Bugs & Drugs: The Ying & Yang of the Immune Response in Oncolytic Virus Therapy in Brain Tumors

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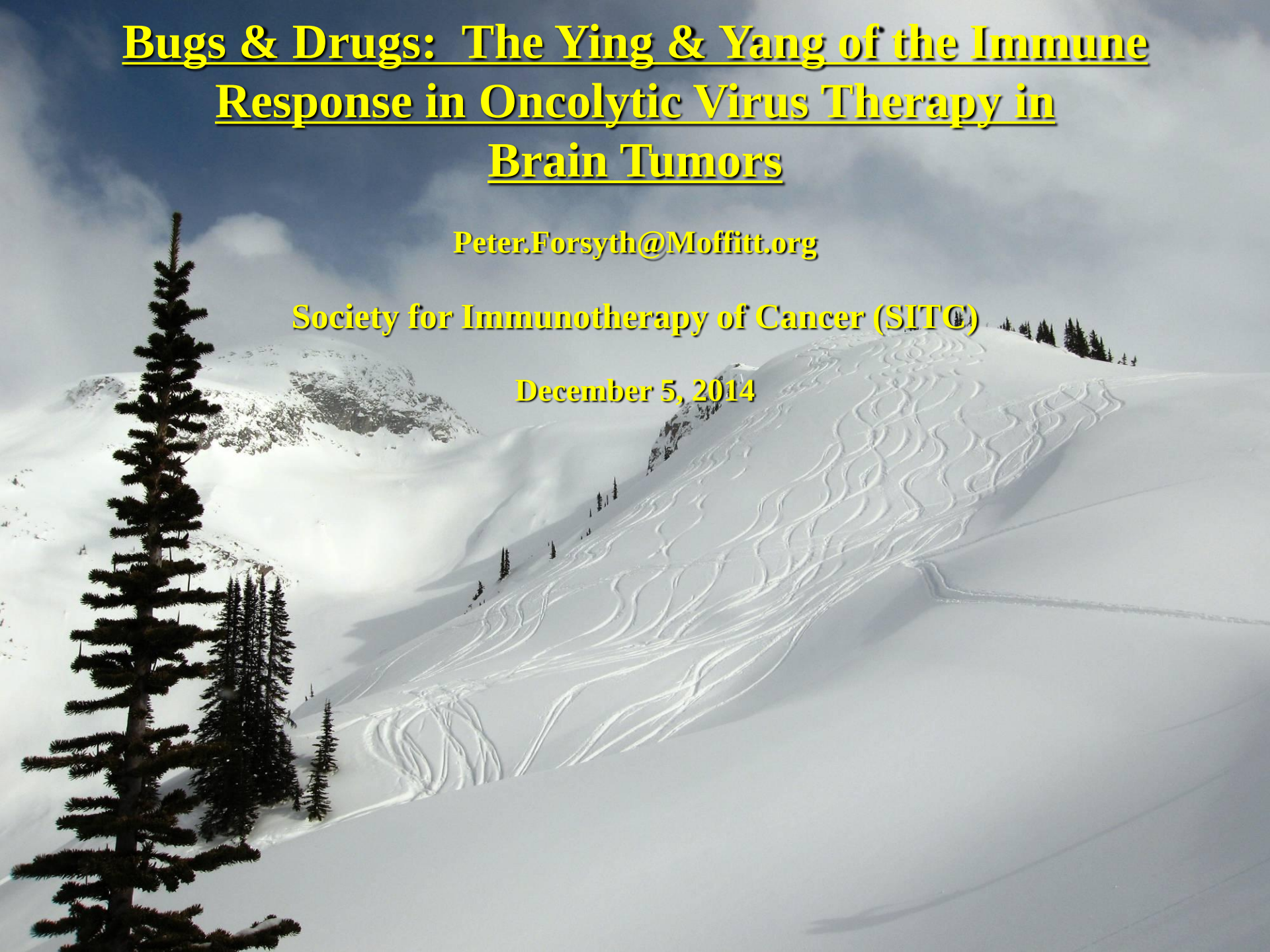
Society for Immunotherapy of Cancer (SITC)

December 5, 2014



Summary

Oncolytic Viruses (Ovs) in Brain Cancer

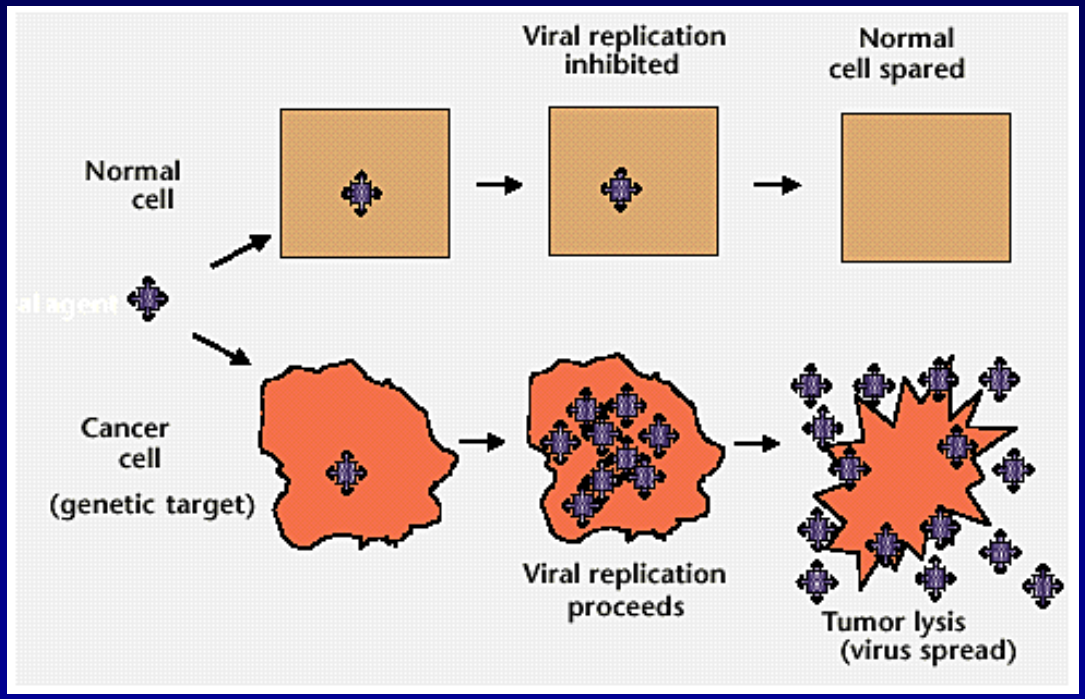
1) **Experiments & Patients**

2) **Myxoma Virus as an Experimental Therapeutic:**

- **Ying = Immune system limits infection and killing**
- **Yang = Immune system is required for killing**

