Integrated mathematical models to personalize cancer radiotherapy

Heiko Enderling, Ph.D.

Quantitative *Personalized* Medicine

Department of Integrated Mathematical Oncology
H. Lee Moffitt Cancer Center & Research Institute
Tampa, Florida, USA

heiko.enderling@moffitt.org
http://labpages.moffitt.org/enderlingh

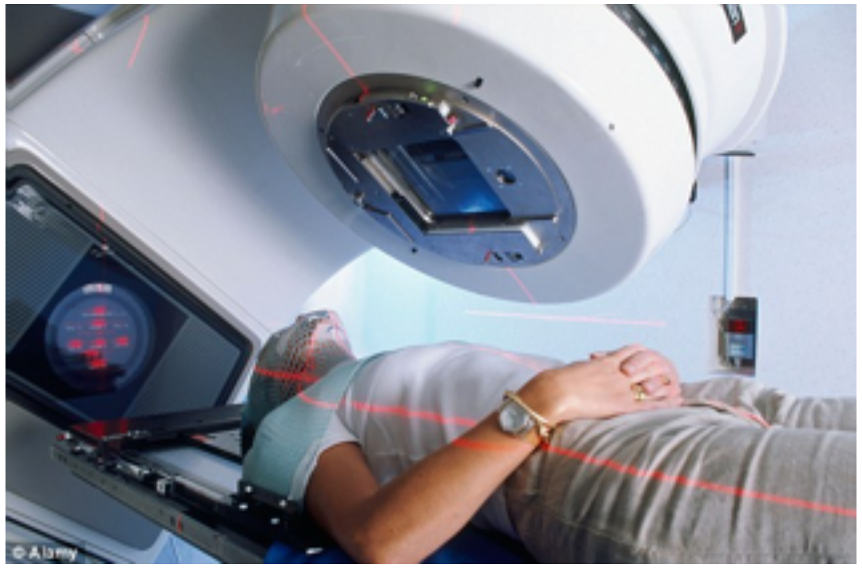
#EnderlingLab

DeBartolo Family
PERSONALIZED MEDICINE INSTITUTE

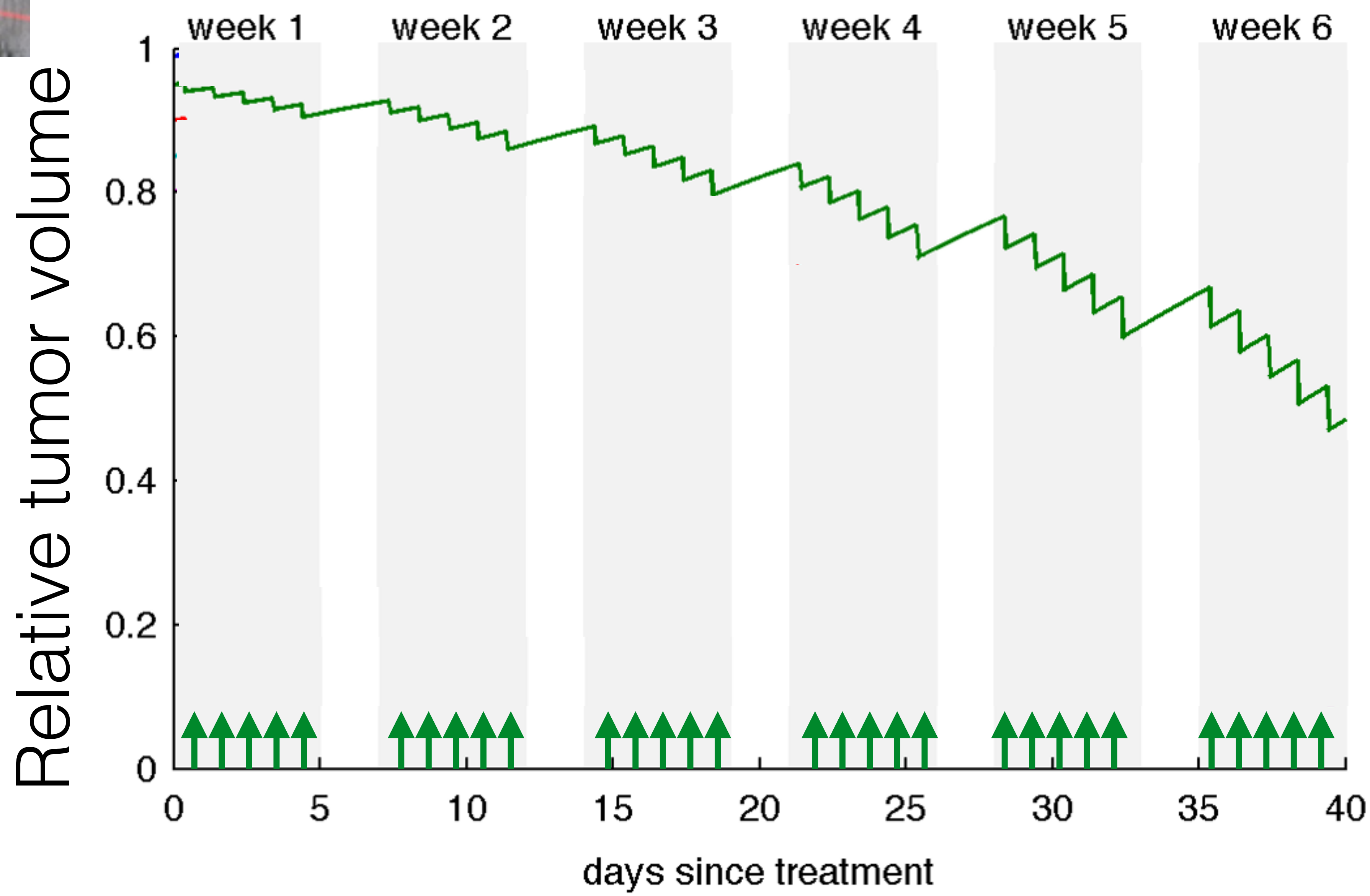
Quantitative *Personalized* Medicine

- Analyze data that is routinely collected from individual cancer patients
- Predict disease progression and response to therapy
- Personalize therapy based on individual data and dynamic model predictions
    - Treatment modalities, dose, sequencing, target

Fractionated Radiotherapy



Standard of care:
daily doses of 2Gy for 6 weeks- no weekends



Altered fractionation schedules

"standard of care"
2 Gy x 25

"hyper-fractionation"
1.2 Gy x 50

"hypo-fractionation"
5 Gy x 10

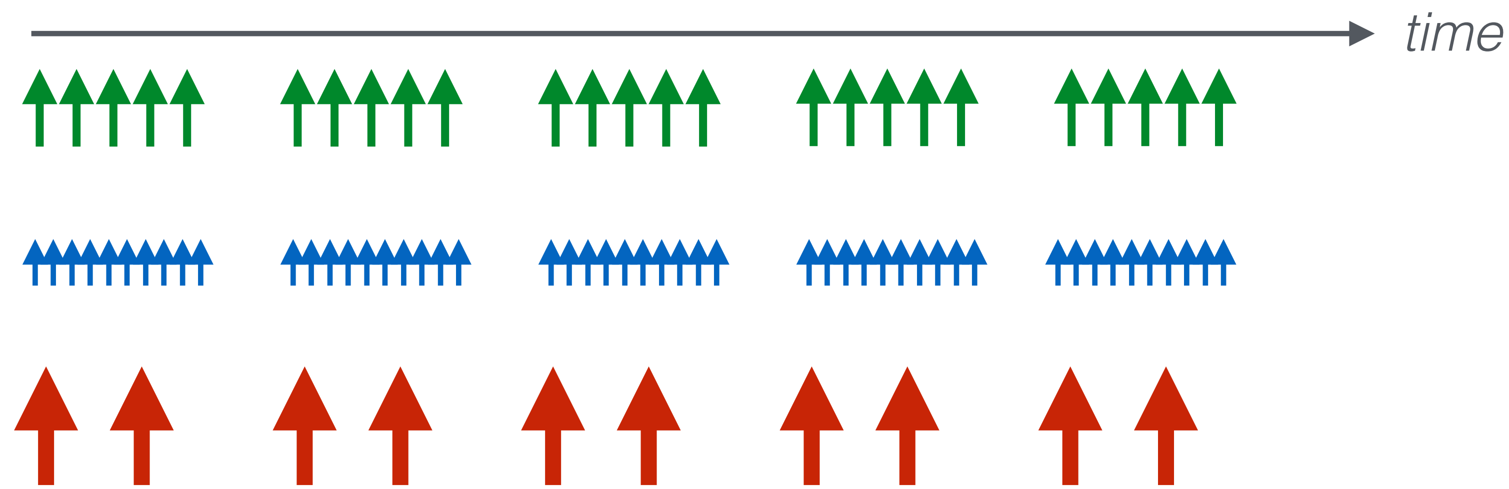


Table 1. Altered Fractionation Schedules Without Chemotherapy in Head and Neck Cancer

	Tumor Site and Type	Median Follow-up	No. of Patients	Dose/Fx (Gy)	Fx/d	Total Dose (Gy)	Tumor Response	Side Effects	Reference
Hyperfractionation (HF)	T2-T3, N0-N1 Oropharyngeal cancer	>200 weeks for living patients	356	1.15	2	80.5	5-yr LRC: 59% *v* 40% (*P* = .02)	More acute mucositis with HF	Horiot et al
				1.8-2	1	70			
	Hypopharynx, stage II of tongue base, various sites stage III- IV	14 years for living patients	1,073	1.2	2	81.6	5-yr LRC: standard fx 45%, 51% for hyperfractionation (*P* = .046) *v* 51% (*P* = .097) for accelerated fx with boost	More acute mucositis with altered fractionation	Fu et al
				1.8	1-2	72			
				1.6	2	67.2			
				2	1	70			
	Oropharynx, stage III-IV	25 months	98	1.1	2	70.4	Overall tumor response 84% *v* 64% (*P* = .02)	Earlier acute reactions with HF	Pinto et al
				2	1	66			
	Various sites, T3-T4, N0 or any T, N+	6.9 years for living patients	331	1.45	2	58	5-yr LRC: 45% *v* 37% (*P* = .01)	Increased acute mucositis with HF	Cummings et al
				2.55	1	51			

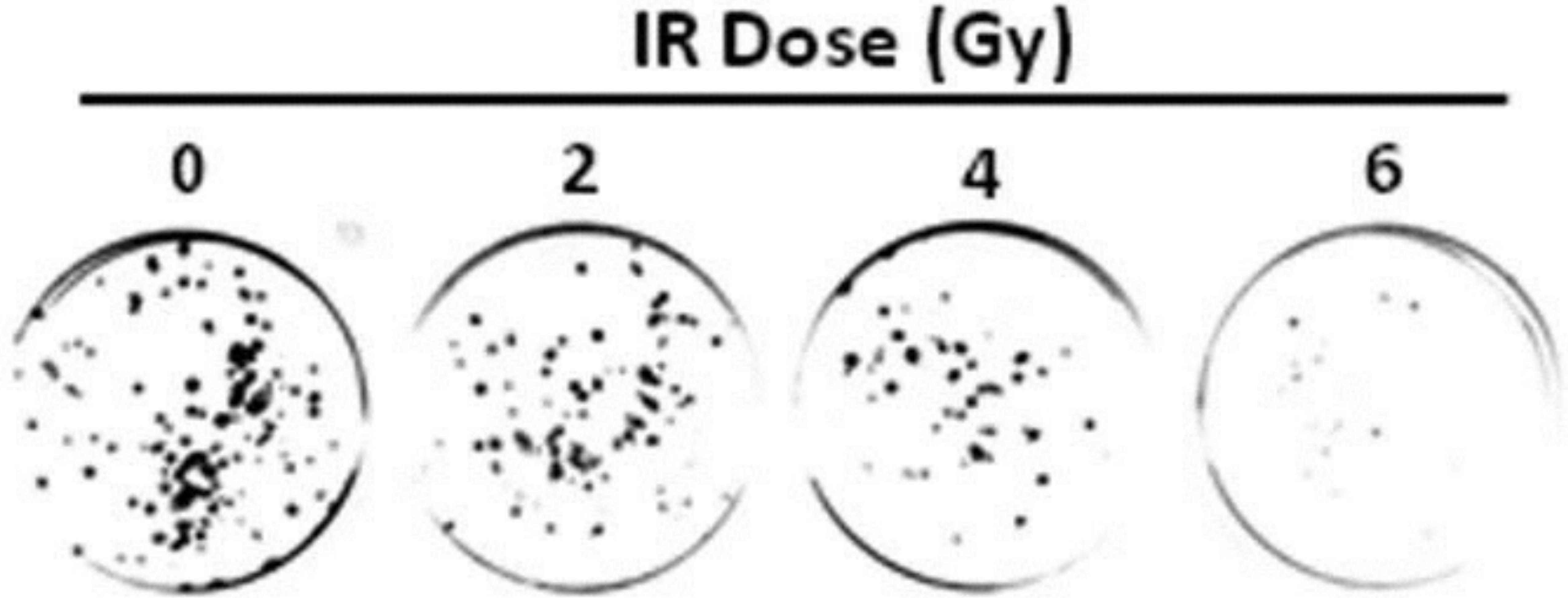
Ahmed et al.. Seminars in Oncology.

Challenge

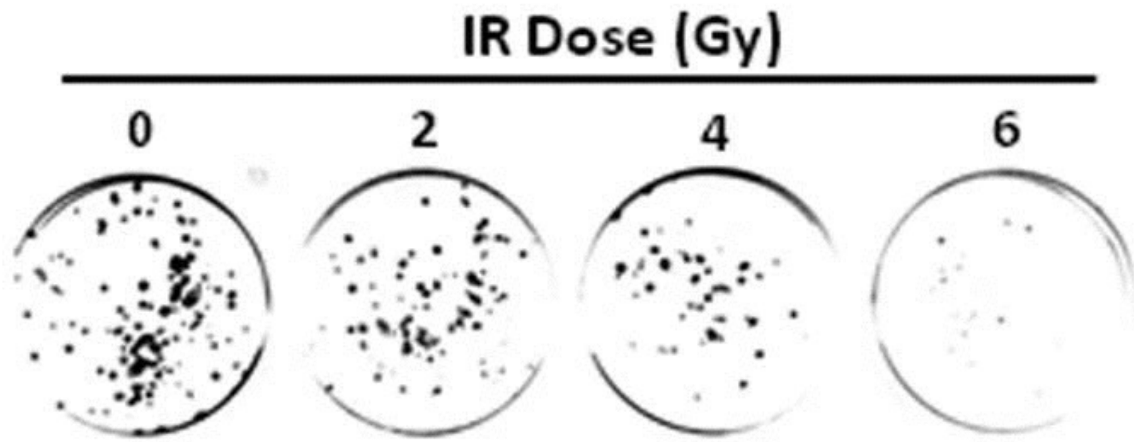
We have little understanding of how to select the most appropriate fractionation schedule for an individual patient.

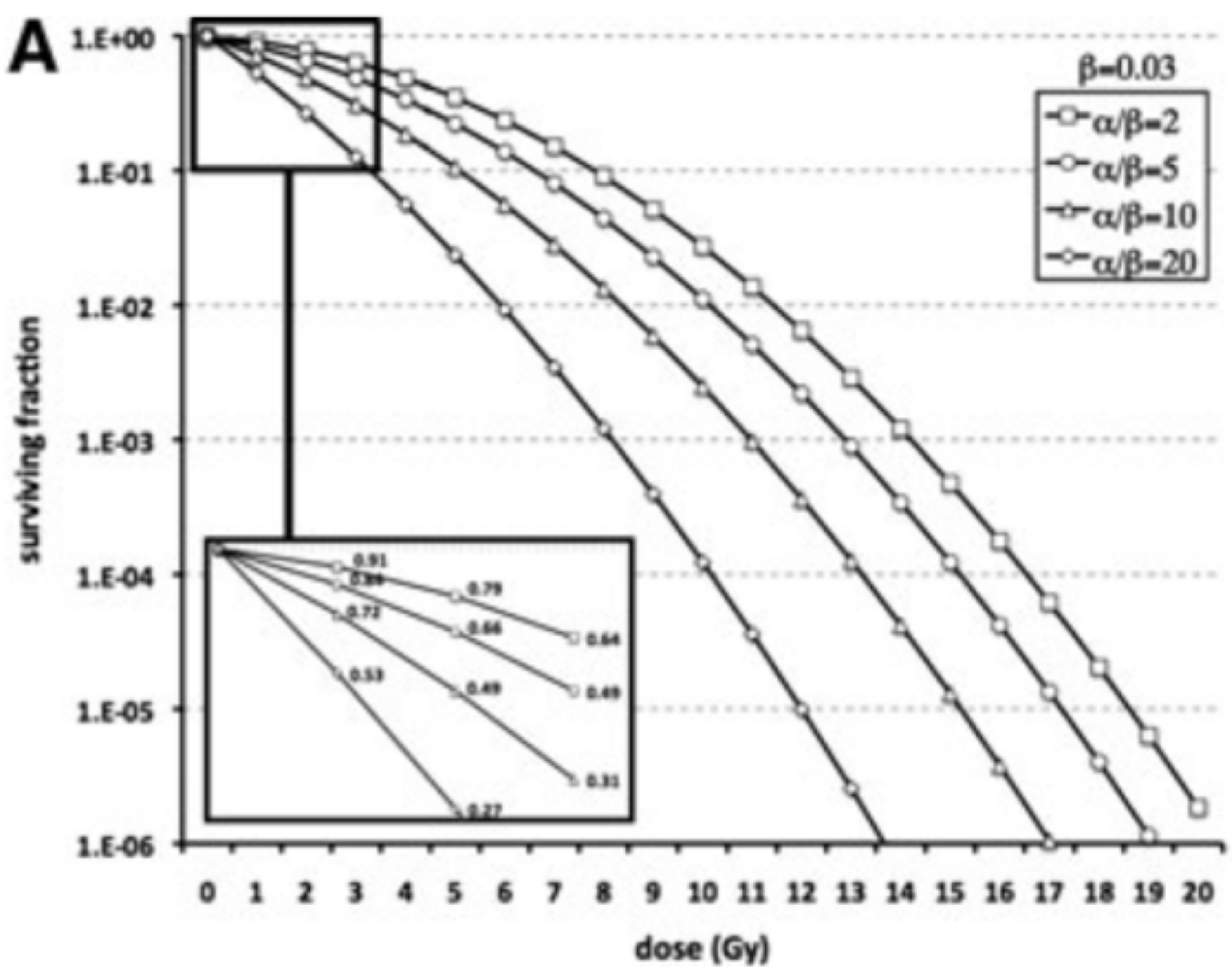
Can we use mathematical modeling
to simulate tumor tumor growth
and predict response to
different radiotherapy protocols
for individual patients?

Modeling radiotherapy



Modeling radiotherapy

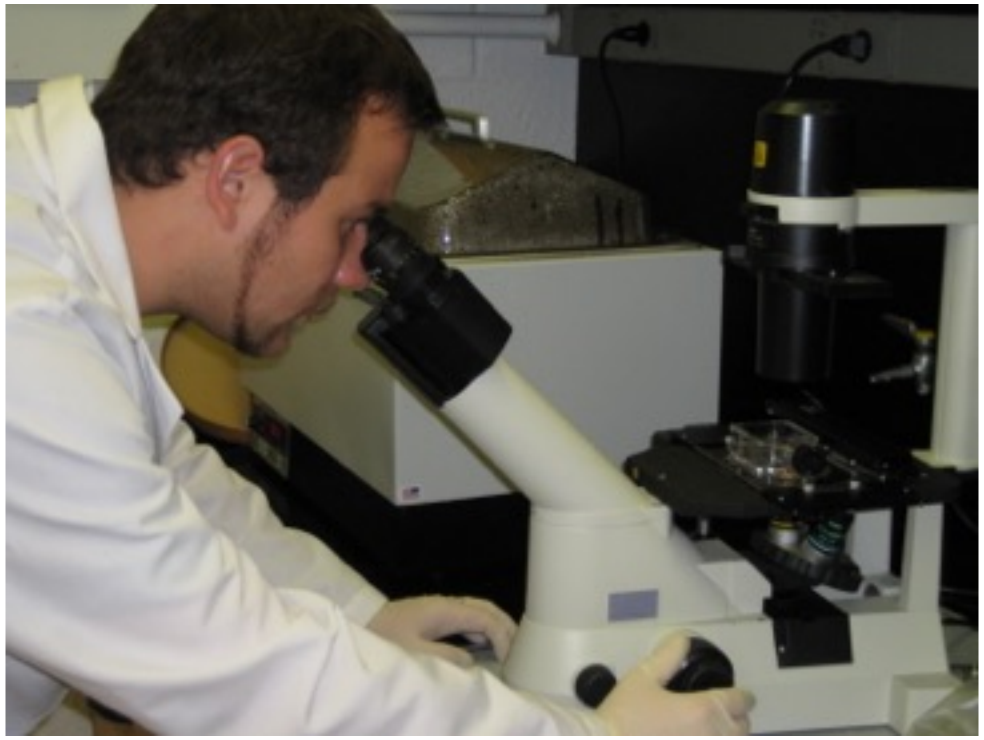


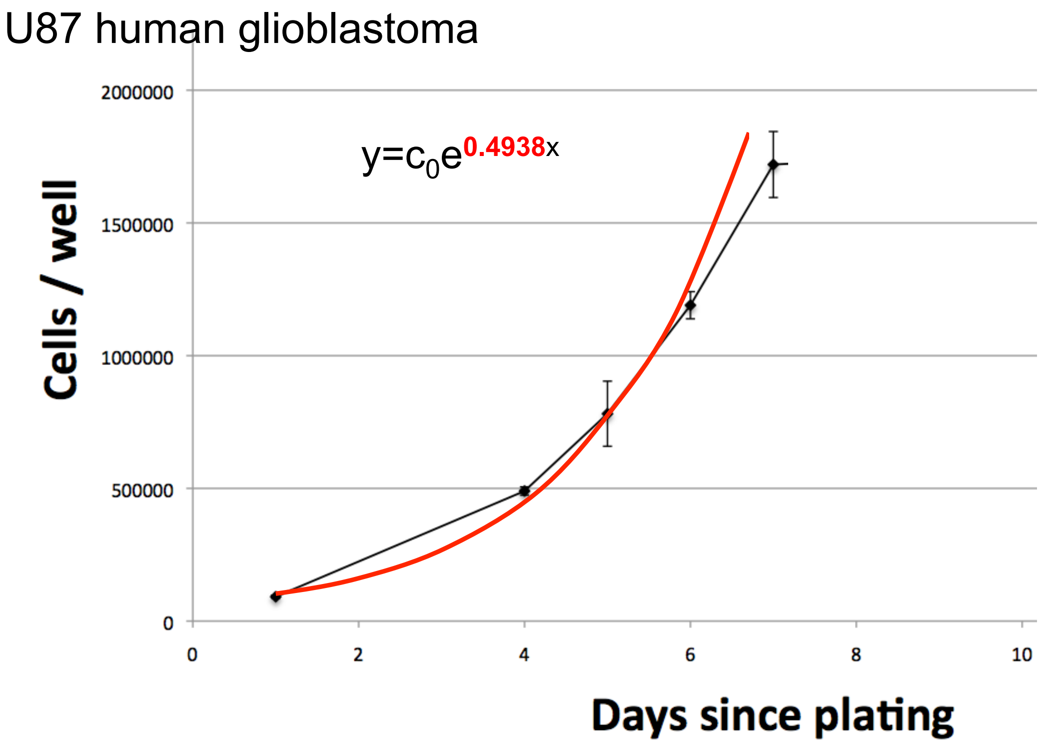


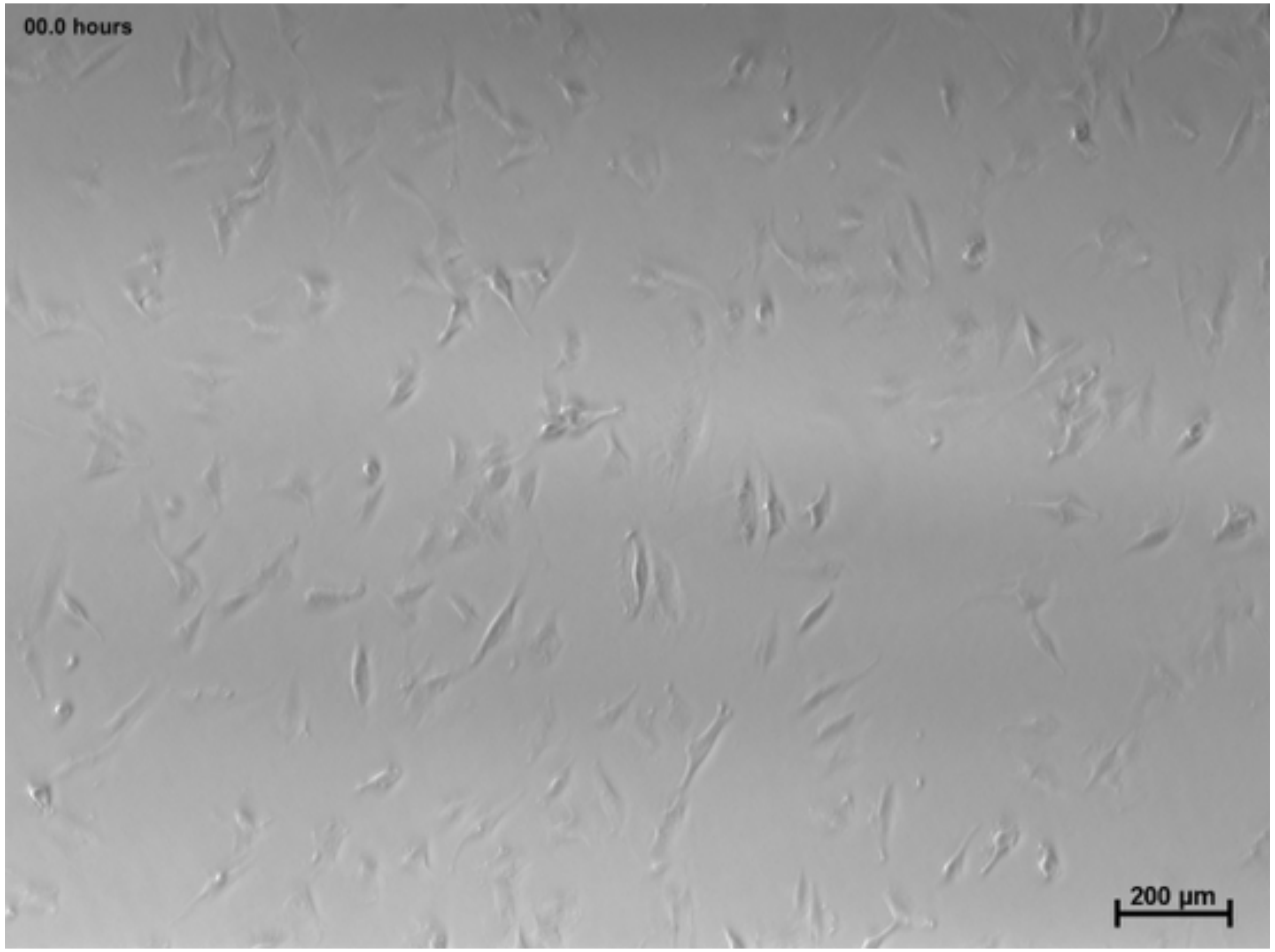
Linear Quadratic Model

$$S=e^{-(\alpha d+\beta d^2)}$$

Tumor growth *in vitro*







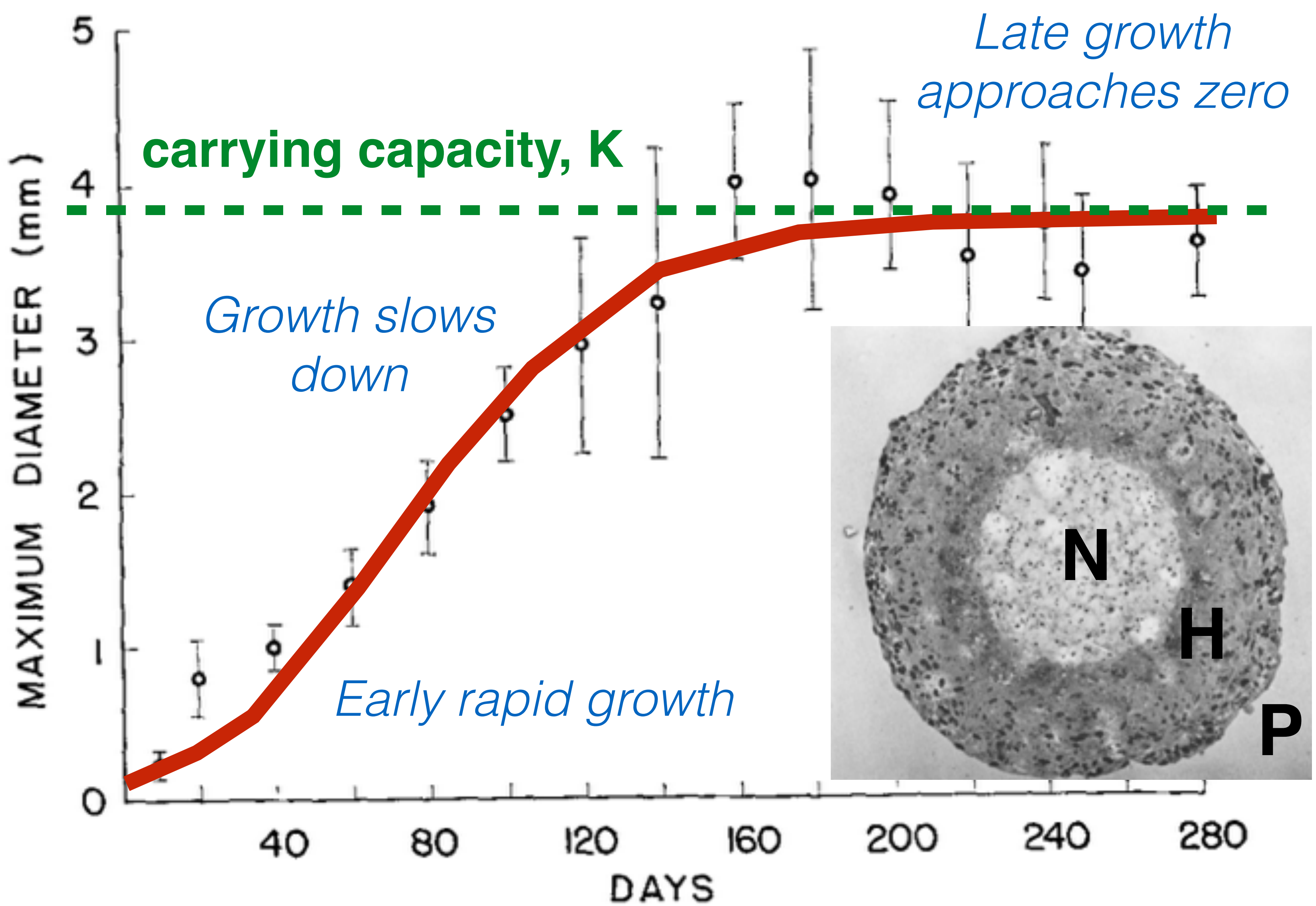
Population level growth

SELF-REGULATION OF GROWTH IN THREE DIMENSIONS*

BY JUDAH FOLKMAN AND MARK HOCHBERG

THE JOURNAL OF EXPERIMENTAL MEDICINE · VOLUME 138, 1973

Vascular Dormancy; await angiogenic switch



Logistic growth with **carrying capacity**

$$\frac{dV}{dt} = \frac{\ln 2}{T_{pot}} V\left(1 - \frac{V}{K}\right)$$

Logistic growth

Logistic growth with **carrying capacity**

$$\frac{dV}{dt} = \frac{\ln 2}{T_{pot}} V \left(1 - \frac{V}{K}\right)$$

*change in **V**olume over **t**ime*

potential doubling time (in vitro growth rate)

reduction of doubling time; current volume-to-carrying capacity ratio

if V is very small: V/K ~0

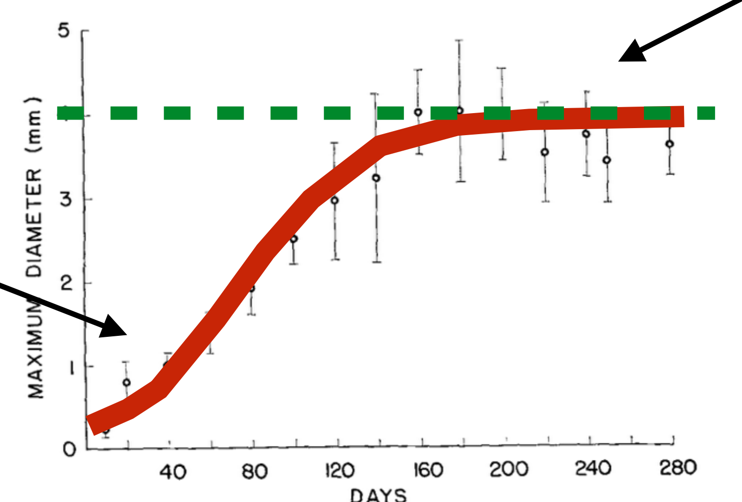
$$\frac{dV}{dt} = \frac{\ln 2}{T_{pot}} V$$

