Modelling dynamics of anti-cancer virotherapy and immunotherapy

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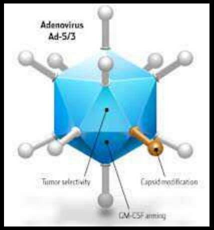
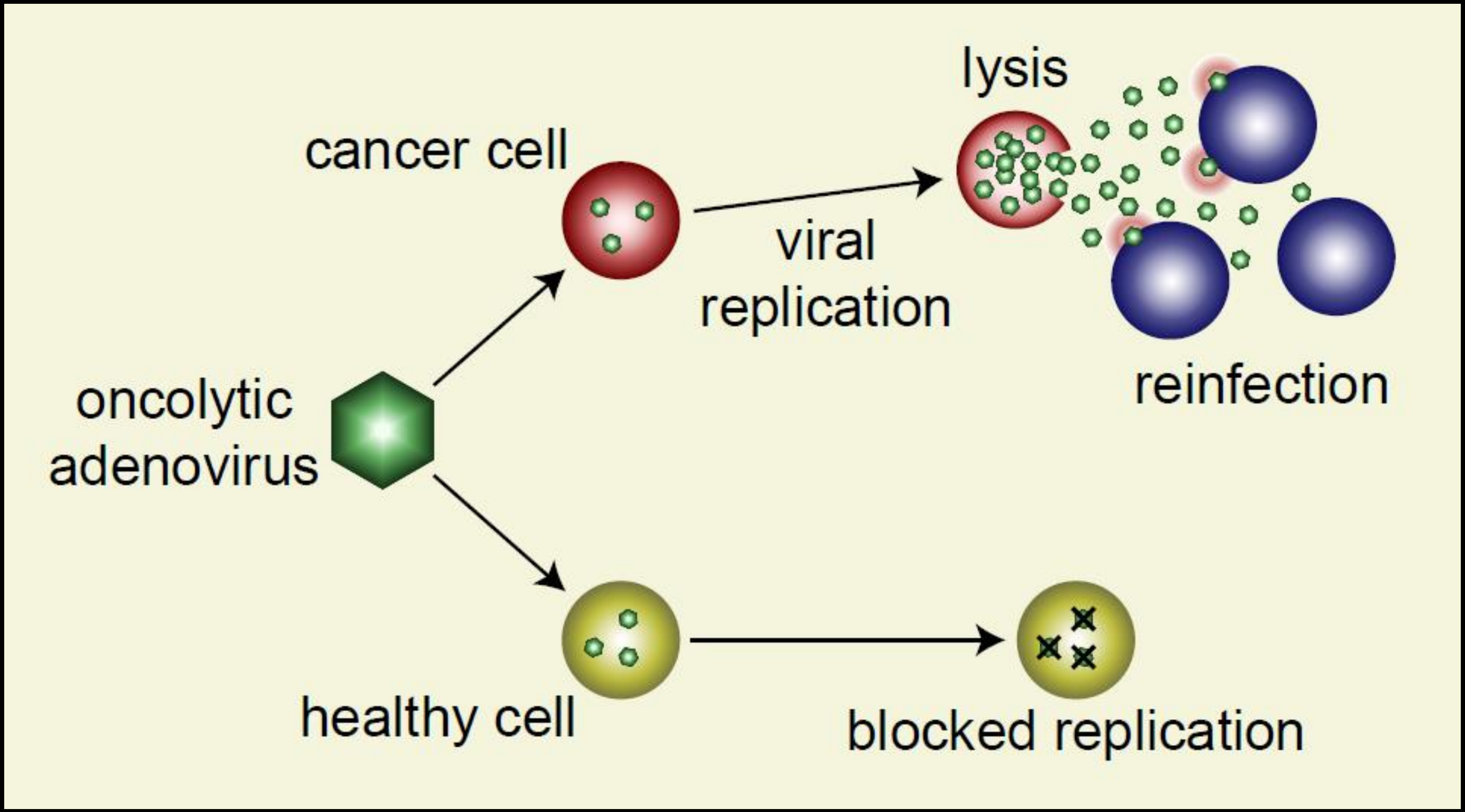
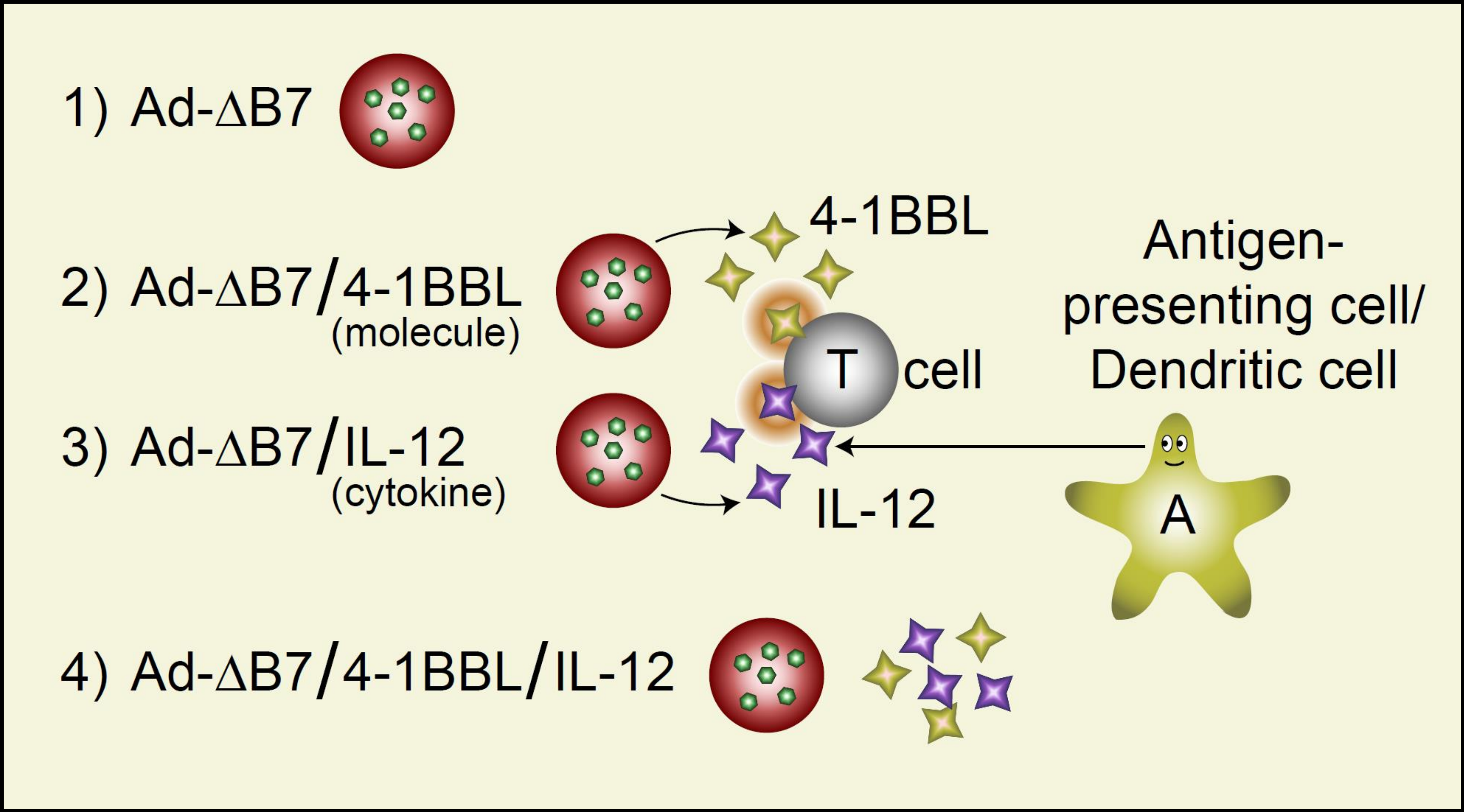


