Mathematical Model Combining Oncolytic Viral Therapy and Immunotherapy

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December 10, 2015

Present Challenges of Mathematics in Oncology and Biology of Cancer: Modelling and Mathematical Analysis

CIRM Marseille, France

Recent News

Cancer

A 'huge milestone': approval of cancer-hunting virus signals new treatment era

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Cancer-fighting viruses win approval

US regulators clear a viral melanoma therapy, paving the way for a promising field with a chequered past.

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Heidi Ledford

28 October 2015

TRANSGENE (ENX:TNG) And SillaJen Announce Revised Agreement For Pexa-Vec Oncolytic Viral Therapy And Provide Update On Clinical Development

11/12/2015 12:23:04 PM

STRASBOURG, France--(BUSINESS WIRE)--Regulatory News: Transgene SA (Paris:TNG) (Euronext: TNG) and SillaJen, Inc. today announced that they have signed an amended agreement for the development and commercialization of oncolytic viral therapy Pexa-Vec to streamline the conduct of clinical trials and to reflect important areas of interest for each company. Key changes to the agreement are outlined below.

Conventional Cancer Treatments

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- Immunotherapy
- Targeted Therapy

Oncolytic Virotherapy

- "Anti-cancer" Oncolytic virus is type of Virotherapy
  - Viral gene therapy

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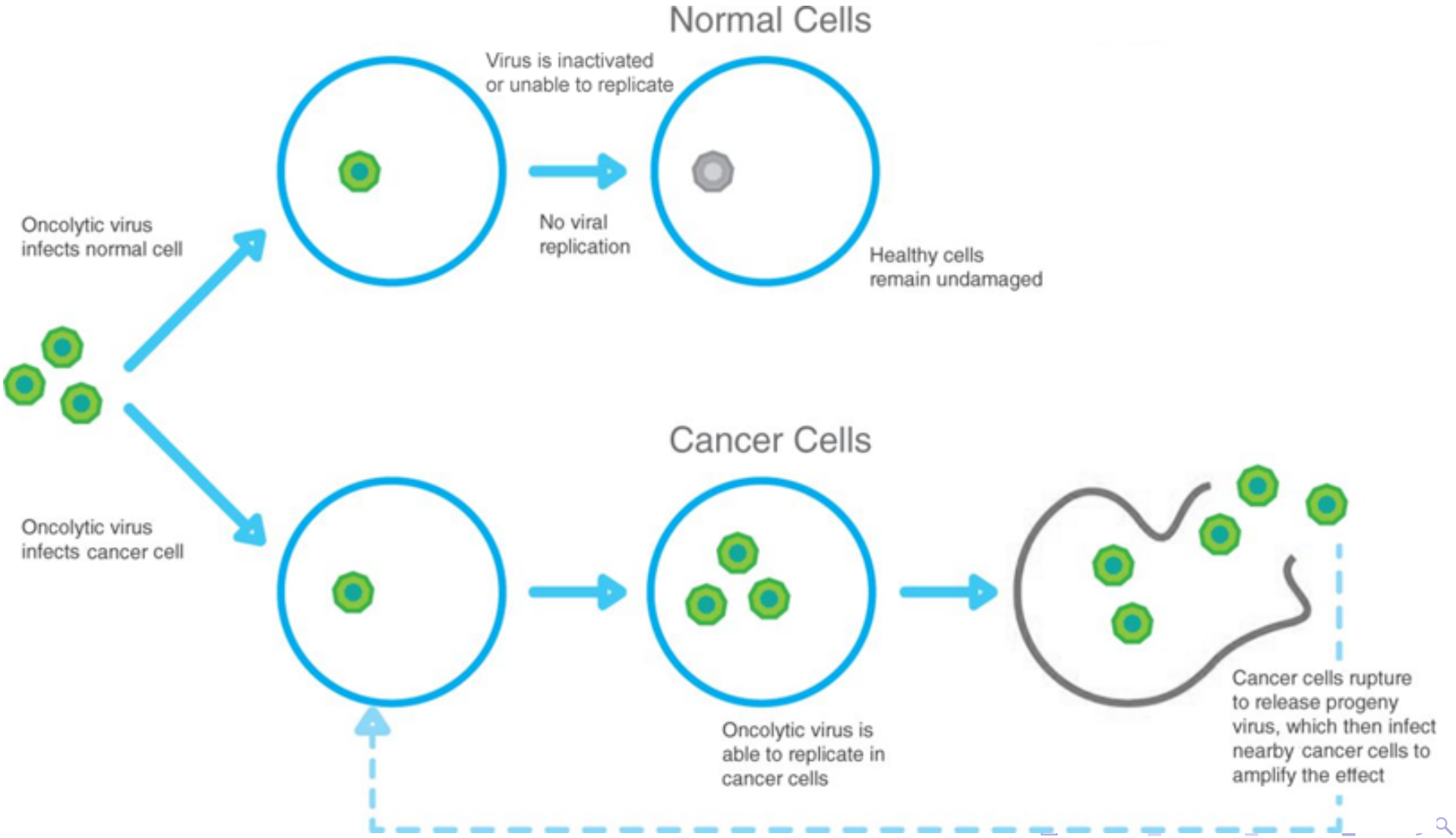


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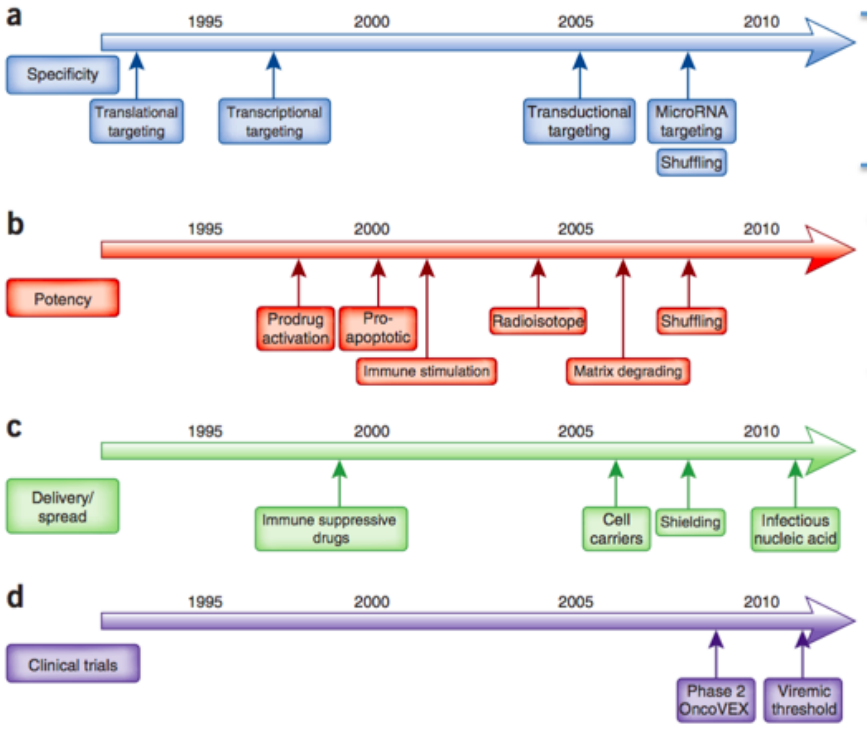
LEGEND

Milestones in Oncolytic Virotherapy



Viral Specificity-
Translational(1991), transcriptional (1997) and transductional (2005) targeting via engineering, and DNA shuffling (2008)

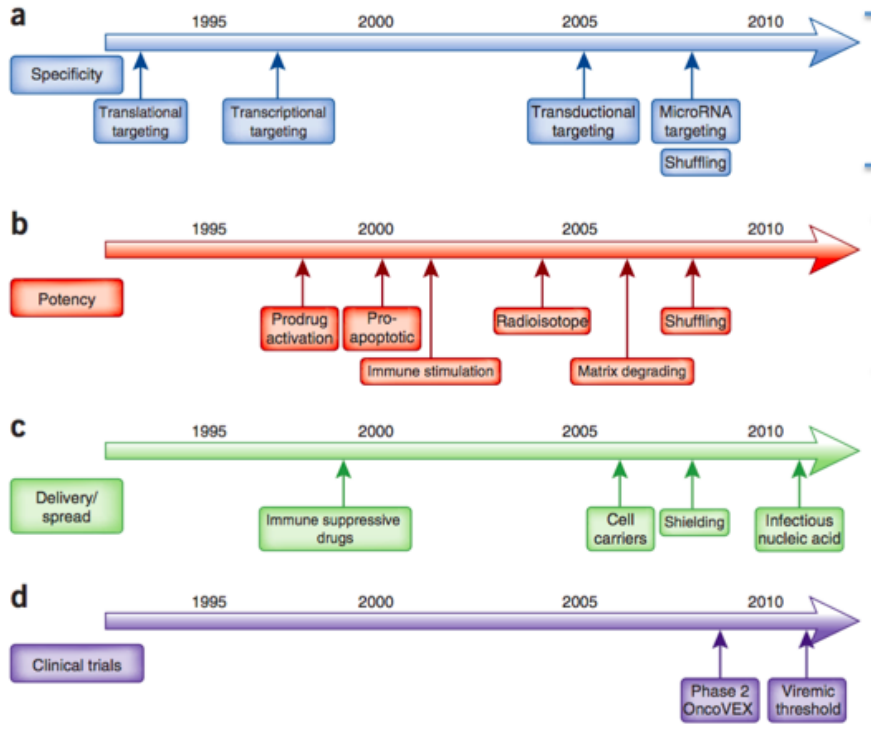
Potency-
Prodrug activation (1998), Introduction of proapoptotic genes (2000), immune stimulation (2001), inclusion of radioisotopic(2004), matrix degrading proteins(2006), DNA shuffling(2008)

Delivery and spread-
Immunosupressibve drugs(1999), introduction to cell carriers(2006), shielding approaches (2008), delivery of oncolyitc porconavirus (2011).