~ exponential growth

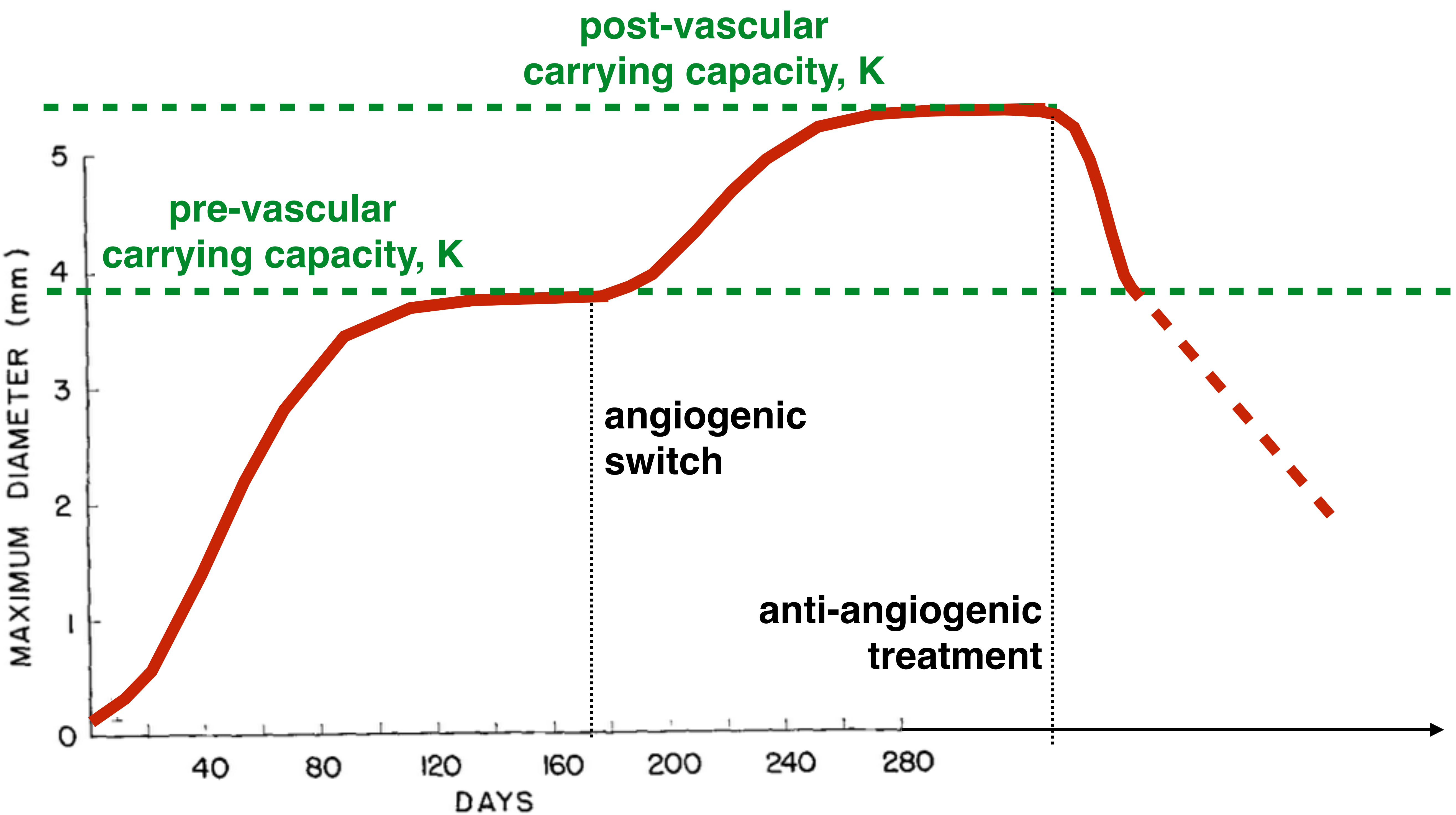
if V approaches K: V/K ~1

$$\frac{dV}{dt} = \mathbf{0}$$

~ saturation; dormancy



Dynamic carrying capacity



Hypothesis

Individual patients have an individual tumor carrying capacity K, which leads to a patient-specific tumor volume - to - carrying capacity ratio V/K.

V/K may serve a serve as prognostic marker for patient-specific treatment response.

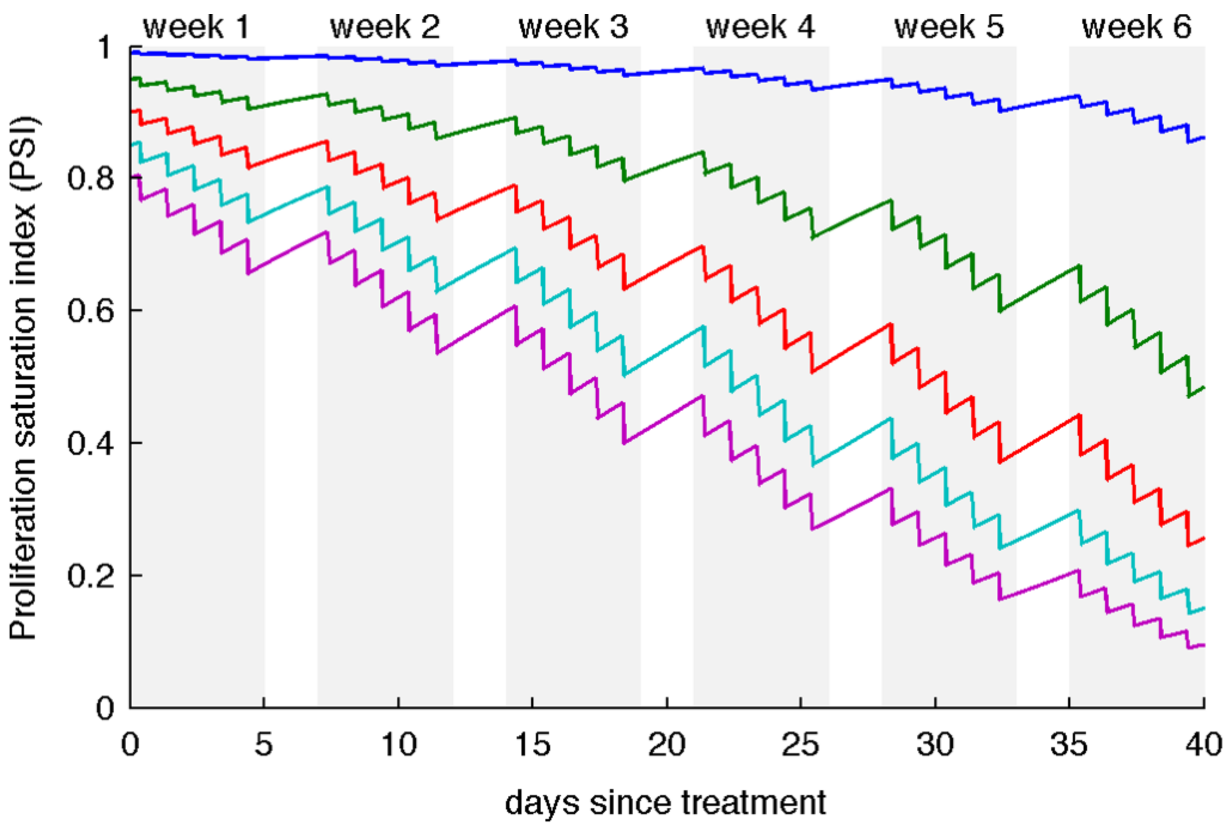
V/K = Proliferation Saturation Index (PSI)

$$\frac{dV}{dt} = \frac{\ln 2}{T_{pot}} V \left(1 - \frac{V}{K}\right)$$

$$V_{postIR} = V - \gamma_d V\left(1 - \frac{V}{K}\right)$$

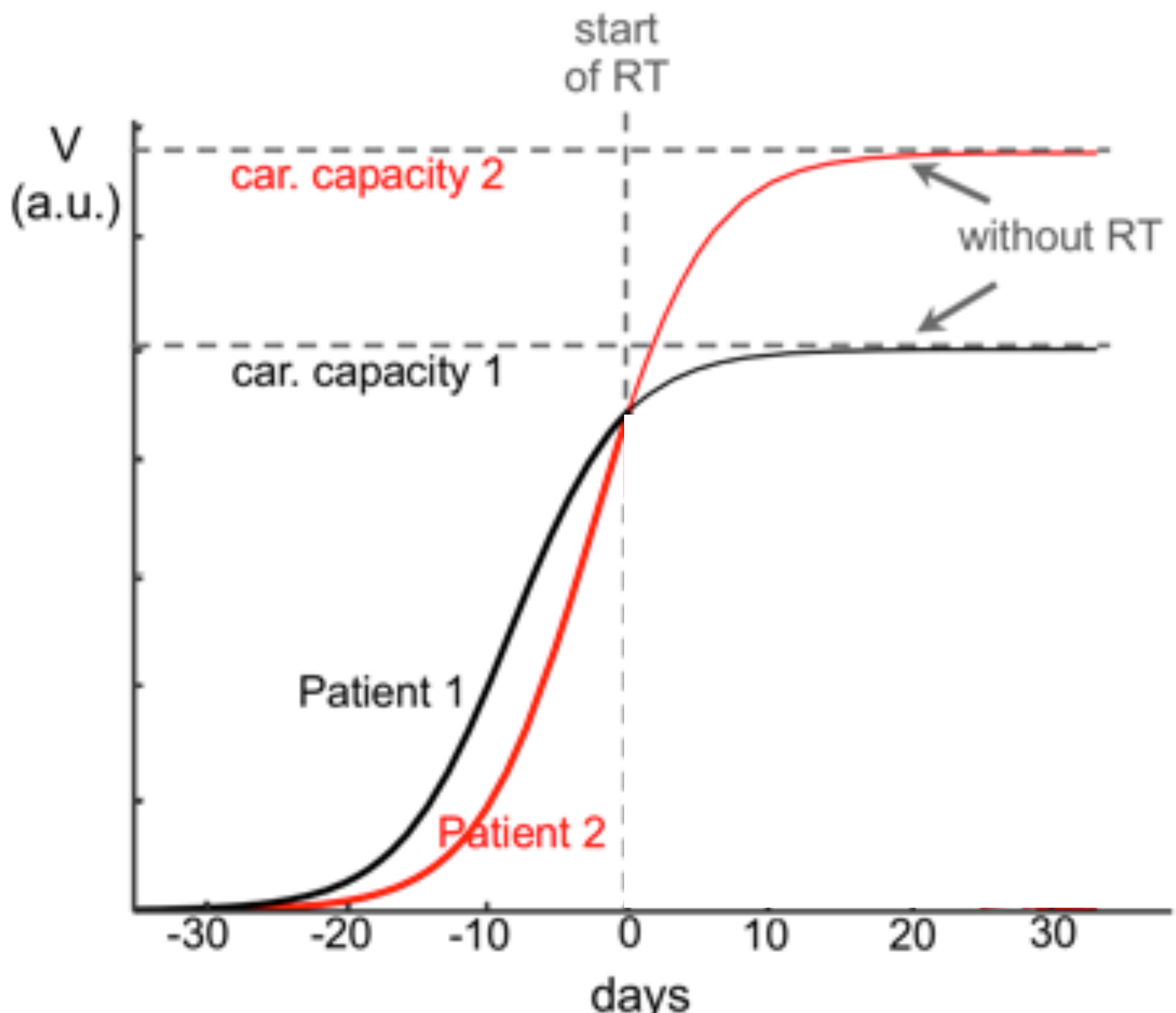
$$\gamma_d = 1 - S$$

$$S = e^{-(\alpha d + \beta d^2)}$$



Prokopiou et al., Radiat Oncol, 2015

V/K dependent radiation response



Prokopiou et al., Radiat Oncol, 2015

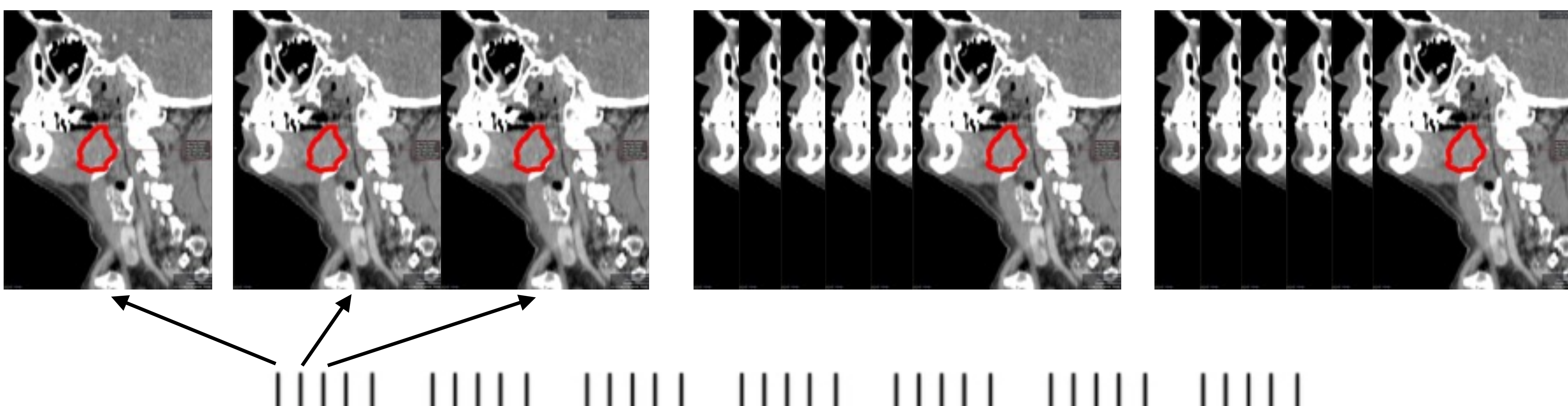
Head and Neck Cancer patient data

Dr. J Heukelom

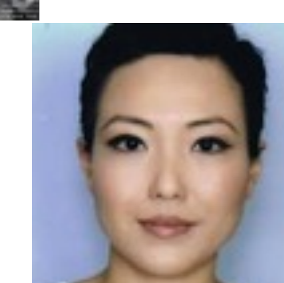
Dr. CD Fuller

PT.nl in St	group	T stage	N stage	age	sex	Tumor location	Detailed tu	PA	HPV	Tumor vol	Tumor vol	GTVnodes	nodal size
2	1	T2	N2B	55	M	Oropharynx	Right tonsil	Squamous	unknown	90.5151		need assistance	
8	1	T1	N2A	61	M	Oropharynx	Right base (	Squamous (	unknown	unknown			
14	2	T3	N2C	51	M	Oropharynx	Right tonsil	Squamous	positive	48.8148		Yes	73.17912
19	3	T4	N2C	52	W	Oropharynx	Base of ton	Squamous (	positive	117.896		Yes	18.1316
24	3	T3	N2B	65	M	Oropharynx	Left base of	Squamous	negative	need assistance		need assistance	
31	4	T1	N2A	44	M	Oropharynx	Right tonsil	Squamous	positive	3.76938		Yes	
32	4	T1	N2A	63	M	Oropharynx	Right base	Squamous	positive	unknown		No	No
35	4	T3	N2B	55	M	Oropharynx	Left tonsil	Squamous	n/a	64.5749		Yes, added	
36	4	T4	N0	78	M	Oropharynx	Base of ton	Squamous	n/a	45.0227		n/a	n/a
40	5	T2	N2B	57	M	Oropharynx	Base of ton	Squamous	positive	25.9172		Yes, added	
42	5	T1	N2A	55	M	Oropharynx	Right tonsil	Squamous	negative	4.76119		Yes	
49	6	T3	N1	69	M	Oropharynx	Left tonsil	Poorly diffe	negative	33.3892		Yes	
52	6	T2	N2B	57	M	Oropharynx	Left Glosso	Poorly diffe	positive	not contoured		Yes	
56	6	T2	N2B	51	M	Oropharynx	Left tonsil	Squamous	positive	18.6597		Yes	
59	7	T2	N2A	68	M	Oropharynx	Base of ton	Squamous	unknown	2.52961		Yes, added	
62	7	T2	N2B	46	M	Oropharynx	Right base	Squamous	unknown	18.5858		Yes, added	
63	7	Tx	N2b	39	M	Oropharynx	Left tonsil	Squamous	positive	not contoured		Yes	
67	8	T4A	N2B	74	M	Oropharynx	Base of ton	Squamous	unknown	39.7394		Yes, added	
69	8	T2	N2	51	M	Oropharynx	Glossophar	Squamous	positive	23.2338		Yes	
71	8	T1	N2A	63	M	Oropharynx	Base of ton	Squamous	negative	2.51173		Yes	
73	8	T2	N2	69	M	Oropharynx	Left tonsil	Squamous	negative	29.1751		Yes, added	
76	9	T2	N2B	61	M	Oropharynx	Left tonsil	Squamous (	negative	9.62848		Yes	
80	9	T4	N2	57	M	Oropharynx	Right base	Squamous	unknown	36.8045		Yes, added	
81	9	T3	N2C	58	M	Oropharynx	Right base	Poorly diffe	unknown	38.3757		Yes, added	
83	9	T3	N1	63	M	Oropharynx	Oropharynx	Squamous	unknown	97.1265		Yes	
84	10	T2	N2B	57	M	Oropharynx	Base of ton	Squamous	unknown	notin pinnacle			
85	10	T3	N2B	56	M	Oropharynx	Right tonsil	Squamous	unknown	need assistance		No	No
86	10	T4	N2B	59	M	Oropharynx	Right base	Squamous	positive	75.2171		Yes, added	
87	10	T3	N2B	51	M	Oropharynx	Left tonsil	Squamous	positive	60.2338		Yes, added	
94	list Ryan	T4	N0	63	W	Oropharynx	Left tonsil	Squamous	positive	77.761		n/a	n/a
95	10	T2	N2B	42	M	Oropharynx	Right tonsil	Squamous	unknown	need assistance		No	No
96	10	T2	N2C	53	M	Oropharynx	Left tonsil	Squamous	positive	12.8364		Yes	
97	10	T2	N0	54	M	Oropharynx	Right base	Squamous	unknown	36.8697		n/a	n/a
1	1	T3	N0	56	W	Oropharynx	Bilateral ton	Squamous	positive	22.5912		n/a	n/a

PT.nl in St	CHEMO TY	CHEMO C	CHEMO AC	DOSE prim	no. of fx	DOSE level	DOSE II	fx	Dose level	DOSE III	fx	Dose level	DOSE IV	fx	Dose level
2	CONCURR	6w	CISPLATIN	69.96	33	intermediat	60	33	low risk	57	33	supraclavic	50	25	boost right
8	CONCURRE	6w		69.96	33	gross diseas	66	33	intermediat	63	33	low risk	57	33	supraclavic
14	INDUCTIO	3induc.then	carboplatin	70	35	high risk	66	35	intermediat	63	35	low risk	57	35	n/a
19	CONCURRE	6w	CISPLATIN	69.96	33	high risk	67	33	intermediat	66	33	low risk	63	35	supraclavic
24	INDUCTIO	6w pacli cet	CISPLATIN	69.89	35	supraclavic	50	25	left neck bo	10	5	low neck pc	6	3	n/a
31	CONCURR	6w	cetuximab	66	33	supraclavic	50	25	mid neck bc	10	5	right neck b	6	3	n/a
32	CONCURR	6w	cetuximab	66	33	supraclavic	50	25	mid neck bc	10	5	n/a			n/a
35	CONCURR	6w	CISPLATIN	70	35	subclinical	56-62	35	mid neck bc	10	5	mid neck bc	6	3	supraclavic
36	CONCURR	6W	CISPLATIN	69.96	33	n/a			n/a			n/a			n/a
40	CONCURR	6W	cetuximab	70	33	subclinical	56-62	35	supraclavic	50	10	right neck b	58	?	n/a
42	CONCURR	6W	cetuximab	70	35	intermediat	60	33	low risk	54	33	supraclavic	50	25	n/a
49	CONCURR	3 out of 3	CISPLATIN	70	33	intermediat	63	33	low risk	57	33	supraclavic	50	25	n/a
52	INDUCTIO	3+3	induction dc	70	33	intermediat	63	33	low risk	57	33	supraclavic	50	25	left mid nec
56	INDUCTIO	3x inductie,	induction: T	66	30	intermediat	60	30	low risk	54	30	supraclavic	50	25	left mid nec
59	CONCURR	6w	cetuximab	66	30	intermediat	intermediate dose?		low risk	low dose		supraclavic	50	25	right mid ne
62	CONCURR	3 weekly	CISPLATIN	69.96	32	supraclavic	50	25	mid neck bc	10	5	mid neck bc	4	2	n/a
63	CONCURR	3 weekly	CISPLATIN	70	33	intermediat	63	33	low risk	57	33	supraclavic	50	25	left mid nec
67	CONCURR	3 weekly	CISPLATIN	70	35	high risk	63	35	low risk	57	30	supraclavic	50	25	right mid ne
69	CONCURR	? 6w?	CISPLATIN	70	33	intermediat	63	33	low risk	57	33	supraclavic	50	25	bilateral mi
71	CONCURR	3 weekly	CISPLATIN	69.96	33	intermediat	62	33	low risk	54	33	supraclavic	50	25	right mid ne
73	CONCURR	5/6 weekly	CISPLATIN	70	33	intermediat	60	33	low risk	54	33	supraclavic	50	25	neck boost
76	CONCURRE	6w	CISPLATIN	70	33	high risk	63	33	low risk	57	33	supraclavic	50	25	n/a
80	CONCURR	2x high dos	CISPLATIN	70	33	high risk	63	33	low risk	57	33	supraclavic	50	25	n/a
81	CONCURR	2x cisplatin,	cisplatin or	69.96	33	supraclavic	50	10	bilateral ne	10	5	right neck b	6	3	n/a
83	CONCURR	Weekly. 6W	cetuximab	70	33	intermediat	63	33	low risk	57	33	supraclavic	50	25	left mid nec
84	CONCURR	2x high dos	CISPLATIN	69.96	33	supraclavic	50	25	right neck b	10	5	right neck b	4	2	n/a
85	CONCURR	3x high dos	CISPLATIN	70	33	intermediat	63	33	low risk	57	33	supraclavic	50	25	right mid ne
86	CONCURRENT		CISPLATIN	70	35	intermediat	63	35	low risk	56	35	n/a			n/a
87	CONCURR	6w	CISPLATIN	70	33	intermediat	63	33	low risk	57	33	supraclavic	50	25	mid neck bc
94	CONCURR	Weekly. 6W	cetuximab	70	35	intermediat	63	35	low risk	57	35	supraclavic	45	35	n/a
95	CONCURR	3 weekly	cisplatin (2)	70	33	supraclavic	50	25	right neck b	10	5	n/a			n/a
96	CONCURR	Weekly. 6W	cetuximab	70	33	intermediat	63	33	low risk	57	33	supraclavic	50	25	bilateral mi
97	CONCURR	2x high dos	CISPLATIN	70	33	uninvolved	57	33	n/a			n/a			n/a
1	CONCURR	6w	CISPLATIN	69.96	33	small volum	66	33	draining no	63	33	prophylacti	57	33	supraclavic



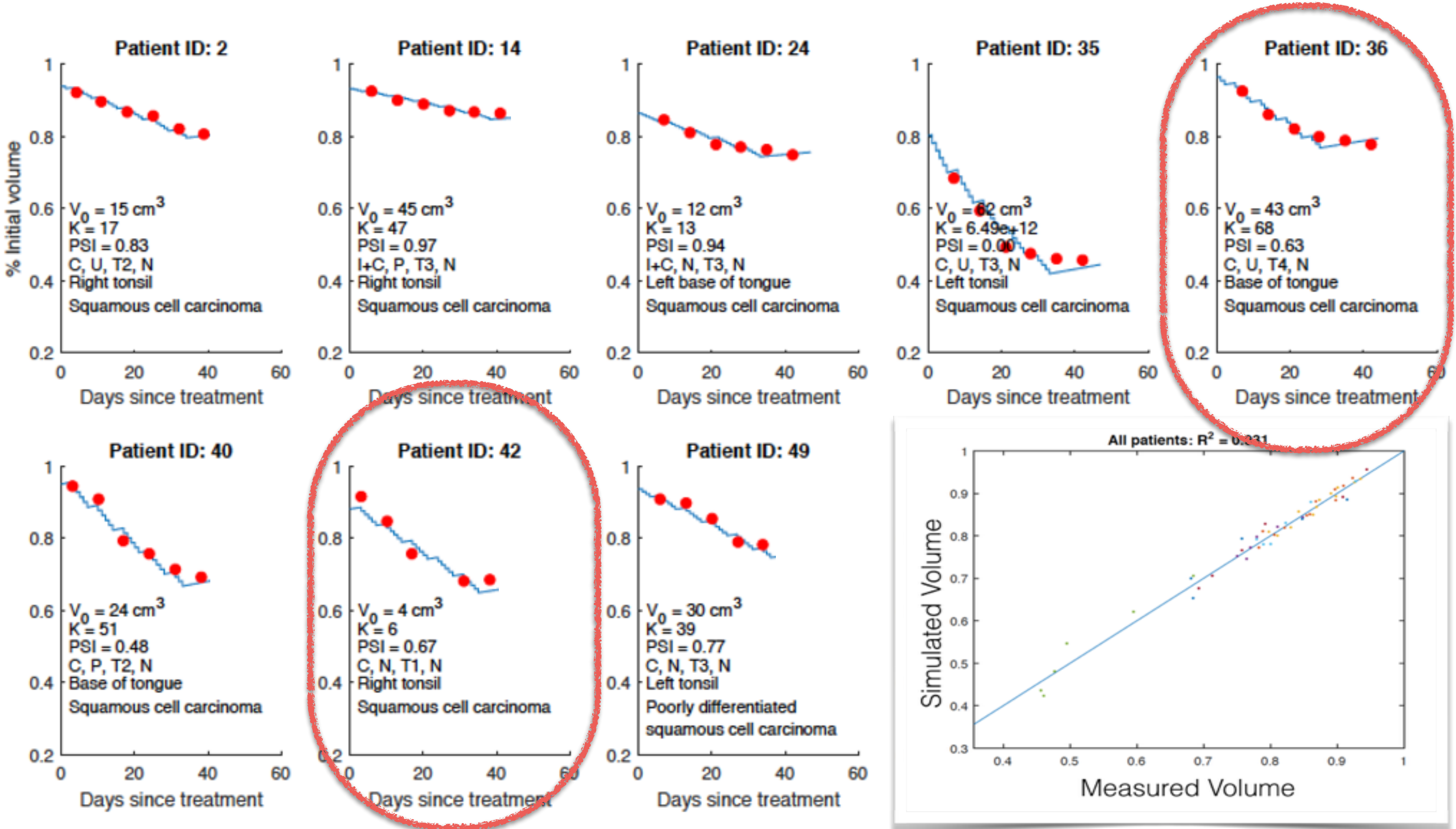
Conventional fractionation 35 fractions, 2 Gy M-F, Total 66-70 Gy; 7 weeks