Oncolytic virotherapy: Genetically-engineered cancer killers

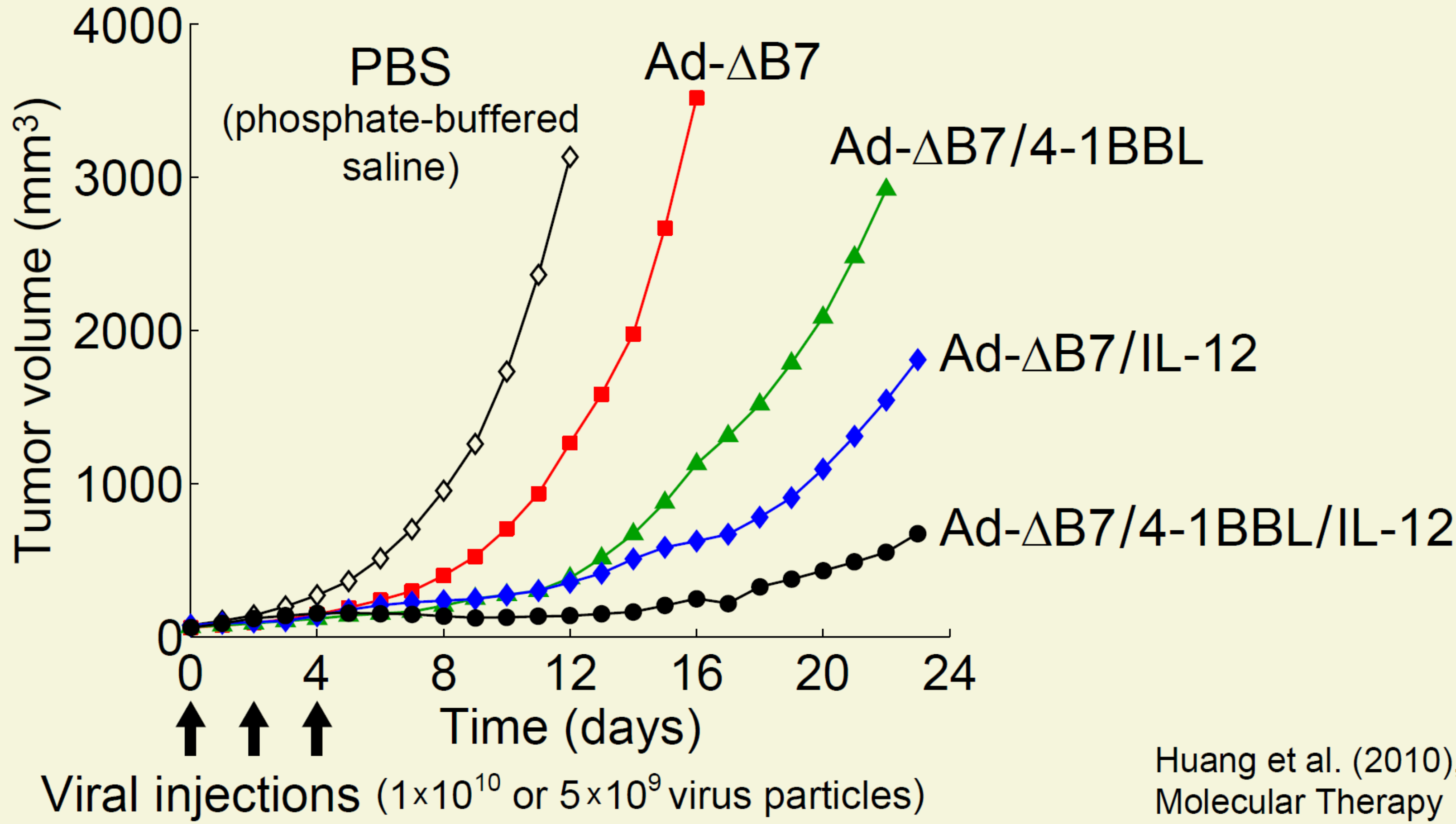


Experimental viruses – plenty of mouse data

(Yun Lab, Hanyang University, Seoul, Korea)

