

# Protocol 1107-1120 RAC Presentation



**A P1 Ascending Dose Trial of the Safety and Tolerability of Toca 511, a Retroviral Replicating Vector, Administered to Subjects at the Time of Resection for rHGG and Followed by Treatment with Toca FC, Extended-Release 5-FC  
(Tg 511-11-01)**

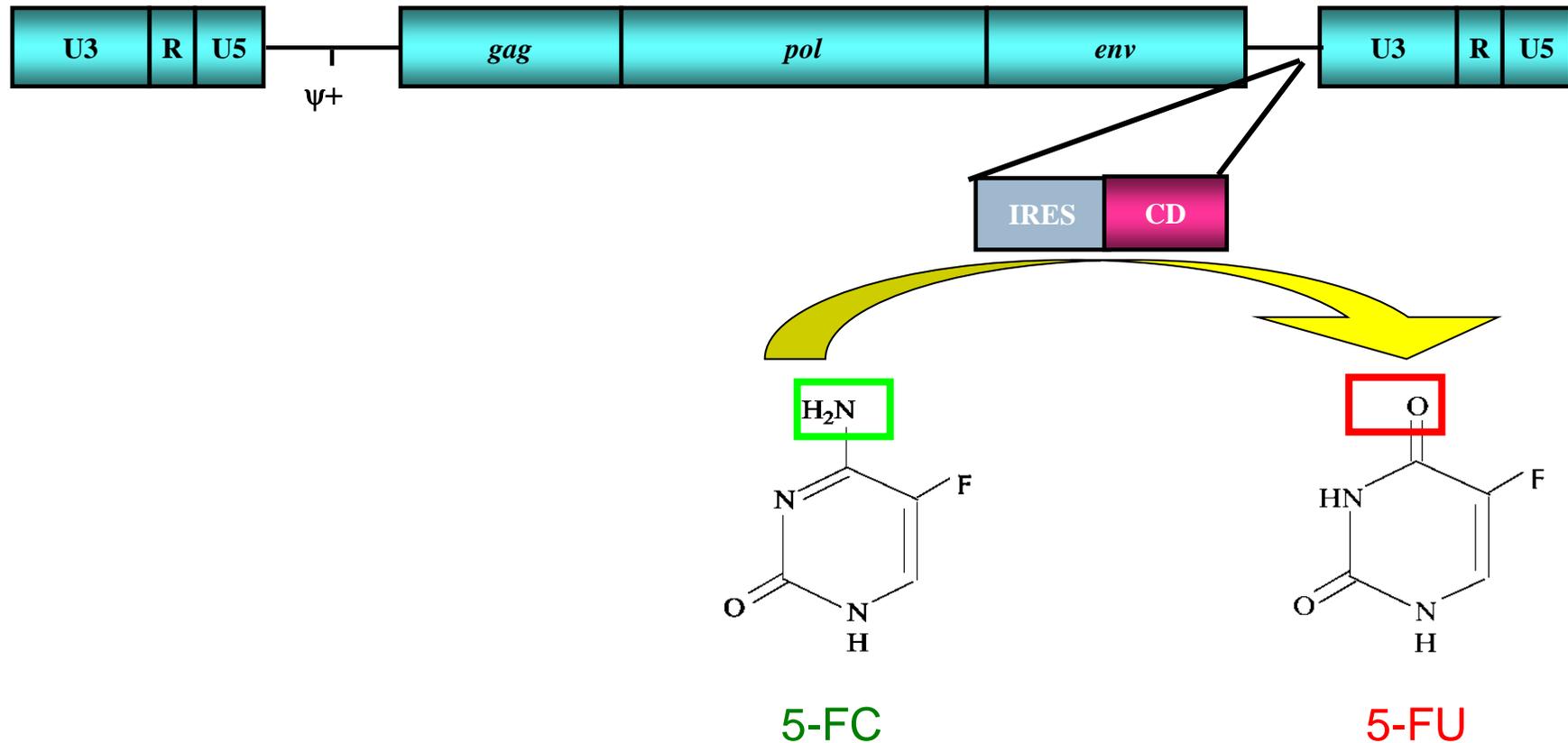
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VP Clinical Development**

# Toca 511 Refresher



- Toca 511 is a Retroviral Replicating Vector (RRV)
- Based on Murine Leukemia Virus (MoMLV)
  - Ecotropic env switched to amphotropic env
  - Cytosine deaminase (CD) gene inserted between env and 3' LTR
    - ✦ CD catalyzes conversion of antifungal drug 5-FC to anti-neoplastic drug 5-FU
  - Internal Ribosome Entry Sequence facilitates CD expression