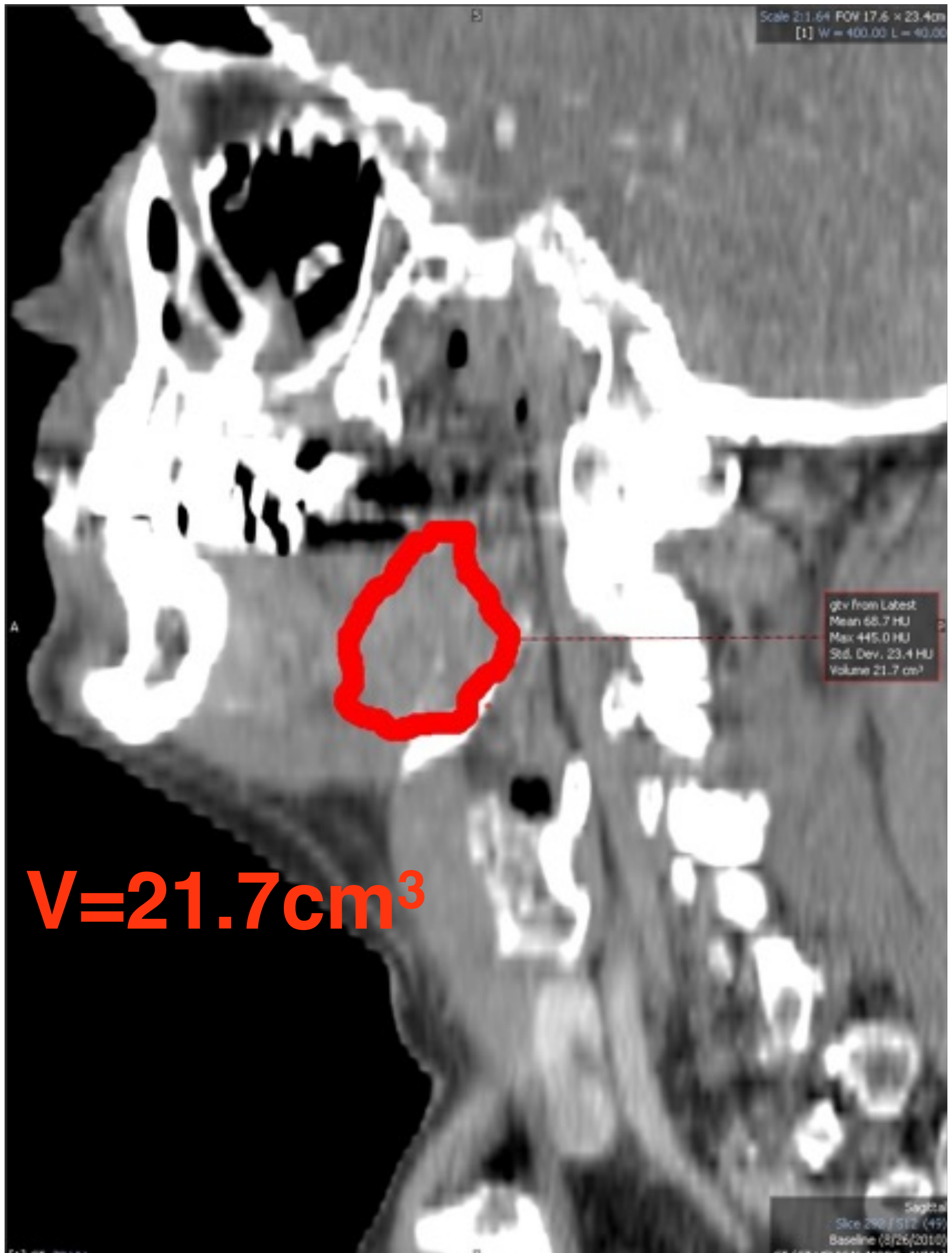
Dr. Joo Kim

Data fitting; Logistic model

$$\frac{dV}{dt} = \frac{\ln 2}{T_{pot}} V \left(1 - \frac{V}{K}\right) \qquad V_{postIR} = V - \gamma_d V \left(1 - \frac{V}{K}\right)$$



Head and Neck Cancer



Diagnosis

Prospective calculation of V/K

$V(t_0)$ $V(t_0+\Delta t)$

$$\frac{dV}{dt} = \frac{\ln 2}{T_{pot}} V \left(1 - \frac{V}{K}\right)$$

- $Tpot$ known from *in vitro* experiments or retrospective cohort analysis
- 2 independent images (diagnostic radiology image and treatment planning image) to determine dV/dt
- explicit solution; solve for K

$$K = \frac{V(diagnosis) \times V(treatment\ \ planning) \times \left(e^{T_{pot}\, t} - 1\right)}{V(diagnosis) \times e^{T_{pot}\, t} - V(treatment\ \ planning)}$$

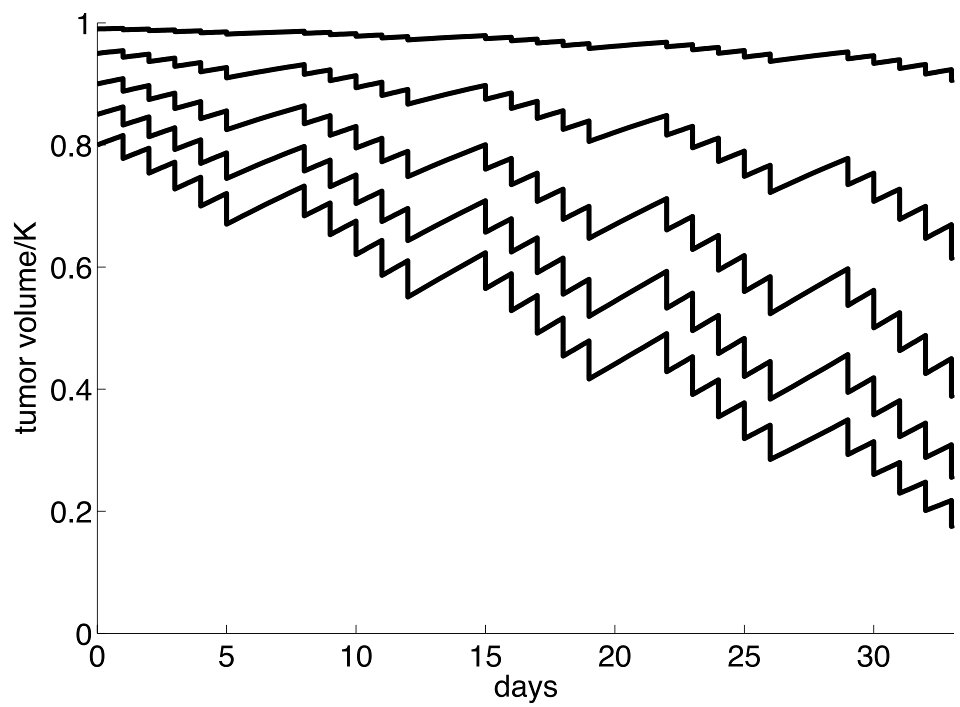
Prokopiou et al., Radiat Oncol, 2015

V/K as prognostic factor for patient-specific radiotherapy response

Estimate patient K

$$\frac{dV}{dt} = \frac{\ln 2}{T_{pot}} V \left(1 - \frac{V}{K}\right)$$

predict response



derive better protocols

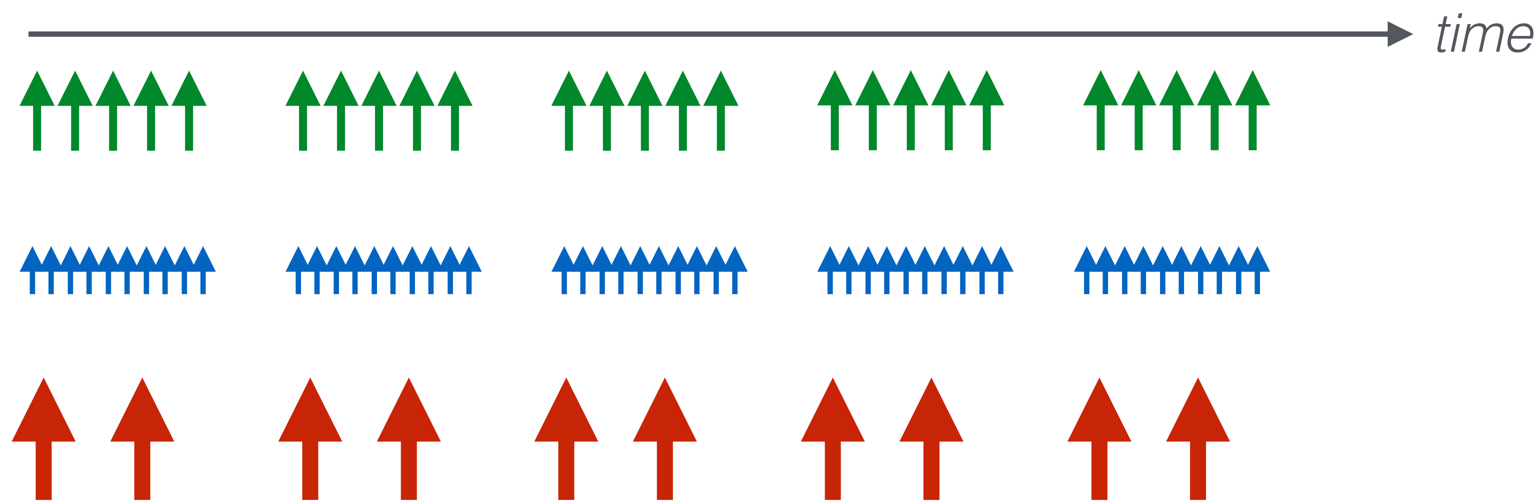
?

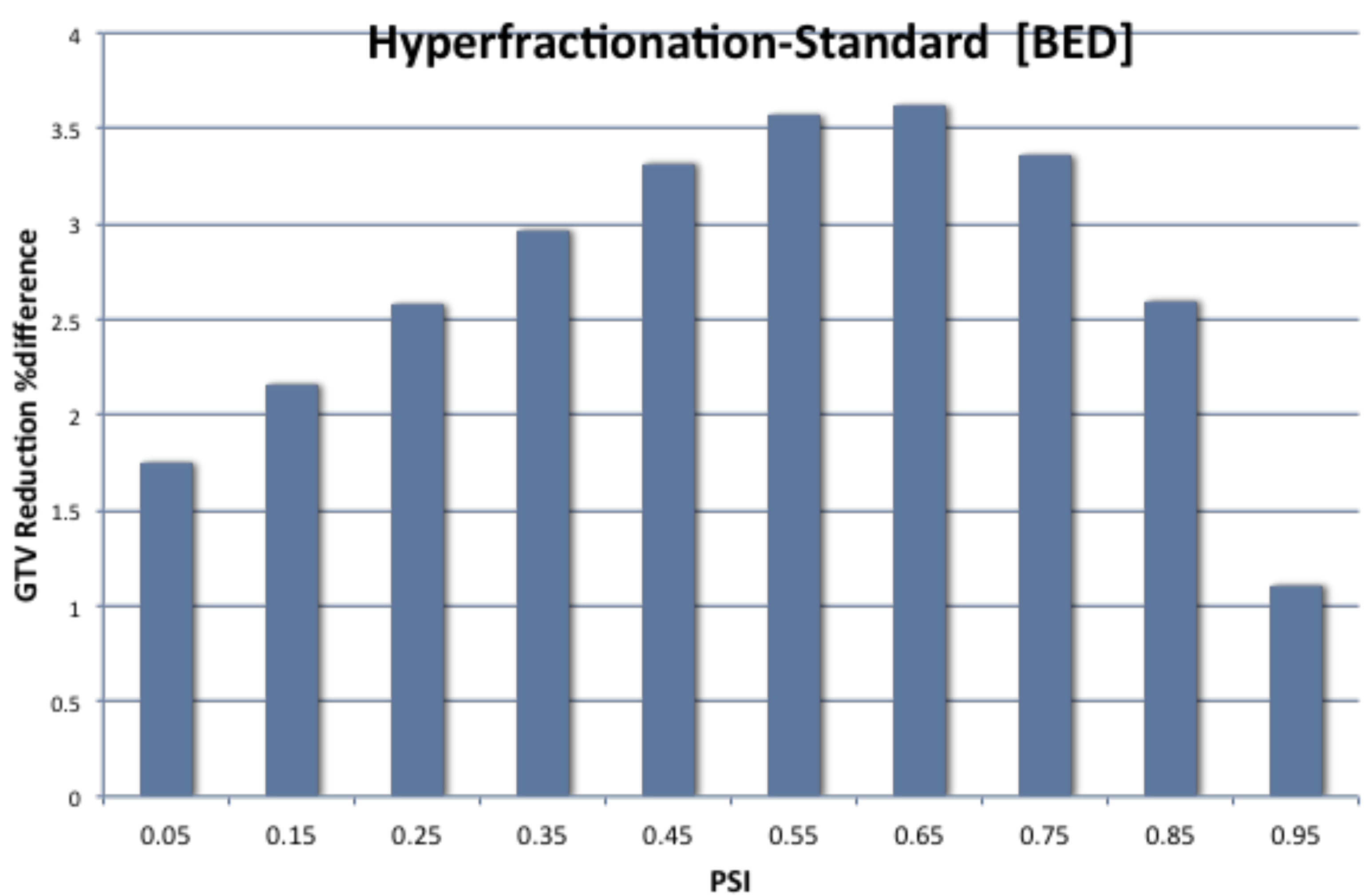
Alternative fractionation

"standard of care"
2 Gy x 25

"hyper-fractionation"
1.2 Gy x 50

"hypo-fractionation"
5 Gy x 10





Prokopiou et al., Radiat Oncol, 2015

Which tumor growth model?

Logistic tumor growth $$\frac{dV}{dt} = \frac{\ln 2}{T_{pot}} V \left(1 - \frac{V}{K}\right)$$

Gompertzian tumor growth $$\frac{dV}{dt} = -\frac{\ln 2}{T_{pot}} V * \ln\left(\frac{V}{K}\right)$$