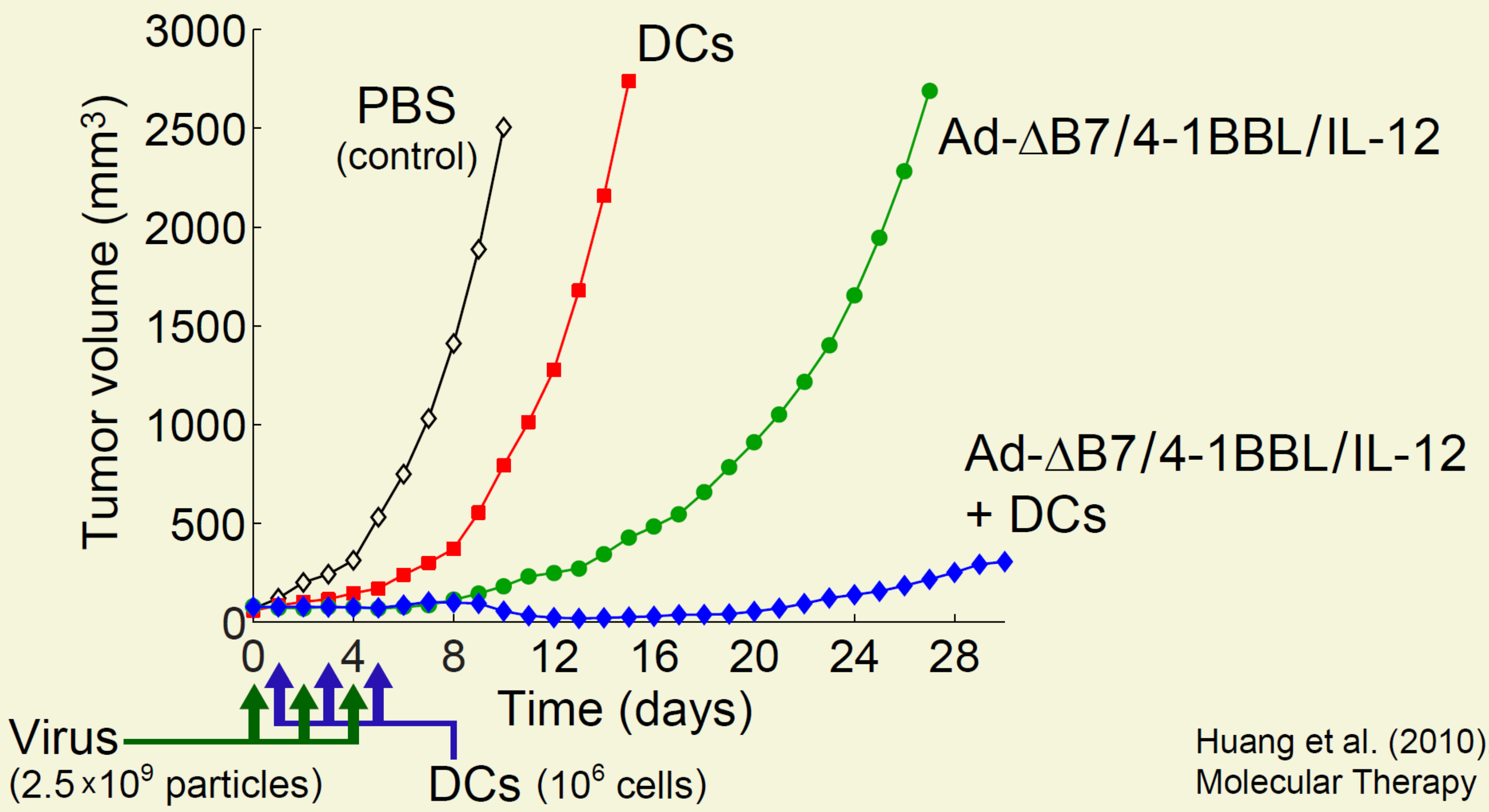


Experimental data set 1: Virus only



Huang et al. (2010), Molecular Therapy

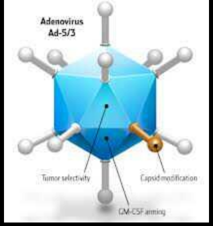
Experimental data set 2: Virus + Dendritic Cell (DC) vaccine



Huang et al. (2010), Molecular Therapy

Fitting model to data

- Yun Lab measures tumor under hierarchically stronger treatments
- Can build models toward more complex dynamics
- Keep it simple!
  We have to fit the model to data

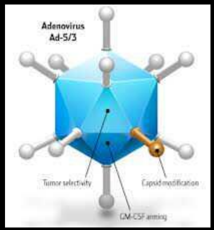


4-1BB ligand and its many functions

- Co-stimulatory molecule on antigen-presenting cells (APCs): dendritic cells (DCs), macrophages, B cells
- Promotes Th1 (killer cell pathway) differentiation
- Boosts killer T cell cytotoxicity
- Boosts T cell proliferation and cytokine secretion
- Decreases T cell apoptosis

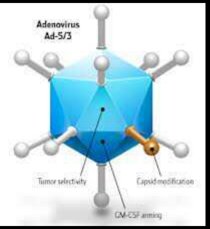
- <u>Keep it simple</u> for the model

  Increases killer T cell activation & cytotoxicity

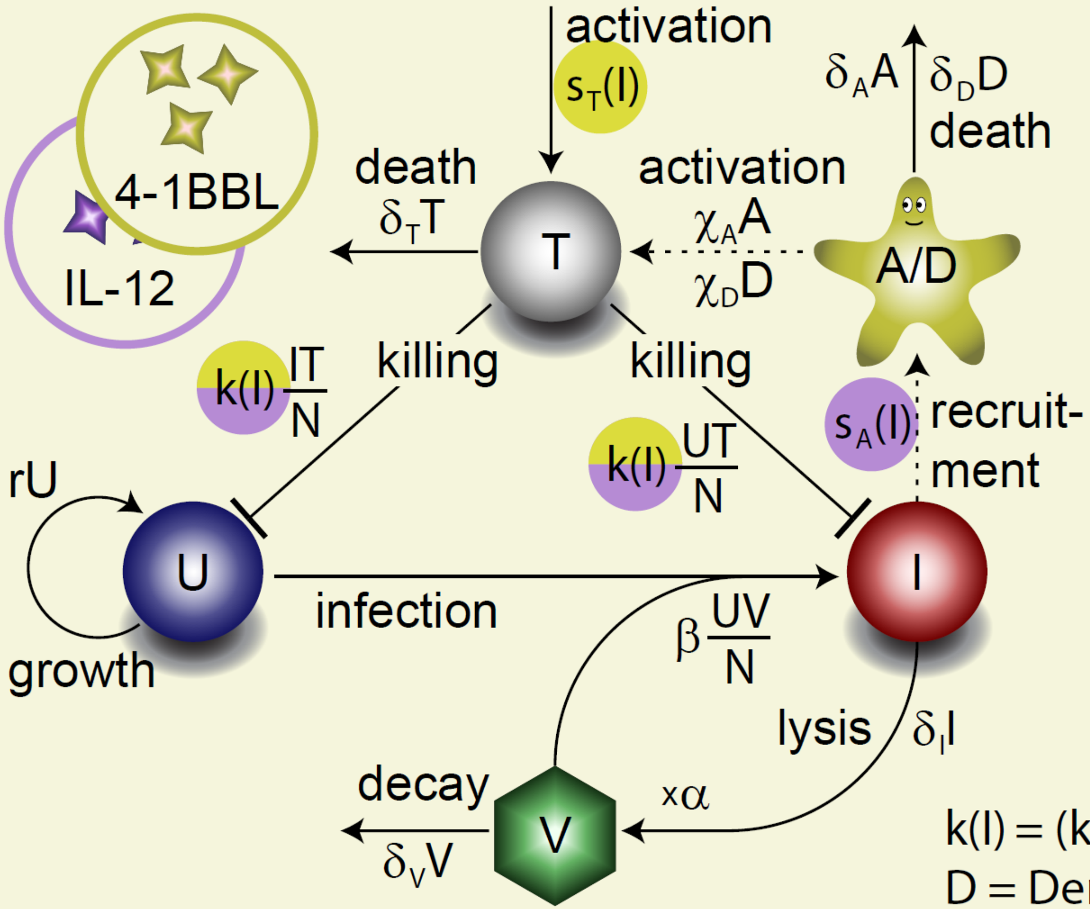


IL-12 cytokine and its many functions

- Promotes Th1 (killer cell pathway) differentiation
- Boosts natural killer and killer T cell cytotoxicity
- Boosts natural killer and killer T cell cytokine activity
- Recruits antigen-presenting cells (APCs), which stimulate cytotoxic T cells
- <u>Keep it simple</u> for the model
  - Increases APC recruitment and T cell cytotoxicity