3) **Lessons & Take Home Messages**

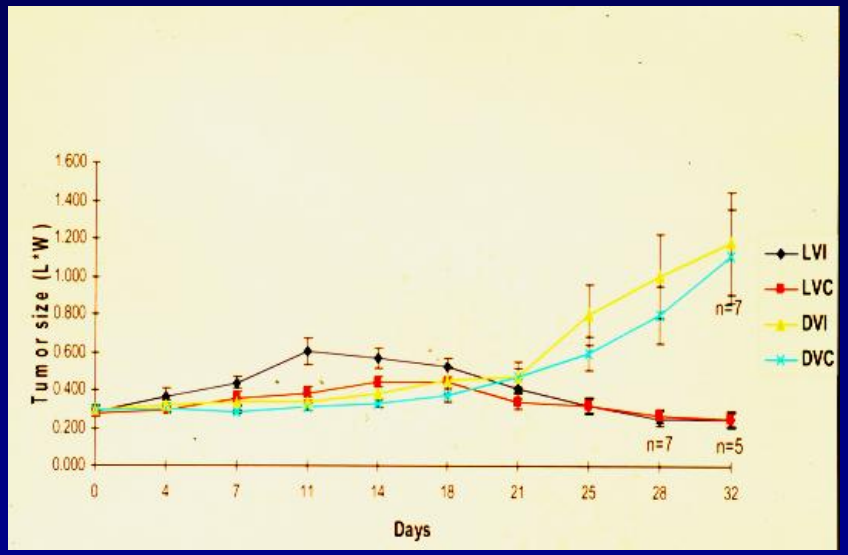
1) Oncolytic Viruses: The Old Concept



Tumor cells & viruses use similar pathways to proliferate & survive

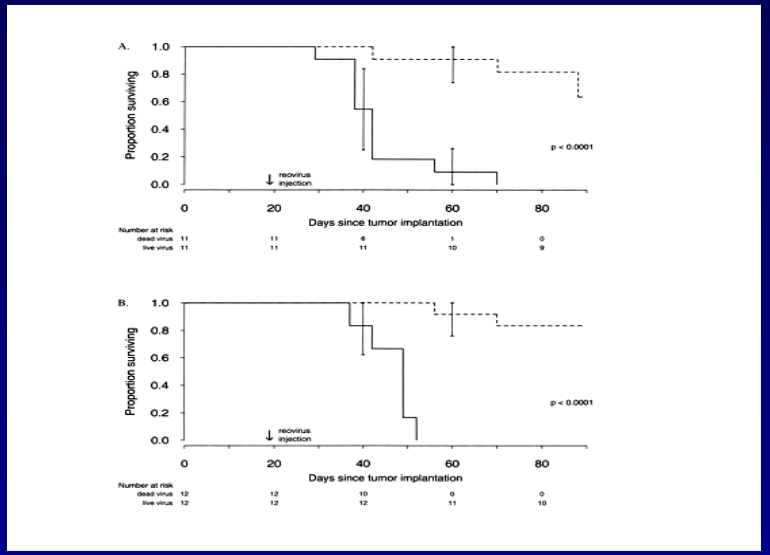
Kirn Nat. Med 7: 781, 2001

Reovirus: naturally occurring segmented DS RNA virus - initial studies



Infected & killed tumors on the contralateral limb (s.c. U87)

Coffey et al, Science 282:1332, 1998



Survival of MGs in the Brain: U251N (A) & U87 (B) tumors in Nudes

Wilcox et. al., JNCI 93: 903, 2001

First Clinical Trial using Reovirus

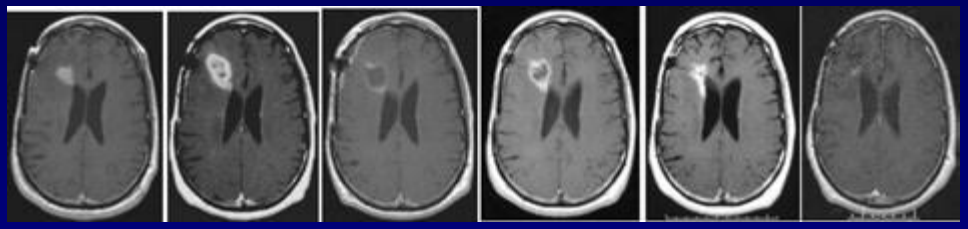
- **Evidence of viral activity in 11/18 (61%) patients**
- **Safe**

Morris DG et al., Invest. New Drugs 31: 696, 2013

Tumor Response To Virus Treatment: Reovirus & New Castle Disease Virus (NDV)

Days after reovirus administration

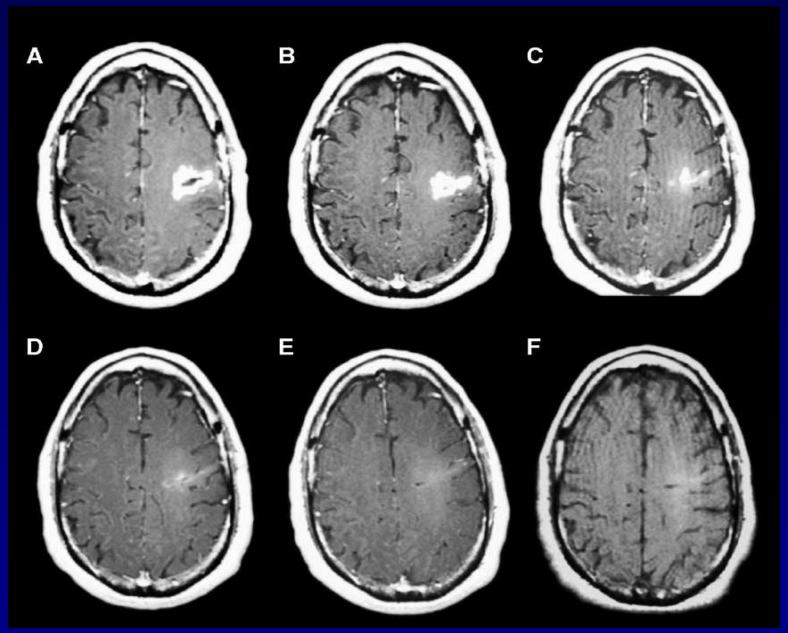
0 3 43 88 167 537



- **I .T. reovirus: 46 y.o. man with second recurrence of anaplastic astrocytoma. Survival > 5yrs**

- **1/12 patients had a CR; 11/12 SD or PD**

Forsyth et al., Mol. Ther., 2008



I.V. NDV. :
(A) Patient at baseline,
(B) (B) SD 1st F/U, (C) PR 2nd F/U,
(D) 20 wks , F) CR at 30 wks from start of virotherapy.

Freeman et al, Mol. Ther., 2006

Clinical Trials of Ovs in MGs

Virus	Genetics	Study Type	#Pts	Dose/schedule/ Route/Response	Reference
HSV-1 (G207)	γ1-34.5 gene deletion lacZ insertion in UL39	Phase I	21	≤ 3x109pfu/single injection/ IT/No MTD	Markert, JM. 2000
HSV-1	γ1-34.5 gene deletion lacZ insertion in UL39	Phase I	9	≤ 1x109pfu/IT/pre-and post-resection/ No MTD	Markert, JM. 2000
HSV-1 (HS-1716)	γ1-34.5 gene deletion	Phase I	9	≤ 1x105pfu/IT/No MTD	Rampling, R. 2000
HSV-1 (HS-1716)	γ1-34.5 gene deletion	Phase I	12	≤ 1x105pfu/ IT/No MTD	Papanastassiou, N. 2002
HSV-1 (HS-1716)	γ1-34.5 gene deletion	Phase I	12	≤ 1x105pfu/IT/resection cavity/ No MTD	Harrow, S. 2004
AdV (ONYX-015)	E1B-55kD gene deletion	Phase I	24	≤ $1x10^{10}$pfu/single injection/tumour bed post-resection/No MTD	Chiocca, EA. 2004
Reovirus	Wildtype virus	Phase I	12	≤ $1x10^{10}$pfu/single injection/ /intratumoural/No MTD	Forsyth, P. 2008
NDV (NDV-HUJ)	selected NDV (lentogenic)	Phase I/II	14	≤ $1.1x10^{10}$IU/No MTD	Freeman, AI. 2006
Reovirus	Wildtype virus	Phase I	18	≤ 10^{8}-10^{10} $TCID_{50}$ /CED	Markart, JM. Unpub.
Measels MV-CEA		Phase I	"40"	IT	Galanis, E. 2013

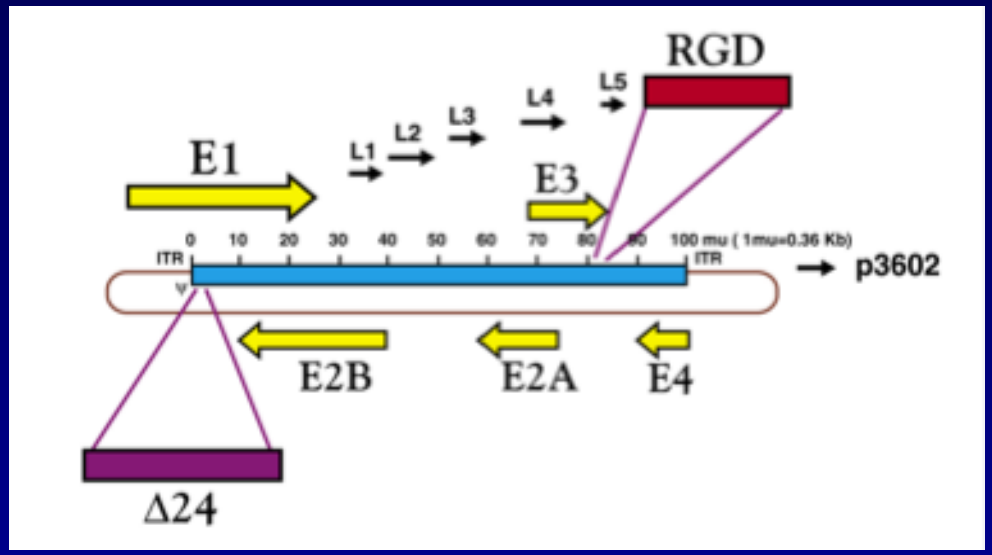
Clinical Trials of Ovs in MGs (cont'd)