# Schematic of Toca 511

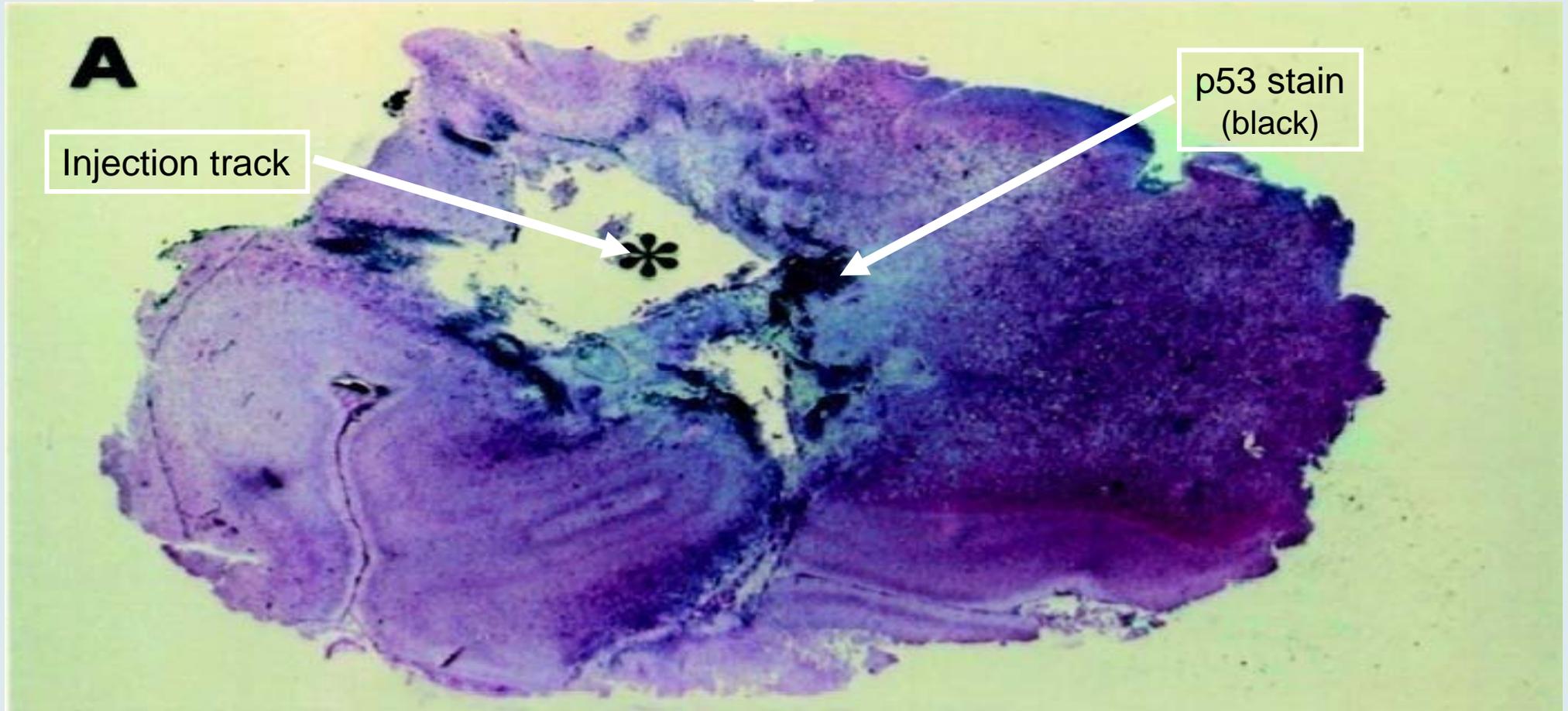


# Rationale for use of RRV



- Many non-replicating vectors have been studied in brain cancer
- Approach was found to be safe but ineffective
- Lack of efficacy due to inability to efficiently transduce tumor cells

# Non-replicating vectors do not spread



Section through a resected human glioma treated with Adp53 vector

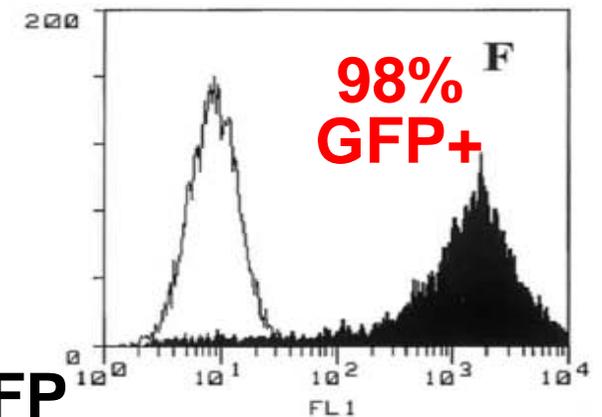
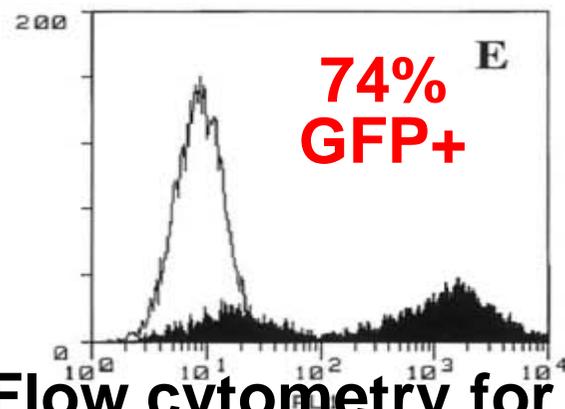
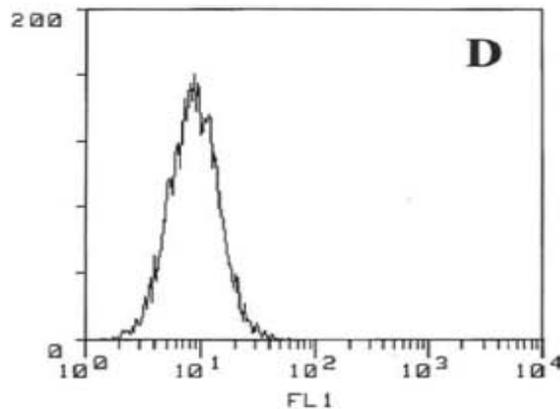
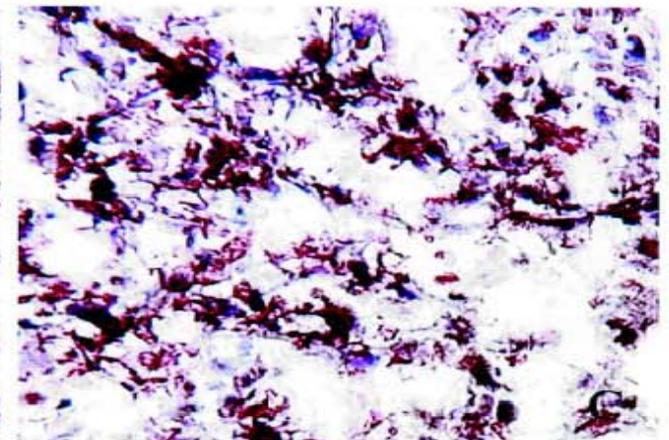
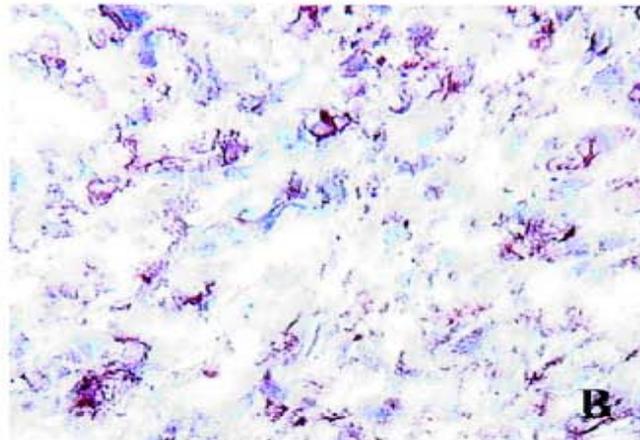
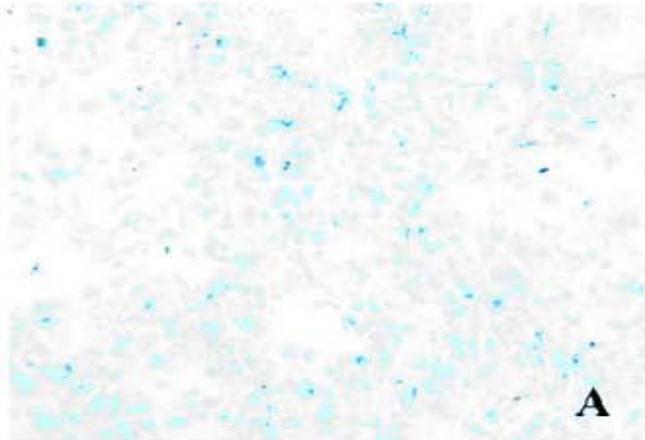
# RRV spreads through intracranial tumors



