- **Efficacy: Lowest effective in mice: $TCID_{50}$ 10^5 (~5 x 10^6/kg); Trial starting dose: 10^6 ~ 1.4 x 10^4/kg in 70 kg human**

Potential toxicities-MV-NIS

Transmission to contacts?

- ***RNA virus – mutation possible, but…***
- ***Vaccine strains of measles never reported to revert and/or to be transmitted***
- ***Vast majority of U.S. citizens vaccinated for measles***

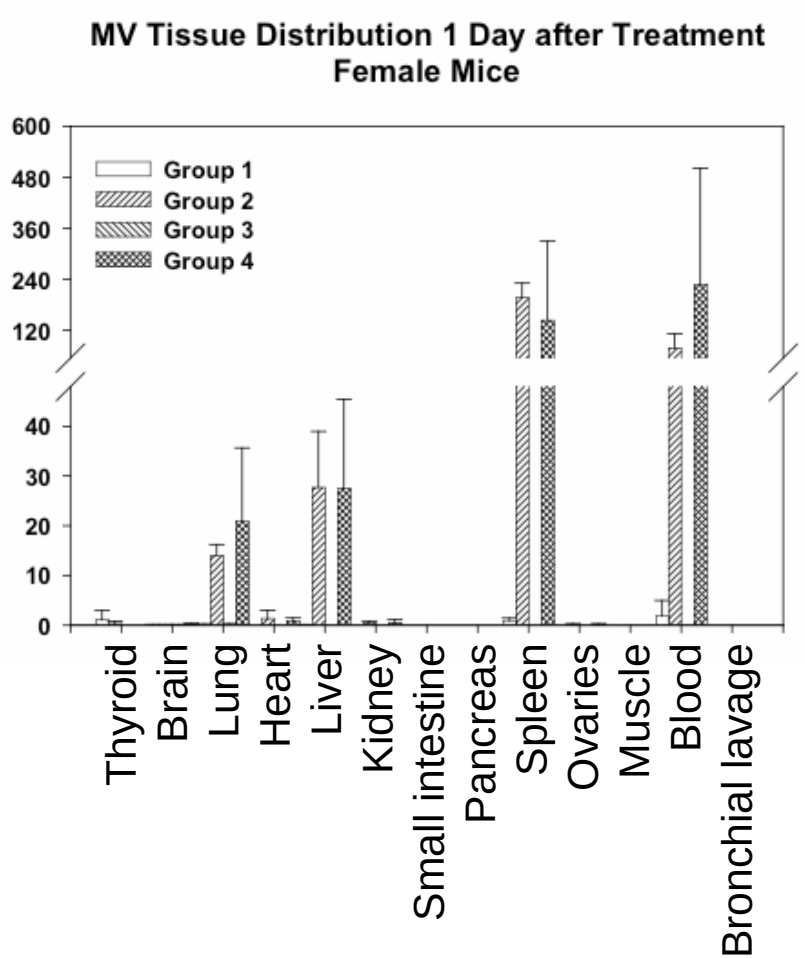
Possible pharmacology/toxicology models

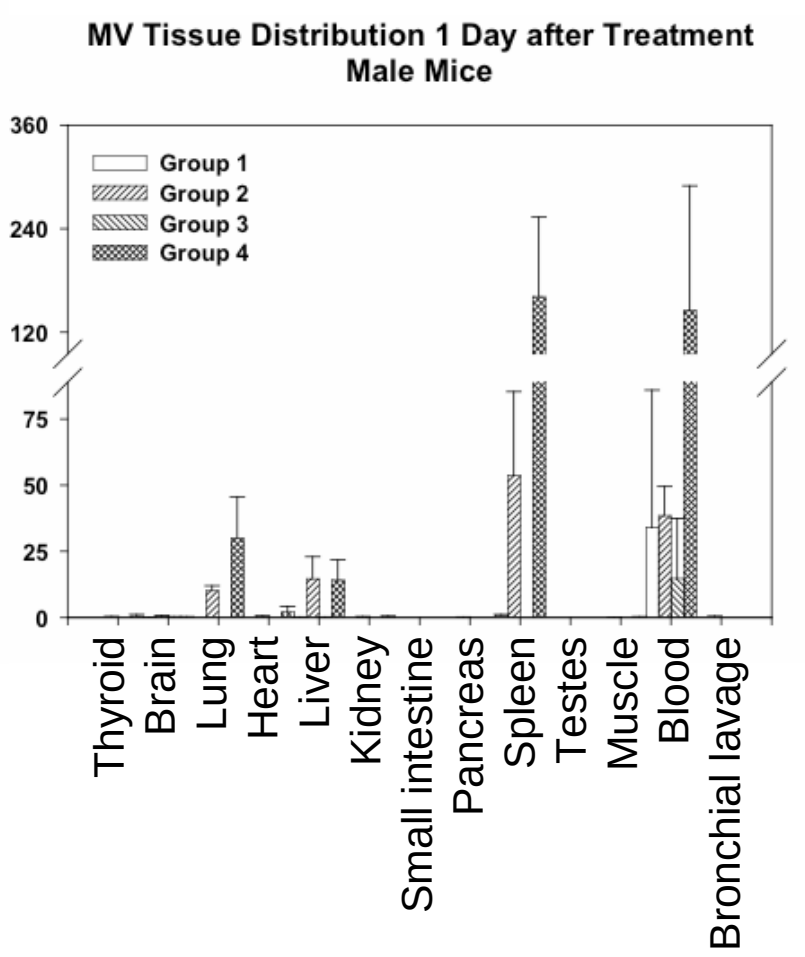
1. CD46 transgenic IFNaRko mice (+/- SCID)
2. CD46 transgenic pigs
3. Cotton rats
4. New world (eg squirrel) monkeys
   Old world (eg rhesus) monkeys