Virus	Genetics	Study Type	#Pts	Dose/Schedule/ Route/	Reference
Ad-24-RGD)	24bp deletion in E1A and RGD fiber	Phase I	28	I.T./≤ 3 X 10E10 PFUs	Lang F, unpubl
HSV-1 (HSV-1716)	ICP34.5 deletions	Phase III			www.crusadelab.com
HSV-1 (M032)	ICP34.5 deletions, expression of human IL-12 subunits	Planned			Parker JN
Poliovirus (PV-RIPO)	Native IRES replaced with human rhinovirus type-2 IRES	Phase I			Gromier M unpubl.

Total = 7 viruses, ~120 patients, 0 DLT or MTD, several L.T. responses

Adenovirus with E1A deleted

(replicates in RB-activated cells & expresses RGD ("Ad-24-RGD")



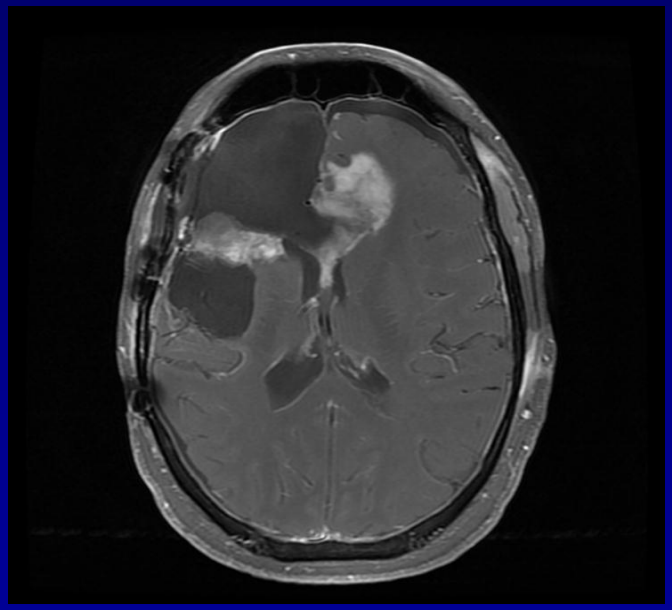
- Infection does not require CAR but is enhanced by α v integrins (present in tumors but not normal brain).

Fueyo J , JNCI 95: 652, 2003

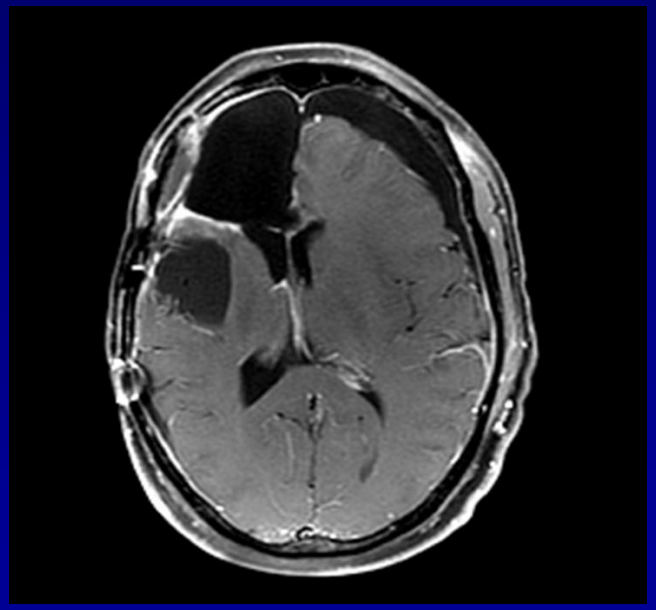
Ad-24-RGD Treatment Results (Rx A)

- 28 pts 1X 10^7 – 3 X 10^{10} pfus I.T.
- Arm A: 4 CR, 3 PR and 6 SD; ? Immune response?
- Mdn. Survival is 15 mos. Longest CR is 40 months.

Patient #4-1: Injection of cavity



9/25/2012

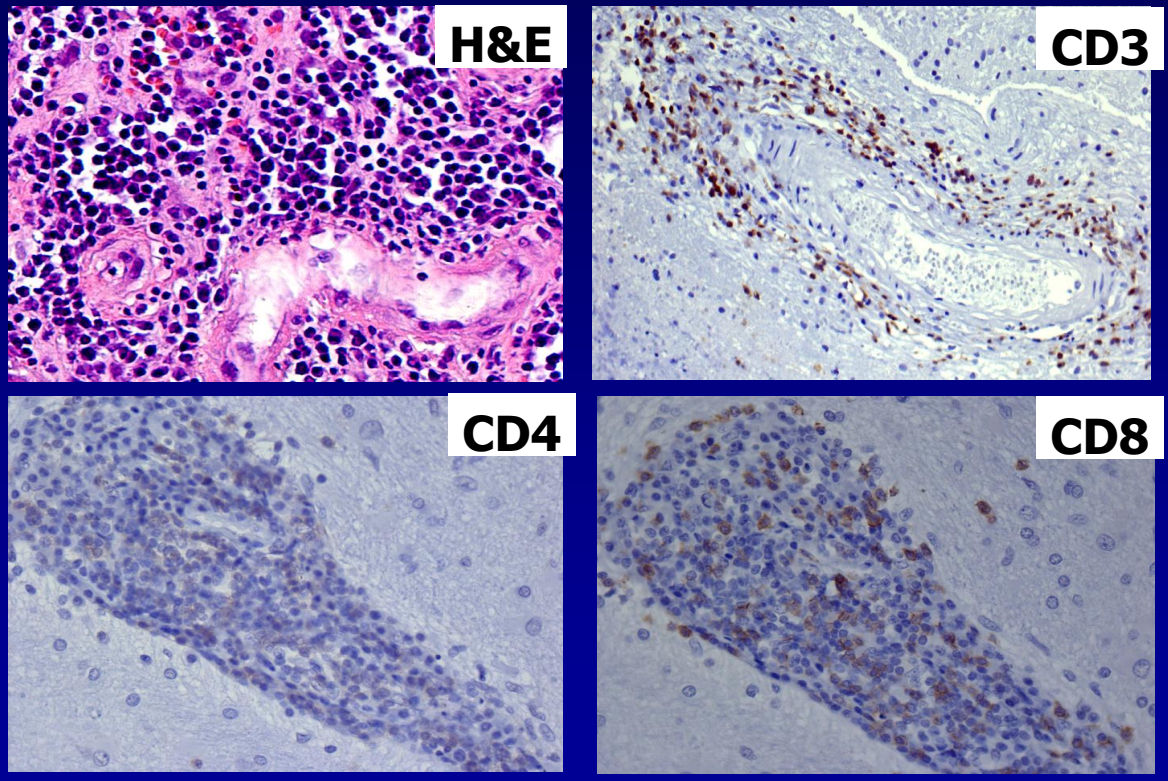


3/19/2013

Courtesy Drs. F Lang, Fueyo, Conrad MDA & Tufaro DNAtrix; *unpubl.*

Ad-24-RGD Treatment (Rx B)

- Inflammatory infiltrates



Courtesy Drs. F Lang, Fueyo, Conrad MDA & Tufaro DNAtrix; *unpubl.*

What have we learned from clinical trials in MGs?

- Safe and well tolerated, no MTD
- All have a few "responders" and one "cure".
- MRIs may have to get worse before getting better ?immune response?
- Trials are small & little biology
- Immune contribution not understood

Moore PS. Nat Rev Cancer 10: 878, 2010.