Exponential

Mendelsohn

Linear

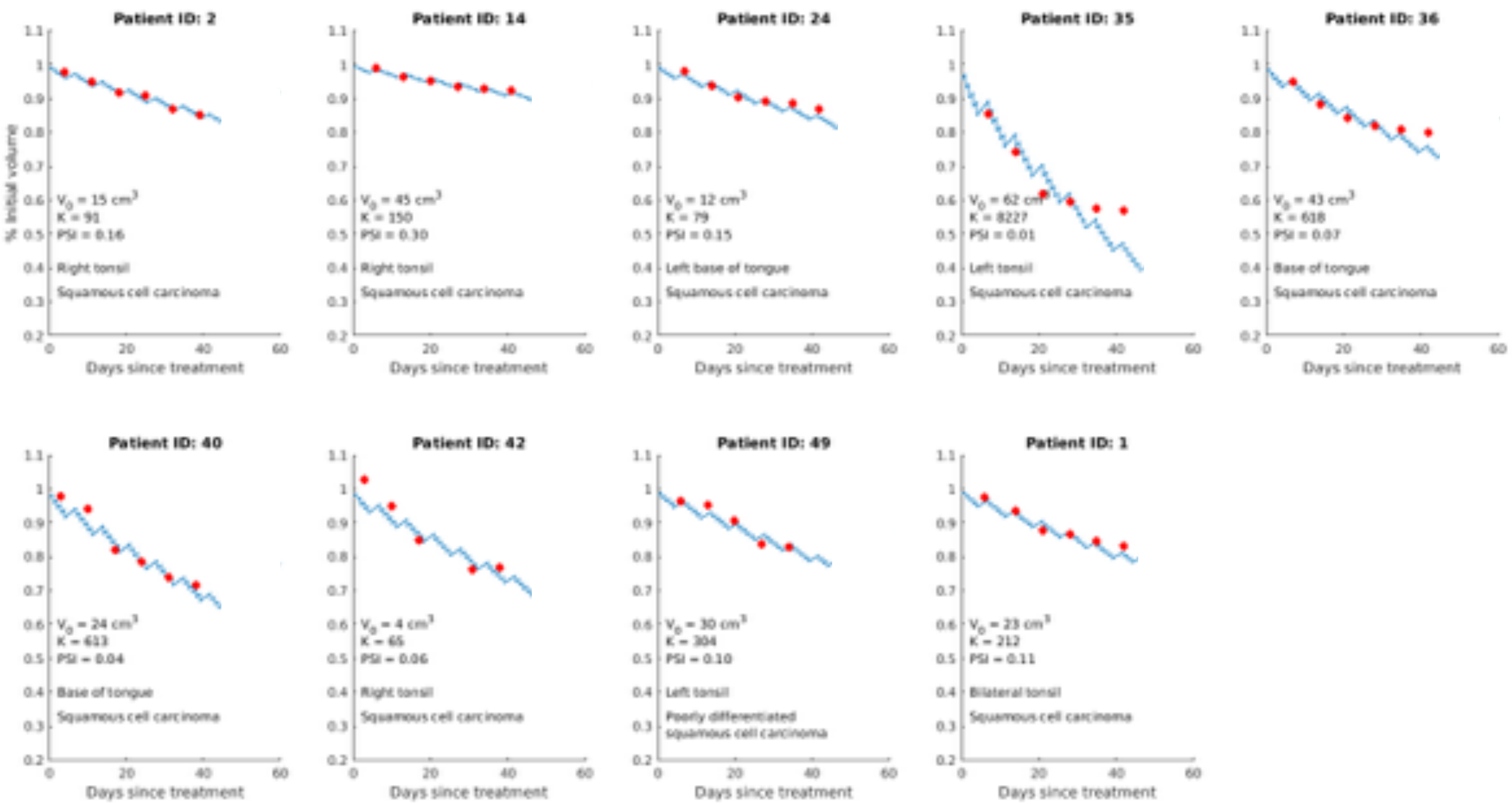
Surface

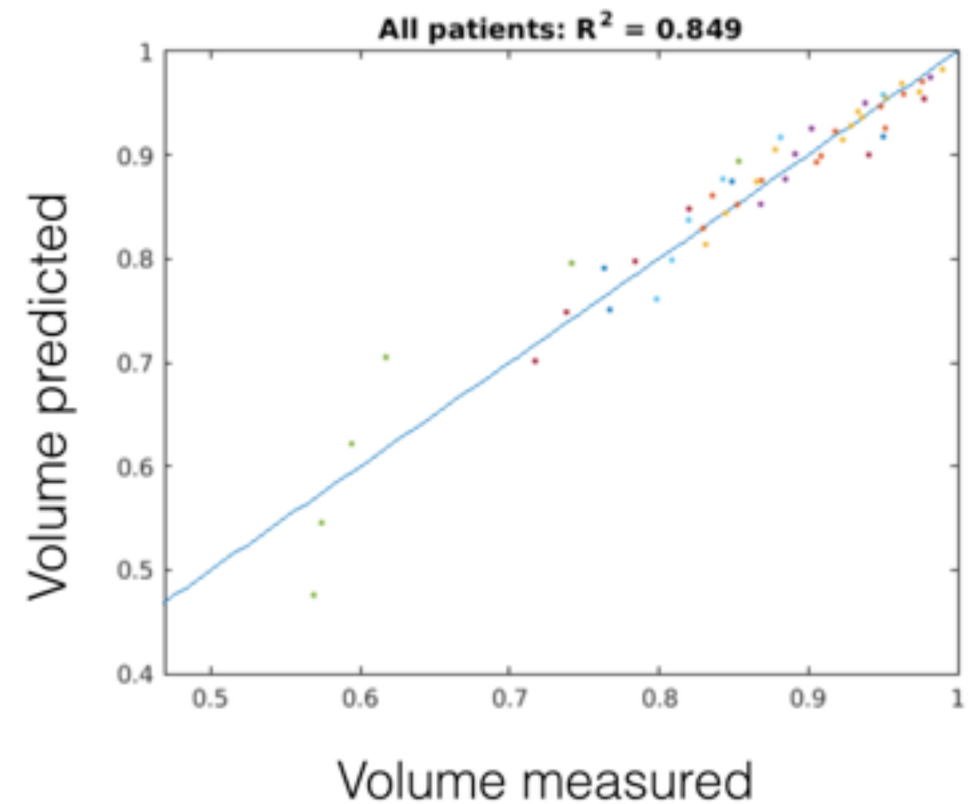
Von Bertalnaffy

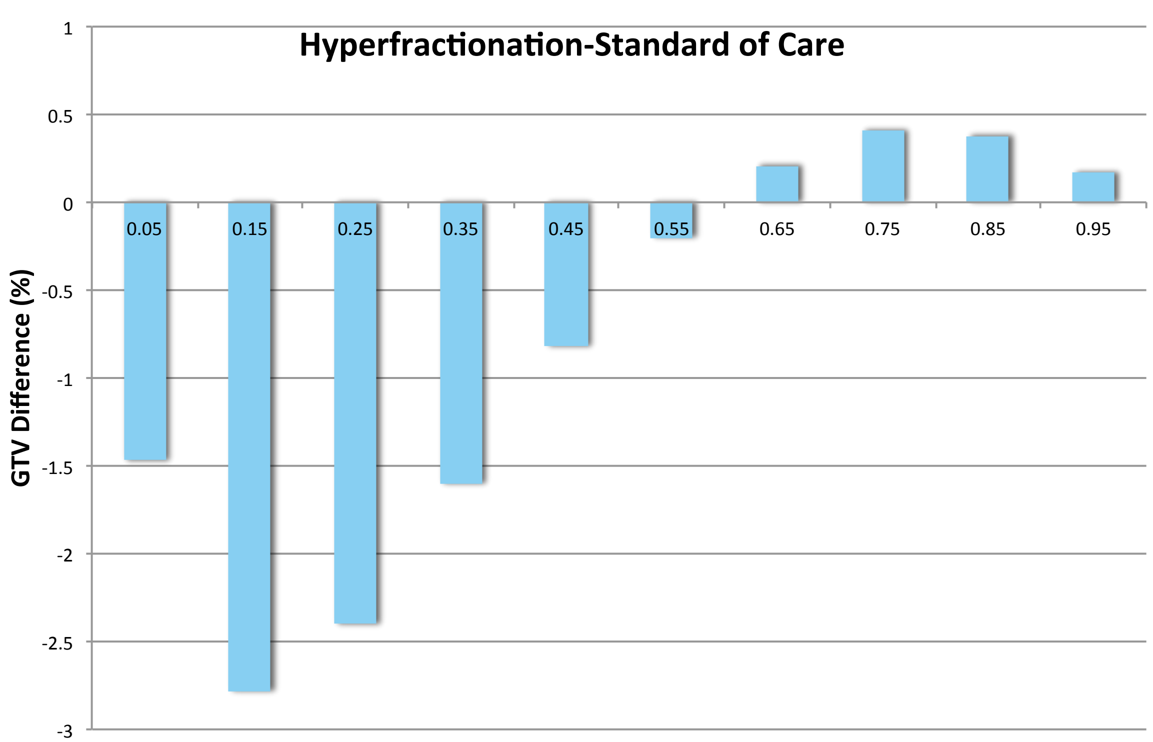
…

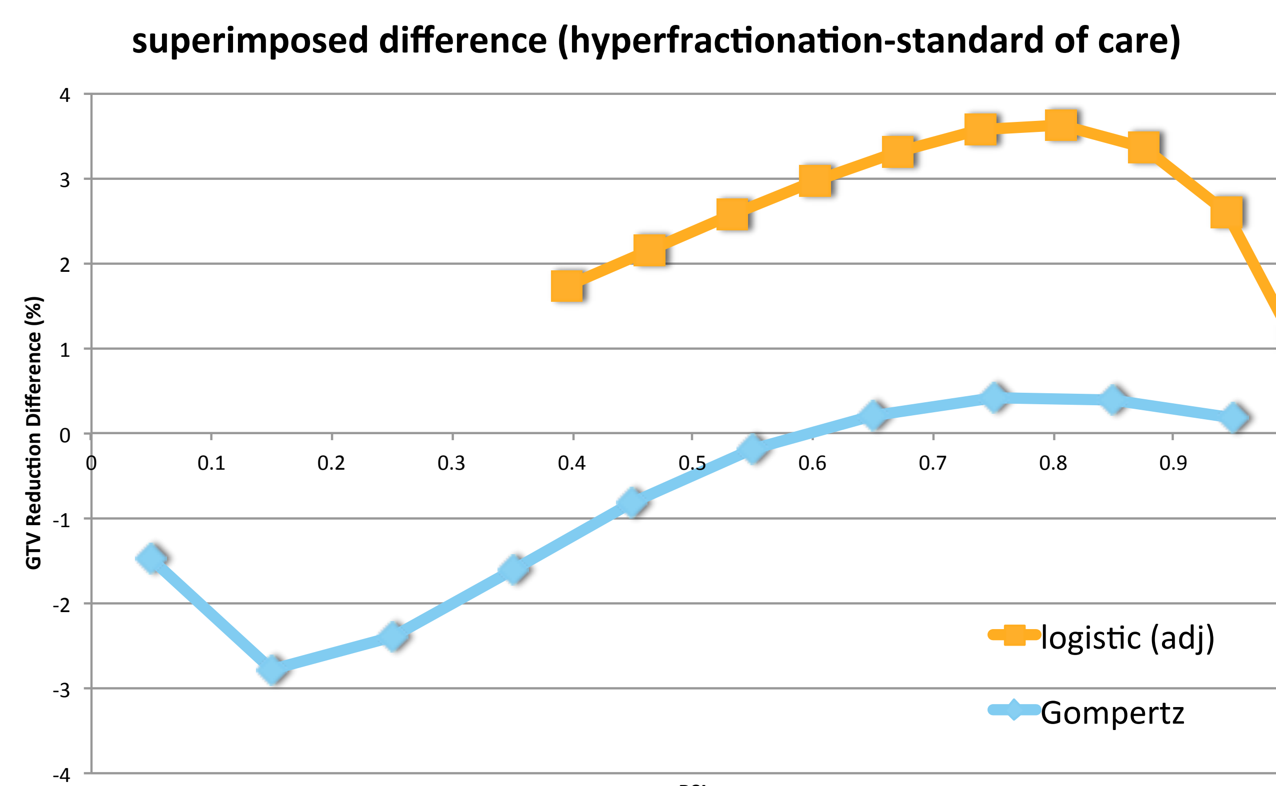
Dr. Dobrovolny lecture, 11/5

Data fitting; Gompertz model







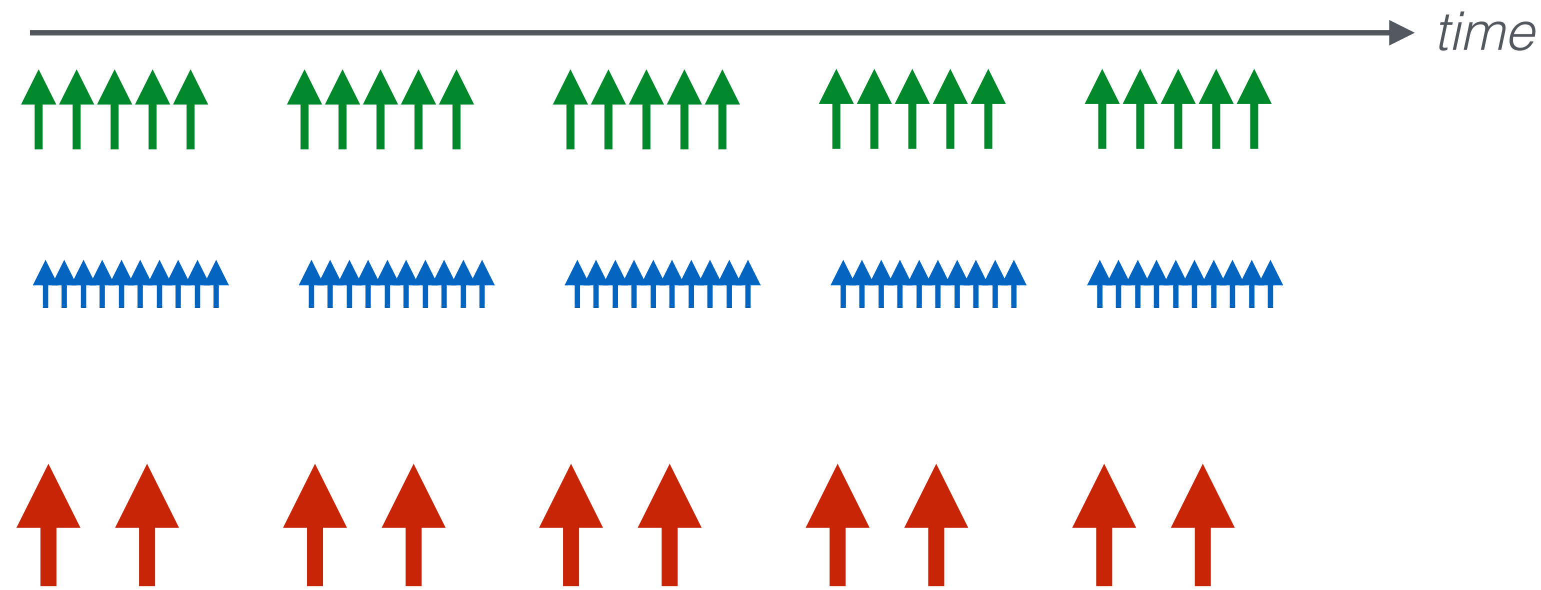


Alternative fractionation

"standard of care"
2 Gy x 25

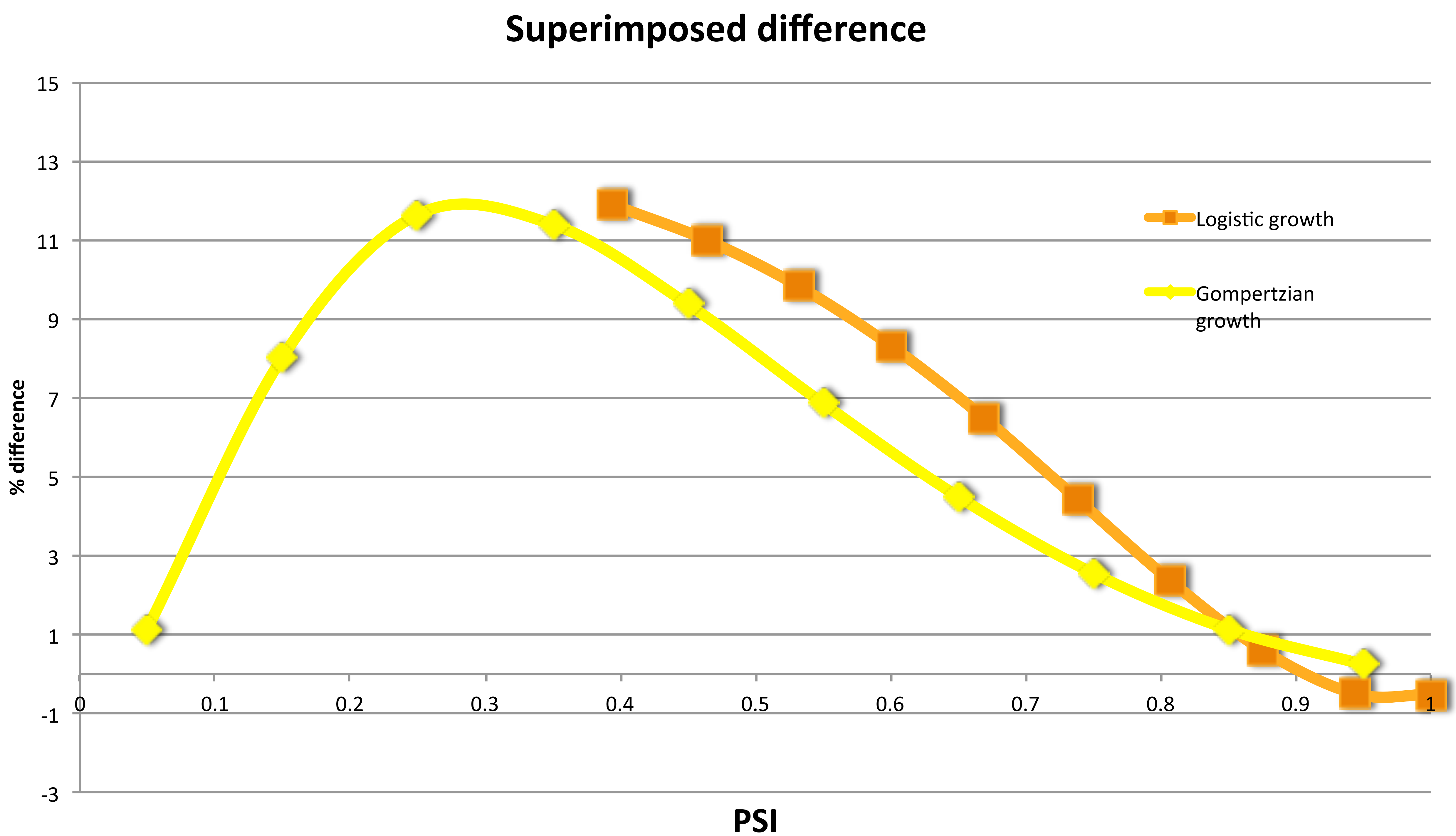
"hyper-fractionation"
1.2 Gy x 50

"hypo-fractionation"
5 Gy x 10

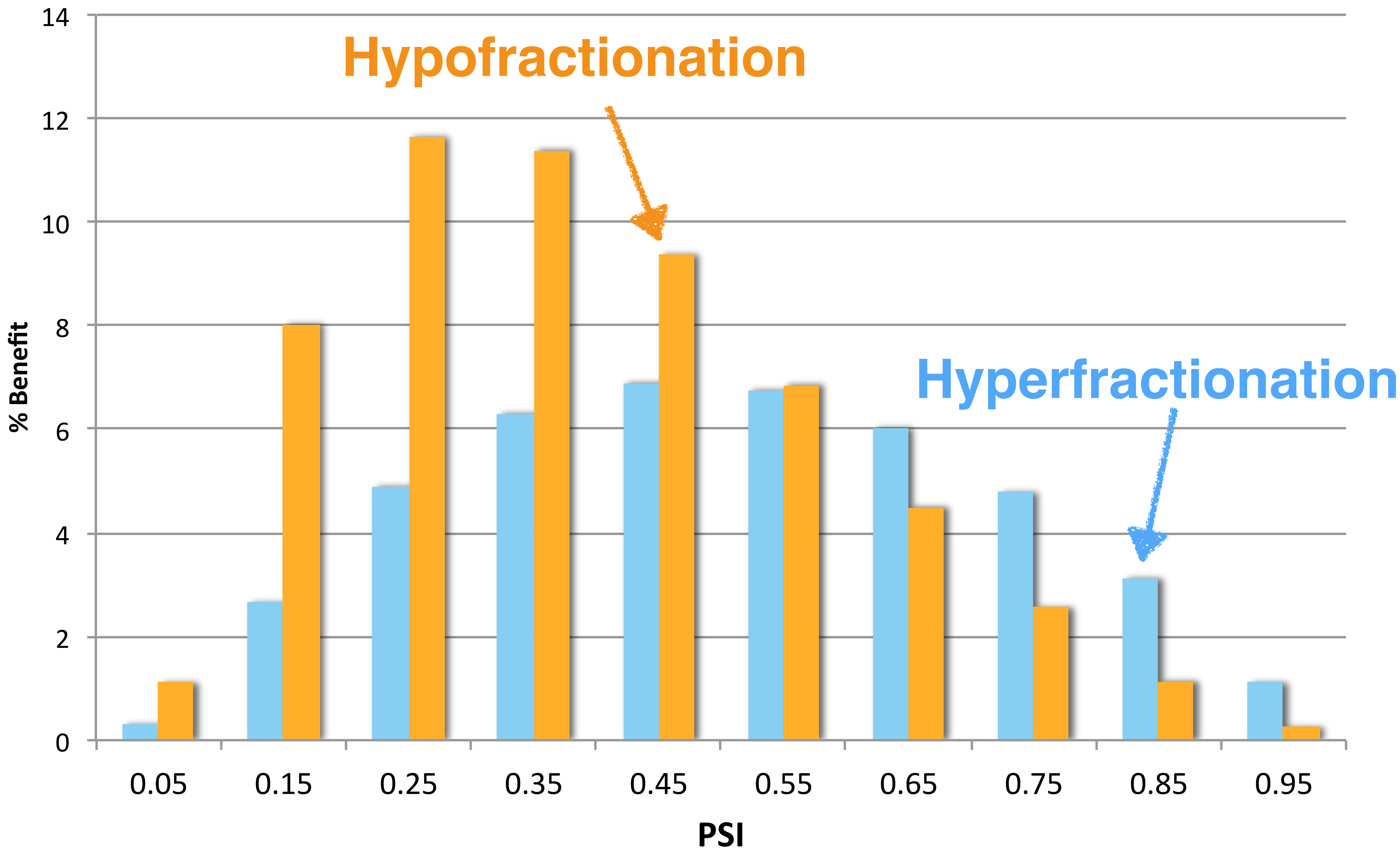


Logistic vs Gompertzian

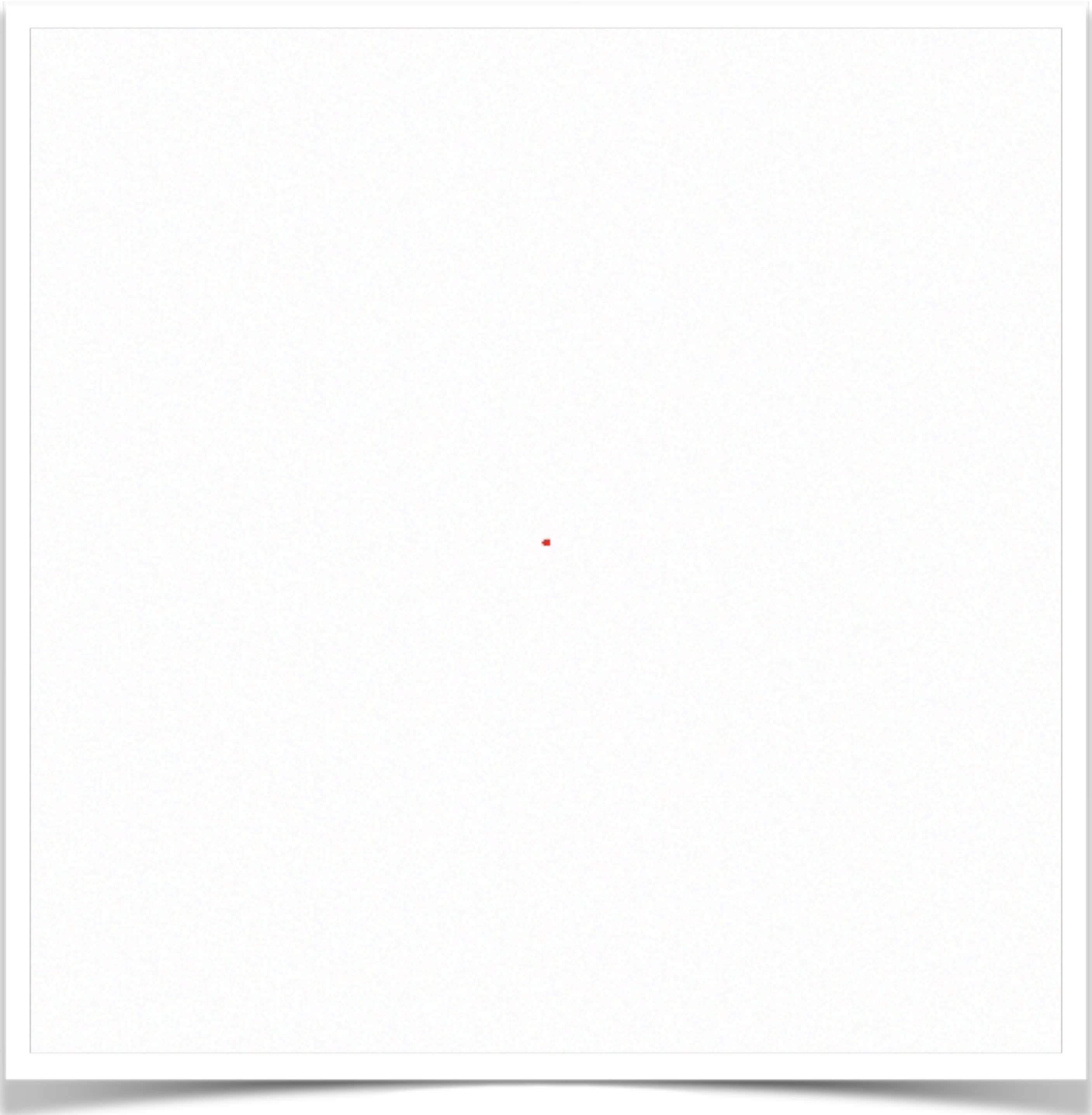
Hypofractionation

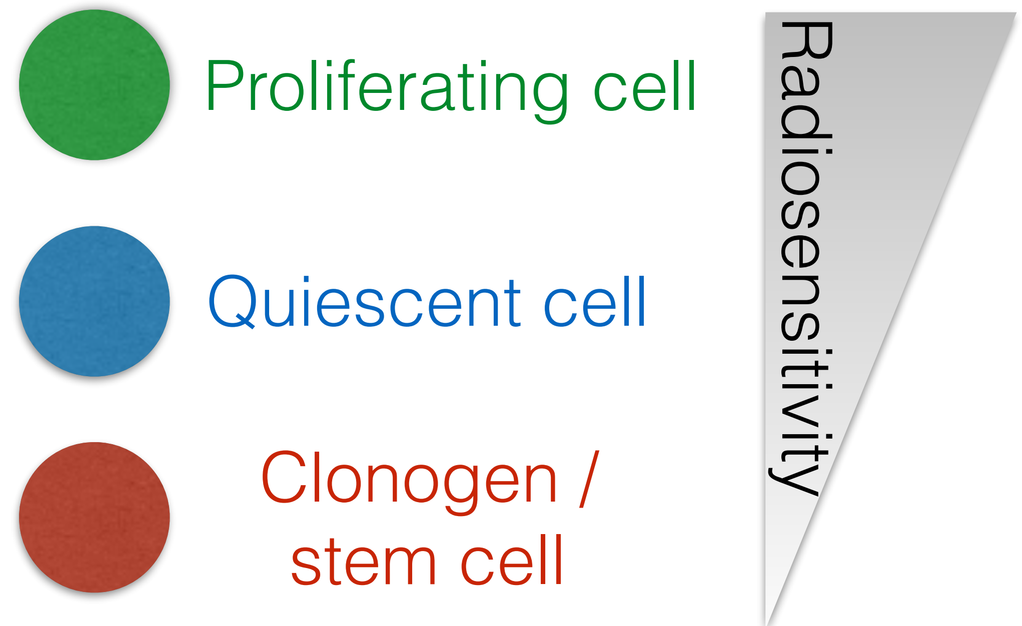


V/K specific fractionation protocol



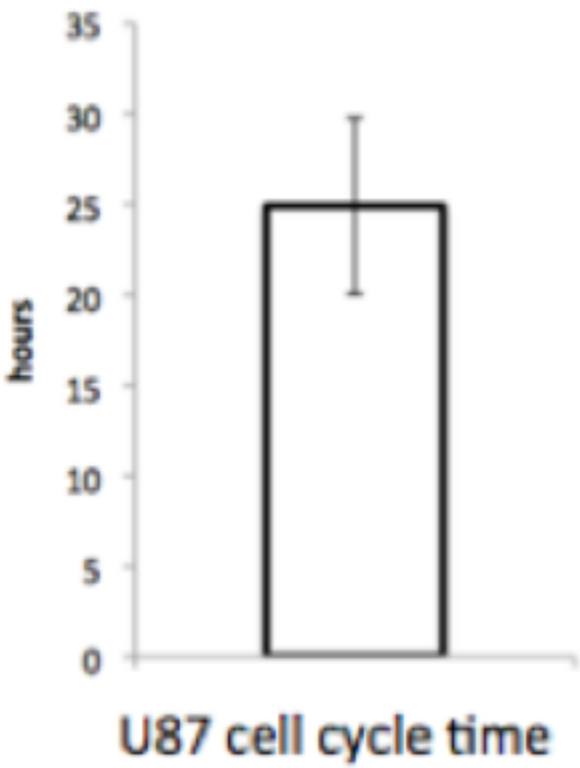
Agent-based model of tumor growth and radiation response

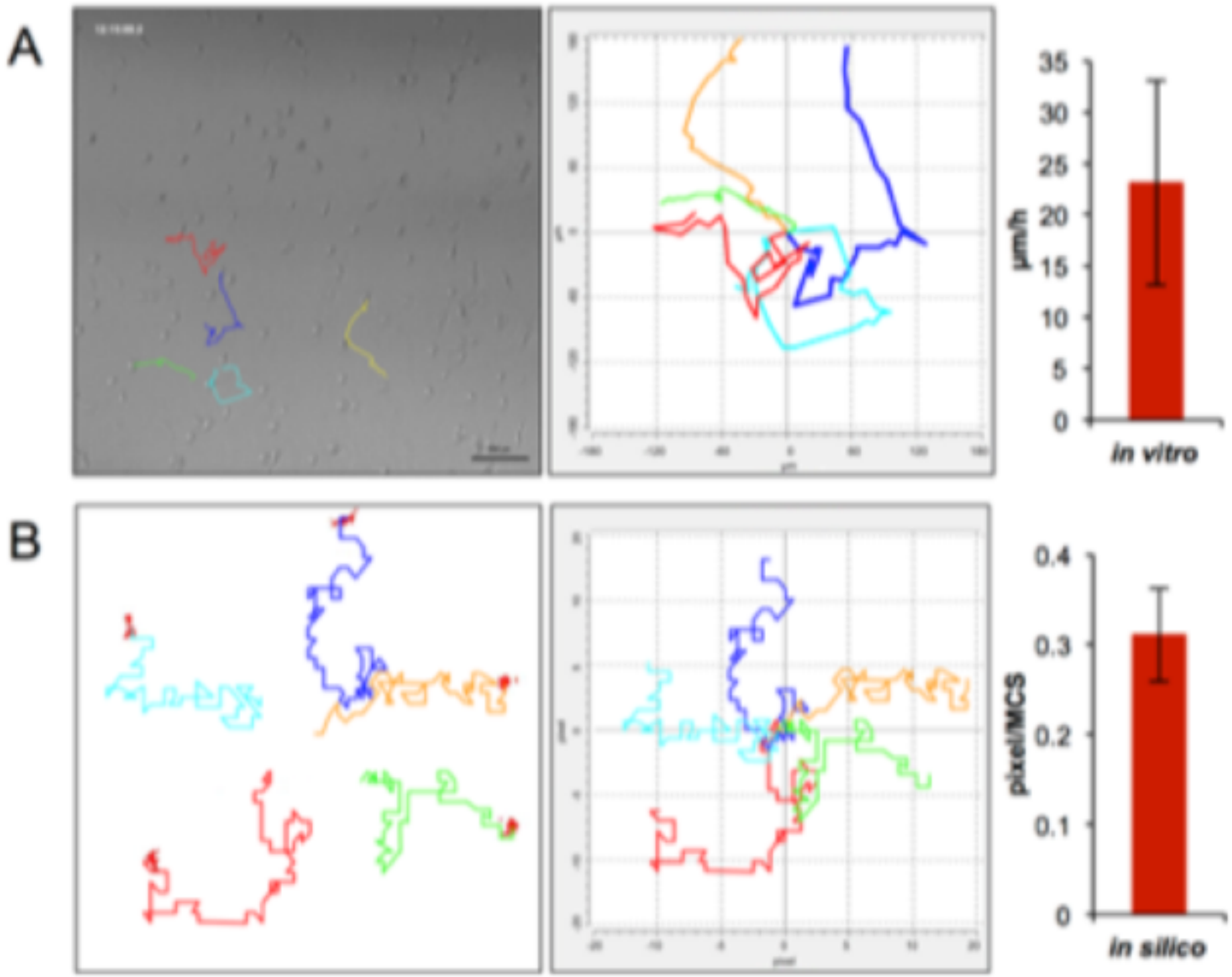


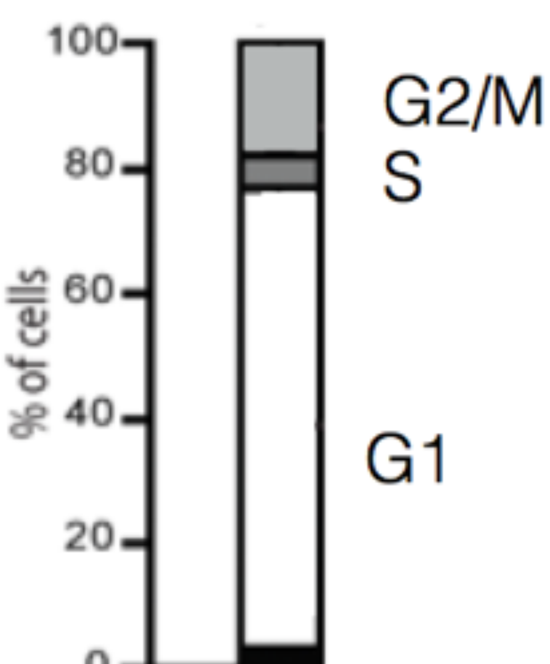


- follow the fate of each cell
- high biological resolution
- **can be calibrated with experimental data**

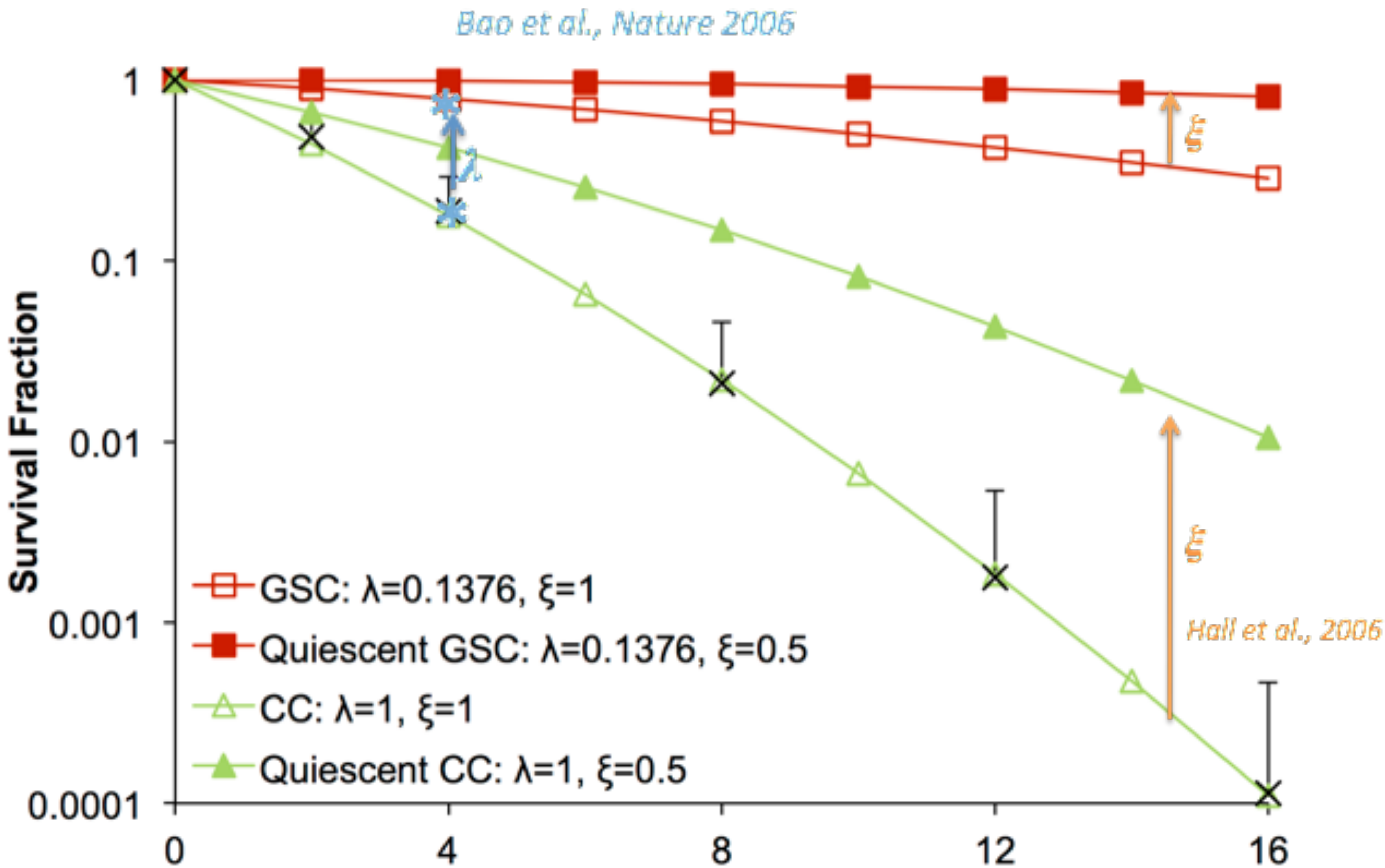
Calibration using experimental data







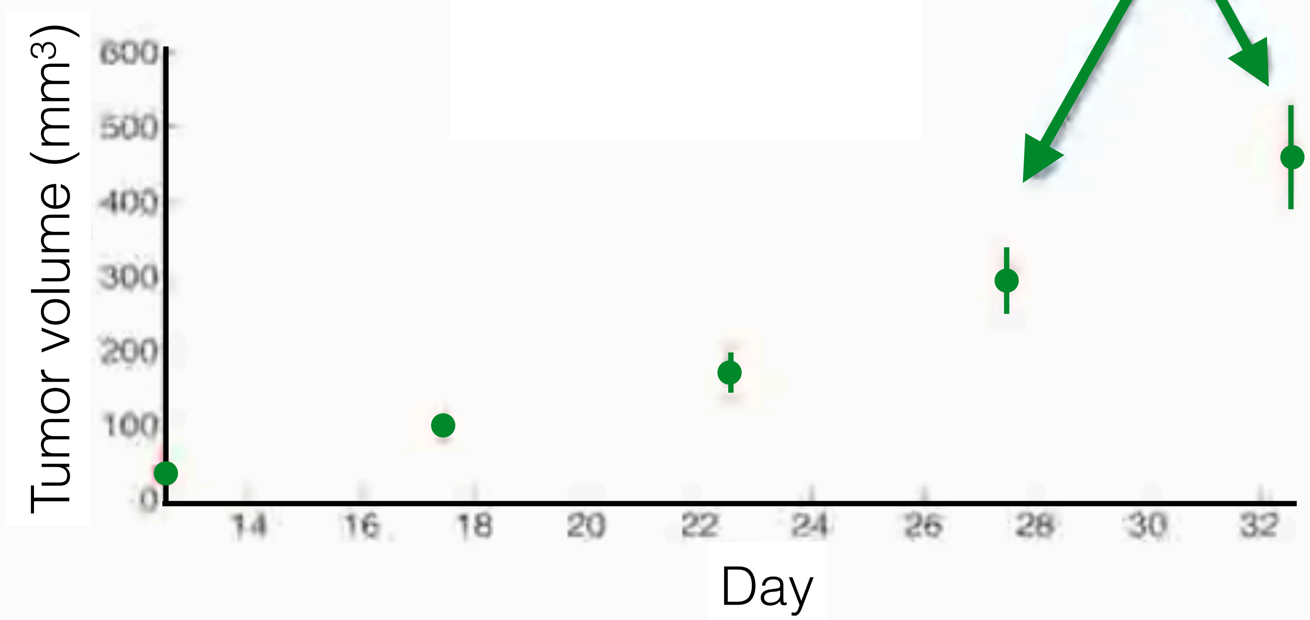
Gao et al. (Enderling), Cancer Res., 2013



$$S = e^{-\xi \lambda \left(\alpha d + \beta d^2\right)}$$

Validate Math Model

Experimental data



Model Simulation

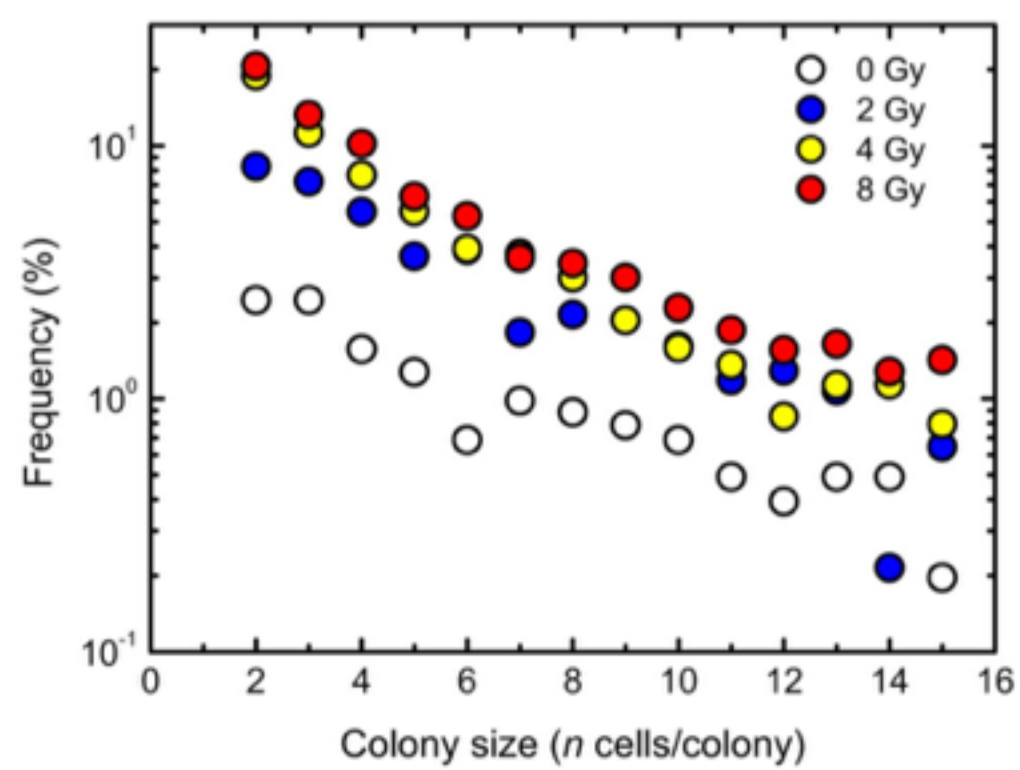
Temporal responses to radiation with therapeutic doses

- immediate cell death
- cell death at next mitosis
- cell death at next mitosis after transient cell cycle arrest
- genomic instability; cell death at future mitosis


OPEN ACCESS Freely available online PLOS ONE

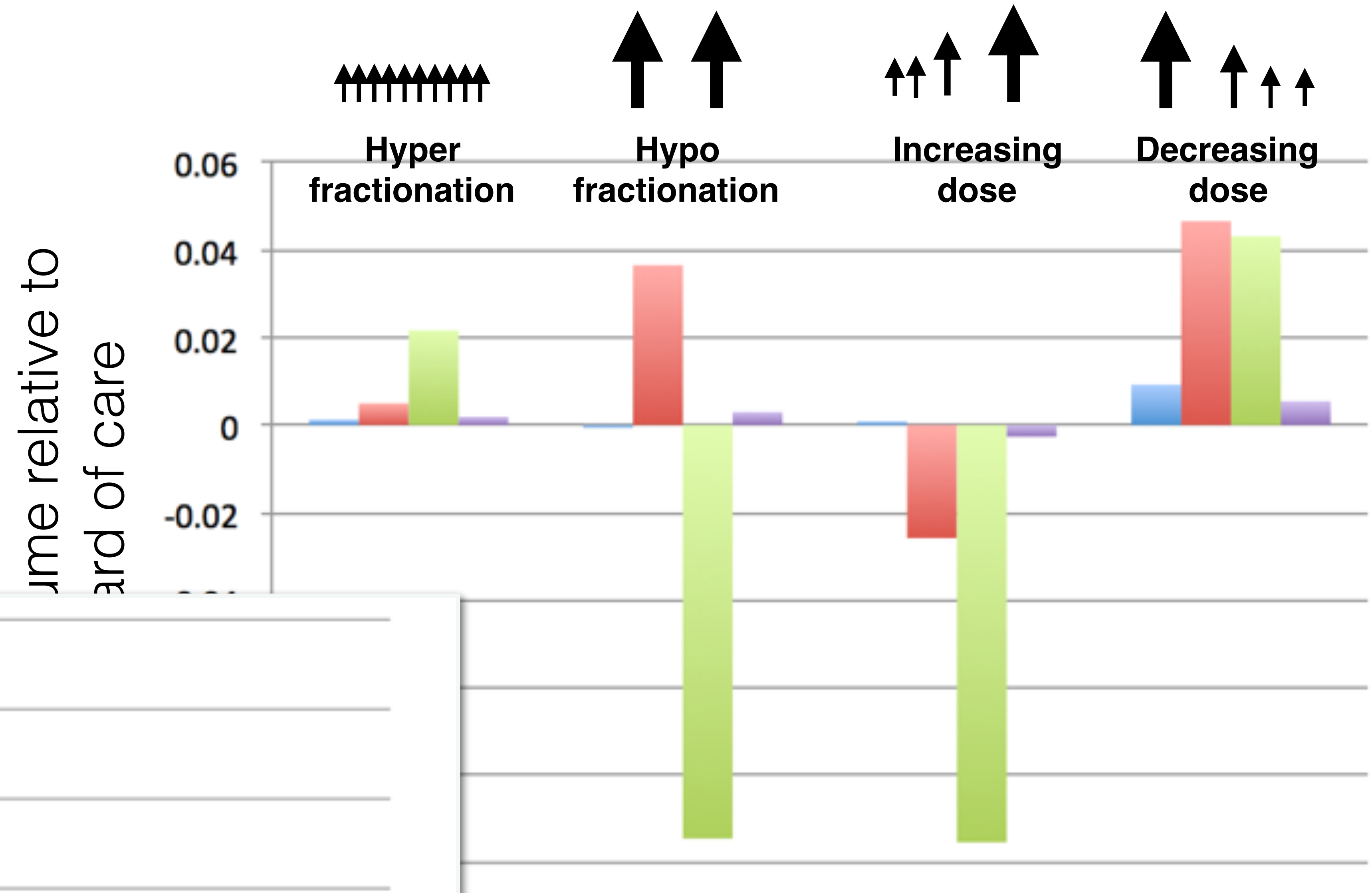
A Framework for Analysis of Abortive Colony Size Distributions Using a Model of Branching Processes in Irradiated Normal Human Fibroblasts