Clinical Trials-
Phase 2 OncoVEX(2009).
Viremic threshold(2011).

Russell et al, 2012

Milestones in Oncolytic Virotherapy



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FDA Approval-
TVEC (2015)

Clinically tested Oncolytic Viruses

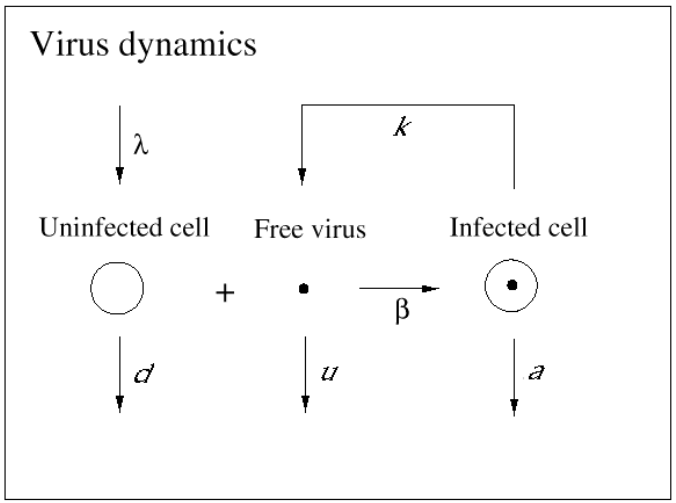
- adenovirus
- reovirus
- measles
- herpes simplex (HSV)
- poxvirus

Question: How sensitive is tumor reduction to combination intermittent oncolytic viral therapy and immunotherapy?

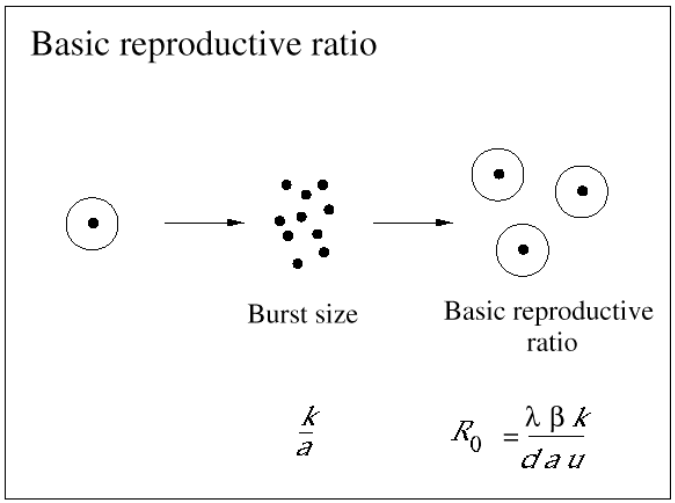
Basic Viral Model

$$\begin{aligned} \frac{dx}{dt} &= \lambda - dx - \beta xv \\ \frac{dy}{dt} &= \beta xv - ay \\ \frac{dv}{dt} &= \kappa y - \delta v \end{aligned} \tag{1}$$

nowak1996population



(a)



(b)

Basic Viral Immune Models

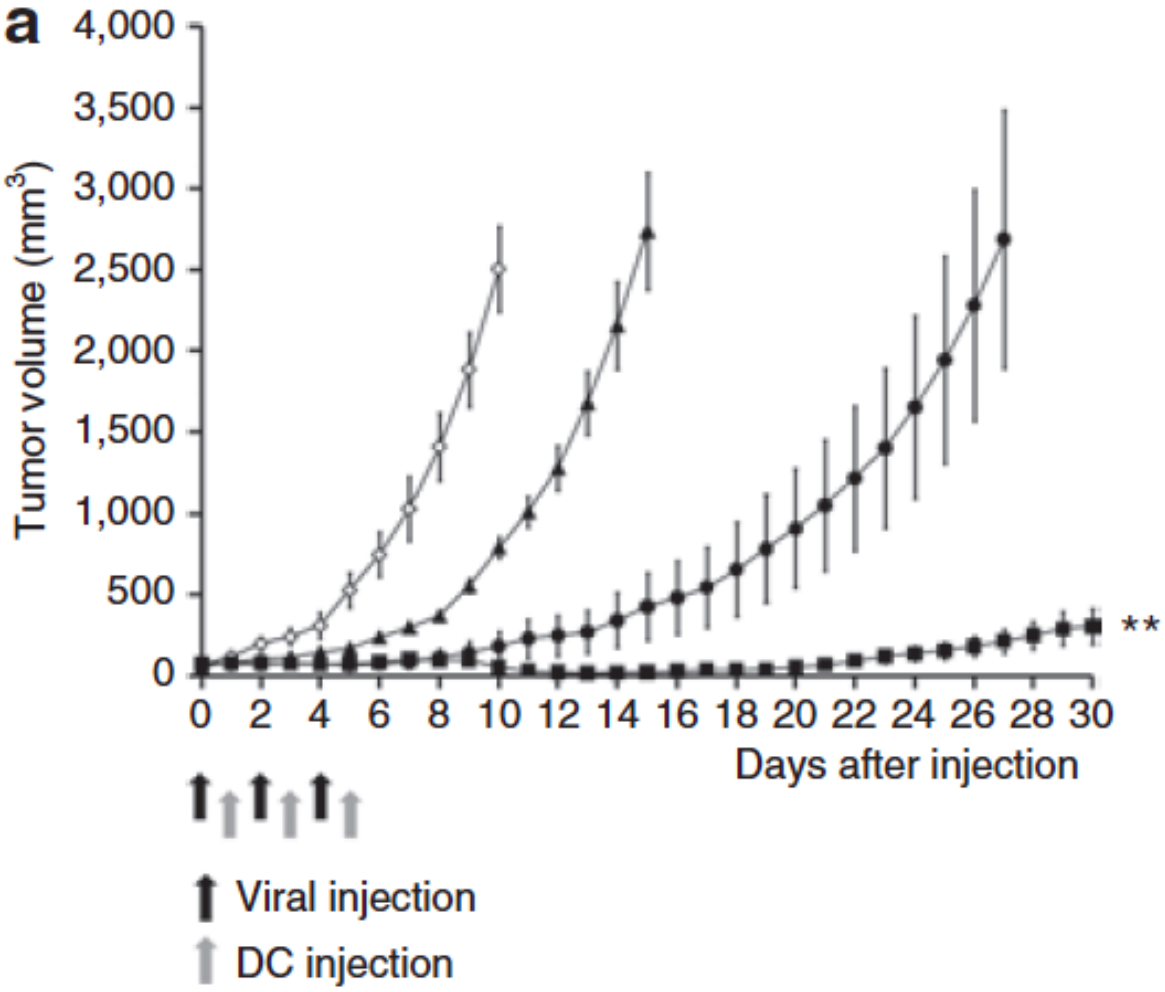
Self-regulating CTL response

nowak2000virus

$$\begin{aligned} \frac{dx}{dt} &= \lambda - dx - \beta xv \\ \frac{dy}{dt} &= \beta xv - ay - pyz \\ \frac{dv}{dt} &= ky - \delta v \\ \frac{dz}{dt} &= c - bz \end{aligned} \tag{2}$$

$$R_0 = \frac{\beta\gamma k}{(a - a^1)d\delta}; \qquad a^1 = \frac{cp}{b}$$

Constructing the model...