negative control

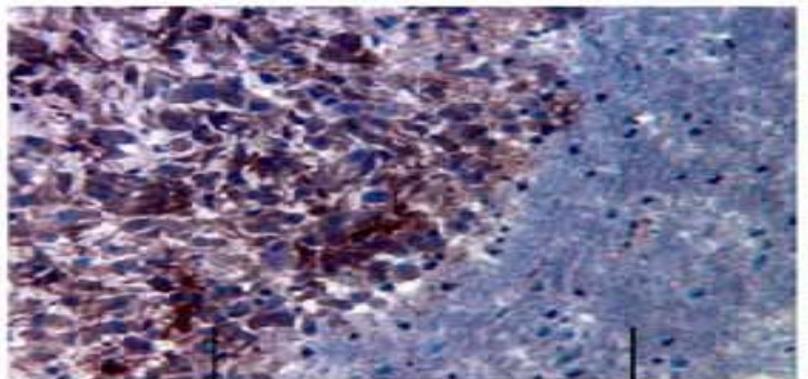
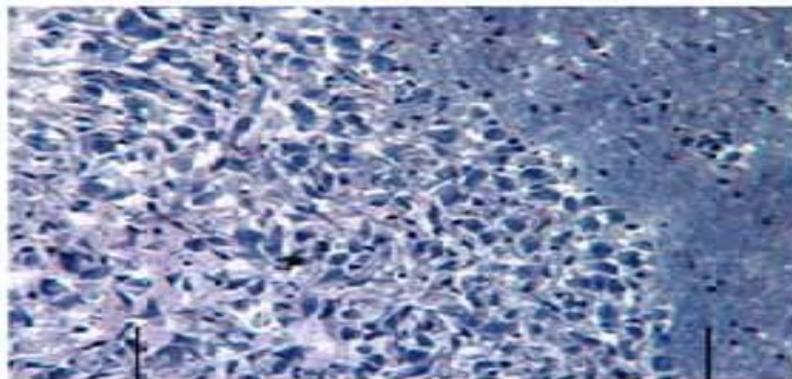
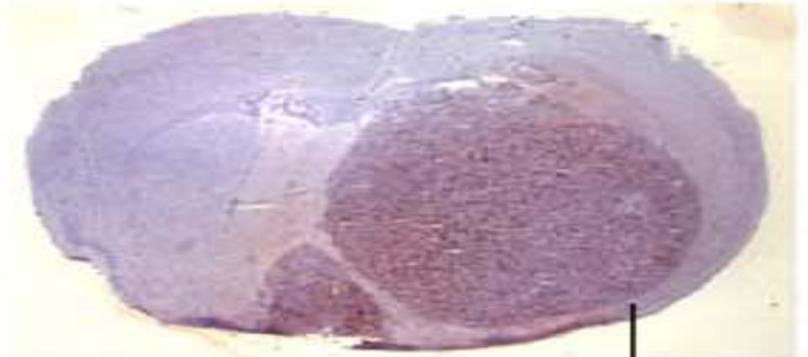
2 weeks post-infection