Full model: DC vaccines + virus



$$N = U + I + T$$

$$\frac{dU}{dt} = rU - \beta\frac{UV}{N} - k(I)\frac{UT}{N}$$

$$\frac{dI}{dt} = \beta\frac{UV}{N} - \delta_I I - k(I)\frac{IT}{N}$$

$$\frac{dV}{dt} = \alpha\delta_I I - \delta_V V - \beta\frac{UV}{N}$$

$$\frac{dT}{dt} = s_T(I) + \chi_A A + \chi_D D - \delta_T T$$

$$\frac{dA}{dt} = s_A(I) - \delta_A A$$

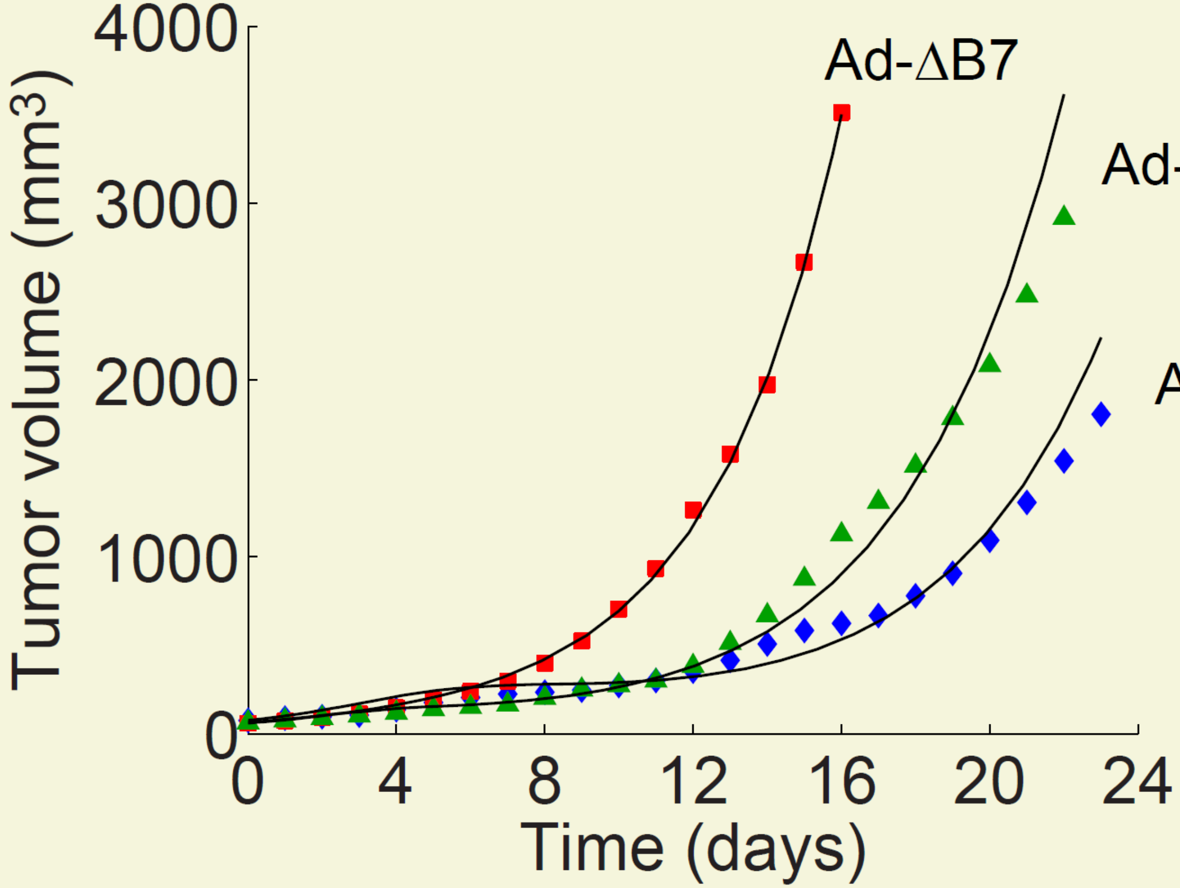
$$\frac{dD}{dt} = -\delta_D D$$

$$s_T(I) = c_4 I$$
$$s_A(I) = c_{12} I$$

$k(I) = (k_0 + c_k)I$, $\quad (k_0 > 0$ when $D > 0)$

D = Dendritic cells from DC vaccine

Some data and model fits



Data from
Huang et al. (2010),
Molecular Therapy

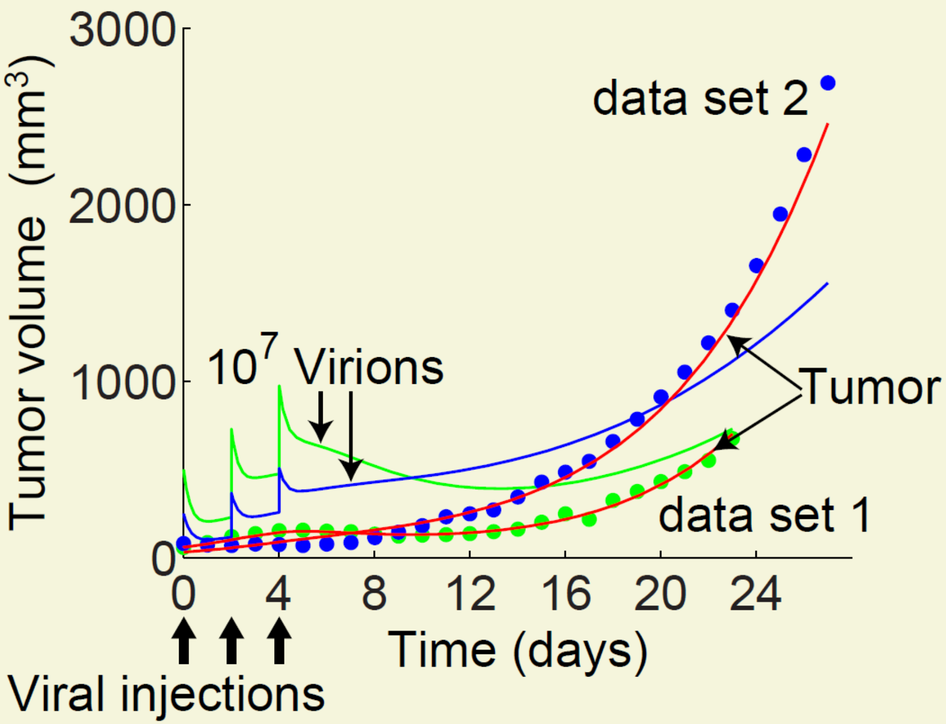
Parameters for four data sets

(Estimated sequentially and hierarchically)