huang2010therapeutic

viruses

MDPI

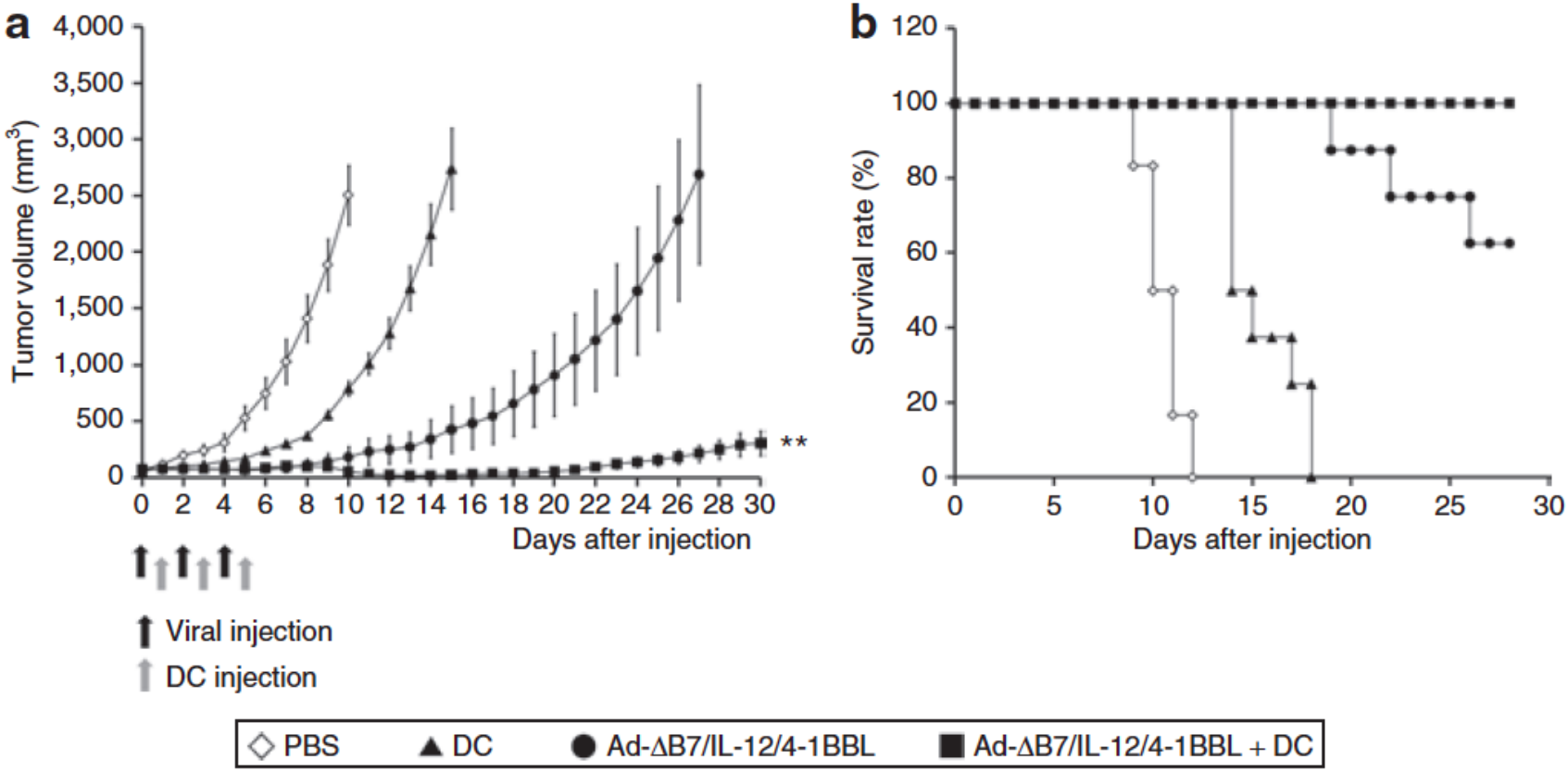
Review

Dendritic Cells in Oncolytic Virus-Based Anti-Cancer Therapy

Youra Kim [1], Derek R. Clements [1], Andra M. Sterea [2], Hyun Woo Jang [3], Shashi A. Gujar [3,4,*] and Patrick W. K. Lee [1,3,*]

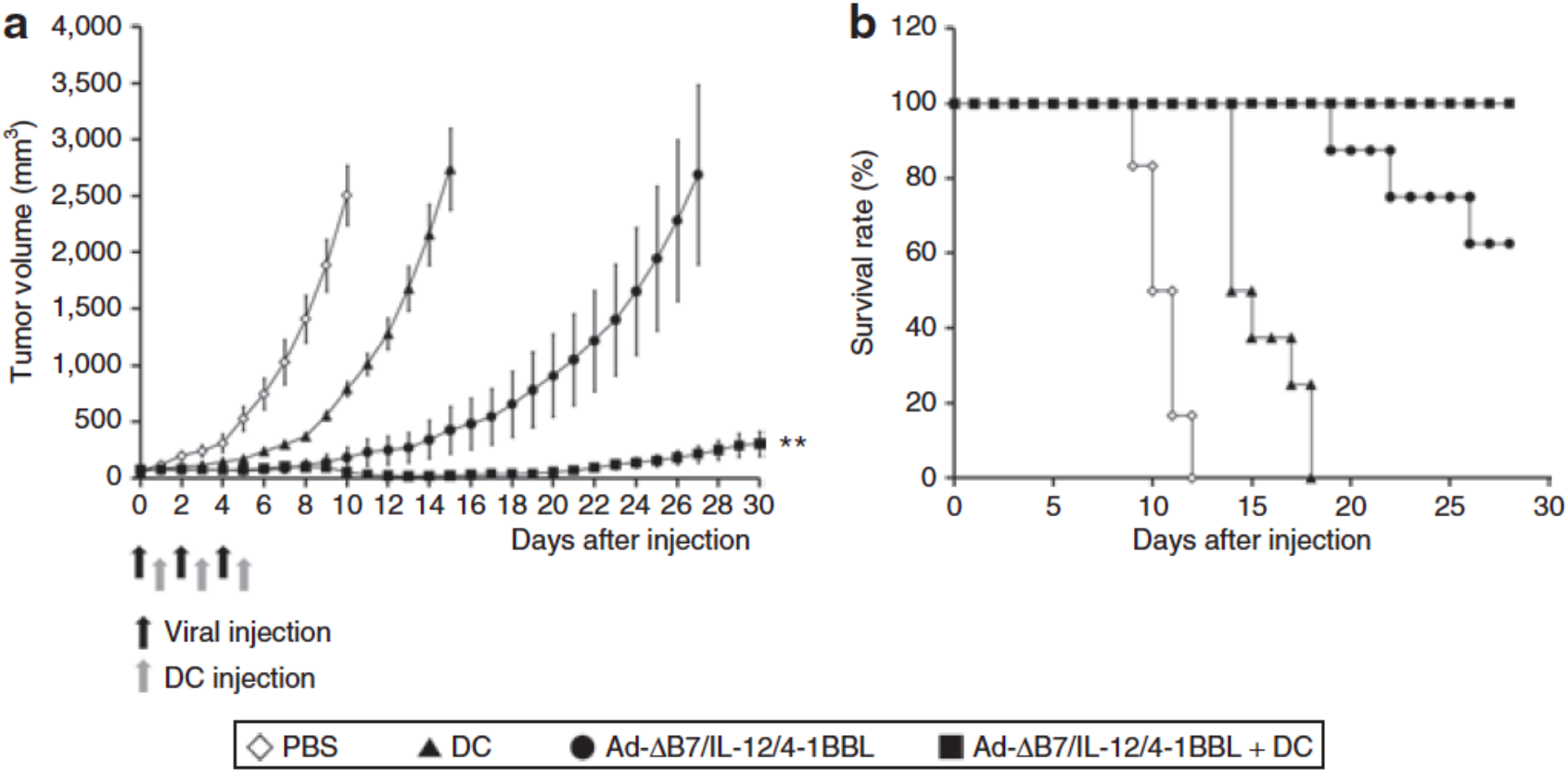
Received: 9 September 2015; Accepted: 27 November 2015; Published: 9 December 2015
Academic Editors: E. Antonio Chiocca and Martine L.M. Lamfers