3 weeks post-infection



Flow cytometry for GFP

# RRV spreads selectively through tumor



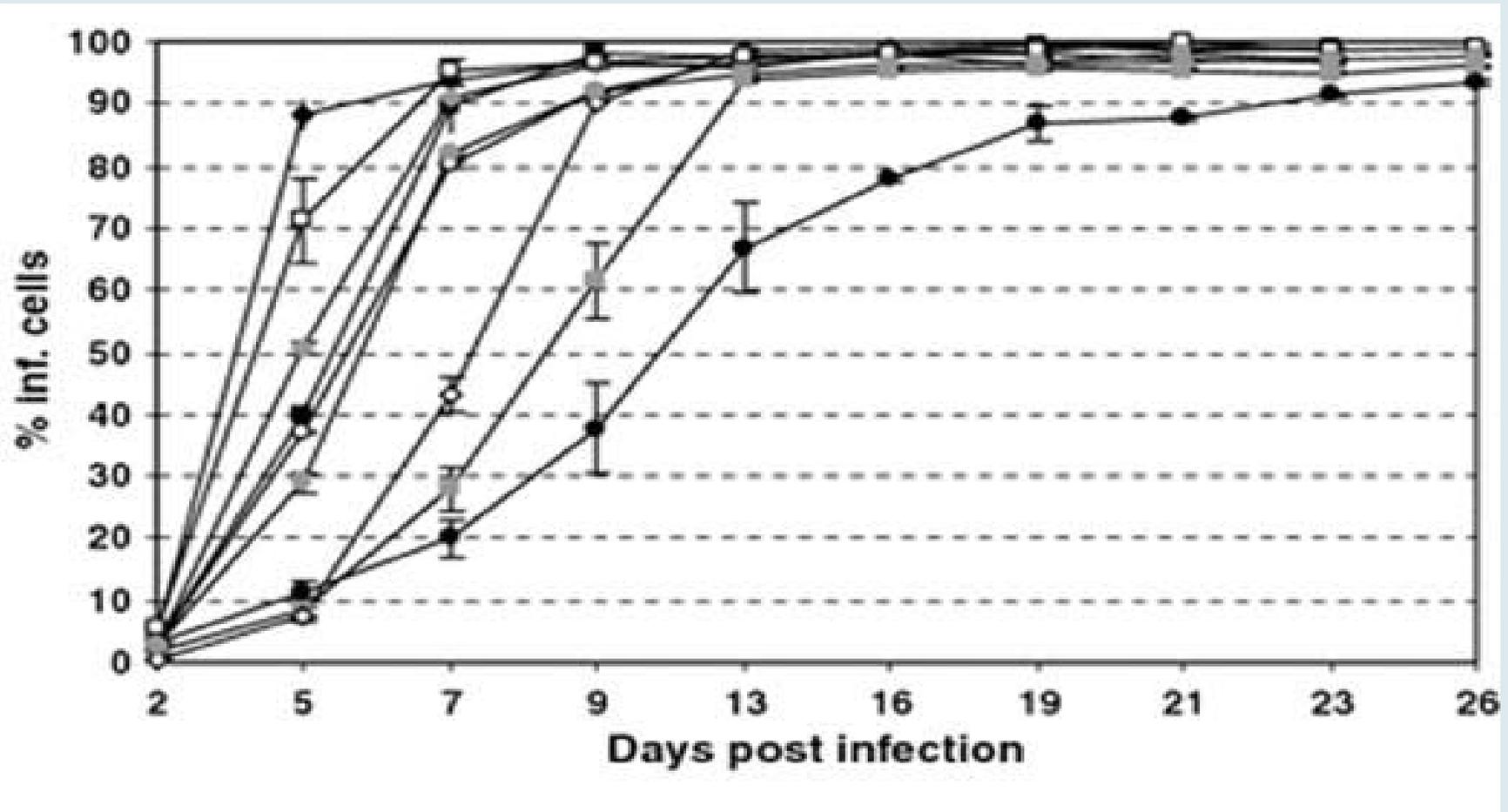
tumor

brain