Myxoma Virus (MYXV)

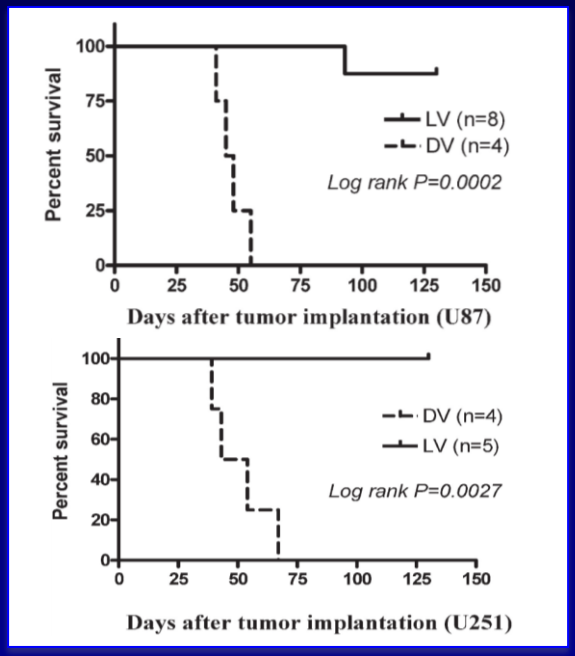
Ying = Immune system limits infection and killing

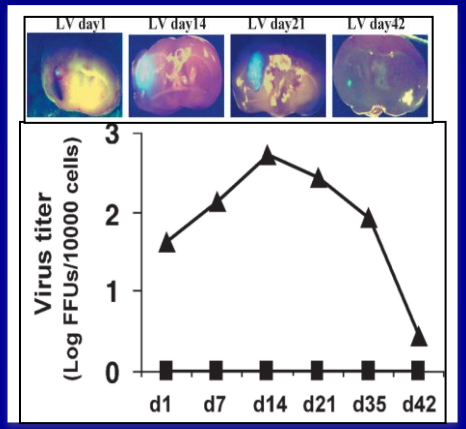
Myxomatosis in European Rabbit

- **Selective for rabbits & cancer cells**
- **Large, engineerable genome**
- **No acquired immune responses**
- **Replicates in cytoplasm**
- **~170 genes**
- **~20 KO/transgenic viruses available**
- **Wonderful collaborator in Gainesville (McFadden)**

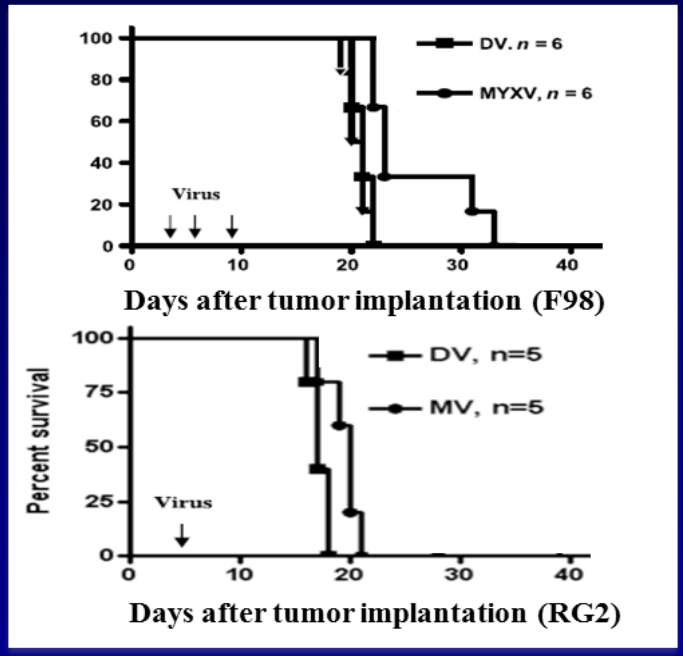
Little replication or cures in immunocompetent or syngeneic MGs

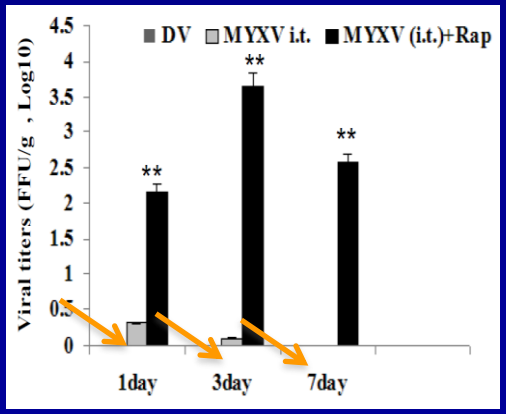
Xenografts in SCIDs



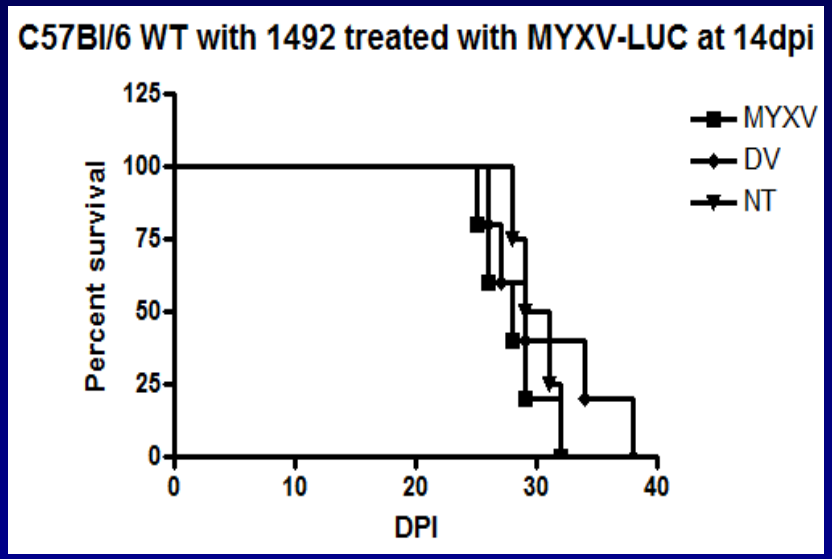


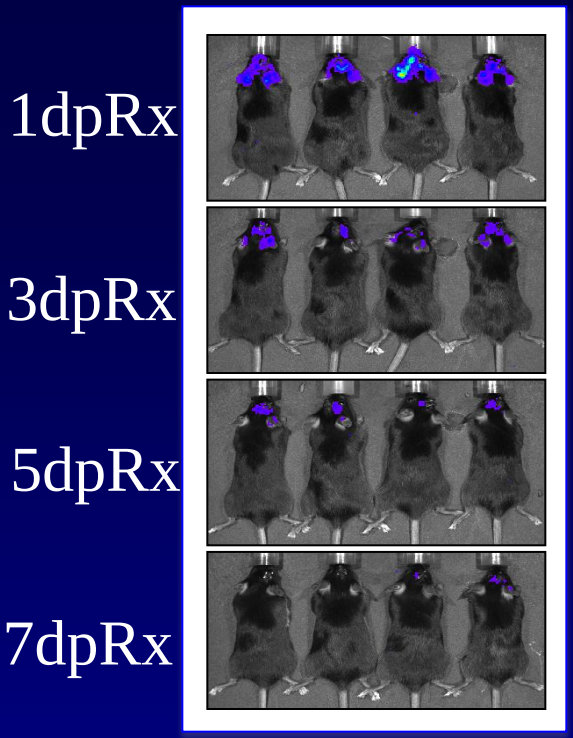
Syngeneic in Rats



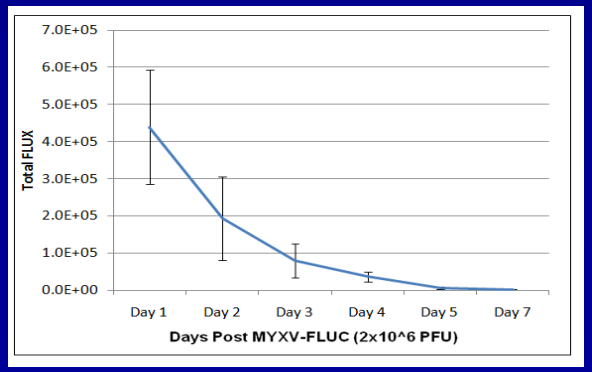


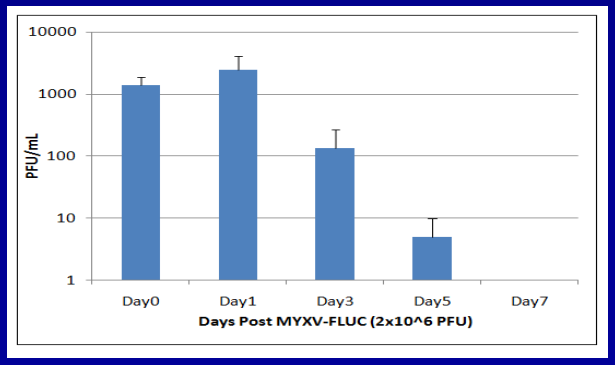
T53$^{+/-}$ / NF$^{+/-}$ line 1492 susceptible *in vitro* but resistant *in vivo*