Data



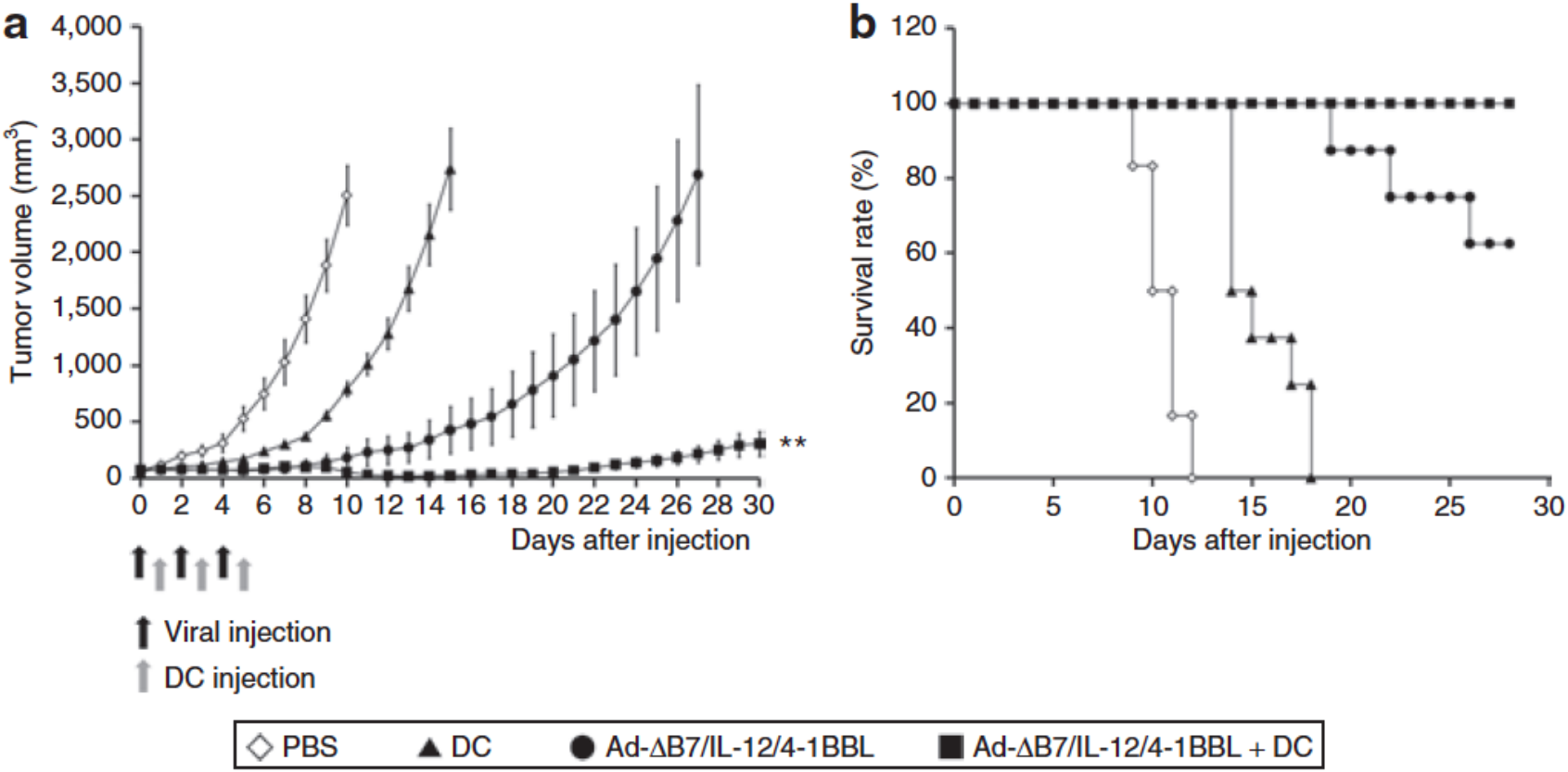
- Gene-based treatment: Enhanced anti-tumor effect via co-expression of IL-12 and 4-1BBL mediated by Oncolytic Adenovirus (Ad)

Data



- Gene-based treatment: Enhanced anti-tumor effect via co-expression of IL-12 and 4-1BBL mediated by Oncolytic Adenovirus (Ad)
- (6-8) Mice/group

Data



- Gene-based treatment: Enhanced anti-tumor effect via co-expression of IL-12 and 4-1BBL mediated by Oncolytic Adenovirus (Ad)
- (6-8) Mice/group
- Subjects: contained B16-F10 subcutaneous murine melanoma

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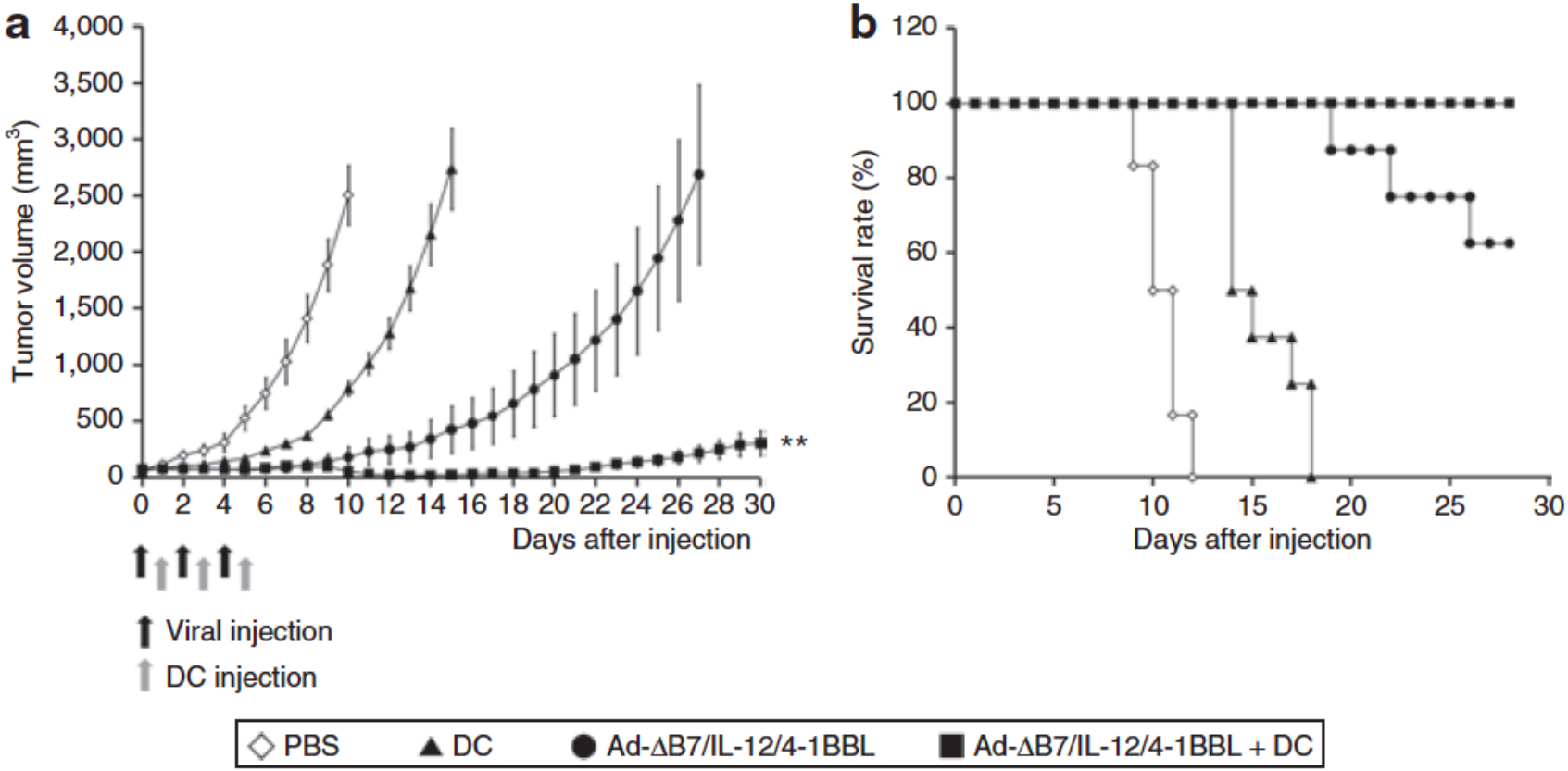

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- (6-8) Mice/group
- Subjects: contained B16-F10 subcutaneous murine melanoma
- Administration : Intratumorally

Model Combining Oncolytic Viral Therapy and Immunotherapy

$$
\begin{aligned}
\frac{dU}{dt} &= rU - \beta\frac{UV}{N} - (\lambda_u + \kappa I)\frac{UT}{N} \\
\frac{dI}{dt} &= \beta\frac{UV}{N} - \delta_I I - (\lambda_i + \kappa I)\frac{IT}{N} \\
\frac{dV}{dt} &= u_v(t) + \alpha\delta_I I - \delta_v v \\
\frac{dT}{dt} &= \rho D - \delta_t T \\
\frac{dD}{dt} &= \mu_u U + \mu_I I - \delta_d D + u_d(t)
\end{aligned}
\tag{3}
$$