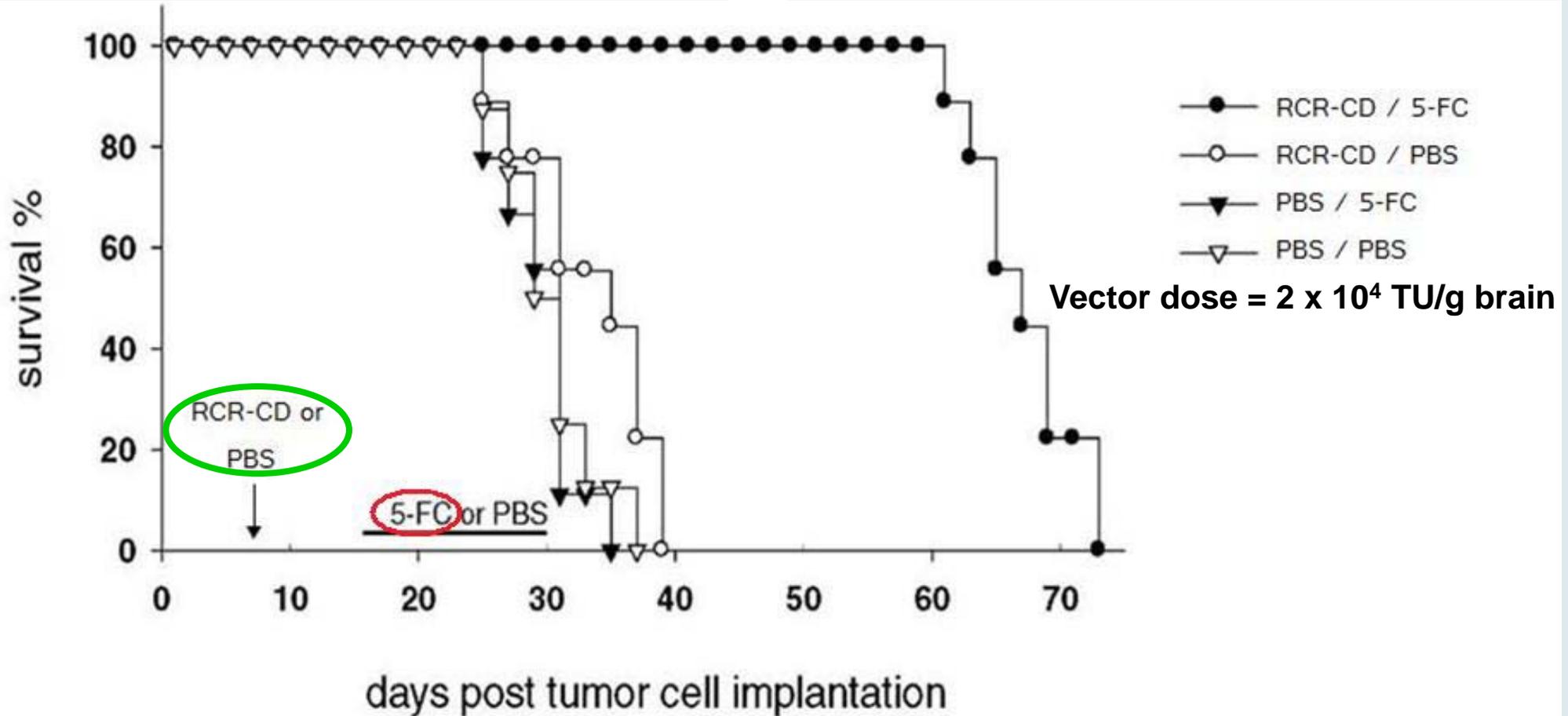
tumor

brain

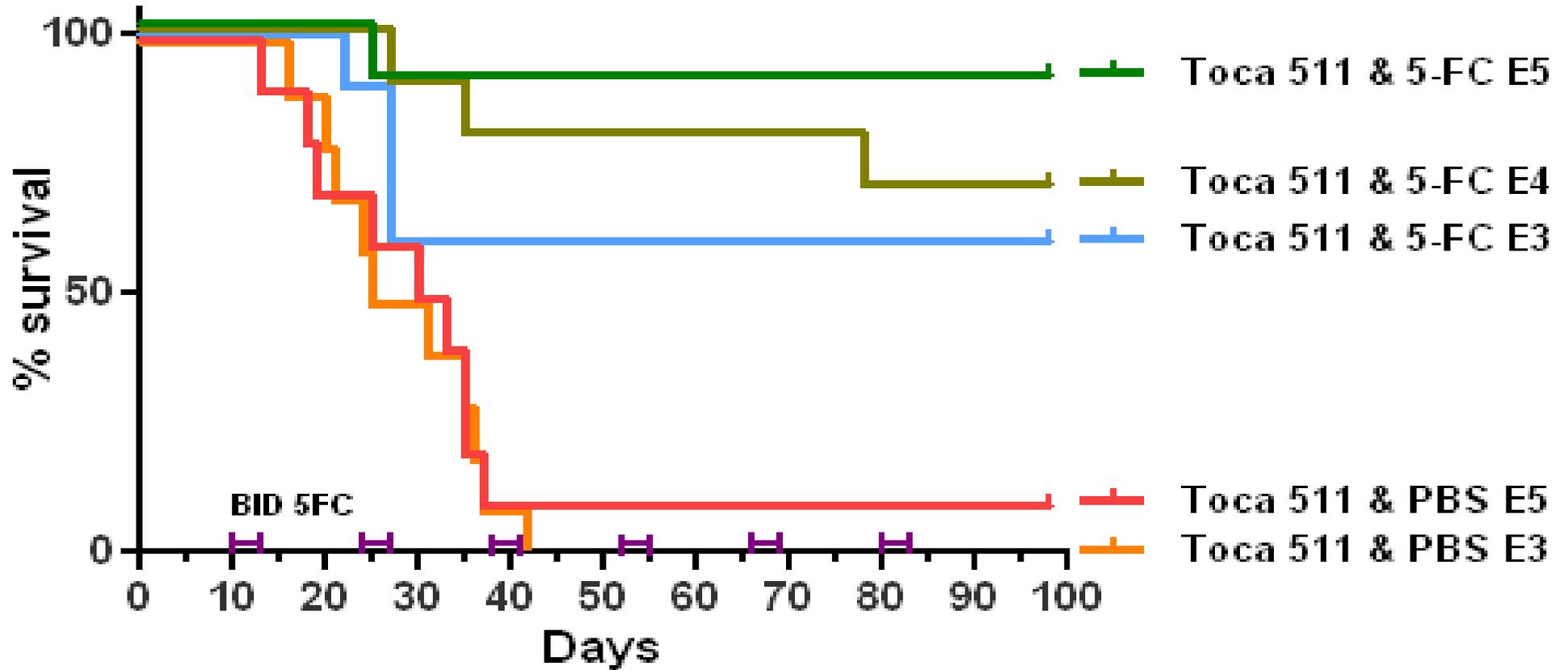
# RRV infects human glioma cells $\approx 100\%$ over 7-26 days