3. +/- cyclophosphamide

Issues: ***CD46 expression***
SLAM expression
intracellular restriction

MV-NIS biodistribution in CD46tg, IFNARko mice (preliminary)





Group1 10^5 **TCID50 MV-NIS**
Group 2 10^7 **TCID50 MV-NIS**
Group 3 **UV-inactivated MV-NIS**
Group 4 **125 mg/kg cyclophoshpamide plus 10^7 TCID50 MV-NIS**

Studies performed day 90 after MV-NIS administration were negative for all organs, all groups.

Potential complications-MV-NIS

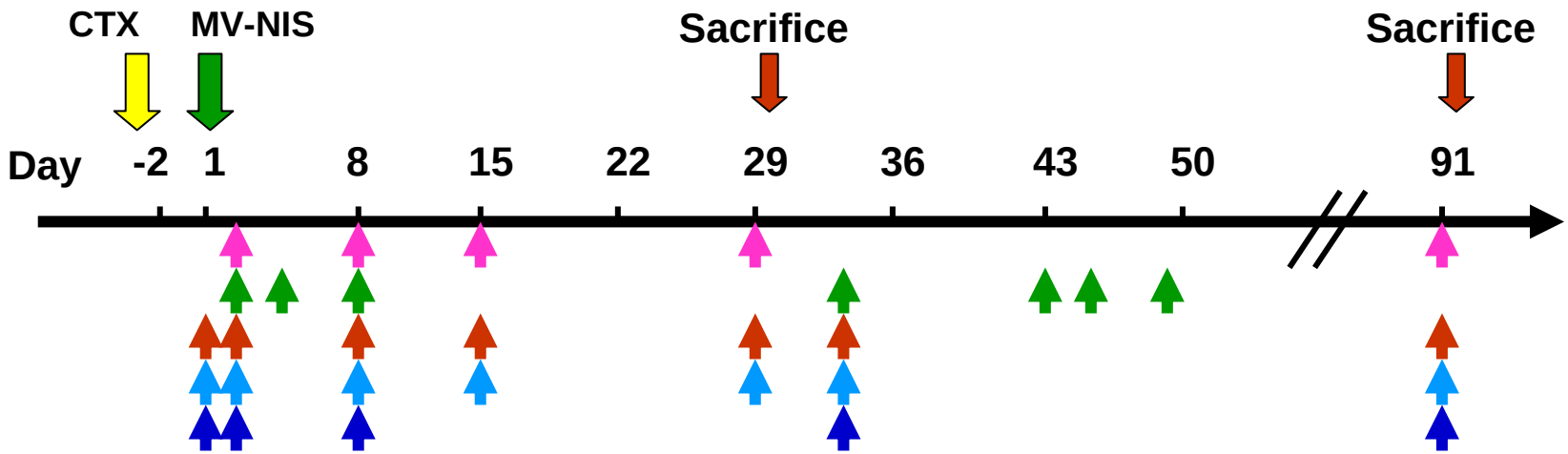
Measles-like illness, virus persistence or transmission?

- **Primate Toxicology**
  (12 Squirrel Monkeys)

- **Primate studies with scheduled sacrifice**
  - Two monkeys from each group: day 29
  - Remaining animals: day 91

Group	MV-NIS ($TCID_{50}$)	CTX (mg/kg)
I	0	0
II	0	31
III	10^8	0
IV	10^8	31

Squirrel Monkey Schema



KEY

- CTX
- MV-NIS
- Sacrifice-necroscopy
- CBC, chemistry, coagulation
- Cytokine measurement
- Anti-MV antibody measurement
- Viral levels, sputum & urine (PCR)
- Viral levels, blood (PCR)

Monkey Necrospy Samples (41)

- Kidneys, bladder, adrenals
- Bone, femoral head with articular surface
- BM: sternum and rib
- Eyes, brain, pituitary, spinal cord, sciatic nerve
- Stomach, esophagus, duodenum, jejunum, ileum, cecum, colon
- Gonads, prostate, epididymides
- Liver, spleen, gall bladder, pancreas
- Gross lesions
- Heart, Aorta
- Lip, salivary gland, tongue, tonsils
- Lungs, trachea
- LN: bronchial, mandibular, mesenteric
- Mammary gland
- Skeletal muscle
- Skin: ventral abdomen, injection site
- Thymus, thyroid, parathyroid

Summary

- Myeloma is an incurable disease with pressing need for innovative therapeutic strategies
- MV-NIS targets myeloma cells preferentially using CD46
- Preclinical data and careful trial design lead us to believe that we can safely administer this therapeutic agent