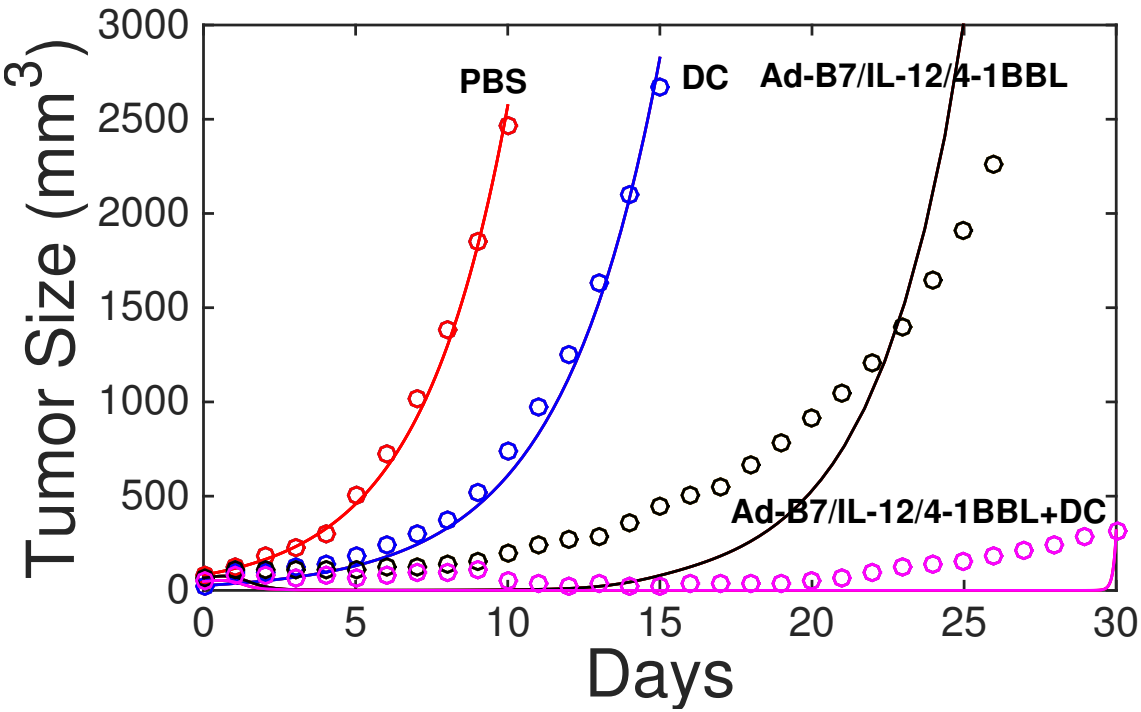
- D denotes Immunotherapy via Dendrites cells; subset of Antigen Presenting Cells (APC's)
- Two types of intermittent treatment; $u_v(t), u_d(t)$
- Enhance immune stimulation; κI

Parameter Fits

Parameter	Description	PBS	DC	Ad-ΔB7/4-1BBL	Ad-ΔB7/4-1BBL+DC
r	**Uninfected tumor cell growth rate**	0.34484	**0.34484**	**0.34484**	**0.34484**
λ_U	**T cell contact rate, uninfected**	-	**0.17206**	**0.17206**	**0.17206**
λ_I	**T cell contact rate, infected**	-	**0.17206**	**0.17206**	**0.17206**
μ_U	**dendrite activation from uninfected cells**	-	**0.15113**	**0.15113**	**0.15113**
μ_I	**dendrite activation from infected cells**	-	-	$\mu_U * 1.1$	$\mu_U * 1.1$
β	**Viral infectious rate**	-	-	**0.0053884**	**0.0058385**
κ	**T cell killing rate**	-	-	8.5×10^{-7}	8.5×10^{-7}
δ_T	**T cell decay rate**	-	**0.35**	**0.35**	**0.35**
δ_D	**Dendritic cell death rate**	-	**0.35**	**0.35**	**0.35**
ρ	**T cell activation rate by dendritic cells**	-	**1**	**1**	**1**
u_{0D}	**Dendritic concentration**	-	10^6	-	10^6
u_{0V}	**Adenovirus concentration**	-	-	**2.5 x** 10^9	**2.5 x** 10^9
α	**adenovirus burst size**	-	-	**3500**	**3500**
δ_I	**Infected lysis**	-	-	**1**	**1**
δ_V	**Viral decay rate**	-	-	**2.3**	**2.3**

Table: Parameter estimates for Model (8)

Fit Simulation



Clinical Trial Regimes

Cancer /Stage	O-Virus	Drug Name	Company	Phase Trial	R.O.A$_V$[1] R.O.A$_I$[2]	Quantity$_V$ (pfu/ml)	Schedule	Immune-Combo	Cite

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Cancer /Stage	O-Virus	Drug Name	Company	Phase Trial	R.O.A$_V$ [1] R.O.A$_I$ [2]	Quantity$_V$ (pfu/ml)	Schedule	Immune-Combo	Cite
Melanoma IIIB-IV	HSV-1	T-VEC	AMGen	III	I-LES[3] Sub-C$_I$ [4]	10^6 10^8 10^8	D1-WK1; D2-WK4; DN+/2WKS; $\leq$ 24 wks; $\leq$ 48 wks(1 yr/ D1) $\leq$ 72wks (18mos from D1)	No.Option(OR) GM-CSF $125\mu g/m^2$ 14 Days(daily)	(Andtbacka et al., 2015)
Varied:NSCLC,Col,Mel,Thy, Pan,Ova,Gas, Lei, Mes	Vaccinia Poxvirus	JX-594 (Pexa-Vec)	Jennerex	I	I-VEN	1×10^5,1×10^6, 3×10^6,1×10^7, 1.5×10^7, 3×10^7 *(pfu/kg)	Singe infusion	Express: GM-CSF, β-gal	(Breitbach et al., 2011)
Ova, Mes	Adenovirus	Ad5-D24-GMCSF		I (min)	I-VEN I-CAV	D1; 8×10^9. Doses escalate to: 1×10^{10}, 3.6×10^{10}, 1×10^{11}, 2×10^{11}, 2.5×10^{11}, 3×10^{11},and 4×10^{11}	Single infusion	GM-CSF	(Cerullo et al., 2010)
Liver Cancer	Vaccinia Poxvirus	Pexa-Vec [5]	Jennerex	II	I-VEN	Low 10^8; High 10^9	Infused low and high dose on D1, D15 & D29	No. Inserted GM-CSF and β Gal	(Heo et al., 2013)
Gastrointestinal Carcinoma	Adenovirus	Onyx-015	Onyx Pharmaceuticals	II	HAI	2×10^{12}	D1,D8 . Chemotherapy administered on D22	-	(Reid et al., 2002)

Table 3: NSCLC,non small cell lung cancer; Col,Colorectal; Mel=Melanoma;Thy,Thyroid; Pan,Pancreatic; Ova, Ovarian; Gas, Gastric; Lei,Leiomyosarcoma; Mes,Mesothelioma. HAI, Hepatic Artery Infusion

Patient code	Dose (VP)	Primary Tumor
C3	8×10^9	Jejunum cancer
M3	1×10^{10}	HCC
O12	3.6×10^{10}	Ovarian cancer
O14	1×10^{11}	Ovarian cancer
G15	1×10^{11}	Gastric cancer
K18	2×10^{11}	NSCLC
T19	2×10^{11}	Thyroid cancer
U89	2×10^{11}	Renal cancer
S100	2×10^{11}	Leiomyosarcoma
S108	2×10^{11}	Synovial sarcoma
M50	2.5×10^{11}	Mesothelioma
R8	3×10^{11}	Breast cancer
M32	3×10^{11}	Mesothelioma
X49	3×10^{11}	Cervical cancer
I52	3×10^{11}	Melanoma
I78	3×10^{11}	Choroidal melanoma
C58	4×10^{11}	Colon cancer
R73	4×10^{11}	Breast cancer
O88	4×10^{11}	Ovarian cancer
O9‖	2×10^{11}	Ovarian cancer