# RRV-CD doubles survival after a single cycle of 5-FC



# Toca 511/5-FC increases survival in immune-competent model

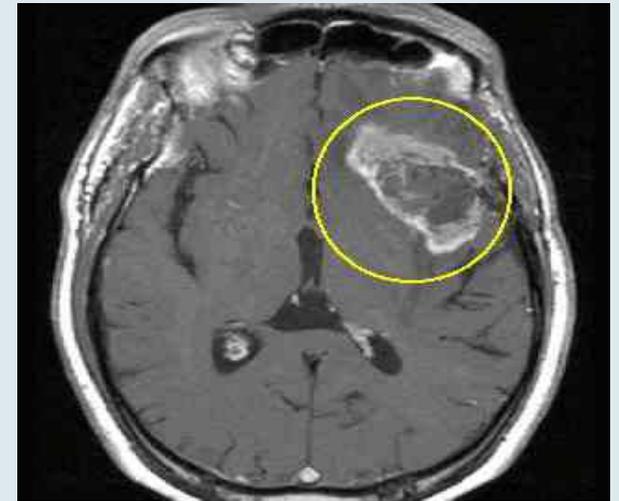


TU-2449 glioma cells in B6C3 F1 mice  
10/group

# Primary brain cancer remains a clinical problem



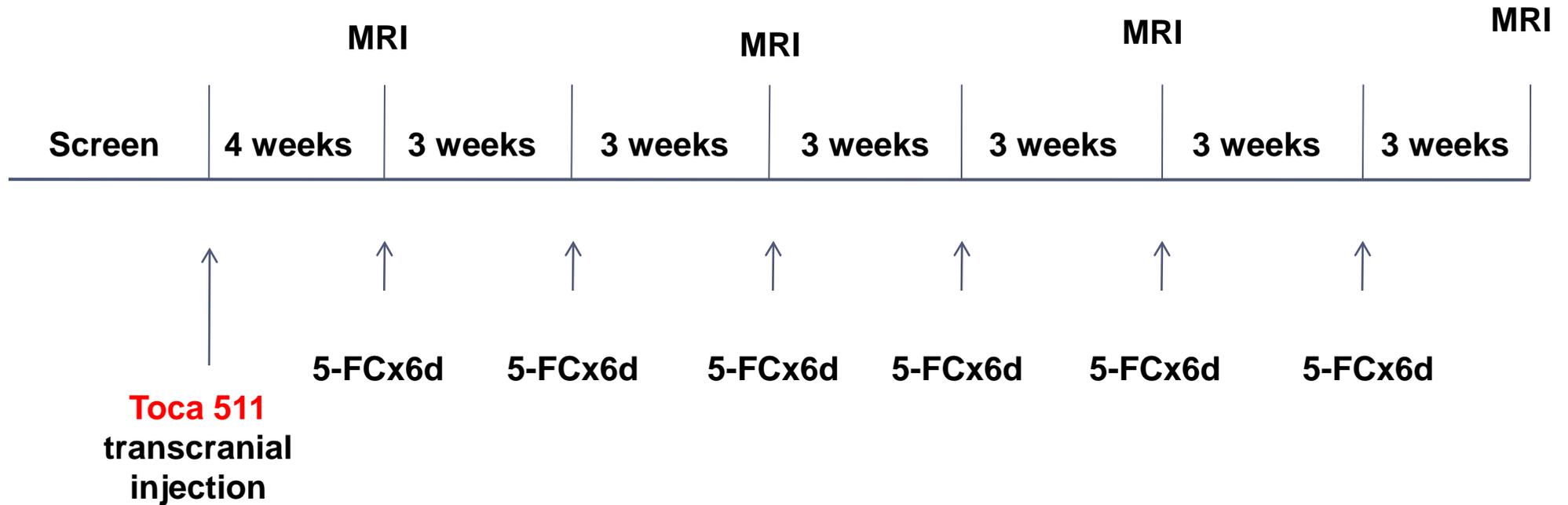
- ≈22,000 primary brain tumors Dx in U.S. in 2011
- 8,000-10,000 will be GBM (grade IV glioma)
- GBM is most aggressive 1° malignant brain tumor
- Tends to affect people in middle life
- Maximal initial Rx = surgery, radiation, temozolomide
  - Median survival 14.6 months
  - < 10% survive two years
  - Temozolomide only benefits ≈ 40% patients
  - rGBM survival ≈ 6-8 months



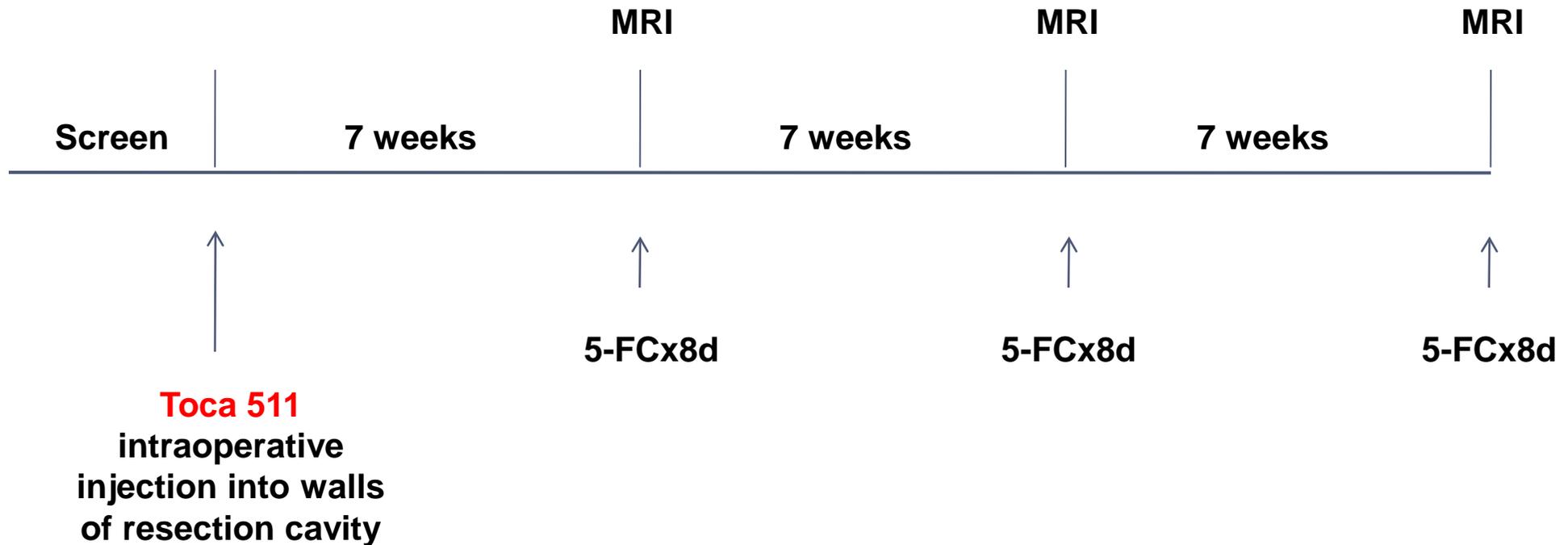
# Intratumoral and post-resection studies

	Tg 511-08-01	Tg 511-11-01
Indication	rHGG	rHGG
Vector	Toca 511	Toca 511
Administration	Intratumoral	Resection bed
Doses (TU/g)	2.6x10 <sup>3</sup> , 9.5x10 <sup>3</sup> , 2.5x10 <sup>4</sup> , 10 <sup>5</sup>	9.5x10 <sup>3</sup> , 2.5x10 <sup>4</sup> , 10 <sup>5</sup> , 3.2x10 <sup>5</sup>
Escalation	½ log	½ log
Design	3+3	3+3
Prodrug	5-FC	5-FC
Weeks to cycle 1	4	7
5-FC days/course	6	8
# cycles	6	3
Objectives	Safety, tolerability, MTD	Safety, tolerability, MTD
LTFU	Yes	Yes