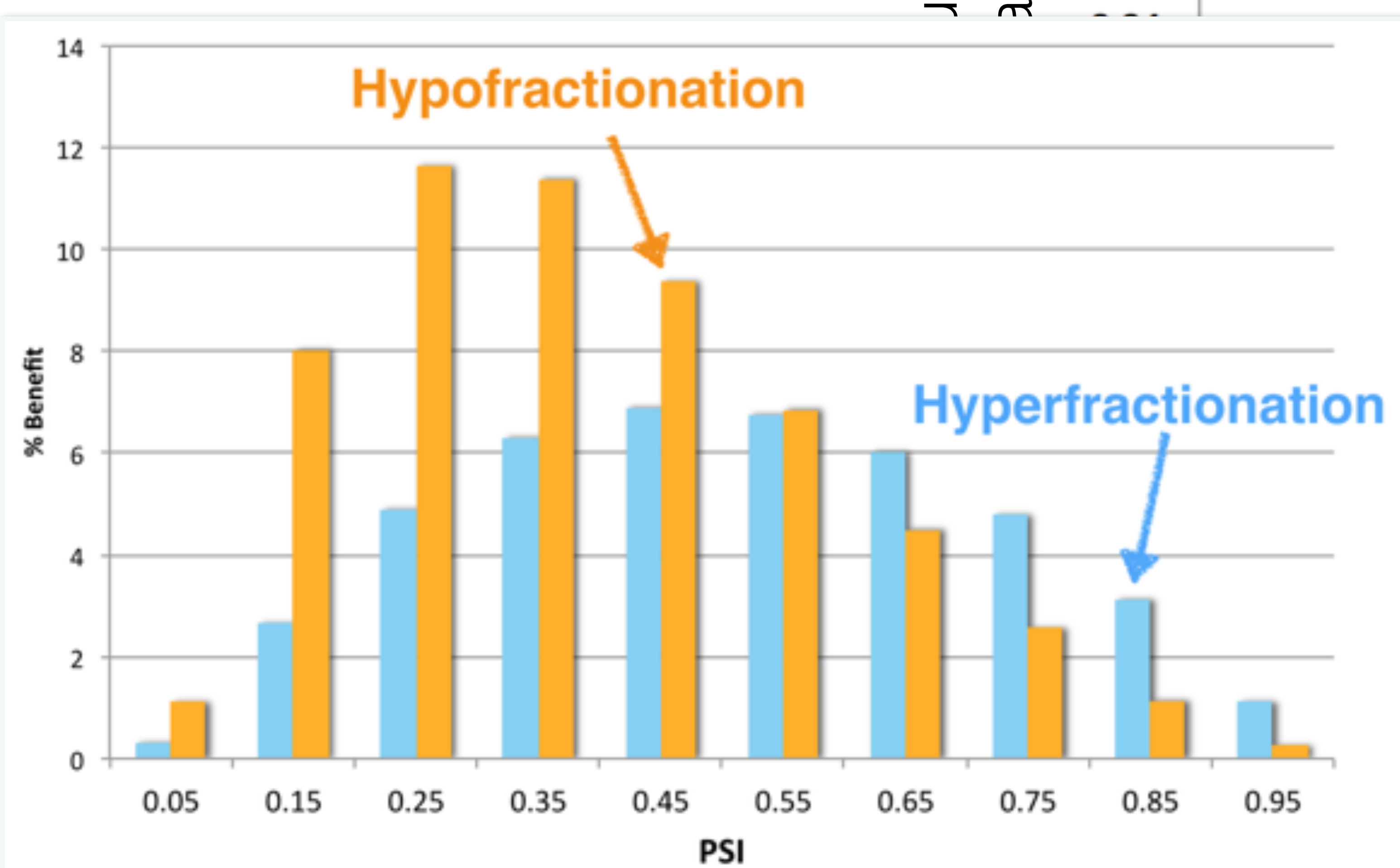
Tetsuya Sakashita[1*], Nobuyuki Hamada[2*], Isao Kawaguchi[3], Noriyuki B Ouchi[4], Takamitsu Hara[5], Yasuhiko Kobayashi[1], Kimiaki Saito[6]



Compare protocols with same total dose

- immediate cell death
- cell death at next mitosis
- cell death at next mitosis after transient cell cycle arrest
- genomic instability; cell death at future mitosis



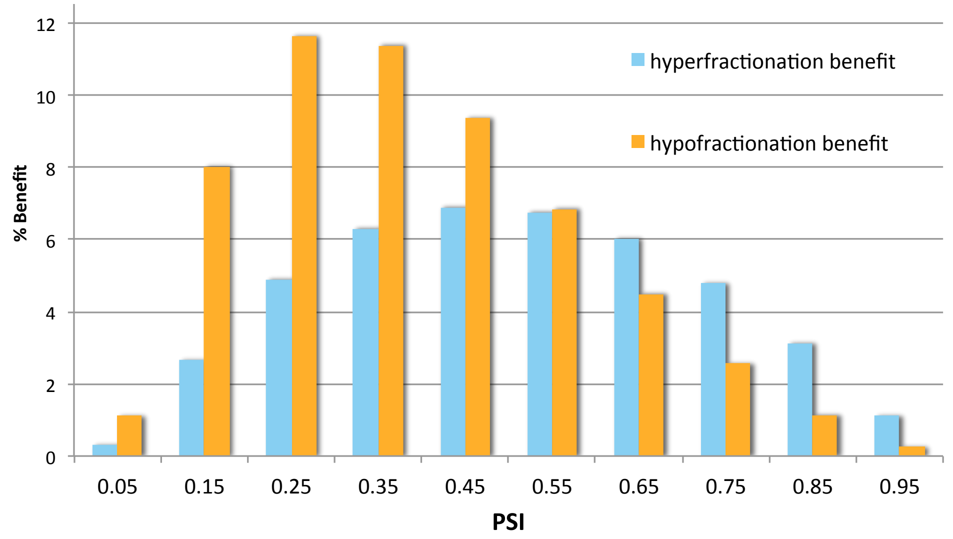


- Motivation for **adaptive radiotherapy**

- not physical beam adaption
- biological dose adaption

Summary

- Logistic + Gompertzian growth models provide excellent fits to retrospective data
  - but forward prediction may be hugely different
- Patient-specific V/K (**PSI; Proliferation Saturation Index**) emerges as prognostic factor for radiotherapy response
- Patient-specific PSI can be calculated from 2 pre-treatment scans
- PSI dependent fractionation protocols (standard, hyper, hypo)
  - personalization of radiation fractionation
  - dose fractionation adaptation?



Acknowledgements

#EnderlingLab

Dr. Jan Poleszczuk

Dr. Rachel Walker

Dr. Sotiris Prokopiou

Thomas Lewin

Joshua Bull

Sid Ramesh

Collaborators

Dr. Eduardo Moros

Dr. Louis Harrison

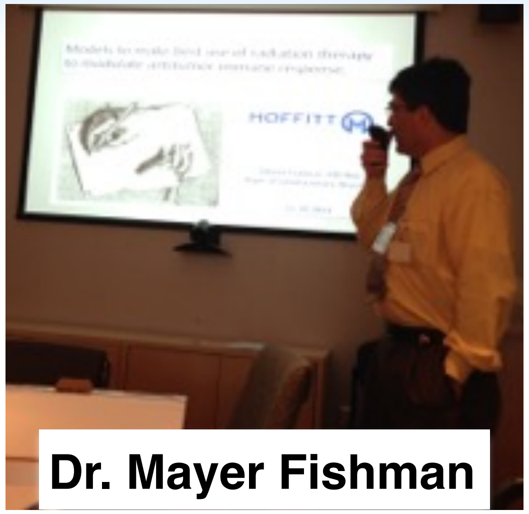
Kimberly Luddy

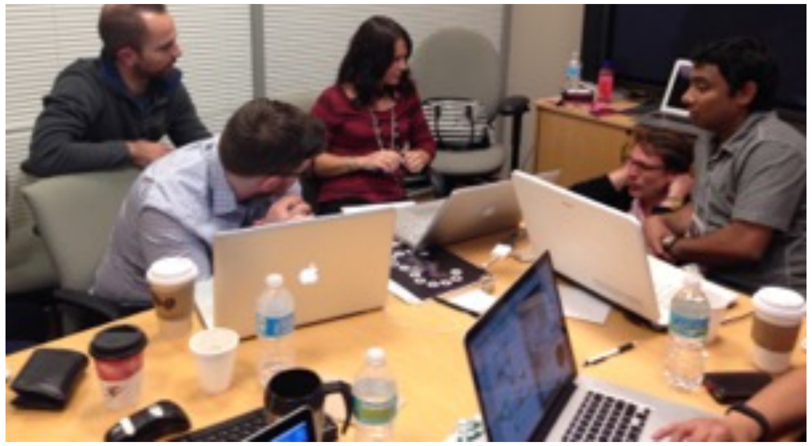
IMO / Moffitt Cancer Center

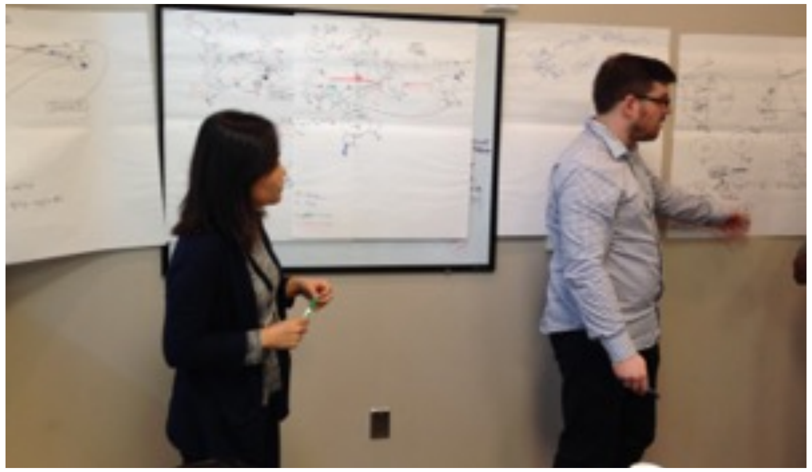
heiko.enderling@moffitt.org
http://labpages.moffitt.org/enderlingh

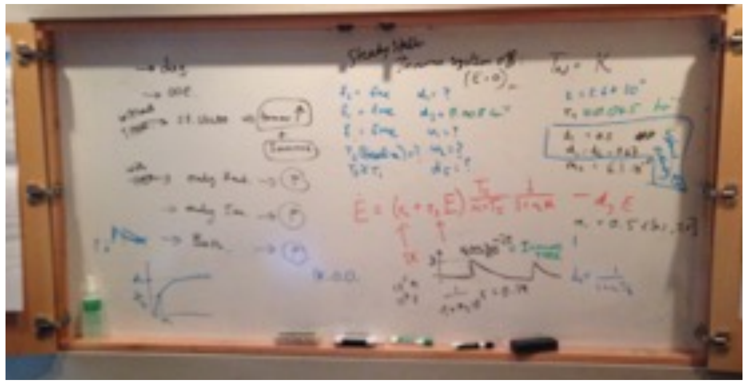
DeBartolo Family
PERSONALIZED MEDICINE INSTITUTE

3rd Integrated Mathematical Oncology
Interdisciplinary, Hands-on Workshop
Personalized Medicine









Abscopal Effect

*"The **abscopal effect** is a phenomenon in the treatment of metastatic cancer where localized irradiation of a tumor causes not only a shrinking of the irradiated tumor but also a shrinking of tumors far from the irradiated area."*

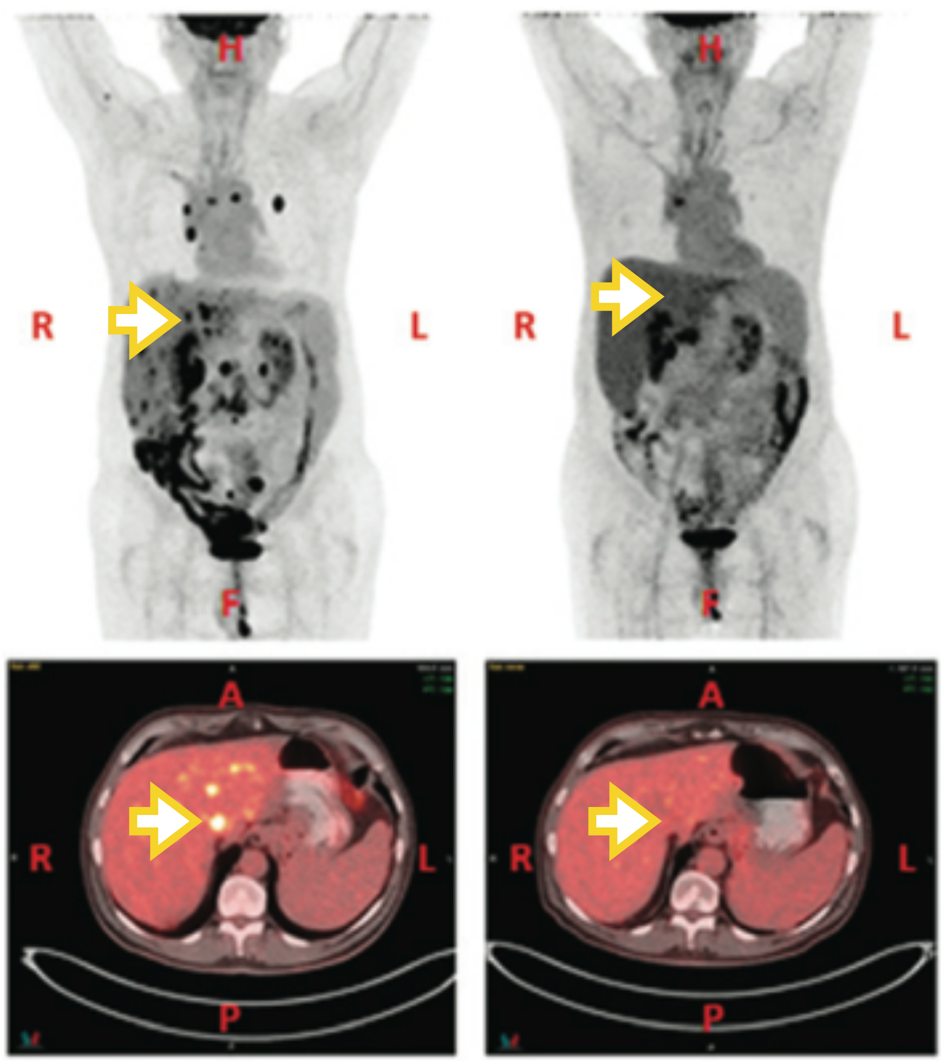
(Wikipedia, 9/12/14)

An untreated distant metastasis on the right ankle resolved after brachytherapy (12 Gy total dose) to lesions on the upper half of the right lower leg. (Cotter, *Arch Dermatol*, 2011)

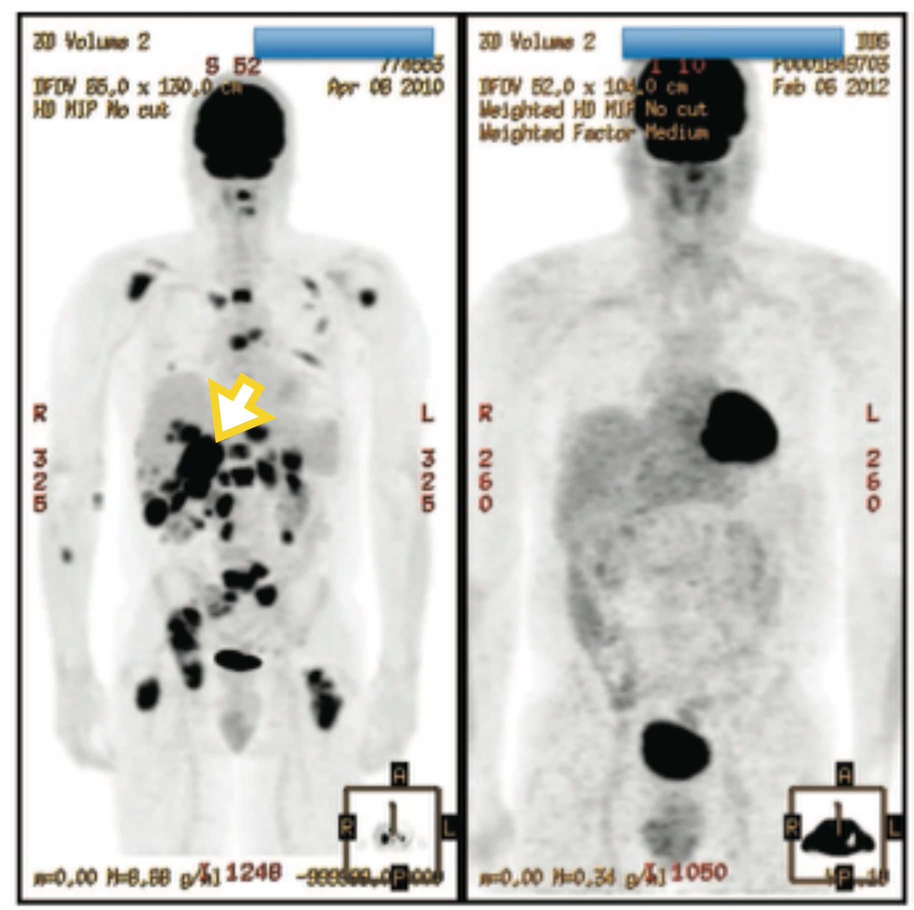
Abscopal Effect

*“The **abscopal effect** is a phenomenon in the treatment of <u>metastatic cancer</u> where <u>localized irradiation</u> of a tumor causes not only a shrinking of the irradiated tumor but also a <u>shrinking of tumors far from the irradiated area</u>.”*

(Wikipedia, 9/12/14)



NSCLC, Golden et al., Cancer Immunol Res, 2013



Melanoma, Seung et al., Sci Transl Med, 2012

MOFFITT CANCER CENTER

Int. J. Radiation Oncology Biol. Phys., Vol. 58, No. 3, pp. 862–870, 2004

0360-3016/04/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2003.09.012

BIOLOGY CONTRIBUTION

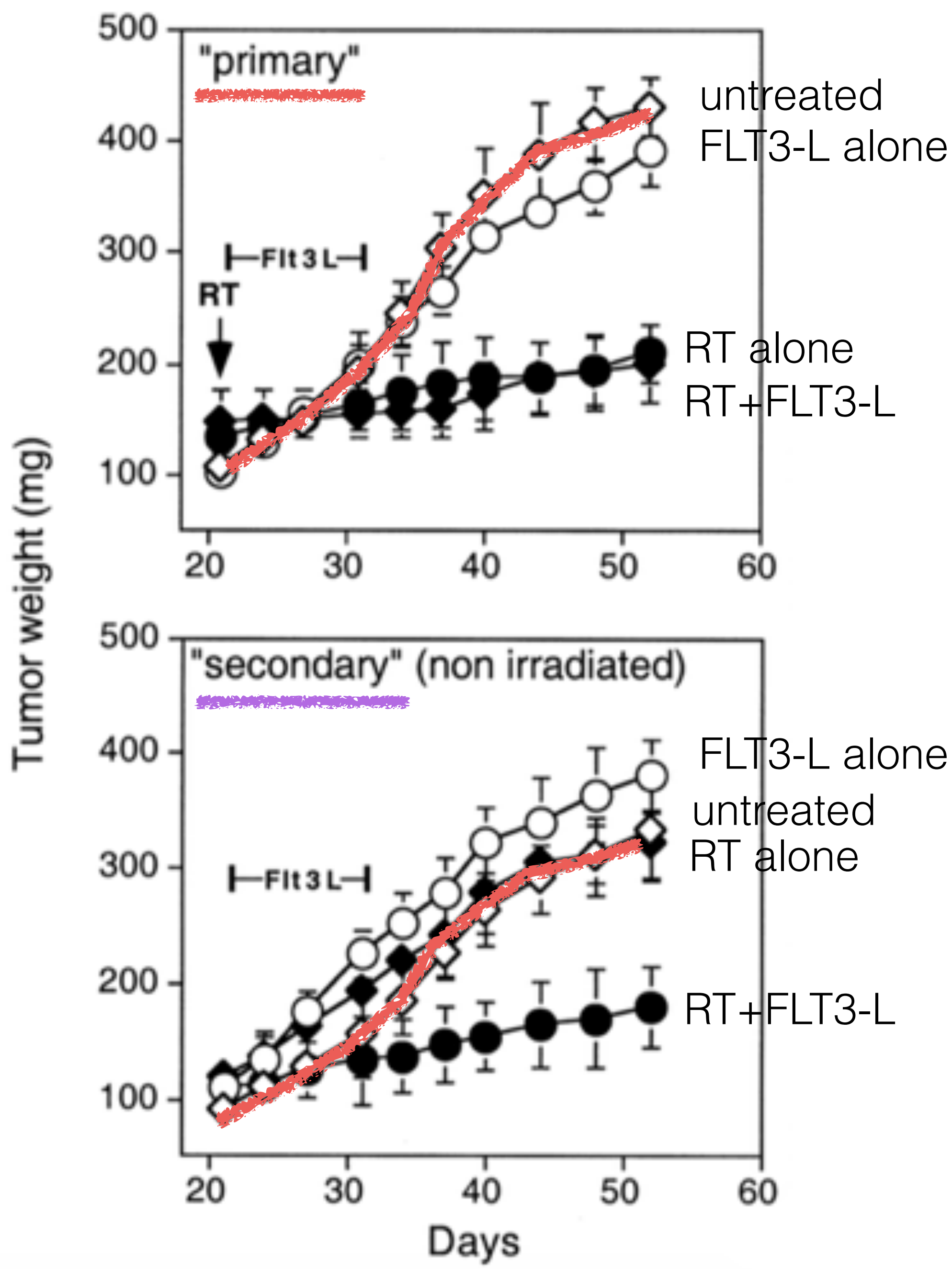
IONIZING RADIATION INHIBITION OF DISTANT UNTREATED TUMORS (ABSCOPAL EFFECT) IS IMMUNE MEDIATED

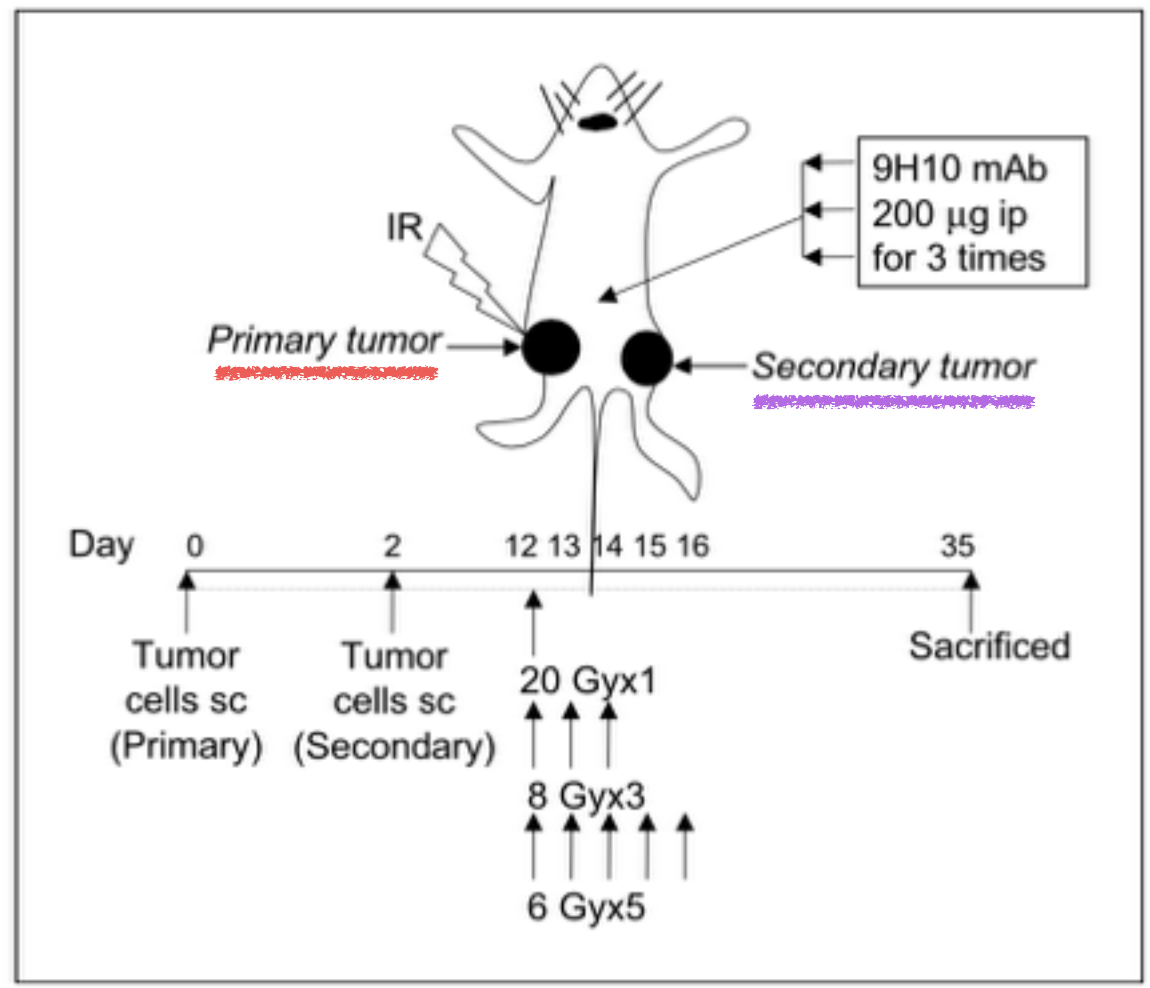
Sandra Demaria, M.D.,* Bruce Ng, M.S.,† Mary Louise Devitt, A.A.S.,‡ James S. Babb, Ph.D.,§ Noriko Kawashima, M.S.,* Leonard Liebes, Ph.D.,† and Silvia C. Formenti, M.D.‡

Departments of *Pathology, †Medicine, ‡Radiation Oncology, and §Radiology, New York University School of Medicine, New York, New York

wild-type female BALB/C mice

67NR cells





Int. J. Radiation Oncology Biol. Phys., Vol. 58, No. 3, pp. 862–870, 2004

0360-3016/04/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2003.09.012

BIOLOGY CONTRIBUTION

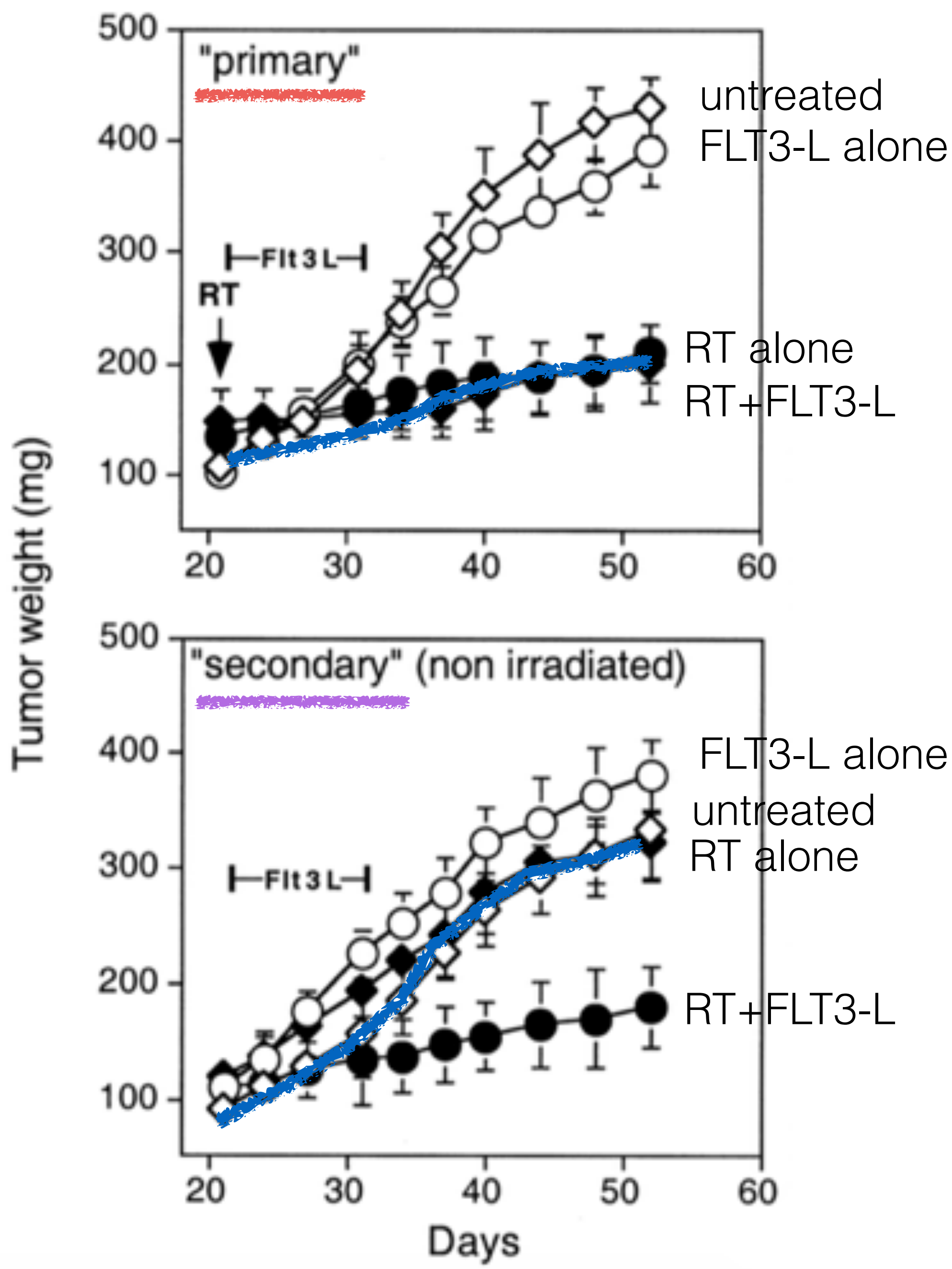
IONIZING RADIATION INHIBITION OF DISTANT UNTREATED TUMORS (ABSCOPAL EFFECT) IS IMMUNE MEDIATED