Patient code	Dose (VP)	Primary Tumor
C3	8×10^9	Jejunum cancer
M3	1×10^{10}	HCC
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G15	1×10^{11}	Gastric cancer
K18	2×10^{11}	NSCLC
T19	2×10^{11}	Thyroid cancer
U89	2×10^{11}	Renal cancer
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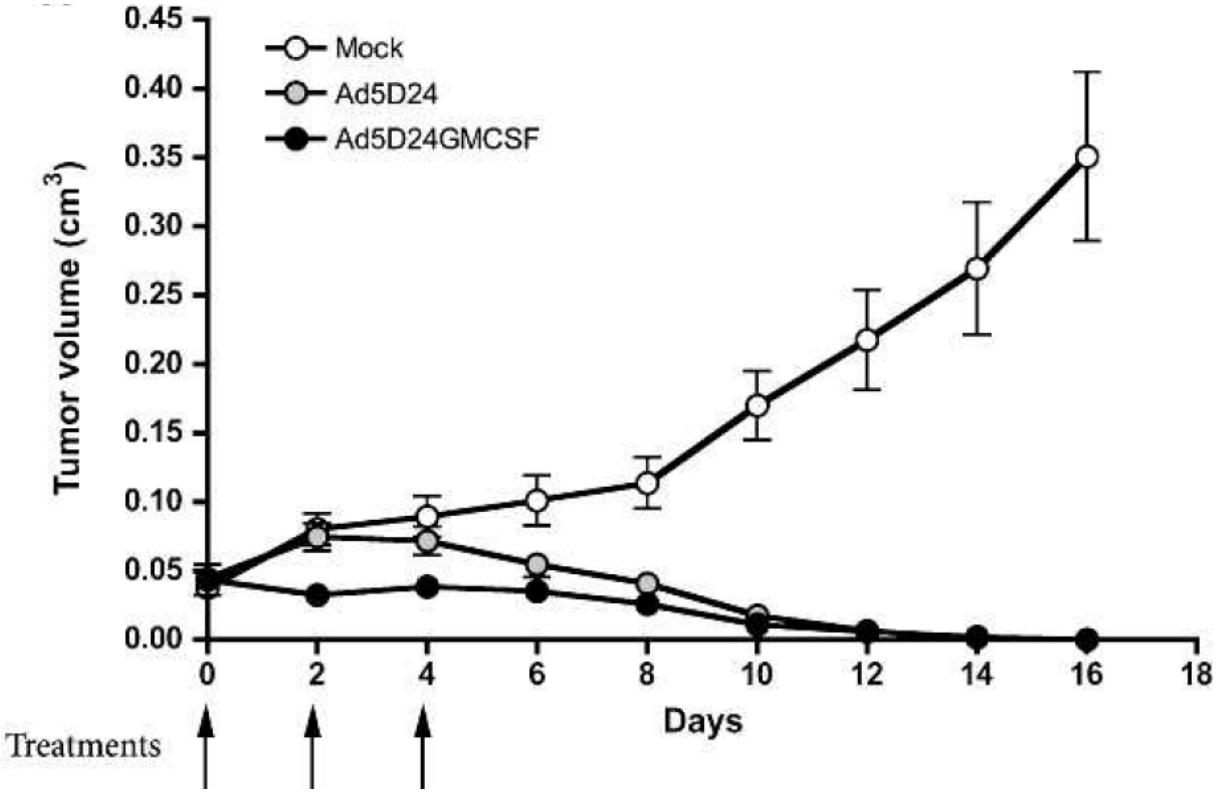
O9[‖]	2×10^{11}	Ovarian cancer



Parameter Fits for Viral Immunotherapy

Parameter	Description	Mock	Ad5D24	Ad5D24+GMCSF
r	Uninfected tumor cell growth rate	0.131	0.43	0.18
λ_U	T cell contact rate, uninfected	-	1.07	0.7
λ_I	T cell contact rate, infected	-	0.27	0.4
β	Viral infectious rate	-	10^{-7}	1.08×10^{-5}
μ_U	dendrite activation from uninfected cells	-	0.59	1
μ_I	dendrite activation from infected cells	-	1	$1.1 \times \mu_U$
κ	T cell killing rate	-	0	7×10^{-5}
δ_T	T cell decay rate	-	0.35	0.35
δ_D	Dendritic cell death rate	-	0.35	0.35
ρ	T cell activation rate by dendritic cells	-	1	1
u_{0D}	Dendritic concentration	-	0	0
u_{0V}	Adenovirus concentration	-	10^9	10^9
α	adenovirus burst size	-	3500	3500
δ_I	Infected lysis	-	1	1
δ_V	Viral decay rate	-	2.3	2.3

Parameter Fits for Viral Immunotherapy

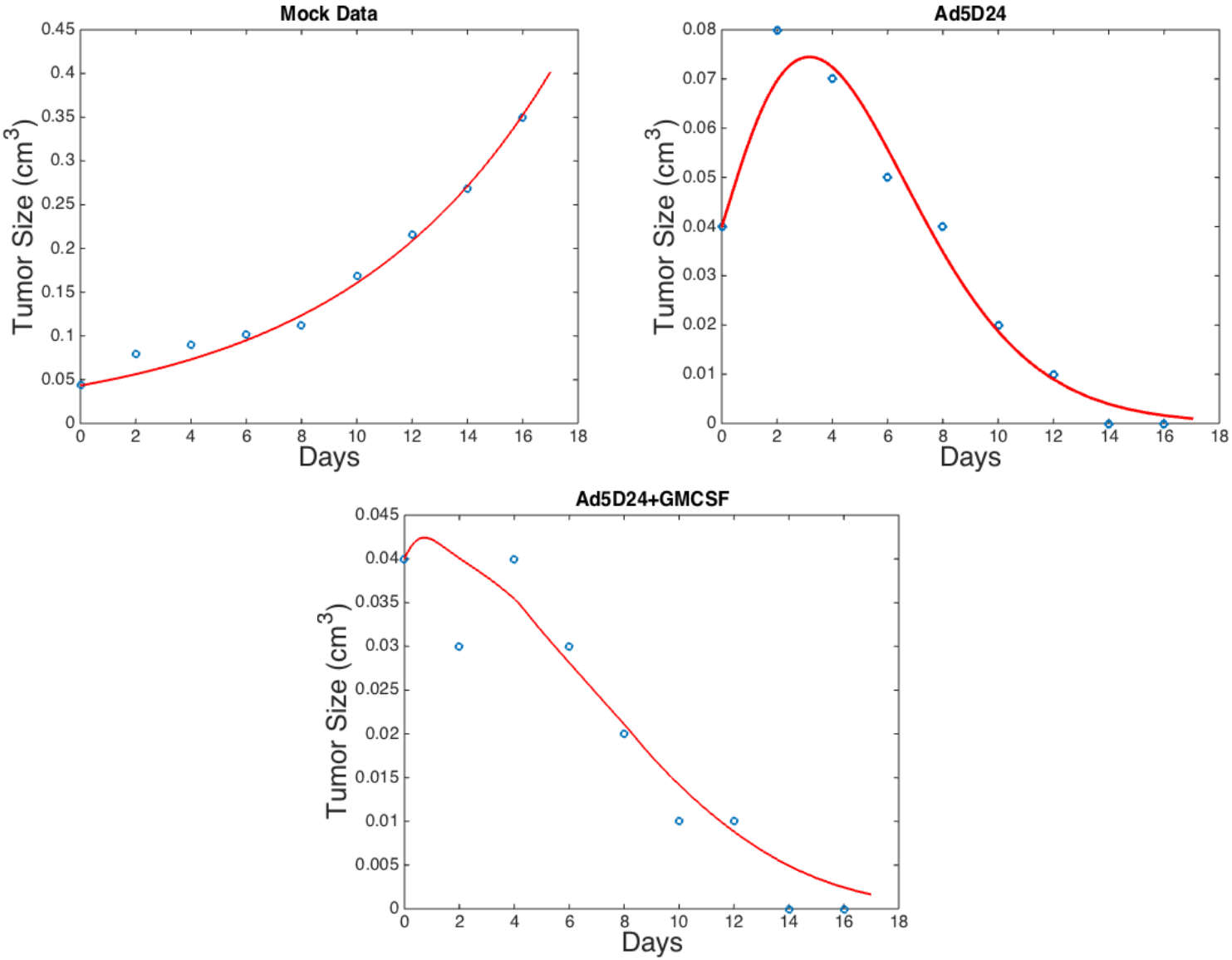
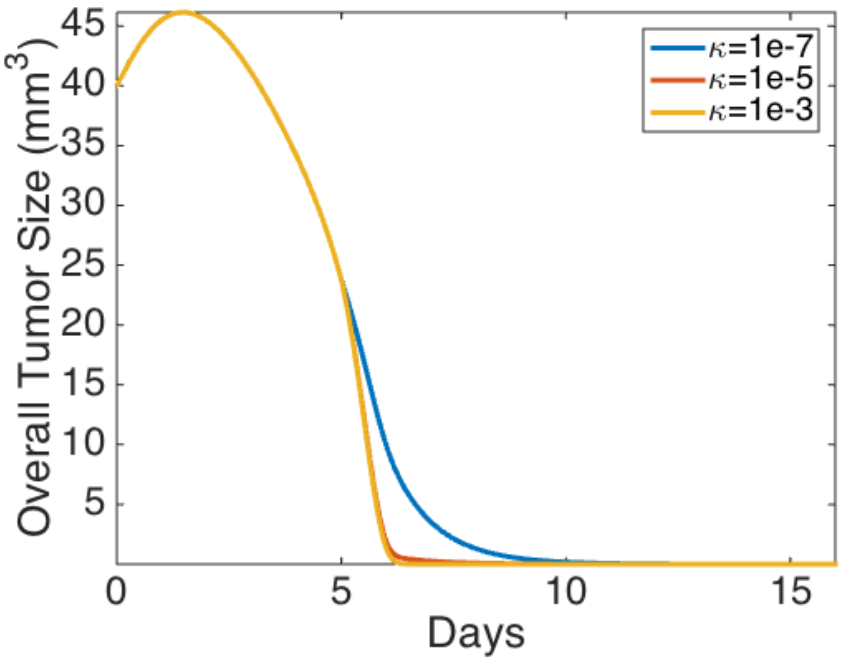