# Intratumoral study schematic



# Post-resection study schematic



# Current status intratumoral study



- Dosing of 3 subjects in cohort 1 completed March 2011-No DLTs
- Data from cohort 1 presented to FDA and study PIs May 2011
- Approval to ascend to second dosing cohort
- Dosing of 3 subjects in cohort 2 complete
- Surgeons suggested administering Toca 511 at time of resection
  - Allows enrollment of subjects with larger tumors
  - Debulking allows increased time for vector spread
  - Allows for injection of larger volumes/dose of Toca 511

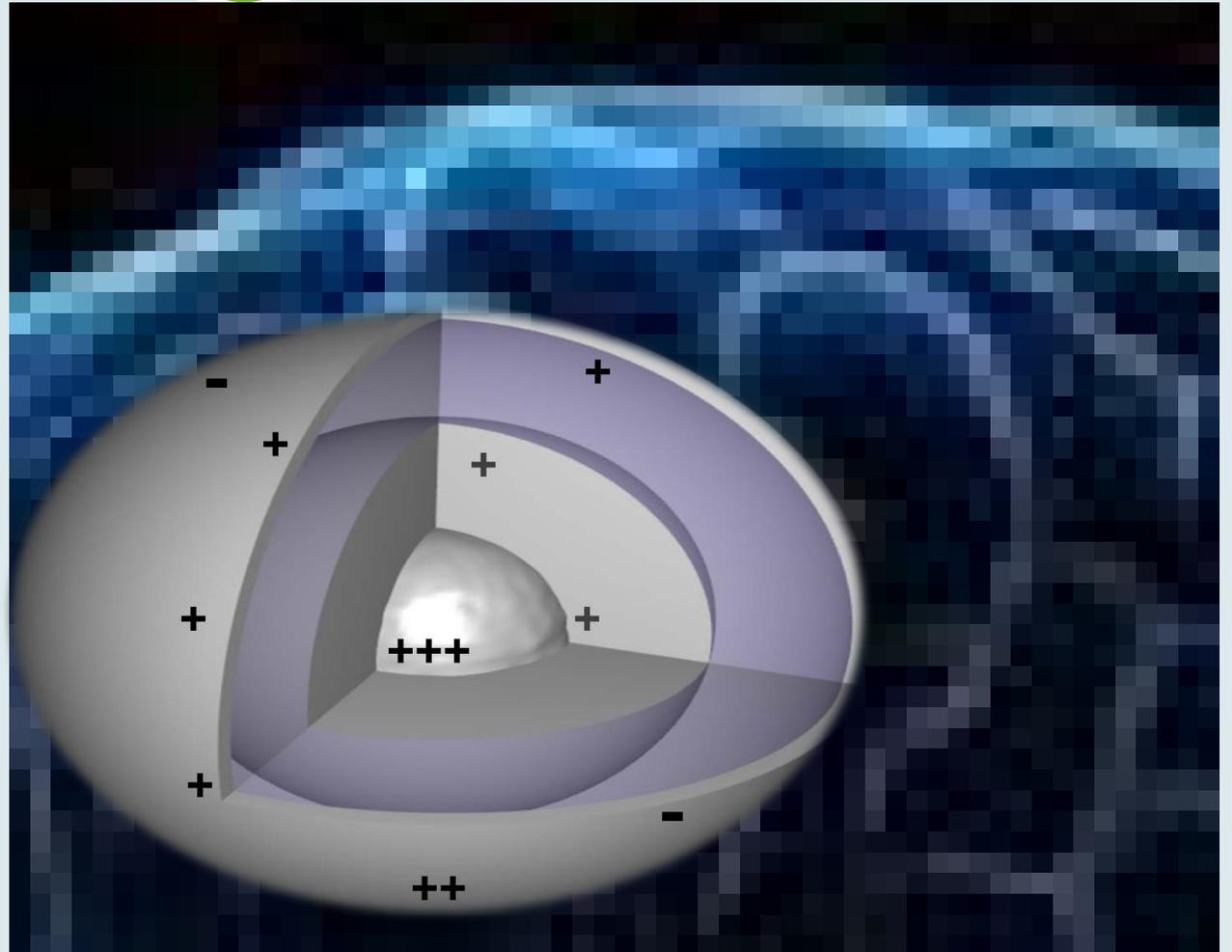
# Summary of human intratumoral study data



- **Dosing Cohort 1 ( $2.6 \times 10^3$  TU/g)**
  - Toca 511/5-FC well tolerated
  - No dose-limiting toxicities observed
  - Some suggestions of drug activity observed
  - Transient viremia detected 9-11 weeks after administration in 2/3 pts
  - Viremia not associated with symptoms or toxicity
  - Viral RNA/DNA cleared after appearance of anti-vector antibodies
  - Vector persisted in tumor after 3 cycles of 5-FC in 2 patients
- **Dosing Cohort 2 ( $9.5 \times 10^3$  TU/g)**
  - No DLTs observed to date
  - No DNA or RNA signal detected to date (7 weeks for first subject)