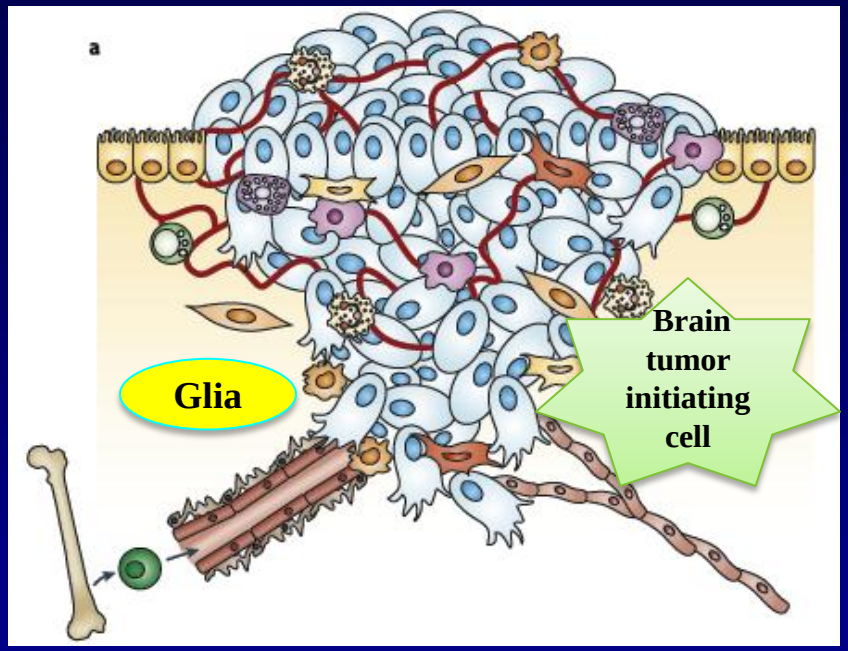


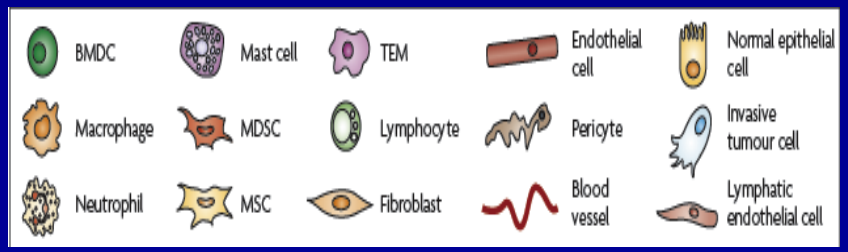
MYXV-FLUC





MGs are a mixture of tumor cells, stromal cells and immunocytes

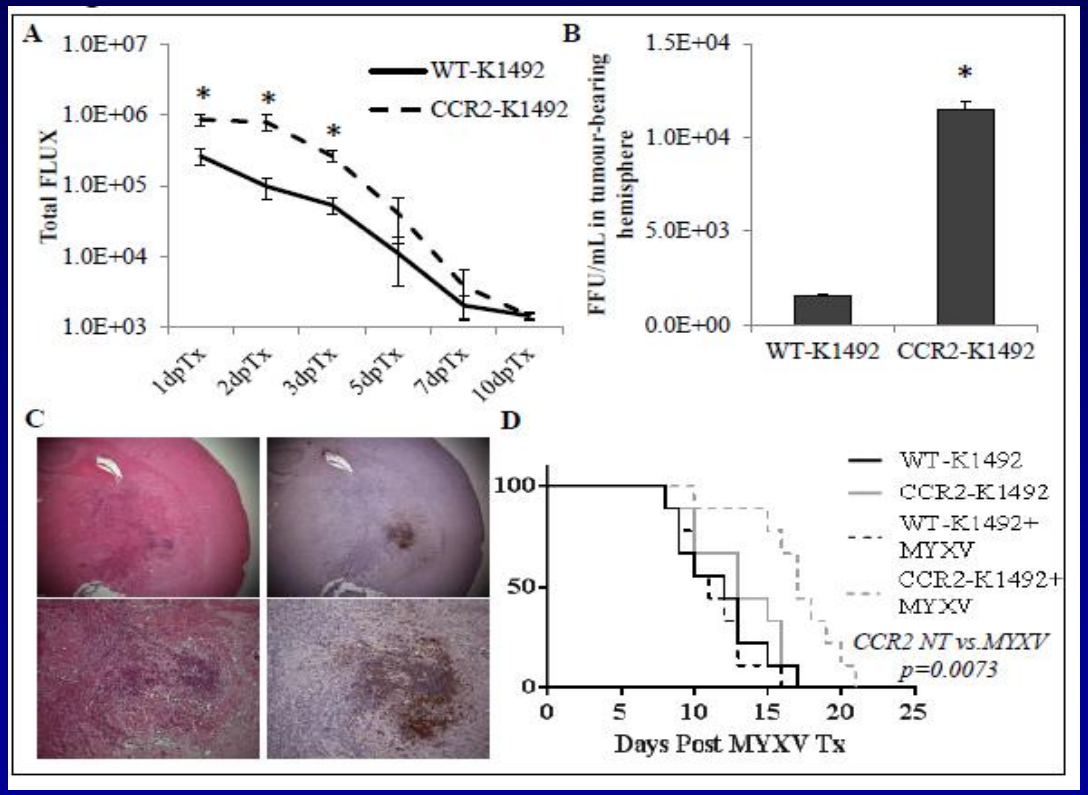




adapted from Joyce & Pollard. Nat. Rev. Cancer 9: 239, 2009

- Different immunocytes in limiting infection/distribution
- Identify factor that inhibits replication *in vivo*
- Macrophage/microglia, T & B cells, NK cells, TLRs) – little importance here individually.
- Many overlapping & redundant immunocytes to protect the brain!