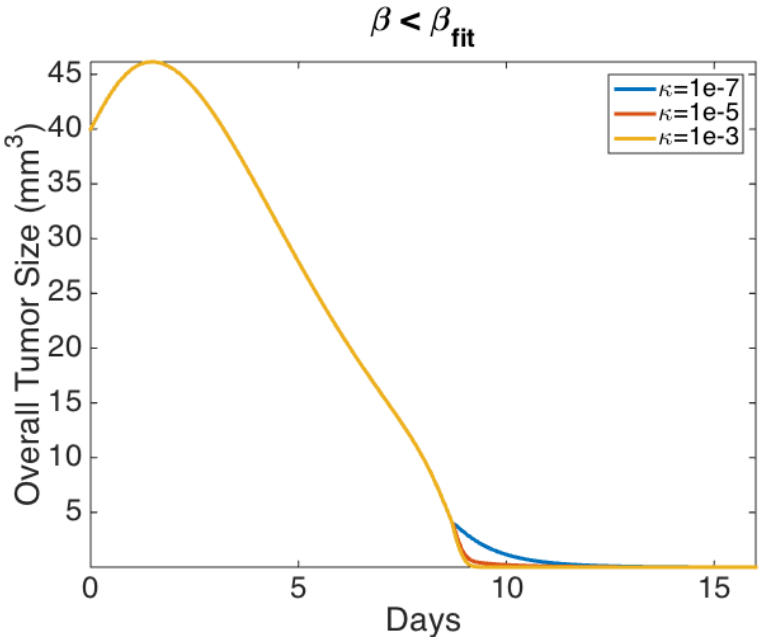
Figure: Parameter fits to adenovirus data **cerullo2010oncolytic**