# Vector DNA distribution in resected tumor

Subject 101



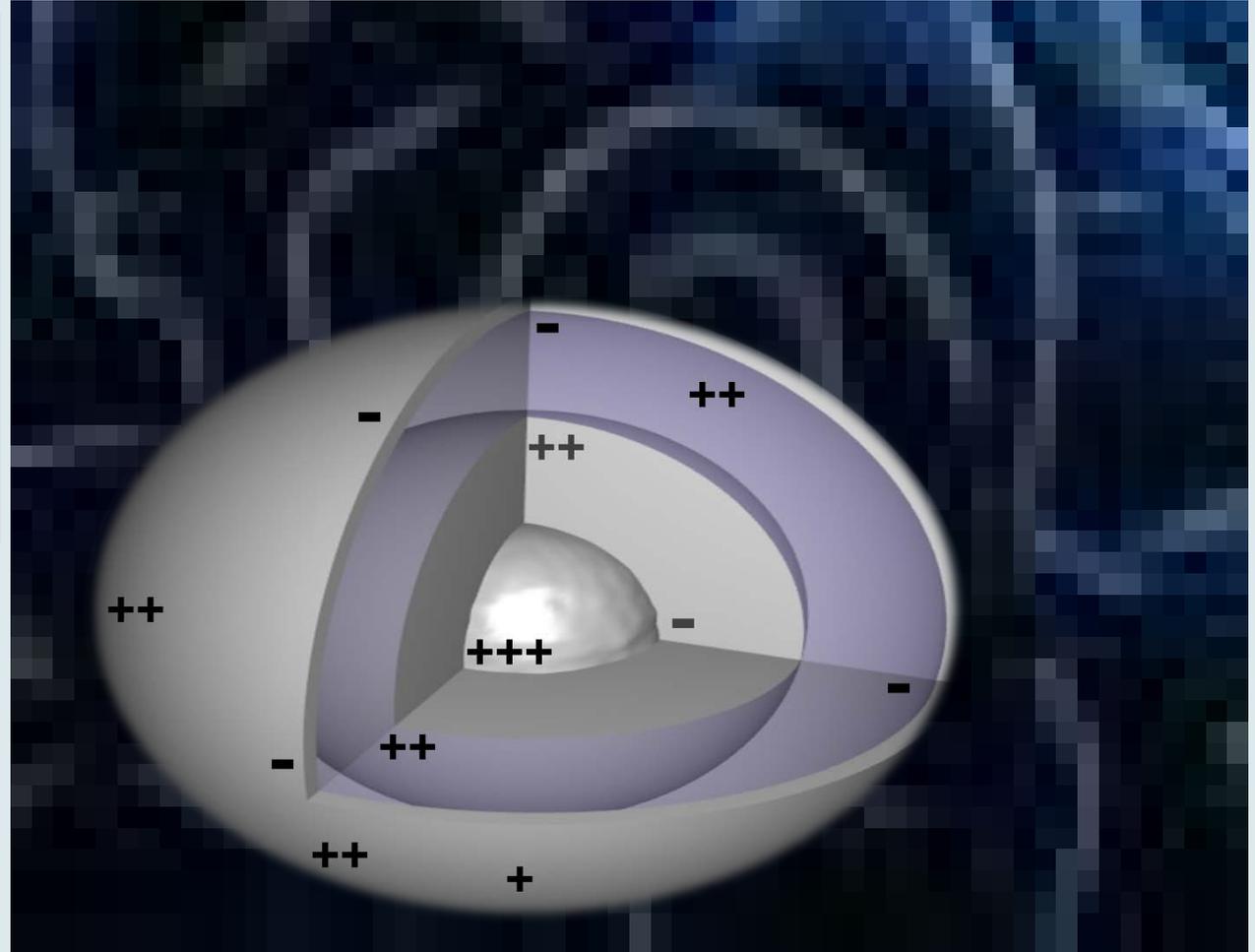
+ Detected

++ 100-1000 copies/ $\mu\text{g}$

+++ > 1000 copies/ $\mu\text{g}$

# Vector DNA distribution in resected tumor

Subject 102



+ Detected

++ 100-1000 copies/ $\mu\text{g}$

+++ > 1000 copies/ $\mu\text{g}$

# Low risk of vector-associated malignancy in humans with non-replicating retroviral vectors



- Over a dozen ex vivo trials with mature T cells
  - no evidence of retroviral vector related cancer
- Several trials with IV, IM or intratumoral injection
  - no evidence of retroviral vector related cancer
- Many ex-vivo HSC trials
  - ADA SCID had no evidence of retroviral vector related cancer
  - SCID-X1 and WAS associated with T cell leukemia

# Potential risk factors for malignancy in ex vivo HSC trials



	SCID-X1	WAS	CGD
Promoter	MoLTR	MPSVLTR	SFFV/MoLTR
Replicating	No	No	No
Transgene	IL2RG	WAS	gp91 <sup>phox</sup>
Designed to persist systemically	yes	yes	yes
Tumor/Disorder	T-cell Leukemia	T-cell leukemia	MDS
Hem. Stem cell target	yes	yes	yes
Cytokine expansion	yes	yes	yes
Transgene survival advantage	yes	yes	no
Infant/child patient	yes	yes	no
Immune-deficient host	yes	yes	yes
BM conditioning	no	yes	yes

# Toca 511 study differs from HSC protocols



- Not infecting hematopoietic stem cells ex vivo
- Not stimulating expansion of infected cells with cytokines
- Not administering to infants with immature immune systems
- Not administering to patients with severe immunodeficiency
- Not designed to persist systemically
- CD not a known growth-promoting gene
- CD does not confer a survival advantage  
-actually the opposite

# Viral testing plan post-resection protocol



- qPCR for viral DNA in whole blood at 8 time points
  - If qPCR > 1500 copies/ $\mu$ g x 2 then clonality testing will commence
- qRTPCR for viral RNA in plasma at 8 time points
- RTPCR for viral RNA in urine and saliva at 7 time points
- Testing in the LTFU protocol Tg 511-09-01
  - Year 1: monthly if positive, every 3 months if negative
  - Years 2-5: monthly if positive, every 6 months if negative
  - Years 6-15: monthly if positive, yearly if negative

# Current precautions



- Ampho-MLV is RG-2 virus
  - HSV, HBV examples of other RG-2 viruses
- Biosafety Level-2 precautions recommended
- Hospitals already operate at BSL-2
  - Universal blood and tissue precautions
- Current recommendations
  - Universal blood and tissue precautions
  - Condoms for men and women until no virus detected

# Risk/benefit conclusions



- Systemic biodistribution of Toca 511 controlled by immune system
- Current trials with Toca 511 differ from trials with vector-associated malignancy
- Toca 511 risk/benefit in 1<sup>o</sup> brain cancer appears appropriate

Thank you.