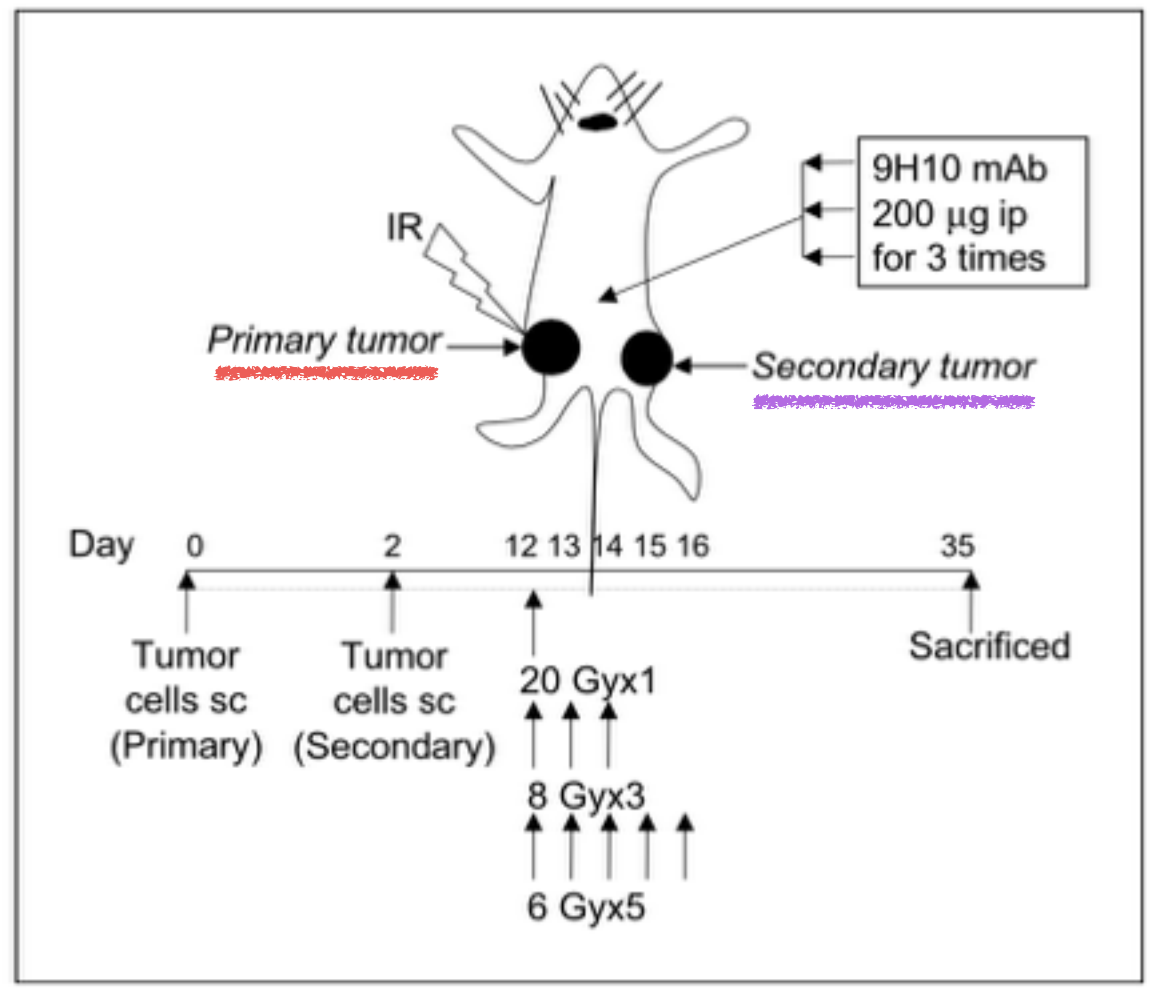
Sandra Demaria, M.D.,[*] Bruce Ng, M.S.,[†] Mary Louise Devitt, A.A.S.,[‡] James S. Babb, Ph.D.,[§] Noriko Kawashima, M.S.,[*] Leonard Liebes, Ph.D.,[†] and Silvia C. Formenti, M.D.[‡]

Departments of [*]Pathology, [†]Medicine, [‡]Radiation Oncology, and [§]Radiology, New York University School of Medicine, New York, New York

wild-type female BALB/C mice

67NR cells





Int. J. Radiation Oncology Biol. Phys., Vol. 58, No. 3, pp. 862–870, 2004
Copyright © 2004 Elsevier Inc.
Printed in the USA. All rights reserved
0360-3016/04/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2003.09.012

BIOLOGY CONTRIBUTION

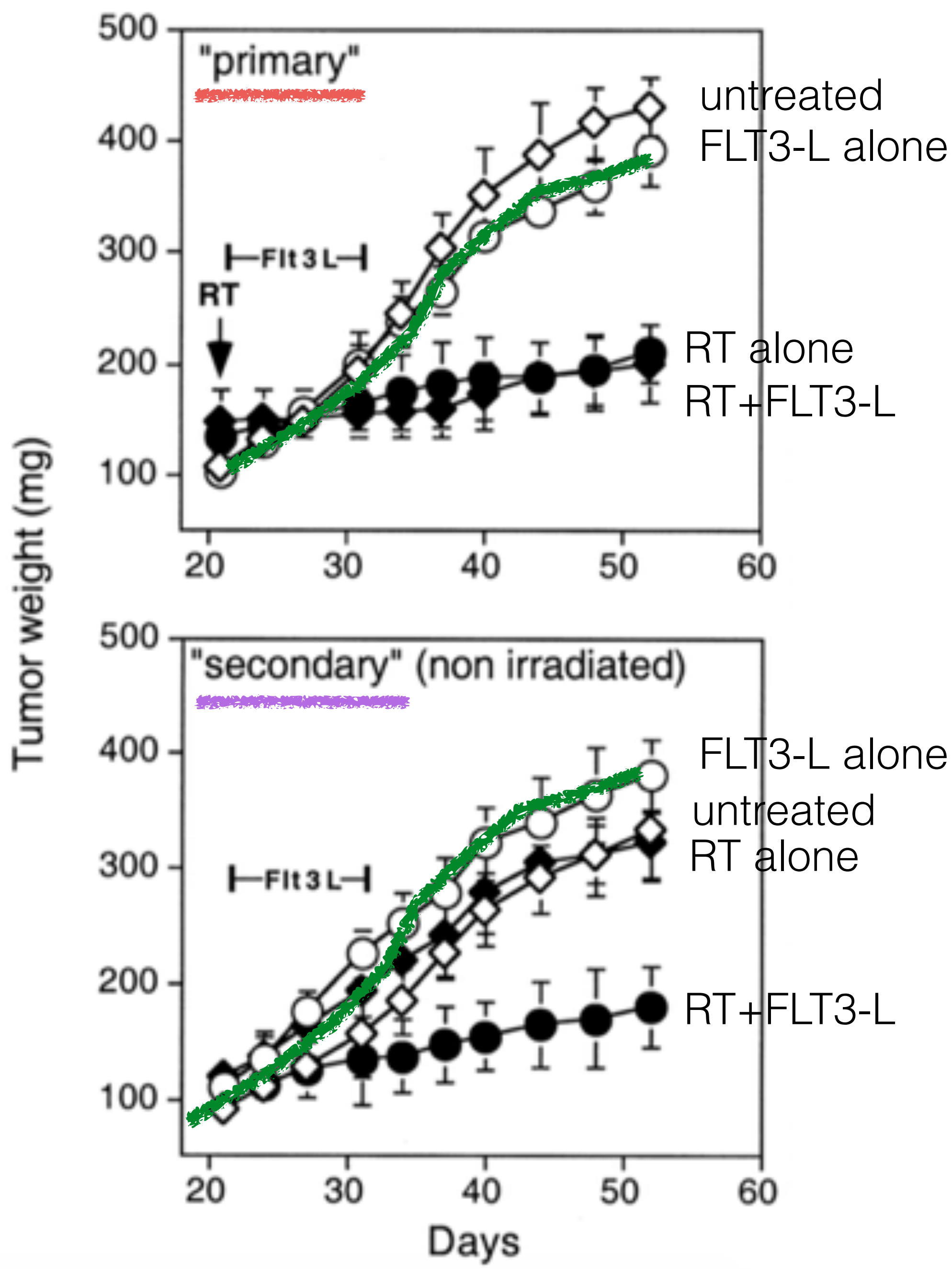
IONIZING RADIATION INHIBITION OF DISTANT UNTREATED TUMORS (ABSCOPAL EFFECT) IS IMMUNE MEDIATED

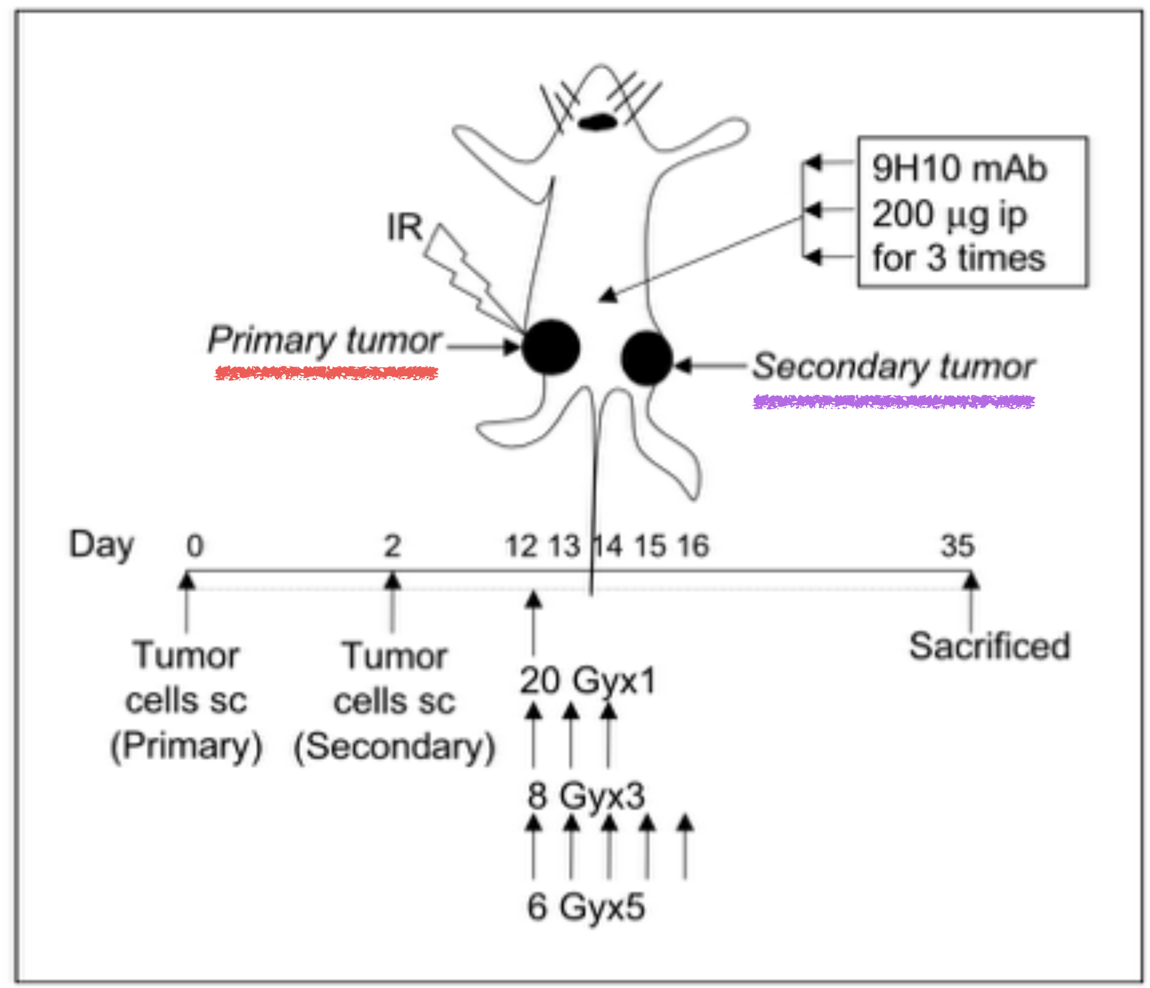
Sandra Demaria, M.D.,* Bruce Ng, M.S.,† Mary Louise Devitt, A.A.S.,‡ James S. Babb, Ph.D.,§ Noriko Kawashima, M.S.,* Leonard Liebes, Ph.D.,† and Silvia C. Formenti, M.D.‡

Departments of *Pathology, †Medicine, ‡Radiation Oncology, and §Radiology, New York University School of Medicine, New York, New York

wild-type female BALB/C mice

67NR cells





Int. J. Radiation Oncology Biol. Phys., Vol. 58, No. 3, pp. 862–870, 2004

0360-3016/04/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2003.09.012

BIOLOGY CONTRIBUTION

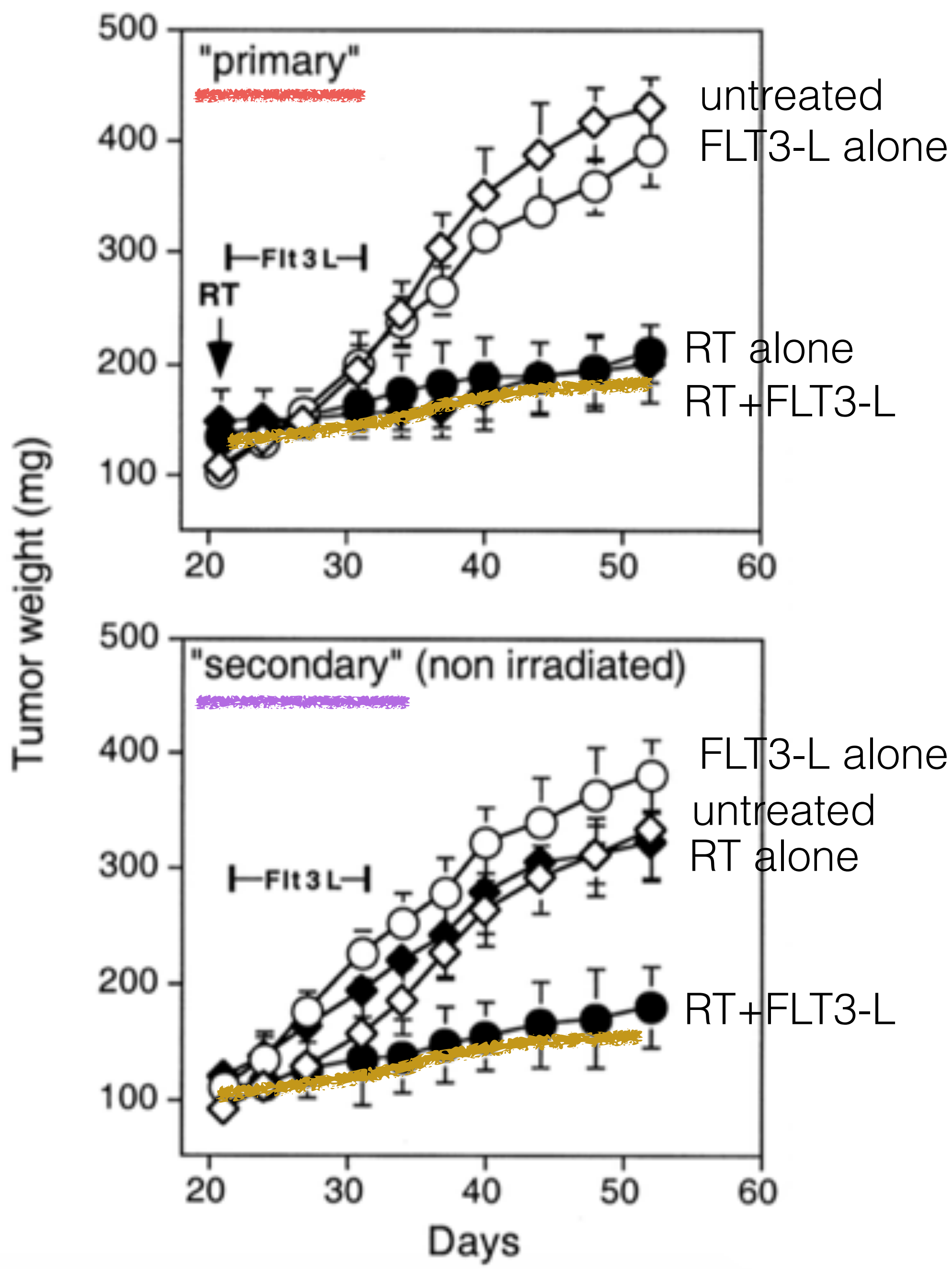
IONIZING RADIATION INHIBITION OF DISTANT UNTREATED TUMORS (ABSCOPAL EFFECT) IS IMMUNE MEDIATED

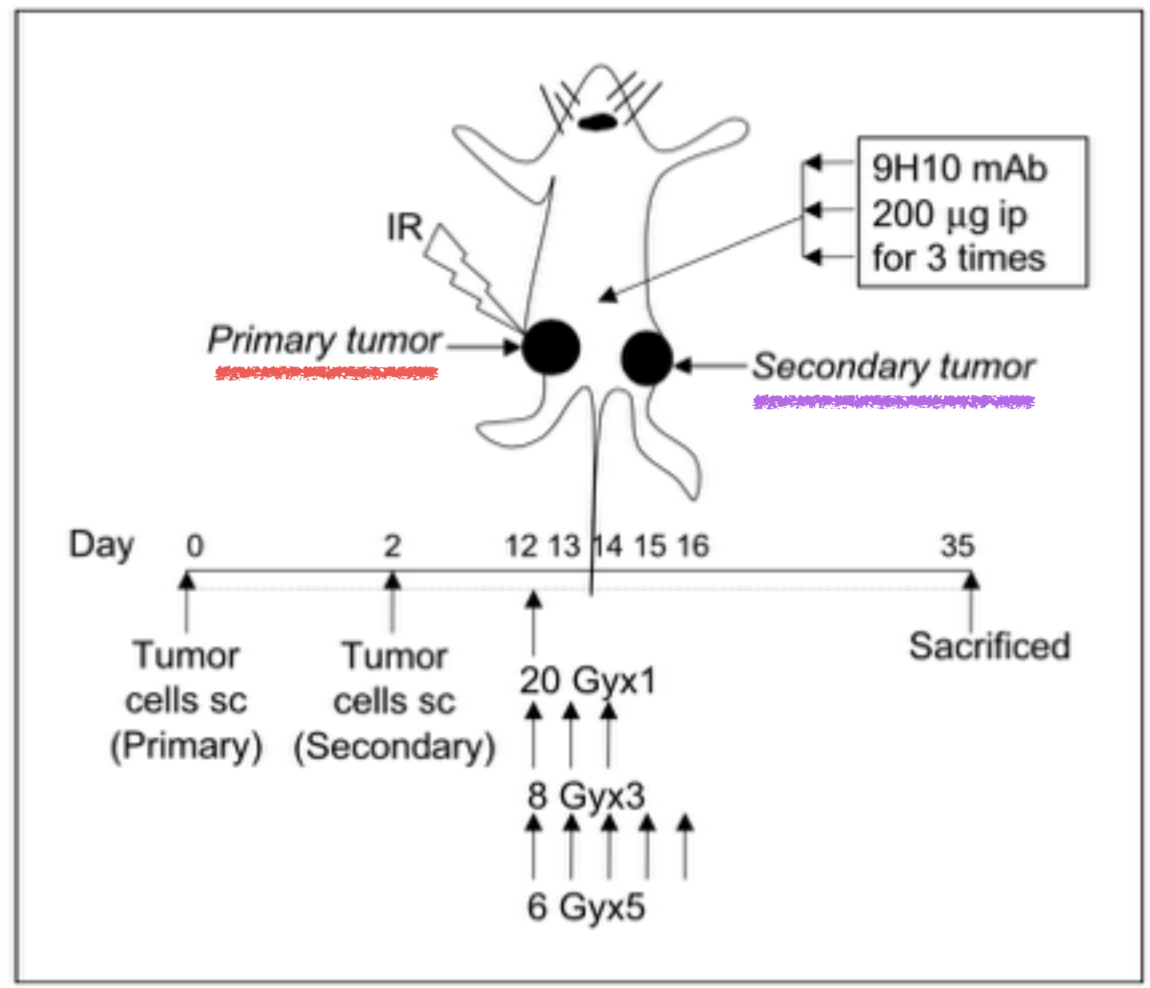
Sandra Demaria, M.D.,* Bruce Ng, M.S.,† Mary Louise Devitt, A.A.S.,‡ James S. Babb, Ph.D.,§ Noriko Kawashima, M.S.,* Leonard Liebes, Ph.D.,† and Silvia C. Formenti, M.D.‡

Departments of *Pathology, †Medicine, ‡Radiation Oncology, and §Radiology, New York University School of Medicine, New York, New York

wild-type female BALB/C mice

67NR cells





Int. J. Radiation Oncology Biol. Phys., Vol. 58, No. 3, pp. 862–870, 2004

0360-3016/04/$-see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2003.09.012

BIOLOGY CONTRIBUTION

IONIZING RADIATION INHIBITION OF DISTANT UNTREATED TUMORS (ABSCOPAL EFFECT) IS IMMUNE MEDIATED

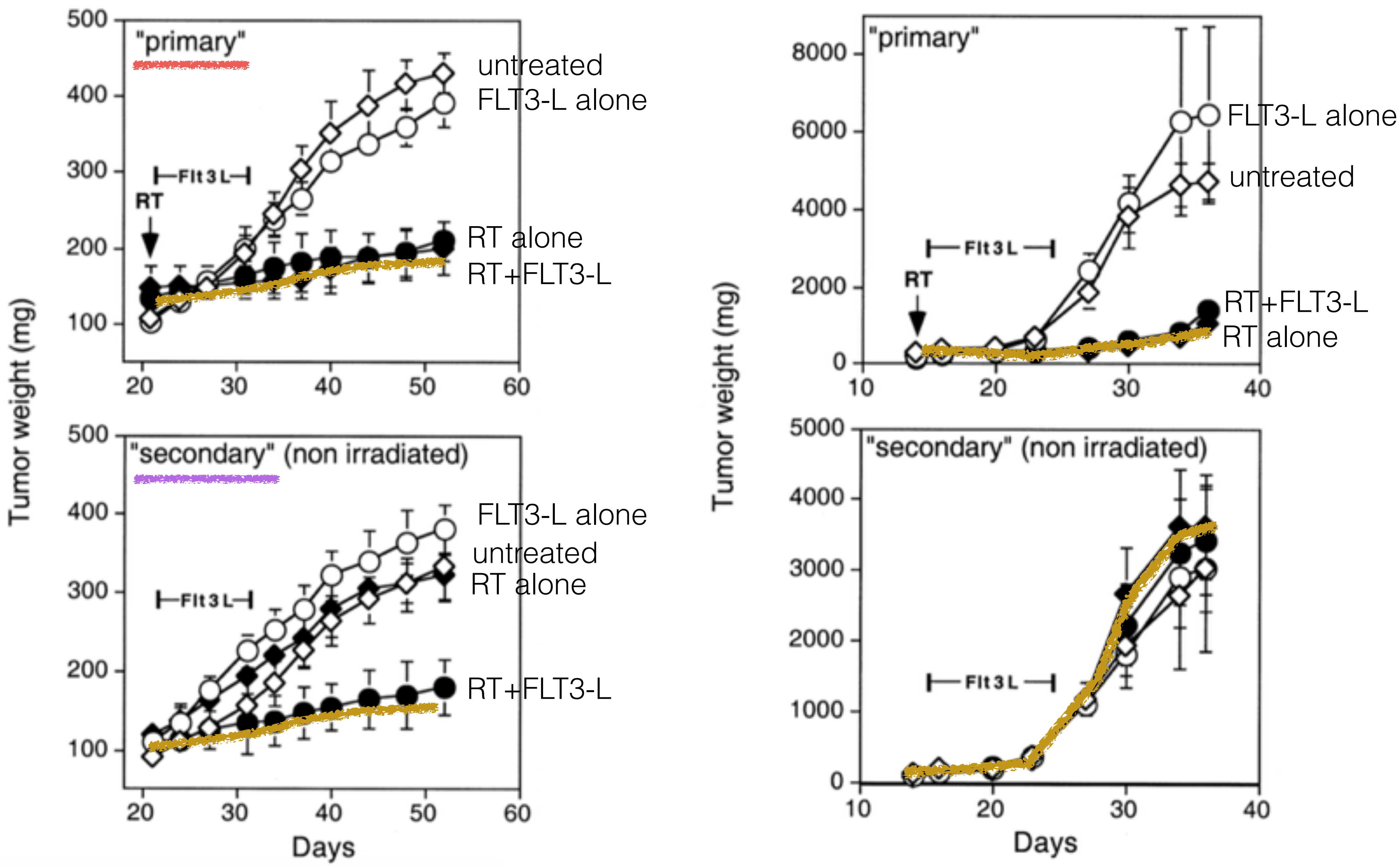
Sandra Demaria, M.D.,* Bruce Ng, M.S.,† Mary Louise Devitt, A.A.S.,‡ James S. Babb, Ph.D.,§ Noriko Kawashima, M.S.,* Leonard Liebes, Ph.D.,† and Silvia C. Formenti, M.D.‡

Departments of *Pathology, †Medicine, ‡Radiation Oncology, and §Radiology, New York University School of Medicine, New York, New York

wild-type female BALB/C mice

nu/nu female BALB/C

67NR cells



Hypothesis

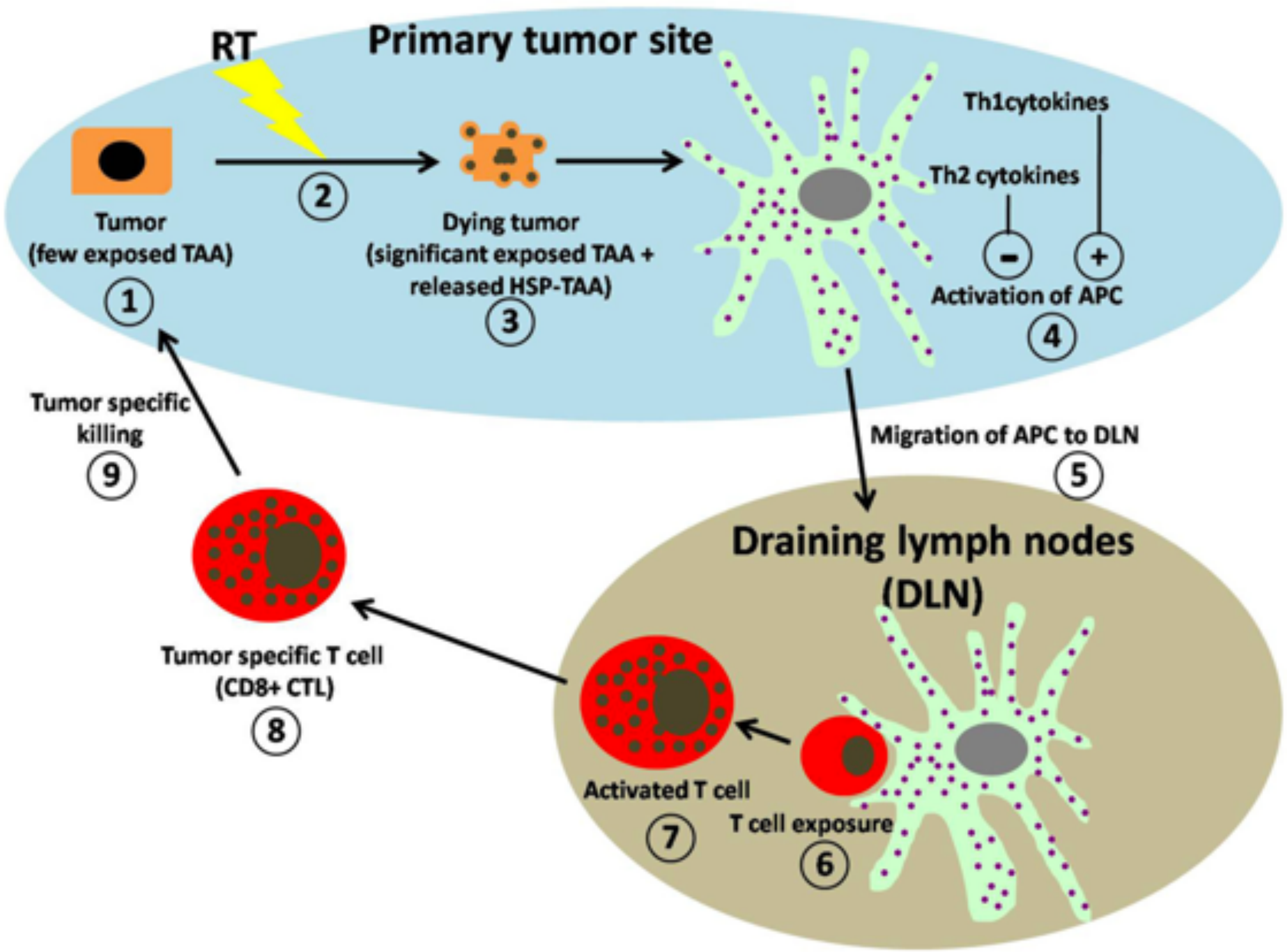
- The induction of the abscopal effects depends on the **trafficking of activated T cells** through the host circulatory system.
  - the **size** and **anatomic location** of each metastatic tumor,
  - the **radiation target** and tissue of immune cell activation after local radiation.

Different metastatic sites within an individual patient have different potentials to induce an abscopal effect.

Question

Can we predict radiation-induced T cell activation, trafficking and systemic distribution to identify best treatment targets for <u>individual</u> patients?