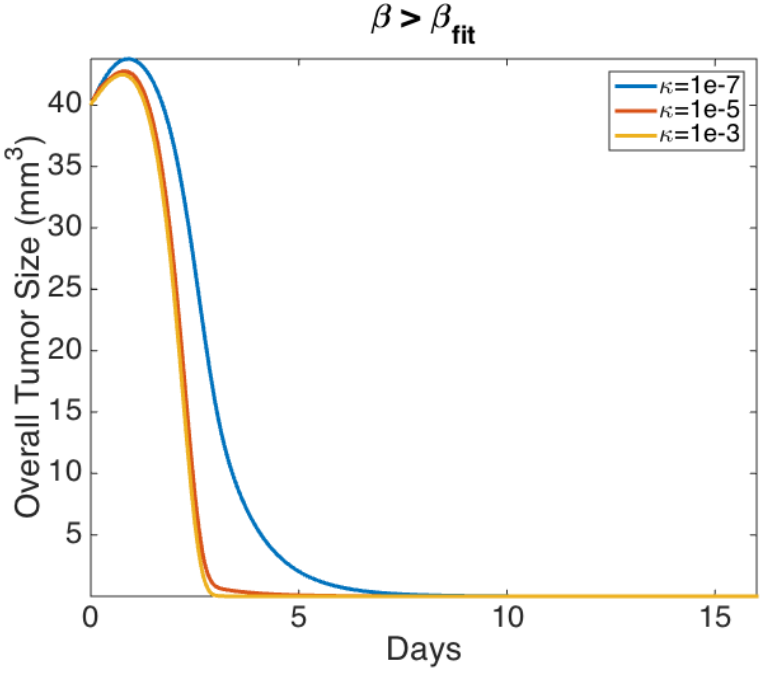

How are the analysis coming?
Almost ready
www.biocomicals.com

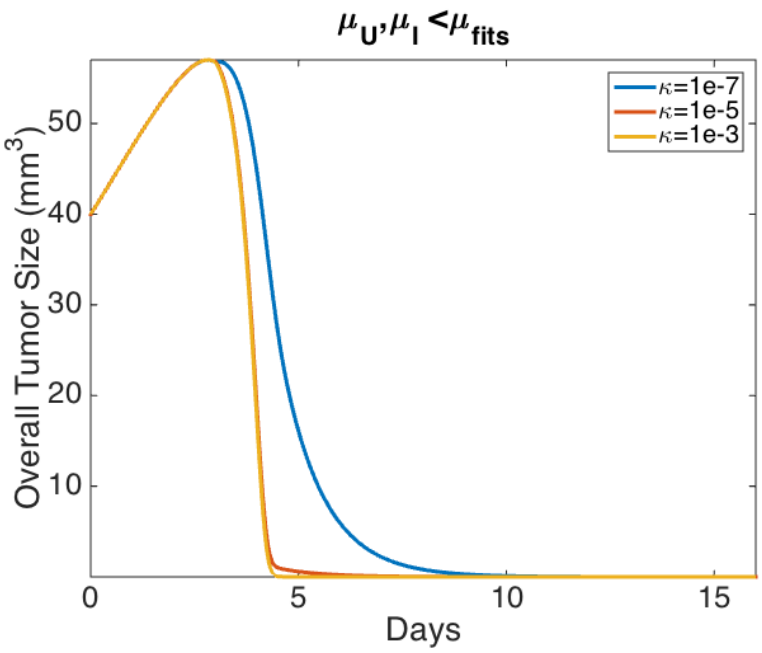
Viral Immunotherapy

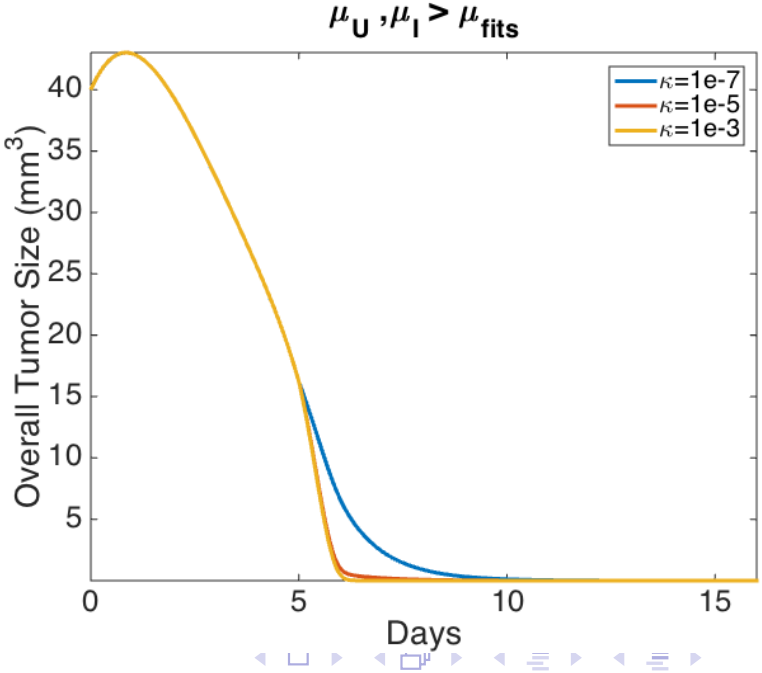


Viral Immunotherapy

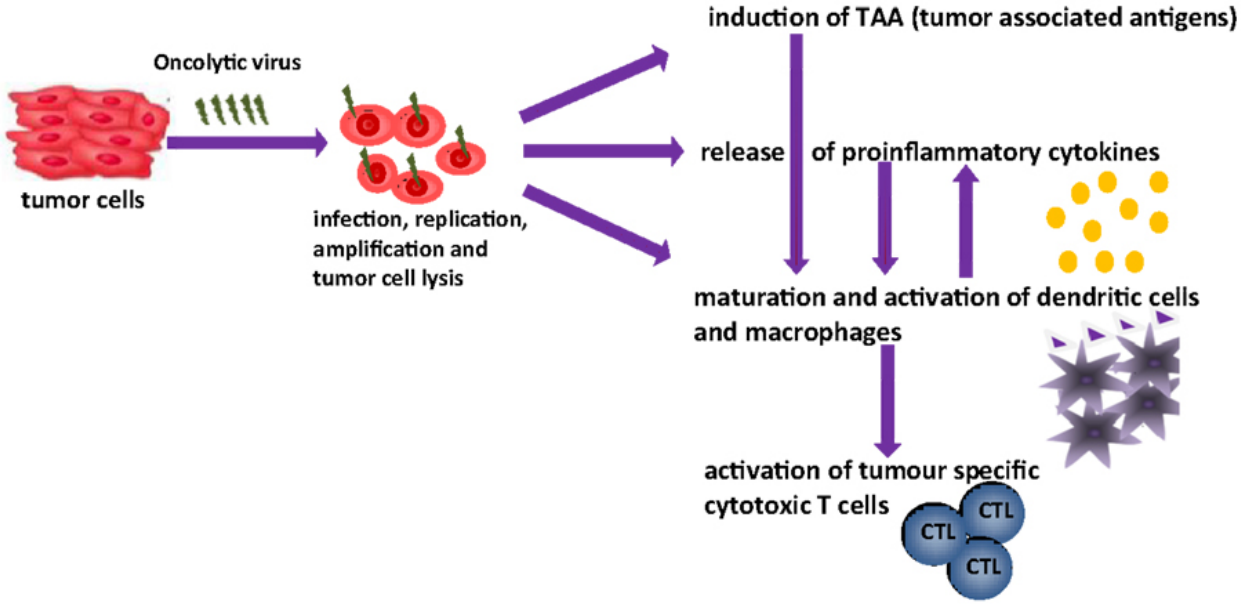




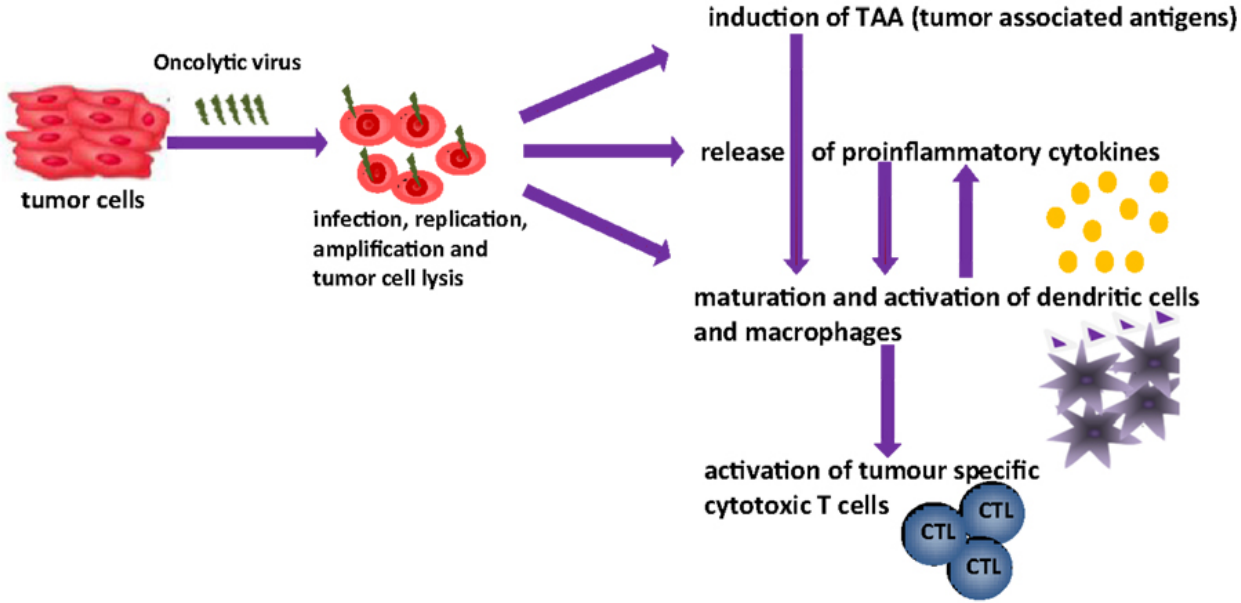


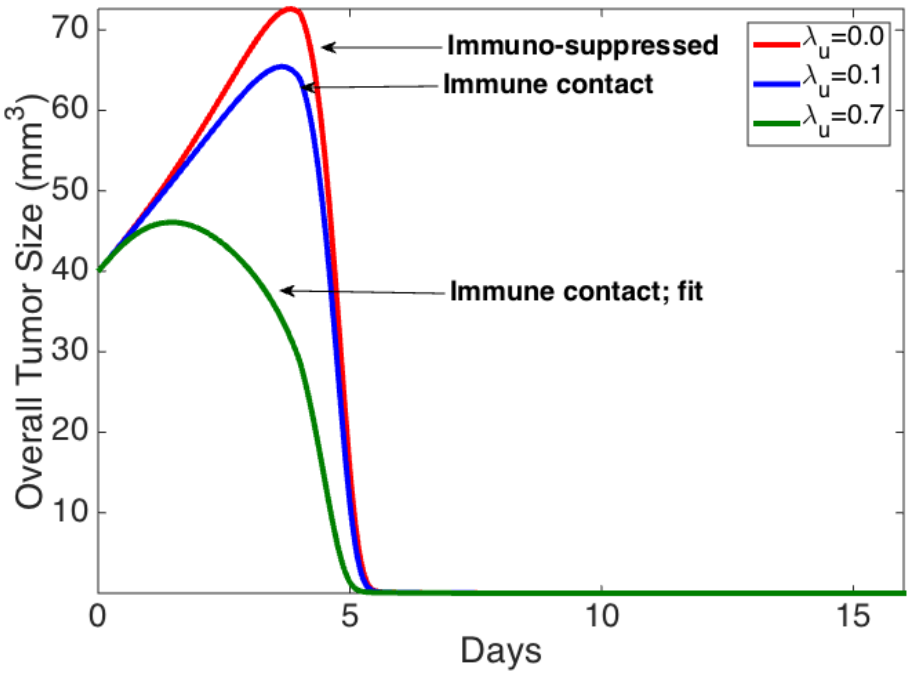


Oncolytic Viral Immunostimulation

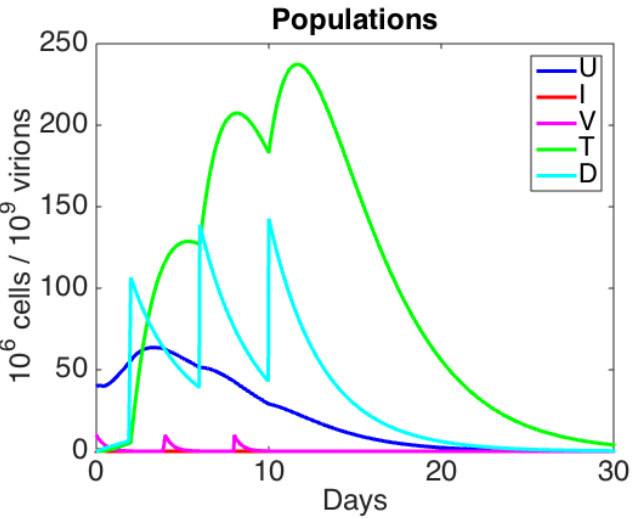


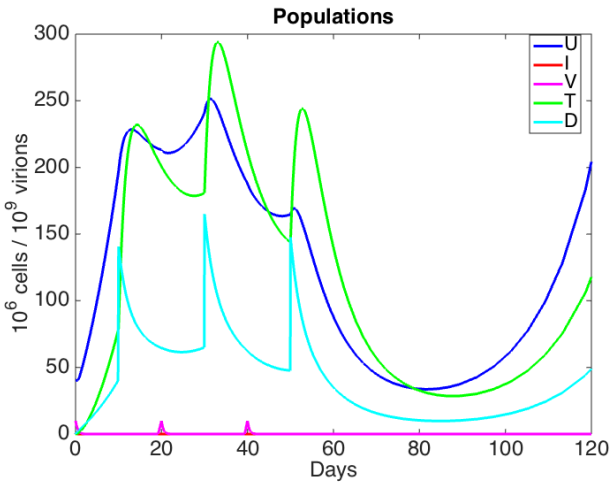
Oncolytic Viral Immunostimulation

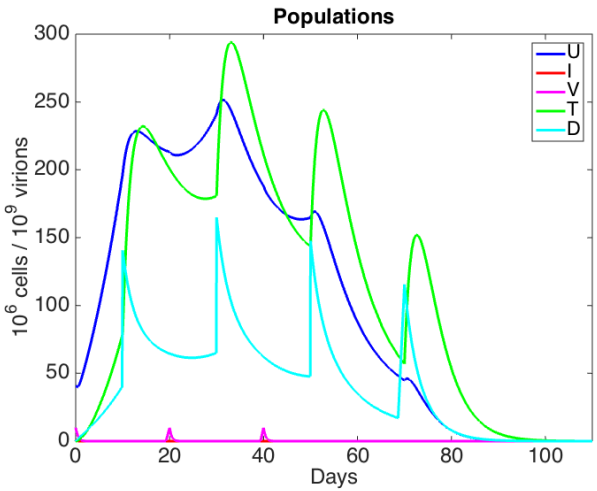




Viral and Dendritic Combination







Model Conclusions

- Increased immuno-stimulation leads to decreased tumor size; prolonged longevity
- Better viral efficacy leads to decrease in tumor size
- The initial size changes of the tumor can depend on dendrite activation rates
- Keeping dense dosage time reduces relapse
- Dense dosage time initially will reduced tumor load; then dose as needed

Future Work

- Immune abundance through numerical analysis
- Match with MTD (Maximum Tolerated Dose)
- Match with human data

"The day may come when the availability of anticancer treatments will include not only chemicals, immune cells, and monoclonal antibodies, but also biologicals such as oncolytic viruses"

lawler2015oncolytic

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Questions

Merci Beaucoup!