Parameter		PBS	Ad	Ad/4-1BBL	Ad/IL-12
r	Tumor growth	0.31	0.31	0.31	0.31
β	Infect rate	--	0.001	0.001	0.001
c_k	Kill const.	--	--	1.6×10^{-7}	7.9×10^{-7}
c_4	T cell const.	--	--	1.8	--
c_{12}	APC const.	--	--	--	0.94
k_0	Kill const w/DC	--	--	--	--
χ_D	T cell-DC rate	--	--	--	--
a	Viral prod.	--	3000	3000	3000
d_I	Infected lysis	--	1	1	1
d_V	Viral decay	--	2.3	2.3	2.3
d_T	T cell death	--	--	0.35	0.35
d_A	APC death	--	--	--	0.35
χ_A	T cell-APC rate	--	--	--	1

1) Ad/4-1BBL/IL-12 data & fit simultaneous fit of 2 data sets

Data & simulations



Model

Uninfected $\frac{dU}{dt} = rU - \beta\frac{UV}{N} - k(I)\frac{UT}{N}$

Infected $\frac{dI}{dt} = \beta\frac{UV}{N} - \delta_I I - k(I)\frac{IT}{N}$

Virus $\frac{dV}{dt} = \alpha\delta_I I - \delta_V V - \beta\frac{UV}{N}$

T cells $\frac{dT}{dt} = s_T(I) + A - \delta_T T$ $\quad k(I) = c_k I$

$s_T(I) = c_4 I$

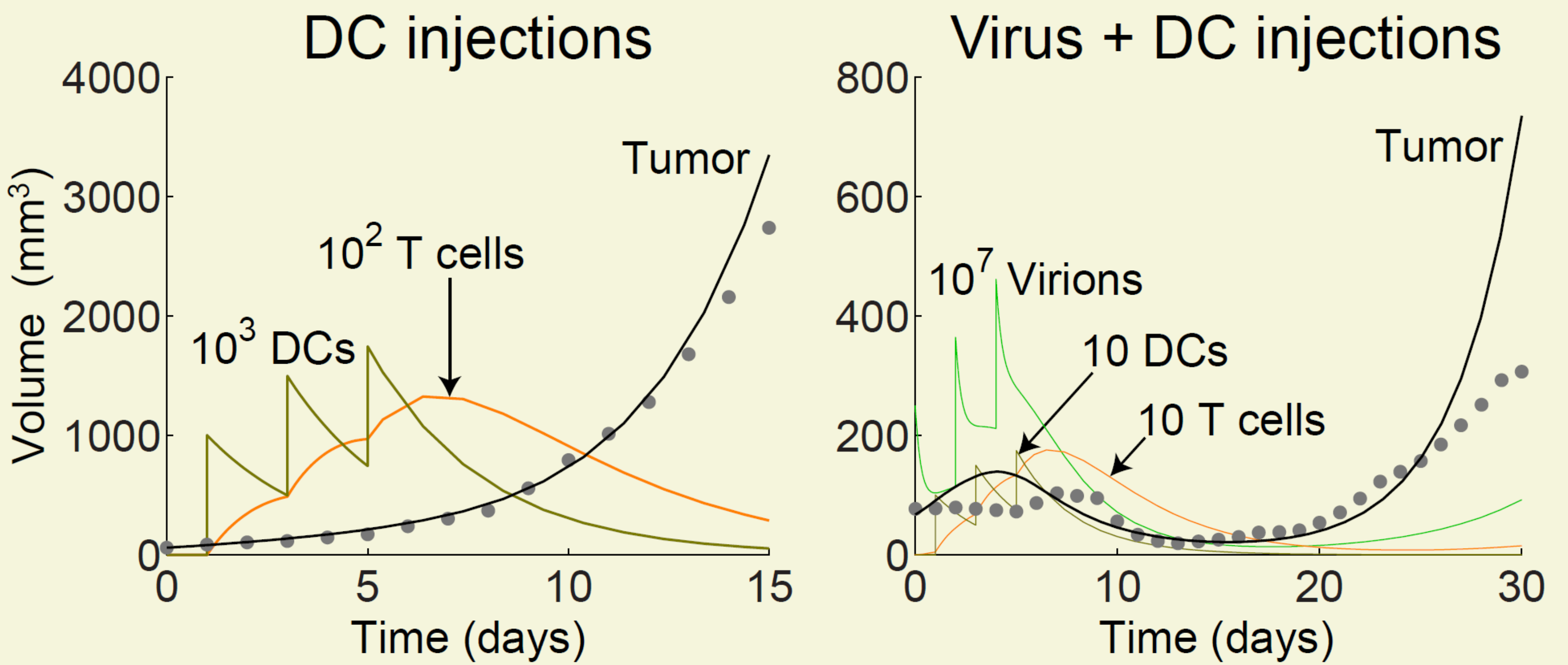
APCs $\frac{dA}{dt} = s_A(I) - \delta_A A$ $\quad s_A(I) = c_{12} I$

Parameter estimates

Previous: Same as before

Current fit: Kill const $c_k = 1.06$
T cell supply const $c_4 = 0.92$
APC supply const $c_{12} = 0.06$

2) DC vaccines + virus data & fit simultaneous fit of 2 data sets



Parameter estimates (current fit)

T cell kill constant $k_0 = 2$ T cell activation by DCs $\chi_D = 4.9$

Parameters for six data sets
(Estimated sequentially and hierarchically)

Parameter		PBS	Ad	Ad/4B	Ad/IL	Ad/4B /IL	Ad/4B/IL + DCs
r	Tumor growth	0.31	0.31	0.31	0.31	0.31	0.31
β	Infect rate	--	0.001	0.001	0.001	0.001	0.001
c_k	Kill const.	--	--	1.6×10^{-7}	7.9×10^{-7}	1.06×10^{-6}	1.06×10^{-6}
c_4	T cell const.	--	--	1.8	--	0.92	0.92
c_{12}	APC const.	--	--	--	0.94	0.06	0.06
k_0	Kill const w/DC	--	--	--	--	--	2.0
χ_D	T cell-DC rate	--	--	--	--	--	4.9
a	Viral prod.	--	3000	3000	3000	3000	3000
d_I	Infected lysis	--	1	1	1	1	1
d_V	Viral decay	--	2.3	2.3	2.3	2.3	2.3
d_T	T cell death	--	--	0.35	0.35	0.35	0.35
d_A	APC death	--	--	--	0.35	0.35	0.35
χ_A	T cell-APC rate	--	--	--	1	1	1

Different combinations of 3 Virus & 3 DC doses

- Experiments considered alternating viruses and DCs (6 doses): V – D – V – D –V – D
- We considered all 20 combinations of 3 virus doses and 3 DC doses