Radiation-immune synergy



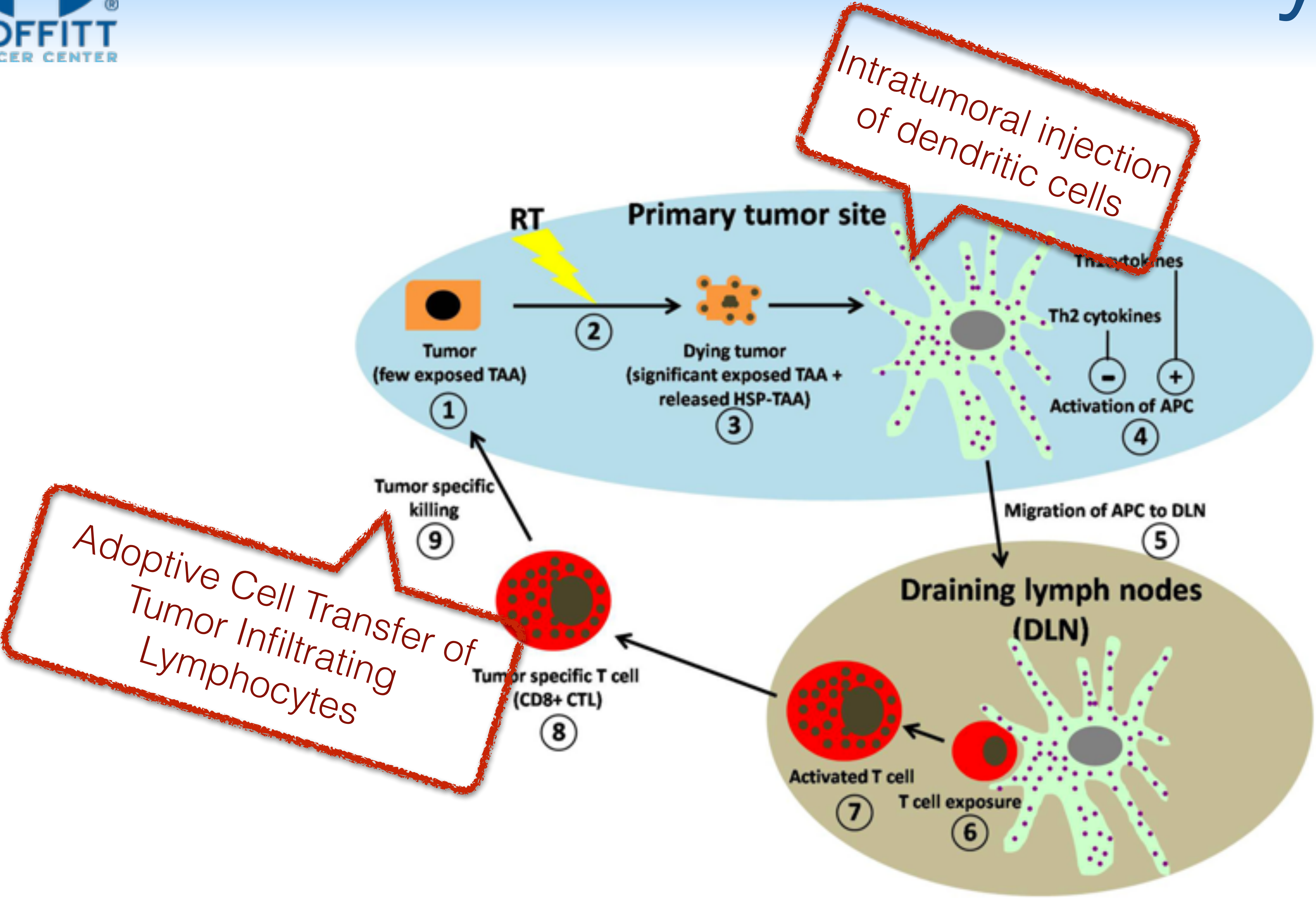
frontiers in ONCOLOGY
REVIEW ARTICLE
published: 17 December 2012
doi: 10.3389/fonc.2012.00191

Radiation-induced effects and the immune system in cancer

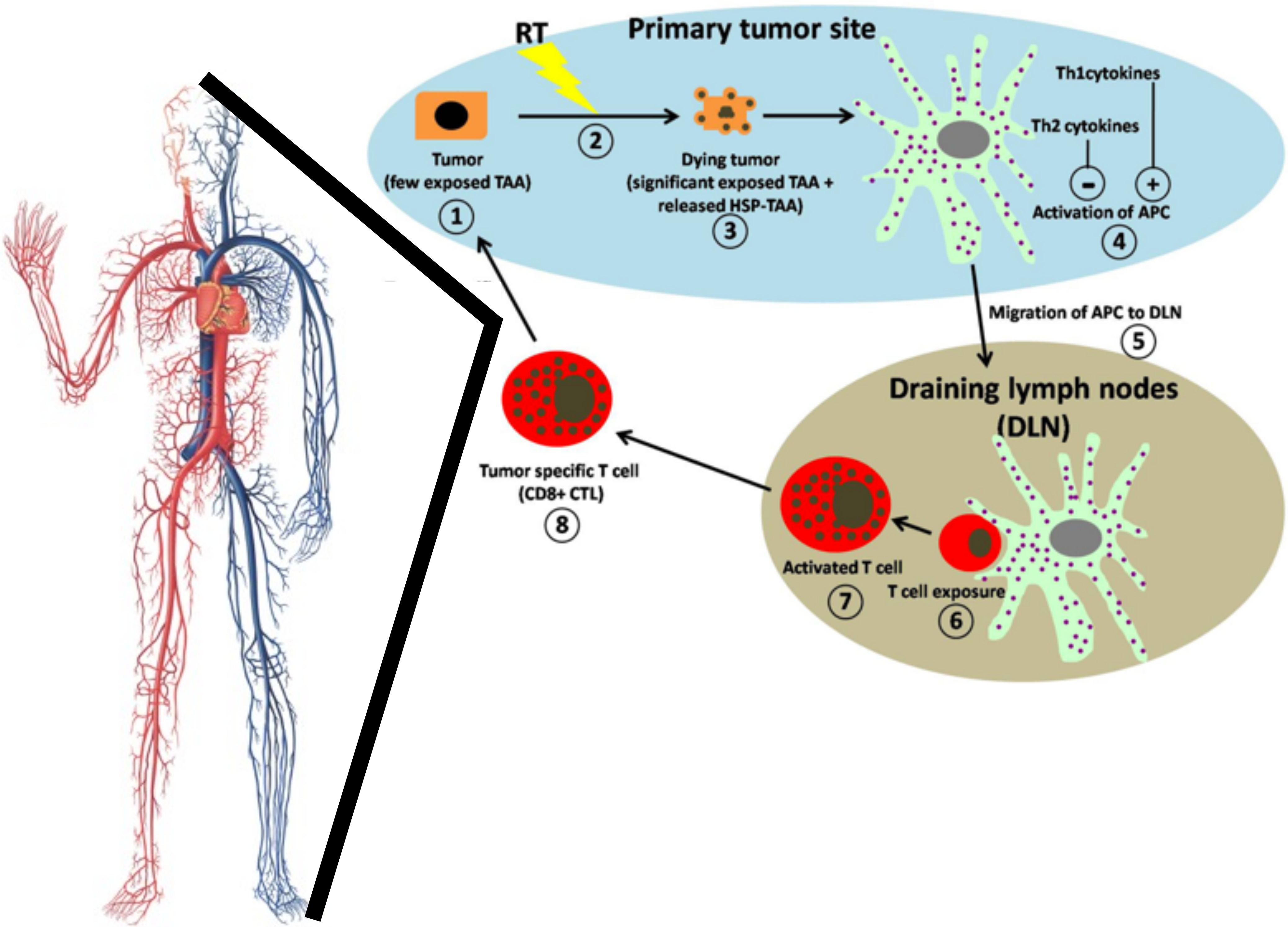
*Punit Kaur and Alexzander Asea**

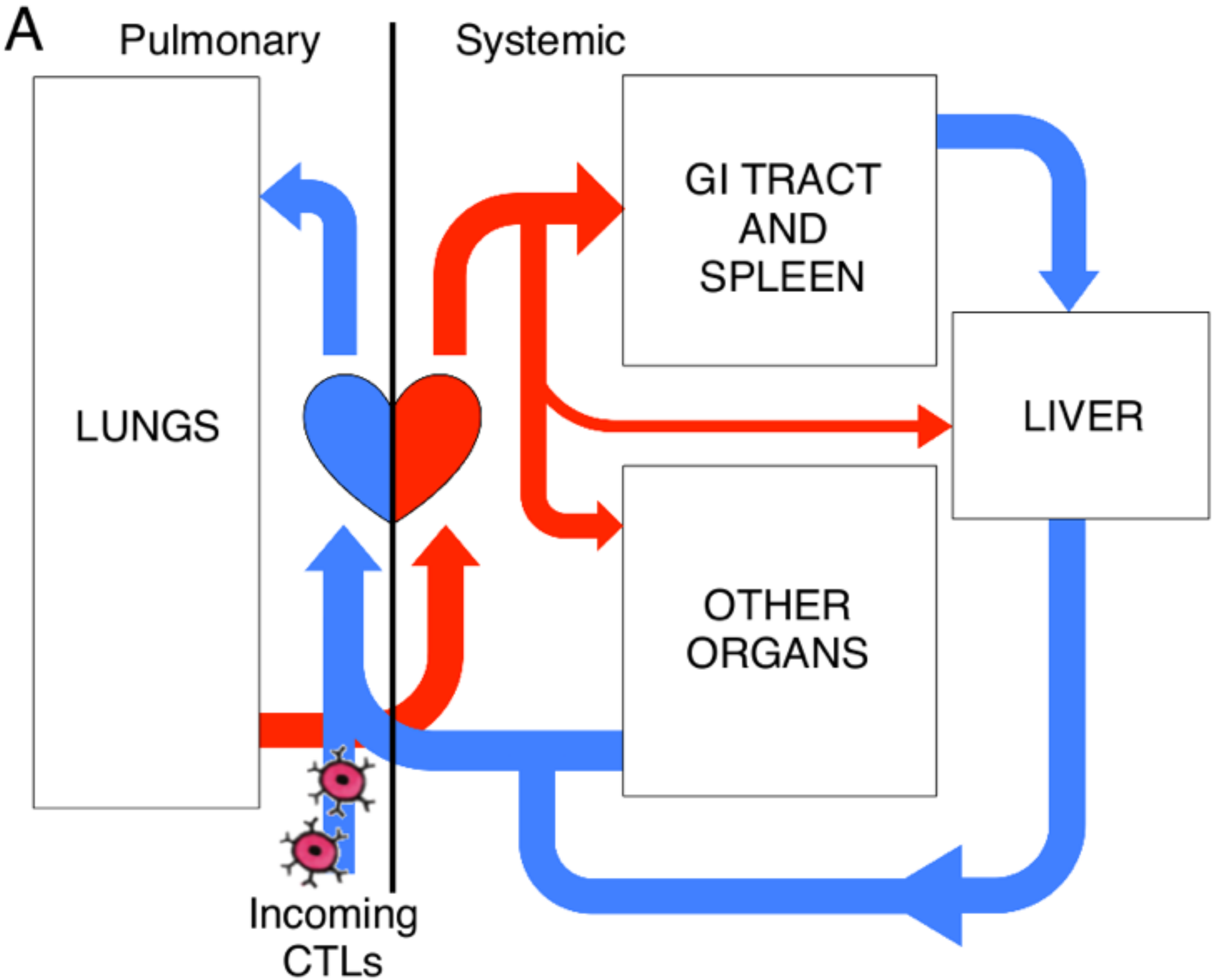
Department of Microbiology, Biochemistry and Immunology, Morehouse School of Medicine, Atlanta, GA, USA

Radiation-immune synergy



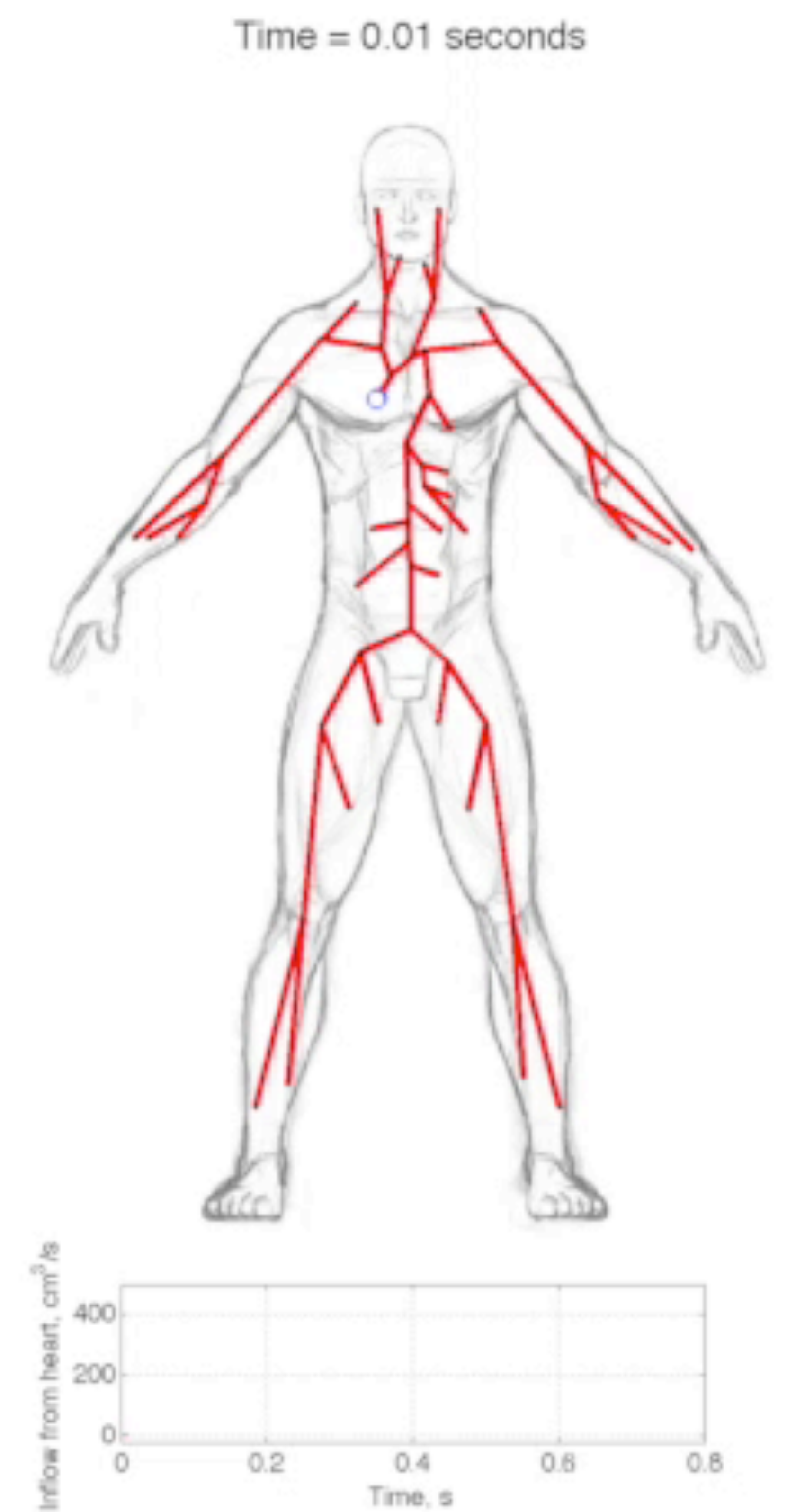
Radiation-immune synergy

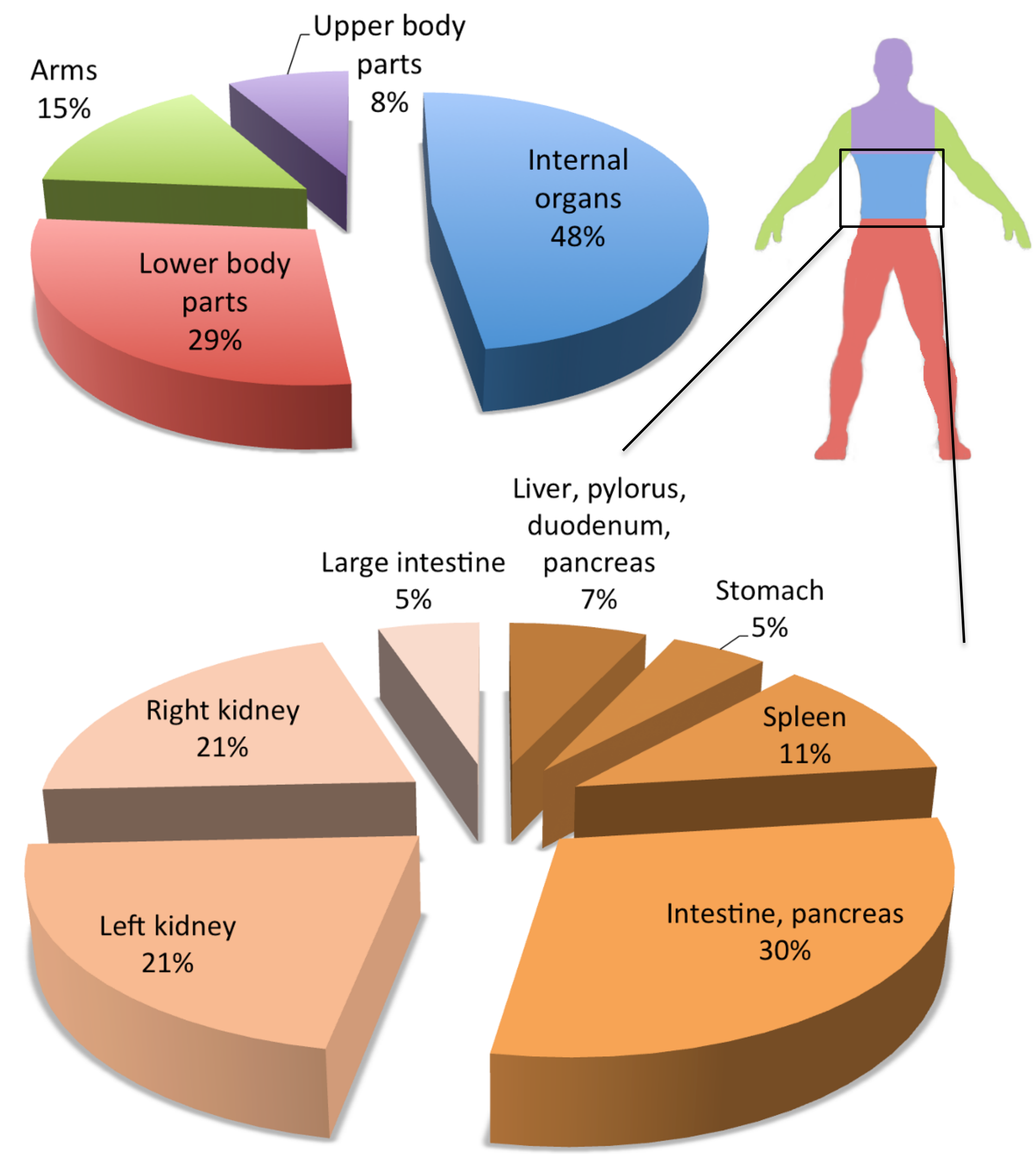



A
Pulmonary
Systemic
LUNGS
GI TRACT
AND
SPLEEN
LIVER
OTHER
ORGANS
Incoming
CTLs

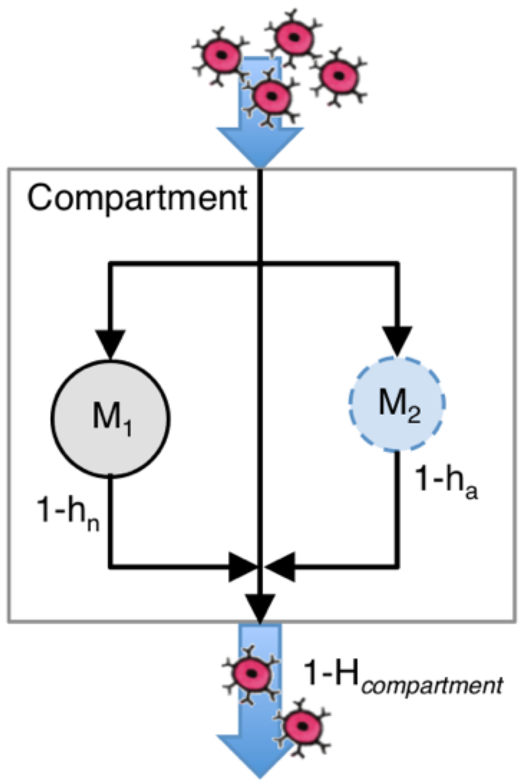
Blood Flow Fractions

At each branching point T cell enters daughter vessels according to the current flow distribution.





MOFFITT CANCER CENTER



patient-specific

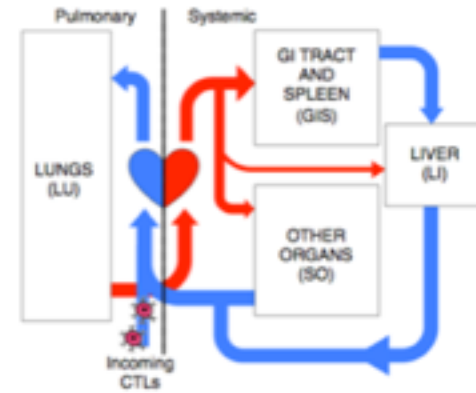
pre-computed

__*Obtain*__
patient-specific diagnostic PET/CT data set

__*Determine*__ **(V_i)**
metastatic tumor volumes in each organ V_{organ}

__*Determine*__ **(BFF_{organ})**
physiologic blood flow fraction to each **tumor bearing organ** from table

__*Determine*__ **($BFF_{compartment}$)**
physiologic blood flow fraction to each **compartment** from table



__*Calculate*__ **(P_i)**
P_i is the probability that the T cell will infiltrate *ith* tumor site after entering a given compartment in each circulatory cycle

__*Calculate*__ **(p_i)**
p_i is the overall probability that the T cell will home to the *ith* tumor site

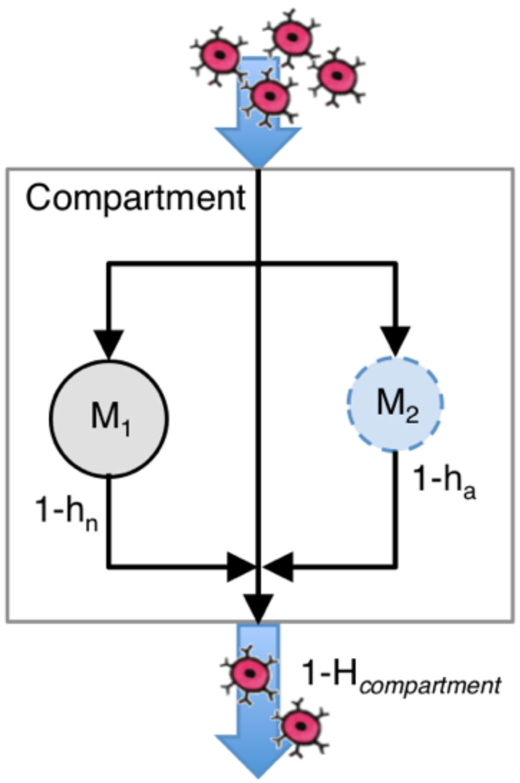
__*Calculate*__ **(E_i)**
Normalized entropy of homing distribution, based on activated T cell dissemination for each metastatic site

__*Calculate*__
Immunogenicity Index, assigned to each site

__*Rank*__
patient-specific treatment targets with highest likelihood of inducing an abscopal effect

__*Rank*__
Combinations of patient-specific treatment targets with highest likelihood of inducing an abscopal effect

MOFFITT CANCER CENTER



patient-specific

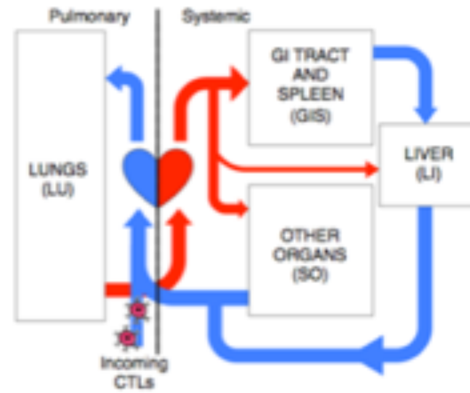
Obtain
patient-specific diagnostic PET/CT data set

Determine **(V_i)**
metastatic tumor volumes in each organ V_{organ}

Determine **(BFF_{organ})**
physiologic blood flow fraction to each **tumor bearing organ** from table

pre-computed

Determine **($BFF_{compartment}$)**
physiologic blood flow fraction to each **compartment** from table



Calculate **(P_i)**
P_i is the probability that the T cell will infiltrate *ith* tumor site after entering a given compartment in each circulatory cycle

$$P_i = h \times \frac{BFF_{organ}}{BFF_{compartment}} \times \frac{V_i}{V_{organ}}$$

h = Extravasation Probability.
Each metastatic site will be evaluated for h_a (activation of T cells by radiation) or h_n (no activation - other site irradiated); where $h_a > h_n$

Calculate **(p_i)**
p_i is the overall probability that the T cell will home to the *ith* tumor site

$$p_i = P_{absorbtion} \frac{P_i}{H_{compartment}}$$

$H_{compartment}$ = sum of P_i in a compartment

$$P_{absorption} = \frac{1}{\Delta} \begin{cases} H_{LU} & \text{in LU} \\ H_{LI}(1-H_{LU})(BFF_{LI} + BFF_{GIS}(1-H_{GIS})) & \text{in LI} \\ H_{GIS} BFF_{GIS}(1-H_{LU}) & \text{in GIS} \\ H_{SO} BFF_{SO}(1-H_{LU}) & \text{in SO} \end{cases}$$

Δ = normalization constant

Calculate **(E_i)**
Normalized entropy of homing distribution, based on activated T cell dissemination for each metastatic site

$$E_i = \left(\sum_{j=1}^{N} p_{ji} \ln p_{ji}\right) / \left(N \ln \frac{1}{N}\right)$$

N = number of metastatic sites
p_{ij} = probability of a T cell activated at site *i* infiltrates tumor at site *j*

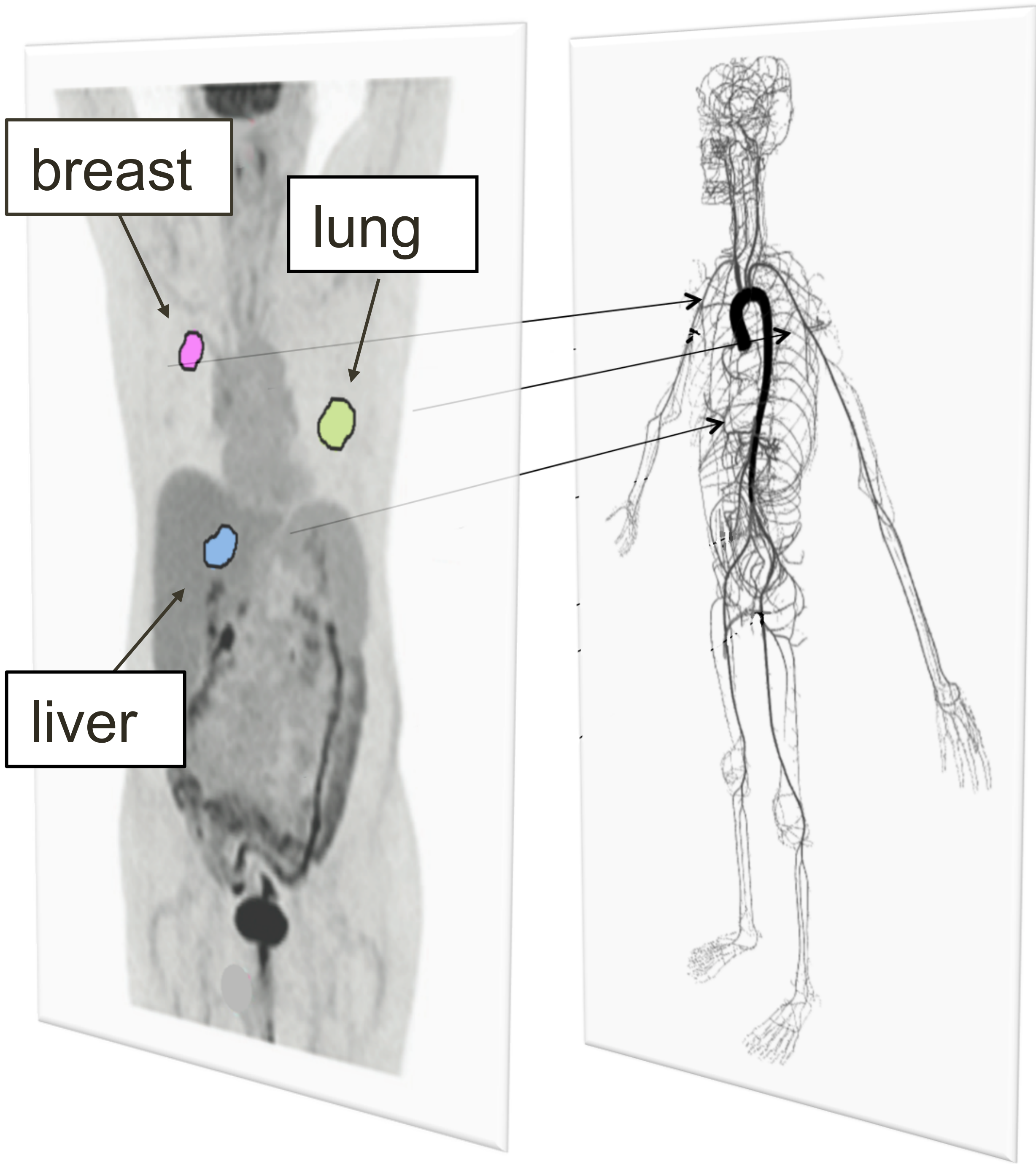
Calculate
Immunogenicity Index, assigned to each site

$$I_i = E_i \frac{V_i}{\max(V_1, \ldots, V_N)}$$

Rank
patient-specific treatment targets with highest likelihood of inducing an abscopal effect

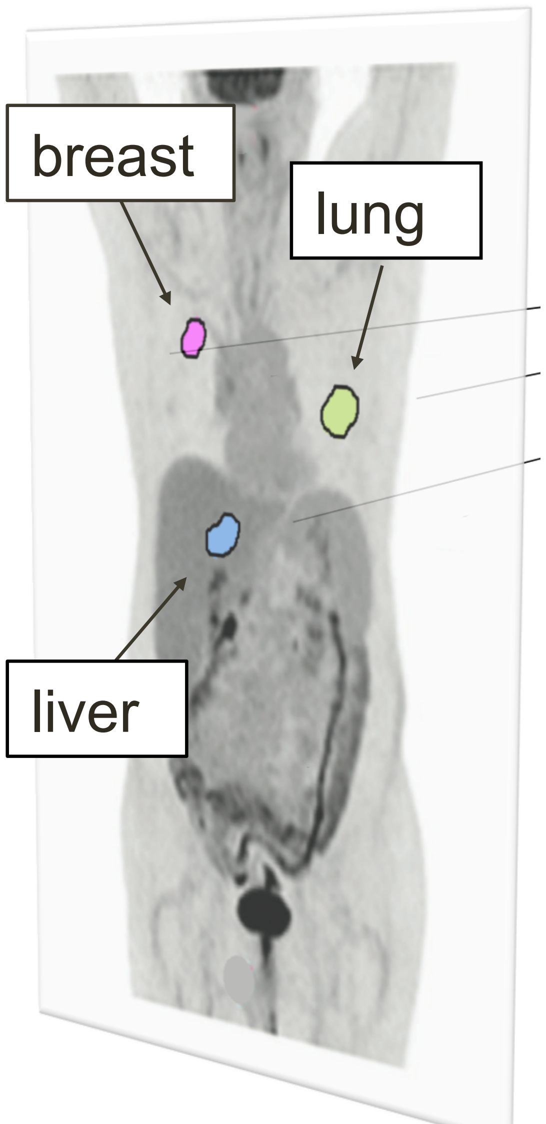
Rank
Combinations of patient-specific treatment targets with highest likelihood of inducing an abscopal effect

Case study

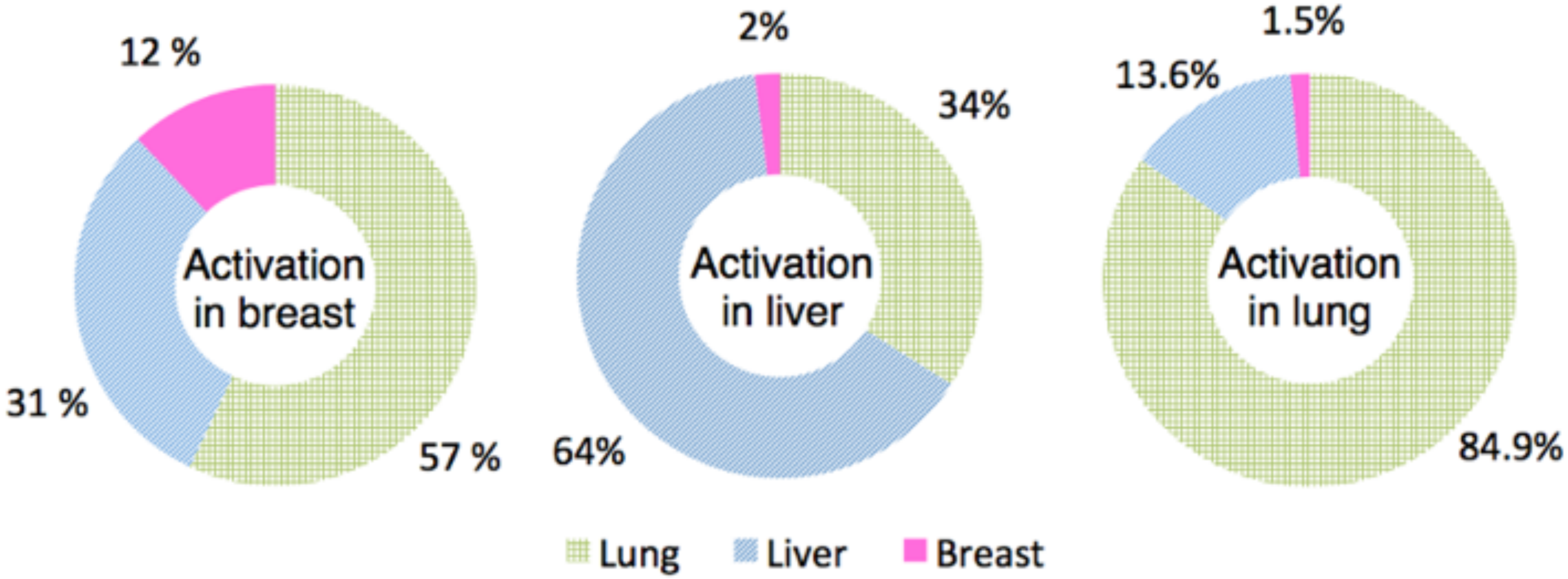


Three metastatic sites in
lung (270cc),
liver (220cc) and
breast (113cc).