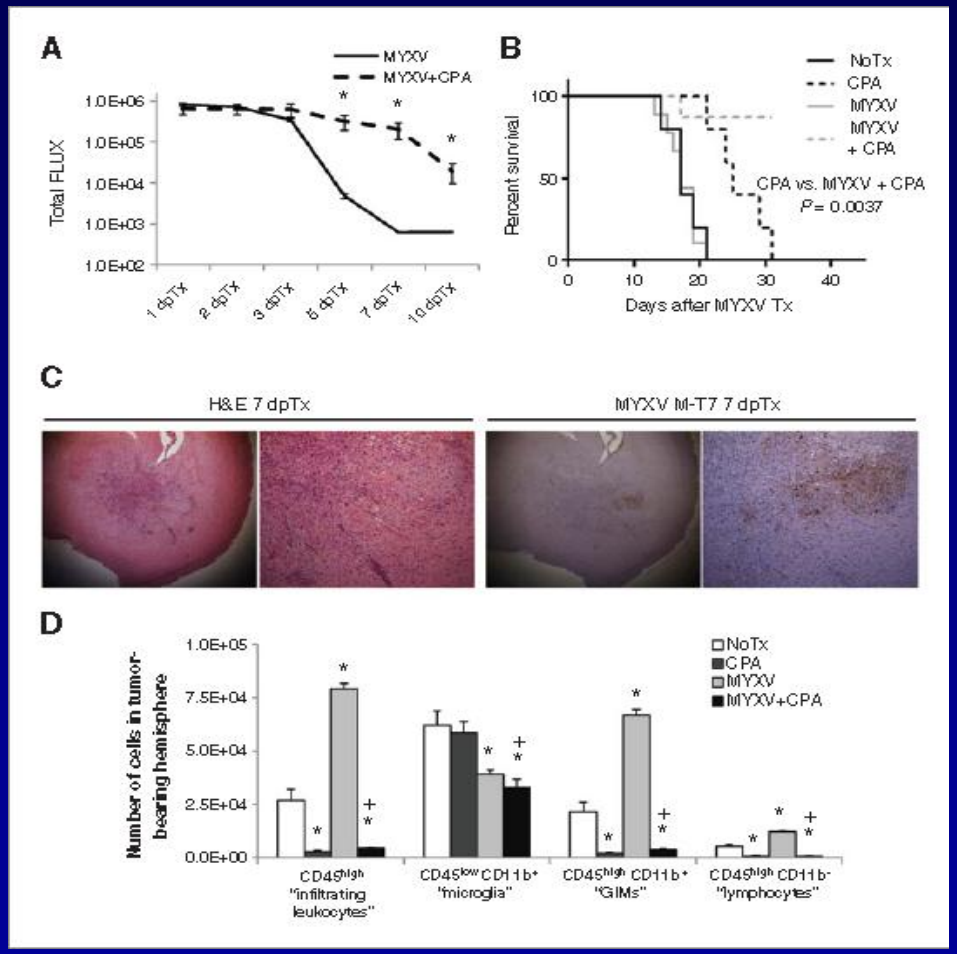
Myxoma virus initial replication is limited by CCL2 resident immunocytes (GIMs)- these will be tricky to deplete



CCR2 -/- mice (don't recruit macrophages/monocytes)

Zemp et al., Cancer Research Oct 21, 2014

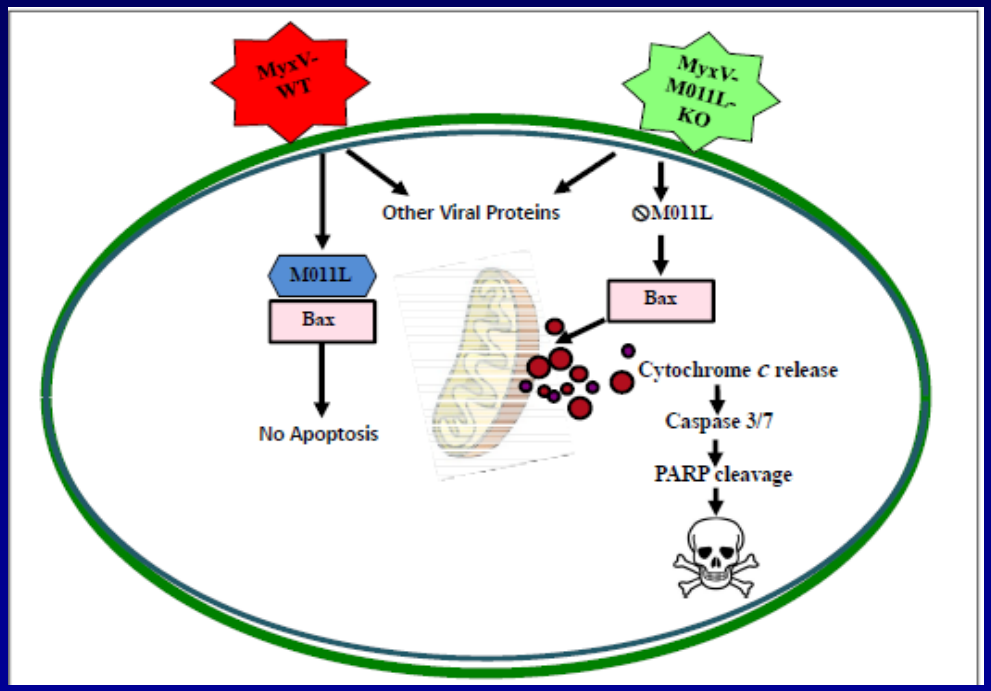
Myxoma Virus & the Immunocyte-depleting Cyclophosphamide Prolongs Survival in Immunocompetent Mice



Zemp et al., Cancer Research Oct 21, 2014

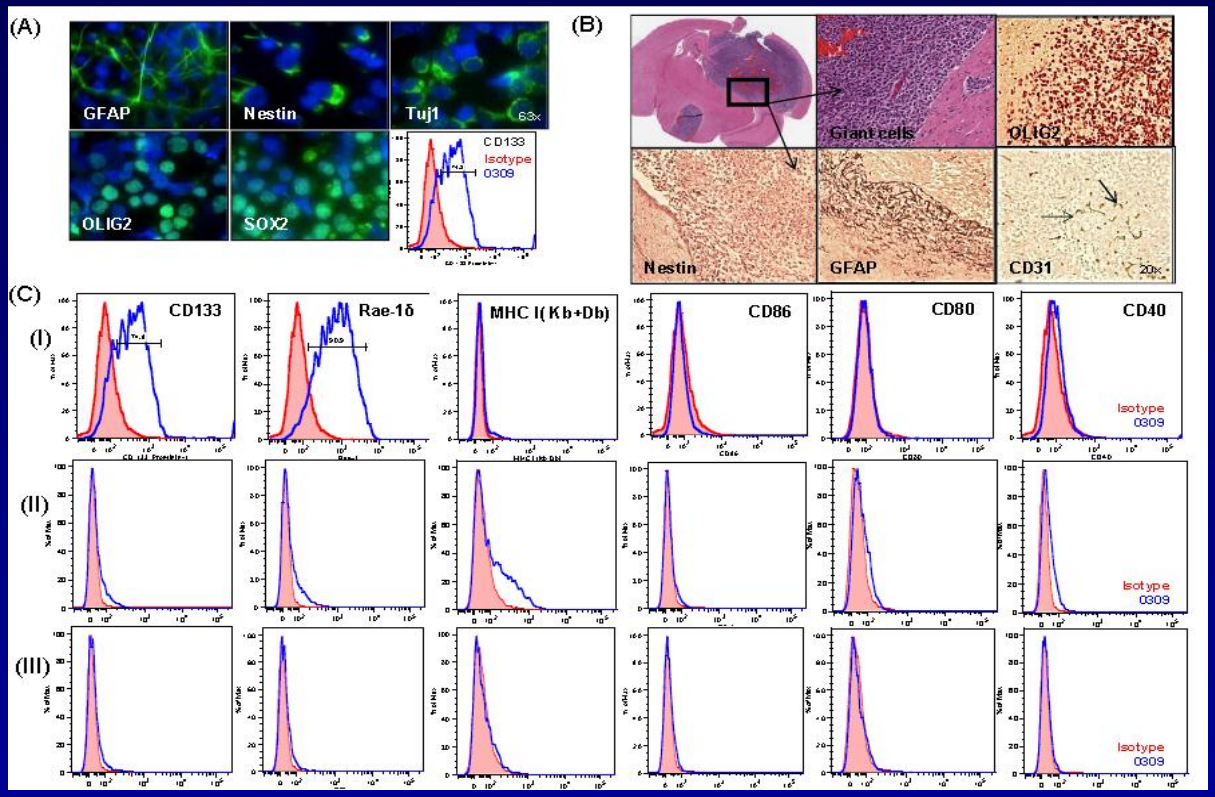
Myxoma virus produces immunomodulatory and anti-death signals