Combinations of Virus-DC doses

Treatment strategy (rank out of 20)	**Tumour vol (mm^3) at 30 days**
1) **V – V – V – D – D – D**	2.8×10^{-7}
2) V – V – D – D – D – V	60.4
4) D – D – D – V – V – V	102.9
11) D – V – D – V – D – V	331.3
15) <u>V – D – V – D – V – D</u>	544.4
20) D – V – V – V – D – D	1,099.0

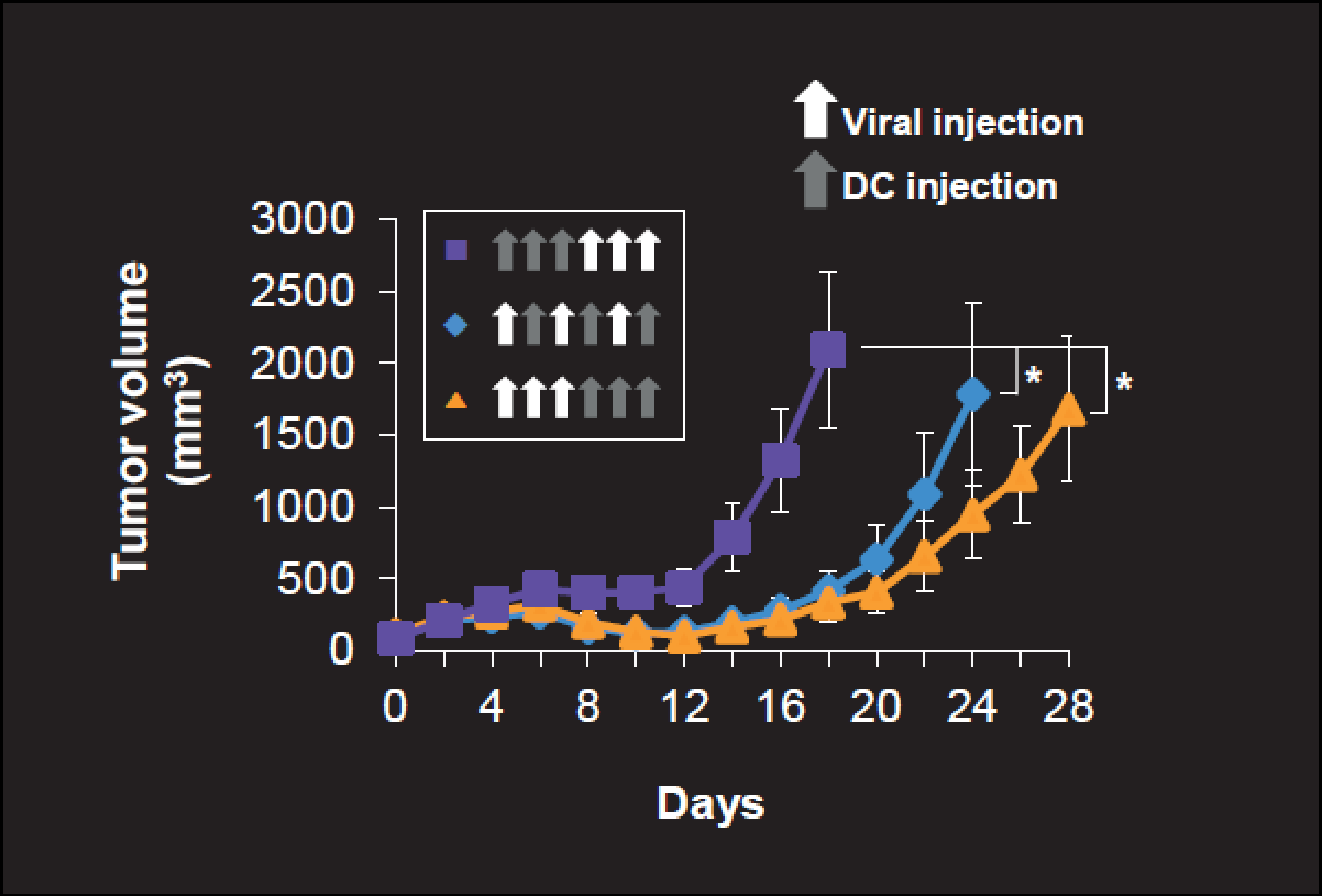
Virus – DC synergy or interference?

- Overall, it seems better to separate Virus doses and DC doses, NOT in an alternating pattern
- It seems better to give Virus first (corroborated by Yun Lab)

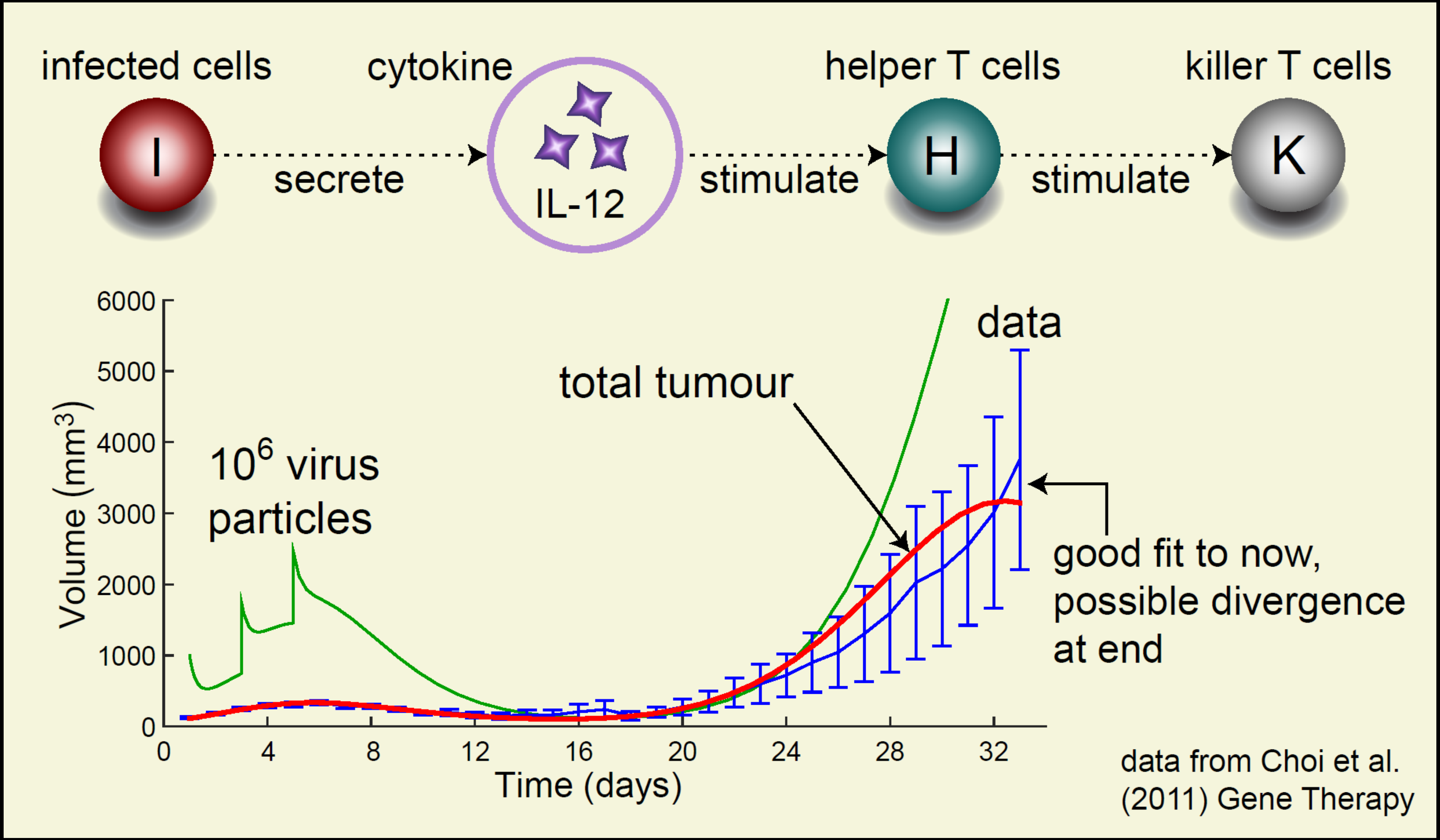
<u>Explanation (maybe)</u>:

- DC-induced immune response eliminates virus
- But virus enhances immune response.

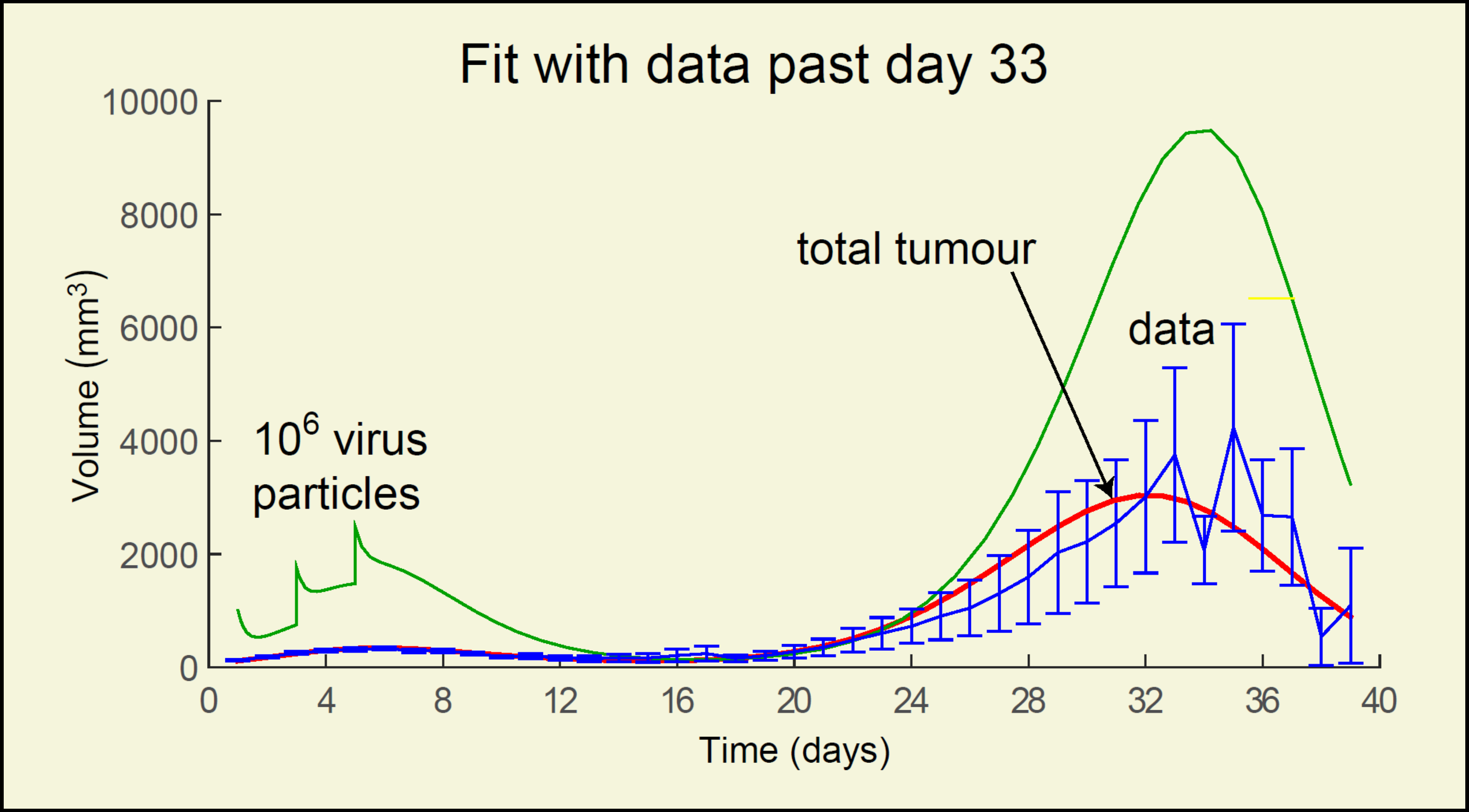
Yun Lab Data: Virus-DC combinations



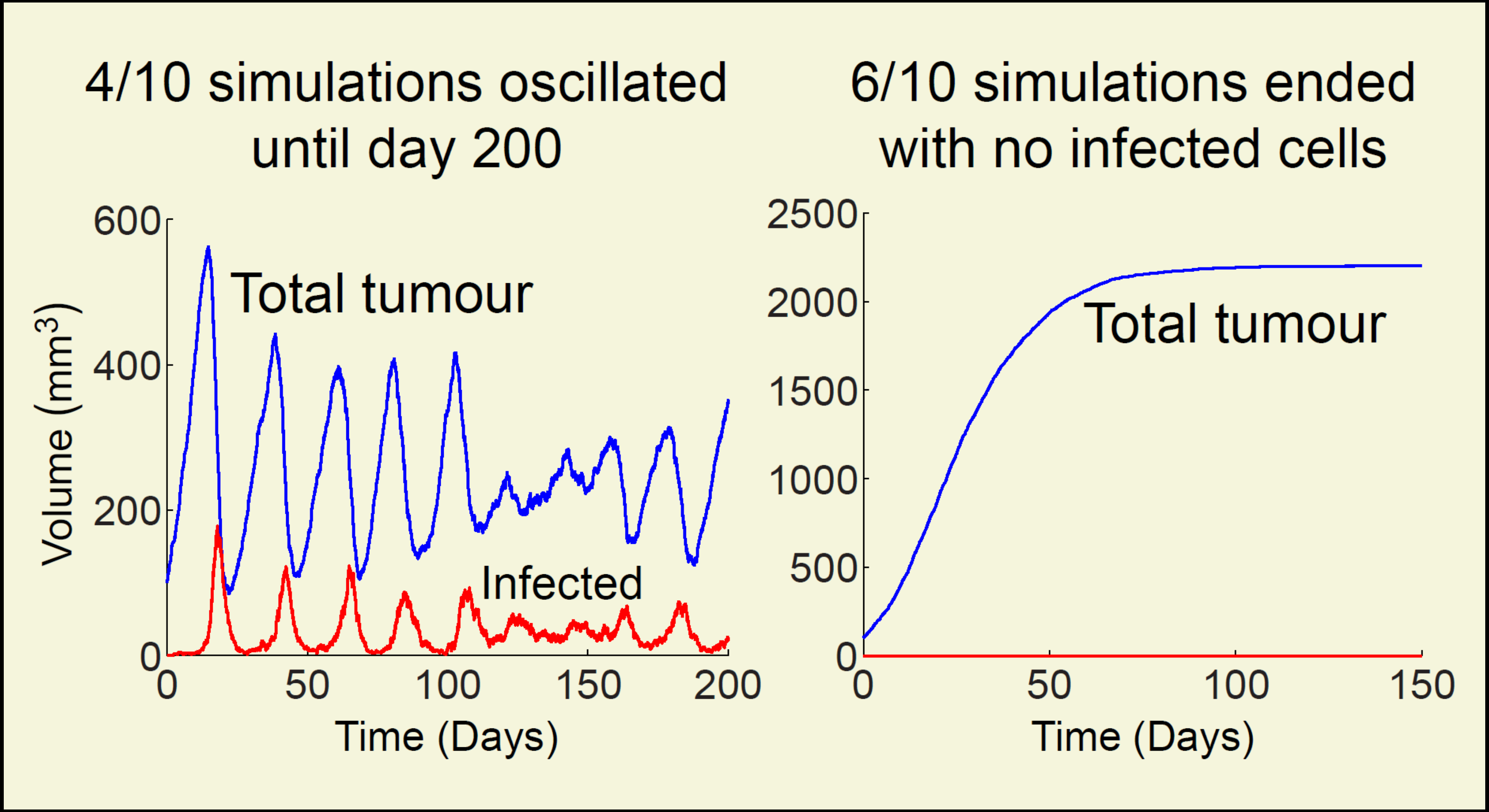
Adrianne Jenner's honours project: Another data set, another model, and fit



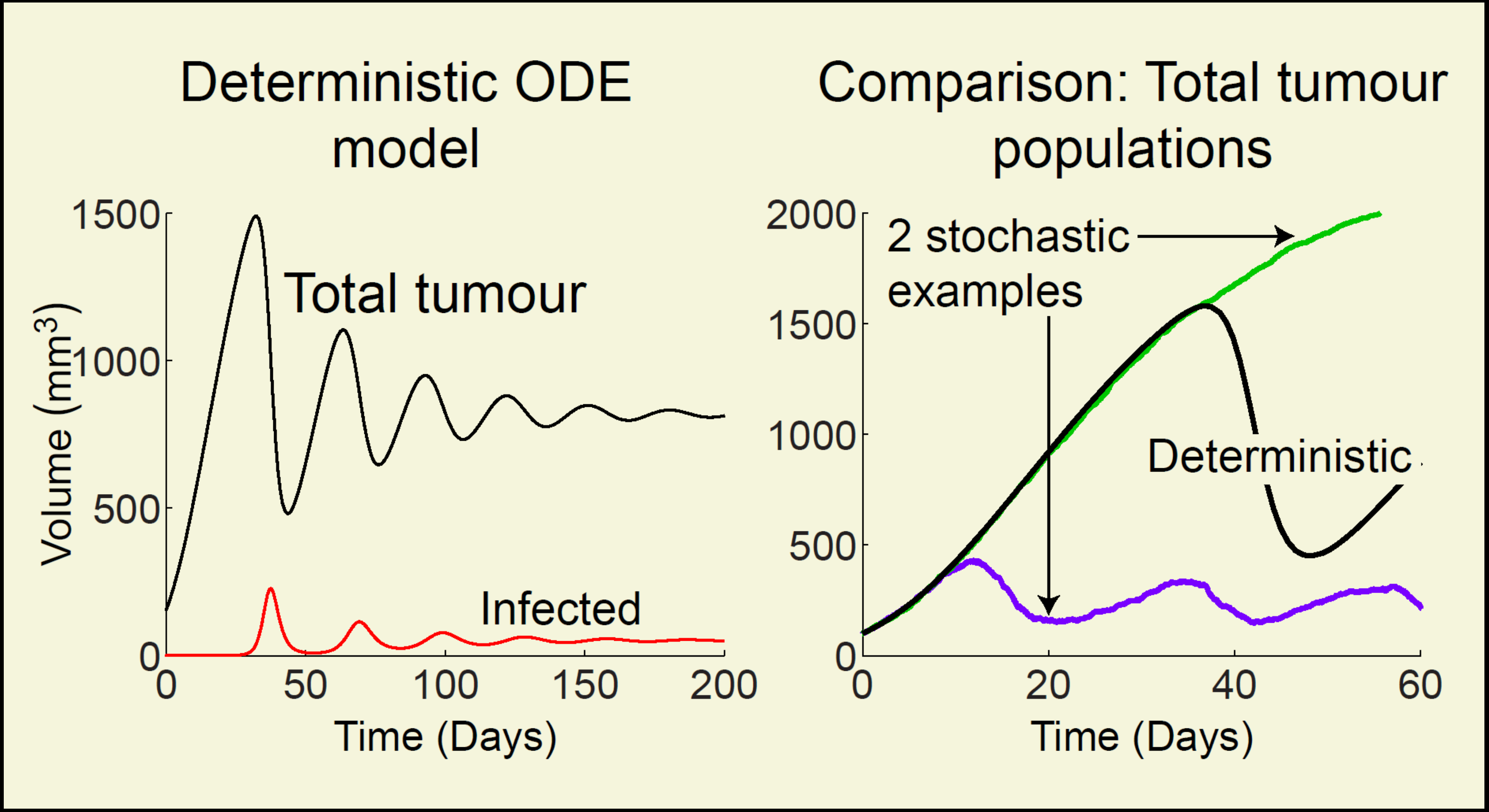
Adrianne Jenner's honours project with additional data from Yun Lab



Adrianne Jenner's honours project: Stochastic oncolytic virus model



Adrianne Jenner's honours project: Deterministic & stochastic comparison



Thank you

The Organizing Committee:
Urszula, Zuzanna, Monika, and Mirek

Collaborators

Adrianne Jenner (U of Sydney); Arum Yoon, Chae-Ok Yun (Hanyang U), Il-Kyu Choi (Harvard Medical School); Joanna Wares (U of Richmond); Joseph Crivelli (Cornell Medical College); Jana Gevertz (The College of New Jersey)