Yang = Immune system is required for killing



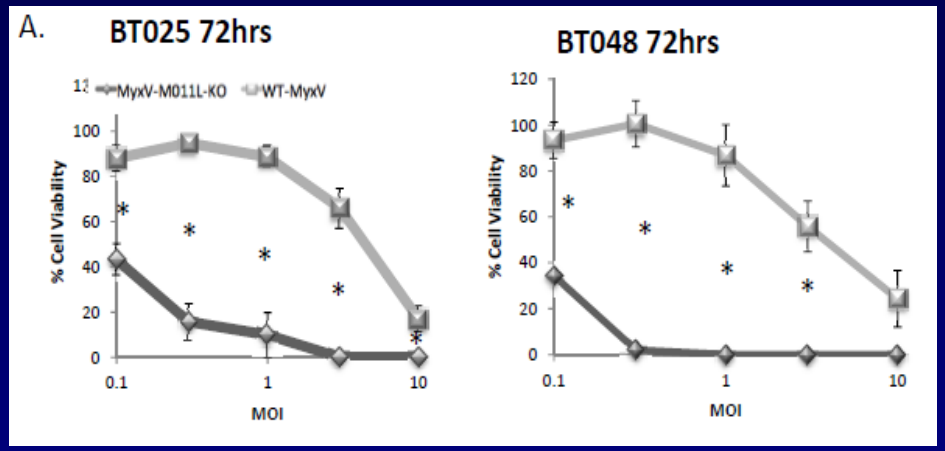
M11L is an anti-apoptotic protein encoded by wild type Myxoma Virus

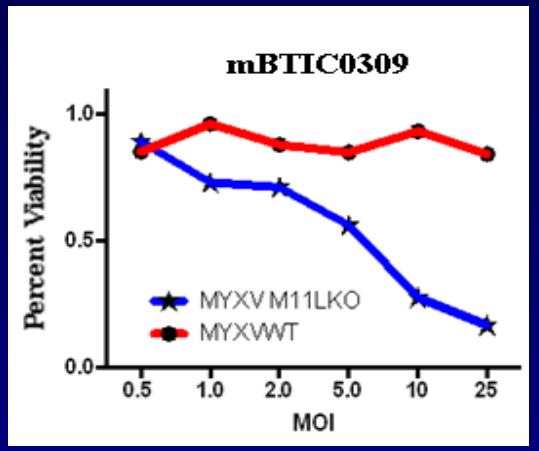
The murine BTIC 0309 in an immunocompetent host resembles a human GBM & stem cells



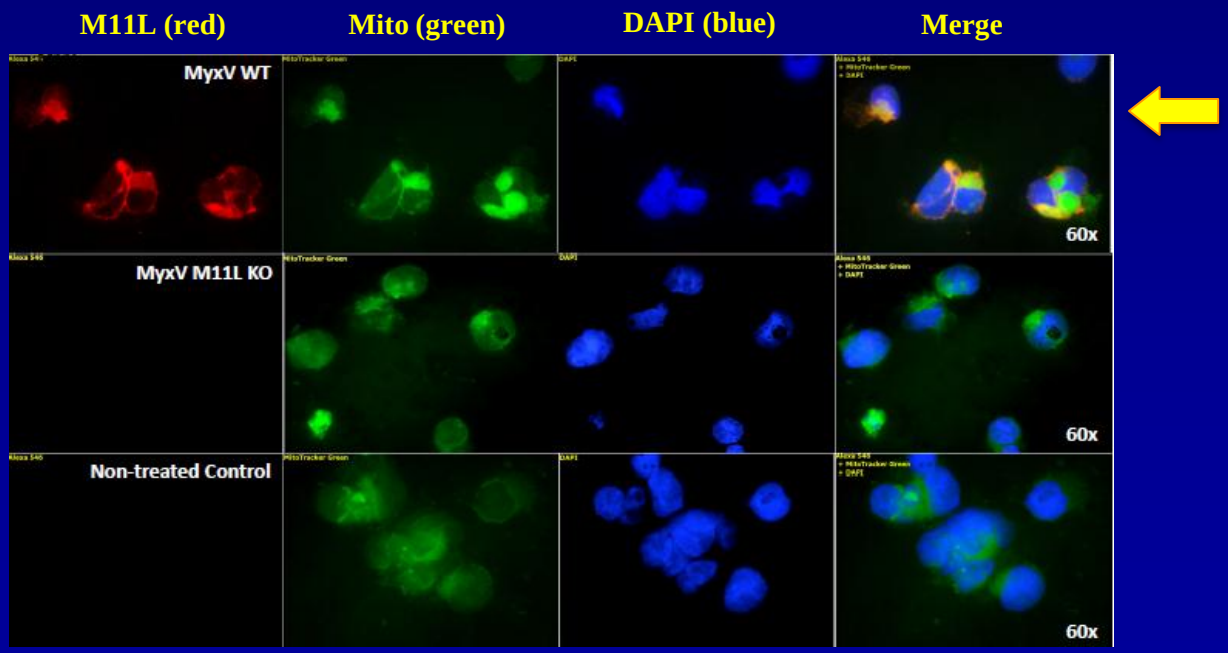
From gliomas arising in NF1+/- Tp53+/- mice & implanted in C57BL6 mice

Myxoma virus deleted for an anti-apoptotic protein (M011L KO) has superior killing *in vitro*

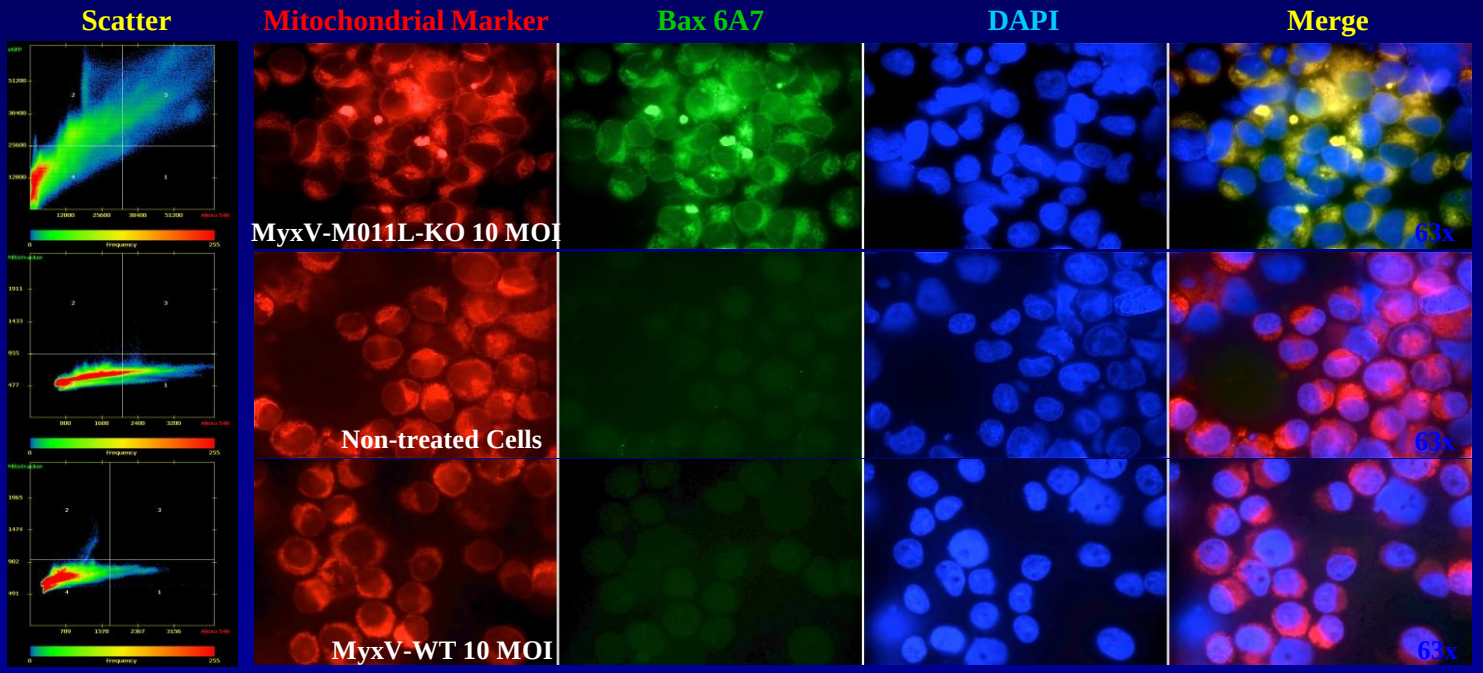




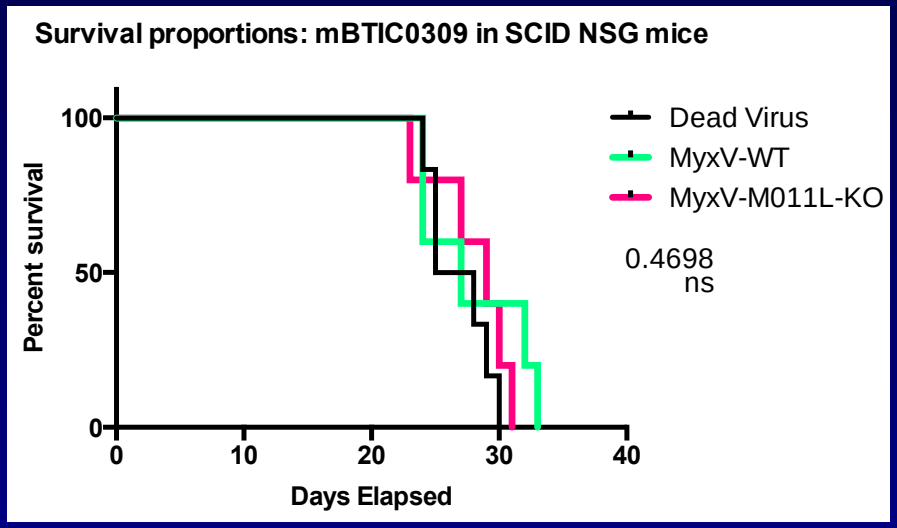
Murine BTIC

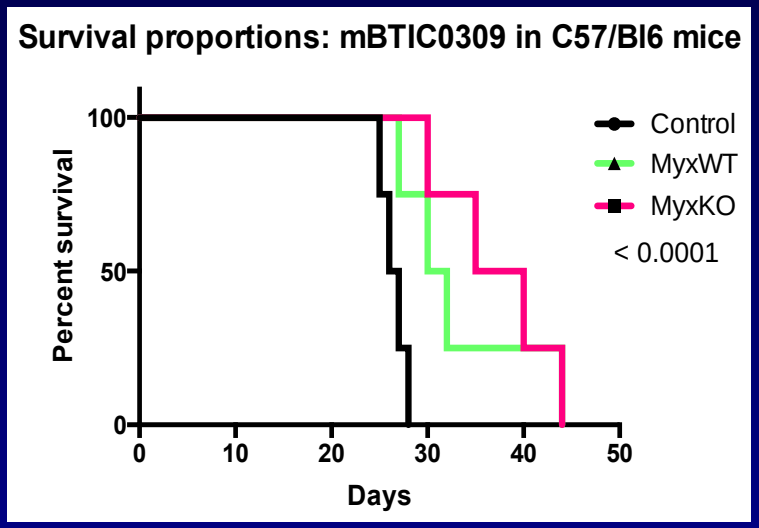


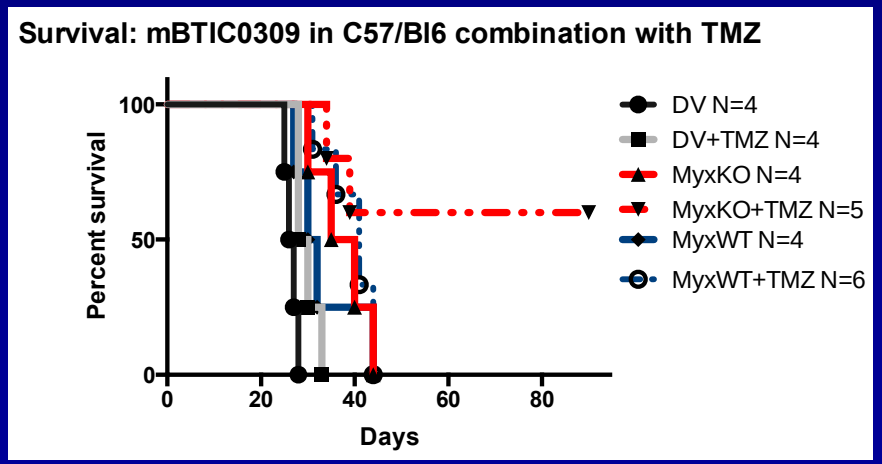
Bax localizes to mitochondria and causes apoptosis in myxoma virus deleted from M11L



M11L-KO MyxV prolongs survival in an immunocompetent murine BTIC model

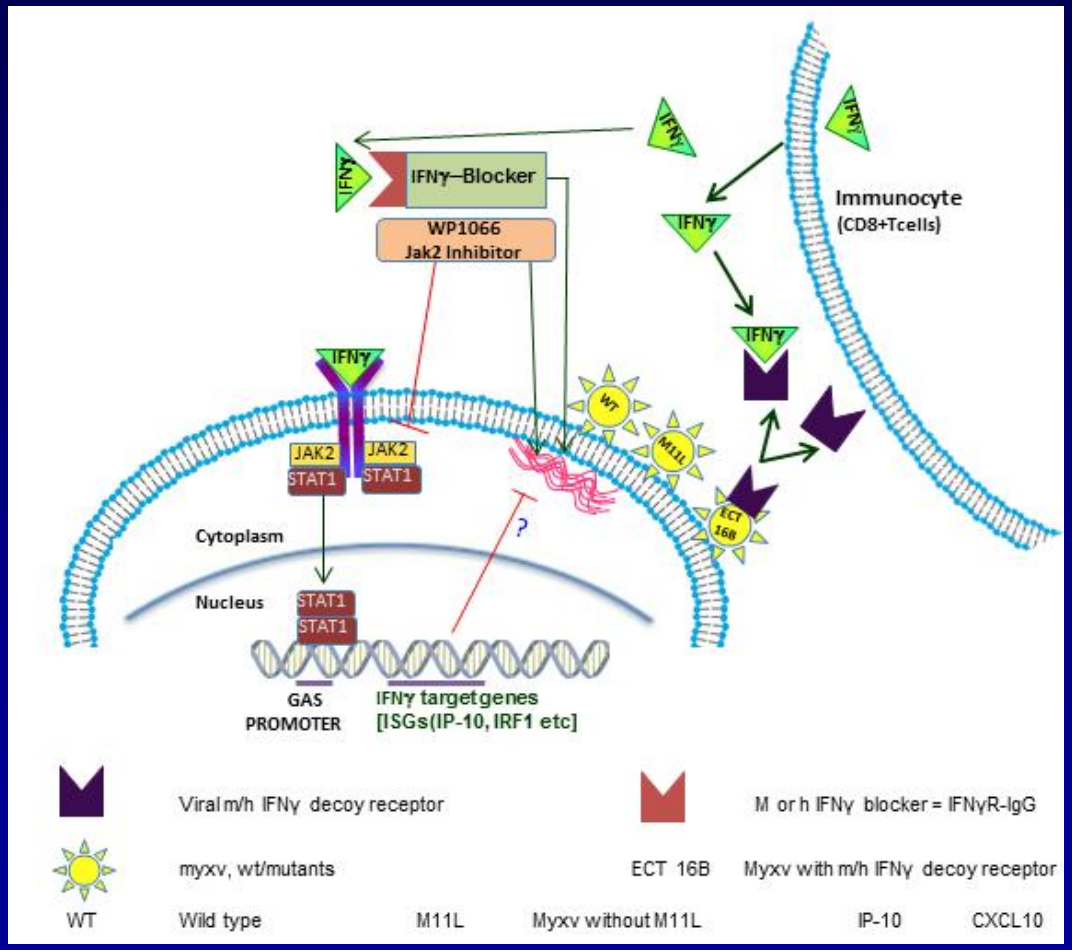






M11L pro-apoptotic virus with Temozolomide (TMZ) produces cures in immunocompetent mice

Manipulate INFg in Host and Virus



Lessons and Take Home Messages

- **Key points:** Human orthografts in immunocomp. mice are misleading
- **Potential impact on the field:** Too early to tell but promising
- **Lessons learned:**

  - Viruses in the brain are potential treatments for gliomas

  - Immune system can both “hurt” and “help” therapy

  - Much work remains to be done

Thanks!

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