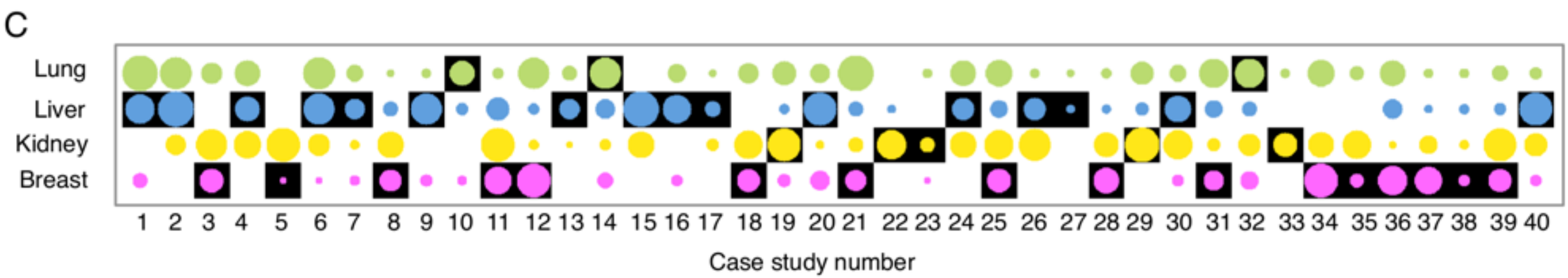
Case study



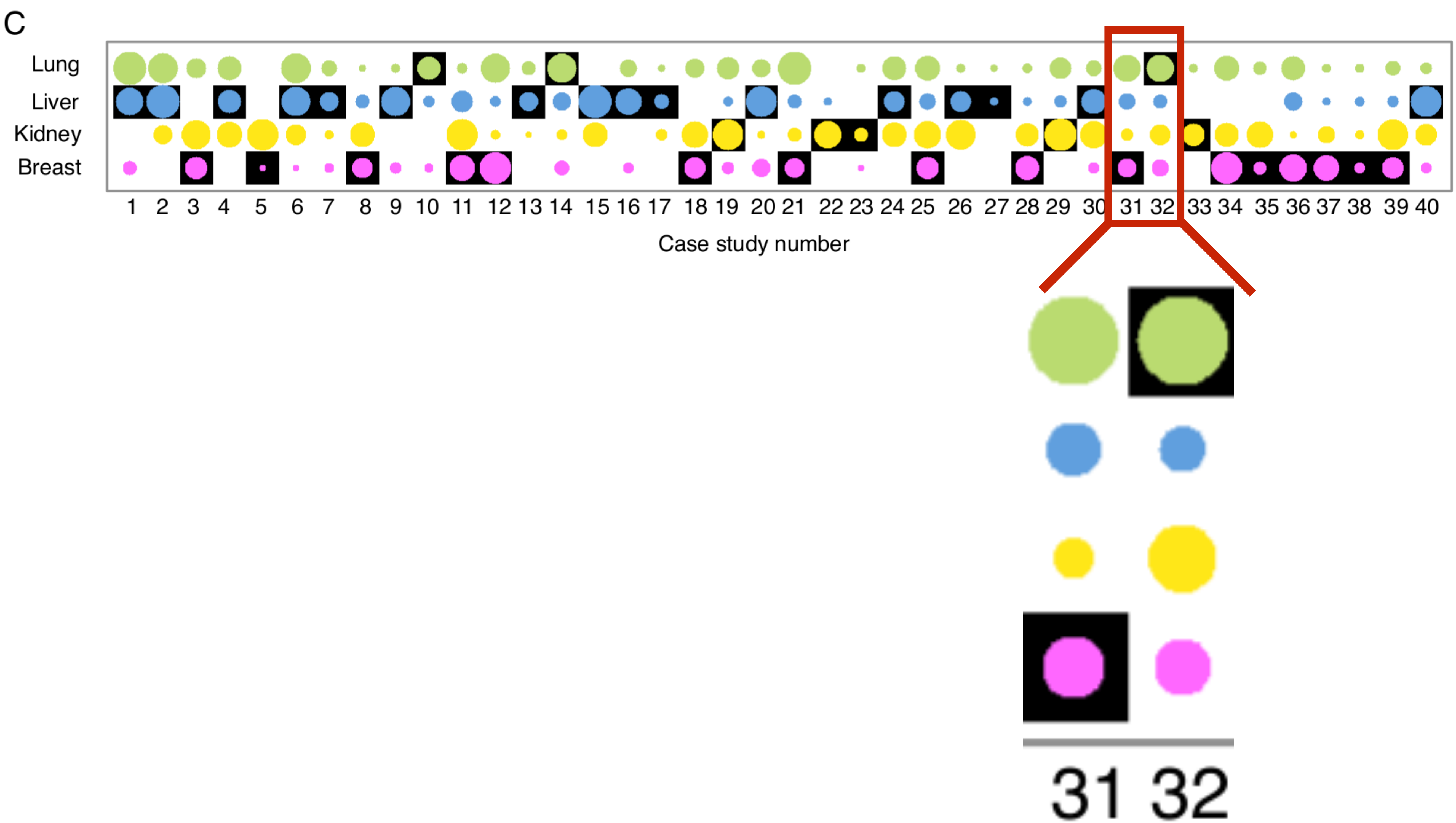
systemic T cell distribution



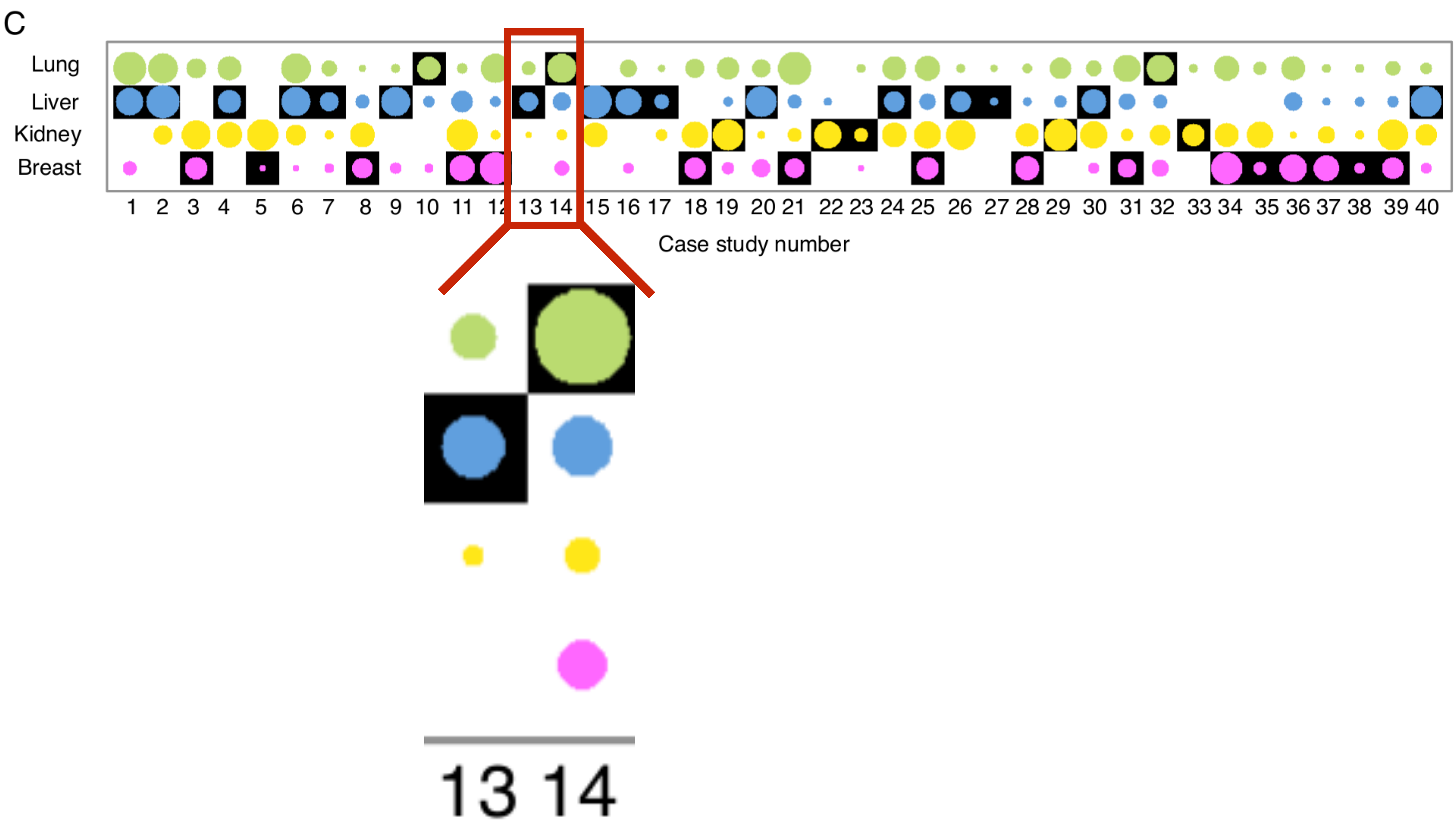
Virtual patient cohort



Virtual patient cohort



Virtual patient cohort



MOFFITT CANCER CENTER

patient-specific

Obtain
patient-specific diagnostic PET/CT data set

↓

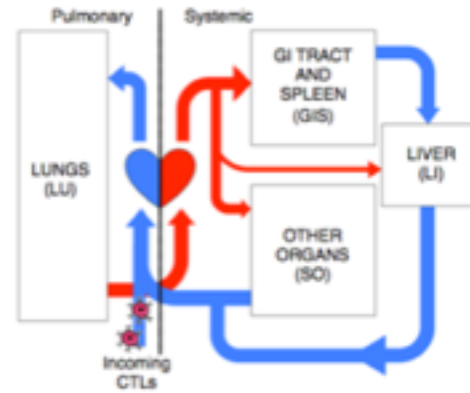
Determine **(V_i)**
metastatic tumor volumes in each organ V_{organ}

↓

Determine **(BFF_{organ})**
physiologic blood flow fraction to each **tumor bearing organ** from table

pre-computed

Determine **($BFF_{compartment}$)**
physiologic blood flow fraction to each **compartment** from table



↓

Calculate **(P_i)**
P_i is the probability that the T cell will infiltrate *ith* tumor site after entering a given compartment in each circulatory cycle

$$P_i = h \times \frac{BFF_{organ}}{BFF_{compartment}} \times \frac{V_i}{V_{organ}}$$

h = Extravasation Probability. Each metastatic site will be evaluated for h_a (activation of T cells by radiation) or h_n (no activation - other site irradiated); where $h_a > h_n$

↓

Calculate **(p_i)**
p_i is the overall probability that the T cell will home to the *ith* tumor site

$$p_i = P_{absorbtion} \frac{P_i}{H_{compartment}}$$

$H_{compartment}$ = sum of P_i in a compartment

$$P_{absorption} = \frac{1}{\Delta}\begin{cases} H_{LU} & \text{in LU} \\ H_{LI}(1-H_{LU})(BFF_{LI} + BFF_{GIS}(1-H_{GIS})) & \text{in LI} \\ H_{GIS} BFF_{GIS}(1-H_{LU}) & \text{in GIS} \\ H_{SO} BFF_{SO}(1-H_{LU}) & \text{in SO} \end{cases}$$

Δ = normalization constant

↓

Calculate **(E_i)**
Normalized entropy of homing distribution, based on activated T cell dissemination for each metastatic site

$$E_i = \left(\sum_{j=1}^{N} p_{ji} \ln p_{ji}\right) \Big/ \left(N \ln \frac{1}{N}\right)$$

N = number of metastatic sites
p_{ij} = probability of a T cell activated at site *i* infiltrates tumor at site *j*

↓

Calculate
Immunogenicity Index, assigned to each site

$$I_i = E_i \frac{V_i}{\max(V_1, \ldots, V_N)}$$

→

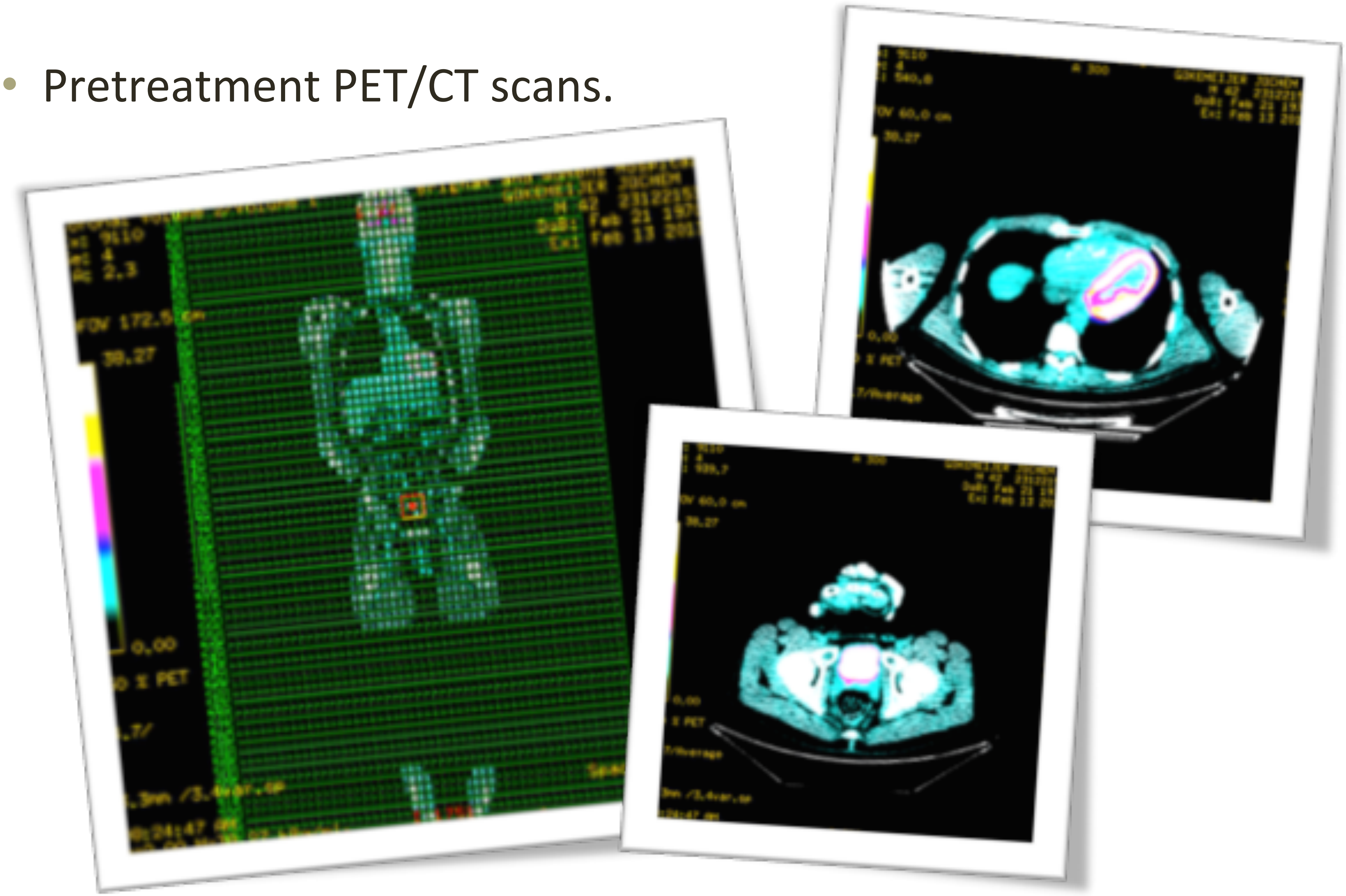
Rank
patient-specific treatment targets with highest likelihood of inducing an abscopal effect

⇢

Rank
Combinations of patient-specific treatment targets with highest likelihood of inducing an abscopal effect

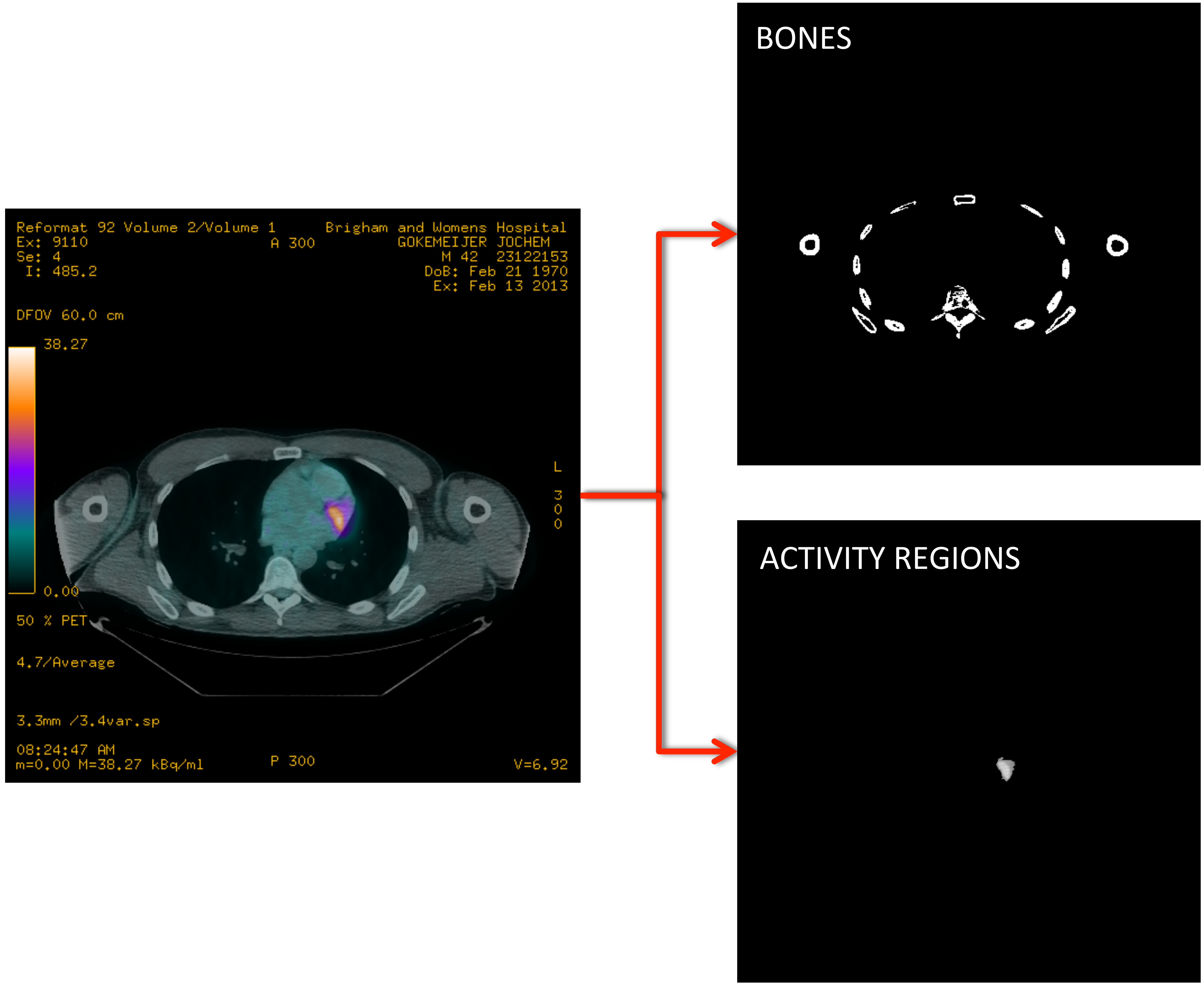
Patient-specific input data

- Pretreatment PET/CT scans.



Metastatic melanoma scans obtained from Jonathan Schoenfeld, DFCC.

Image processing



Extracting anatomical location and size of each metastasis

Extracted body outline + Extracted skeleton + Extracted activity regions = Anatomic map

Summary

- abscopal effect is the observation of regression of metastases outside local treatment field
- different metastases may have potential to induce abscopal effect
- dependent on anatomic distribution, tumor volumes, site of immune activation
- quantitative modeling of T cell trafficking between patient-specific anatomic distribution of metastases may help identifying promising treatment targets
- to be validated in prospective clinical trials

Acknowledgements

Enderling lab

Thomas Lewin

Joshua Bull

Sid Ramesh

Jan Poleszczuk **Rachel Walker** **Sotiris Prokopiou**

Collaborators

Eduardo Moros **Kimberly Luddy**

IMO / Moffitt Cancer Center

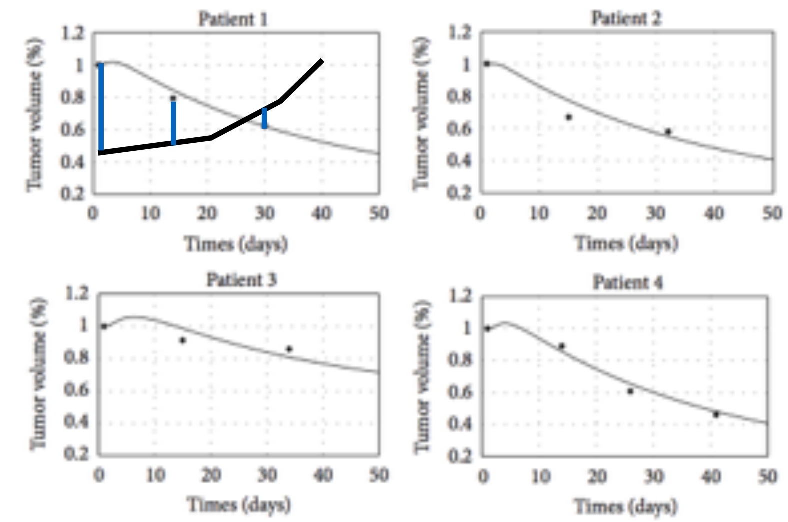
heiko.enderling@moffitt.org
http://labpages.moffitt.org/enderlingh

DeBartolo Family
PERSONALIZED MEDICINE INSTITUTE

MOFFITT CANCER CENTER

Genetic Algorithms

$$\frac{dV}{dt} = \frac{\ln 2}{T_{pot}} V \left(1 - \frac{V}{K}\right) \qquad V_{postIR} = V - \gamma_d V\left(1 - \frac{V}{K}\right)$$



- repeat 1000 times

  - set random value for T_{pot} , γ and K
  - solve the model and estimate *error* to data

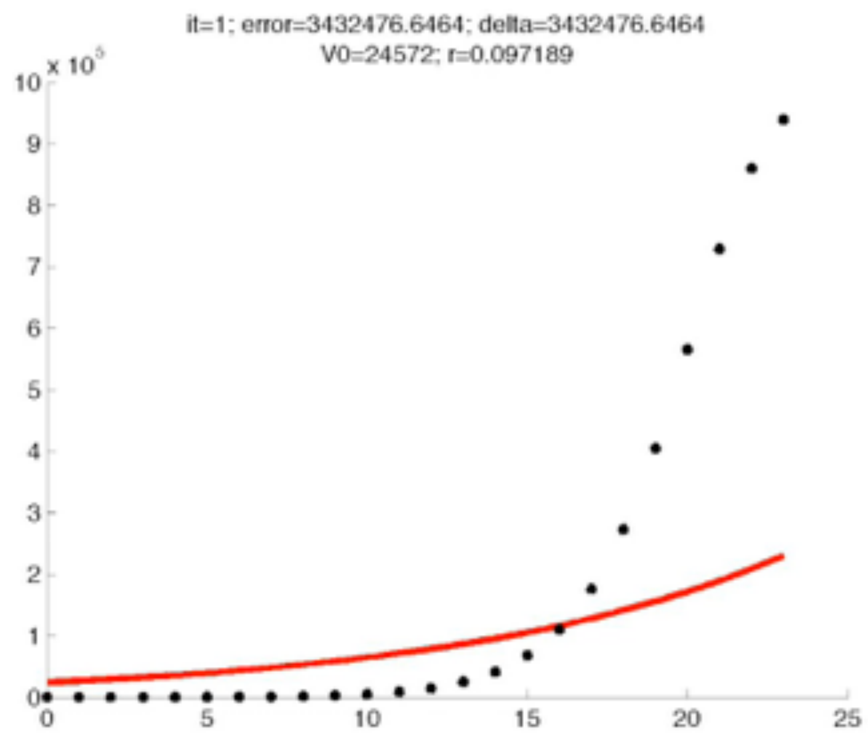
- keep 500 best fits, discard 500 worst fits (***selection***)
- combine choosing random maternal & paternal '*genes*' (***crossover***)
  => 250 new '*individuals*'
- randomly chose 250 '*individuals'* and randomly mutate a '*gene*' (***mutation***)

repeat 1000 times

Genetic Algorithms

exponential growth ?

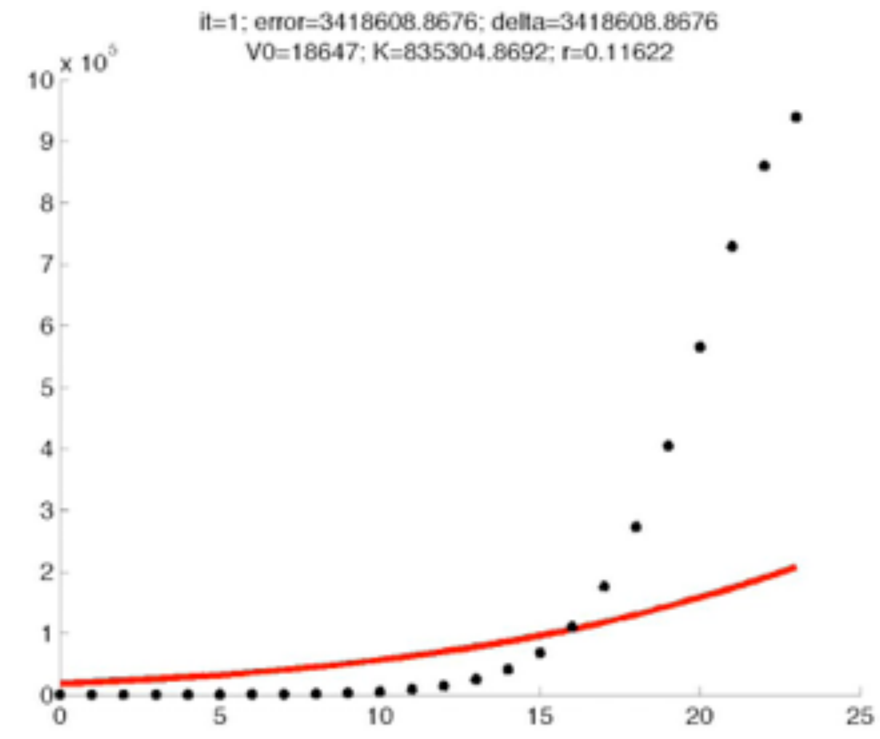
$$\frac{dV}{dt} = \frac{\ln 2}{T_{pot}} V$$



error: 17.5%

logistic growth ?

$$\frac{dV}{dt} = \frac{\ln 2}{T_{pot}} V \left(1 - \frac{V}{K}\right)$$



error: 1.5%

T cell extravasation

- Extravasation is complicated process involving T cell rolling, activation and arrest.
- T cell extravasate more efficiently to the tissue in which they were activated (area code hypothesis).

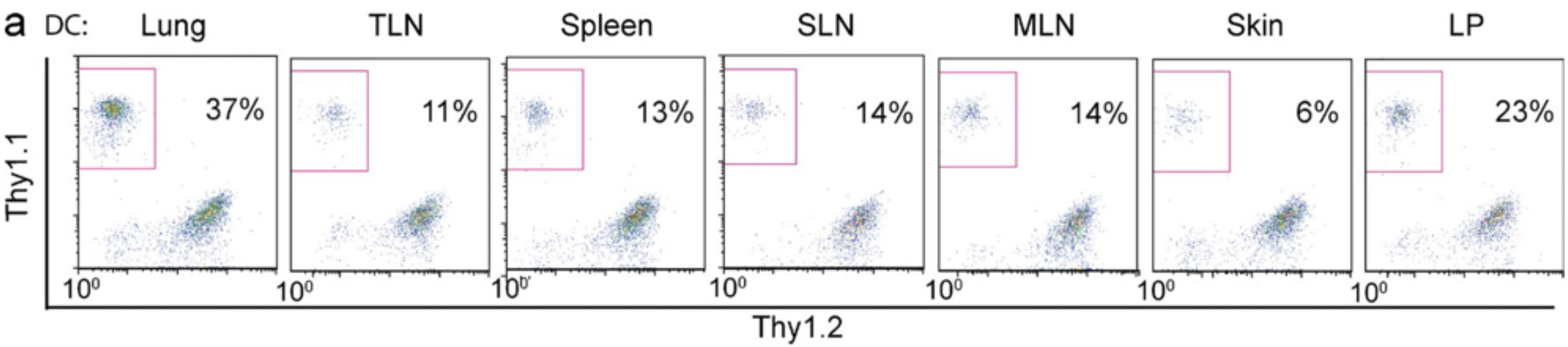
Assumptions:

1. Probability of T cell extravasation in the tissue in which it was activated =: $\mathbf{h_a}$
2. Probability of T cell extravasation in other tissues =: $\mathbf{h_n}$

$$\mathbf{h_a > h_n}$$

T cell homing to activation site

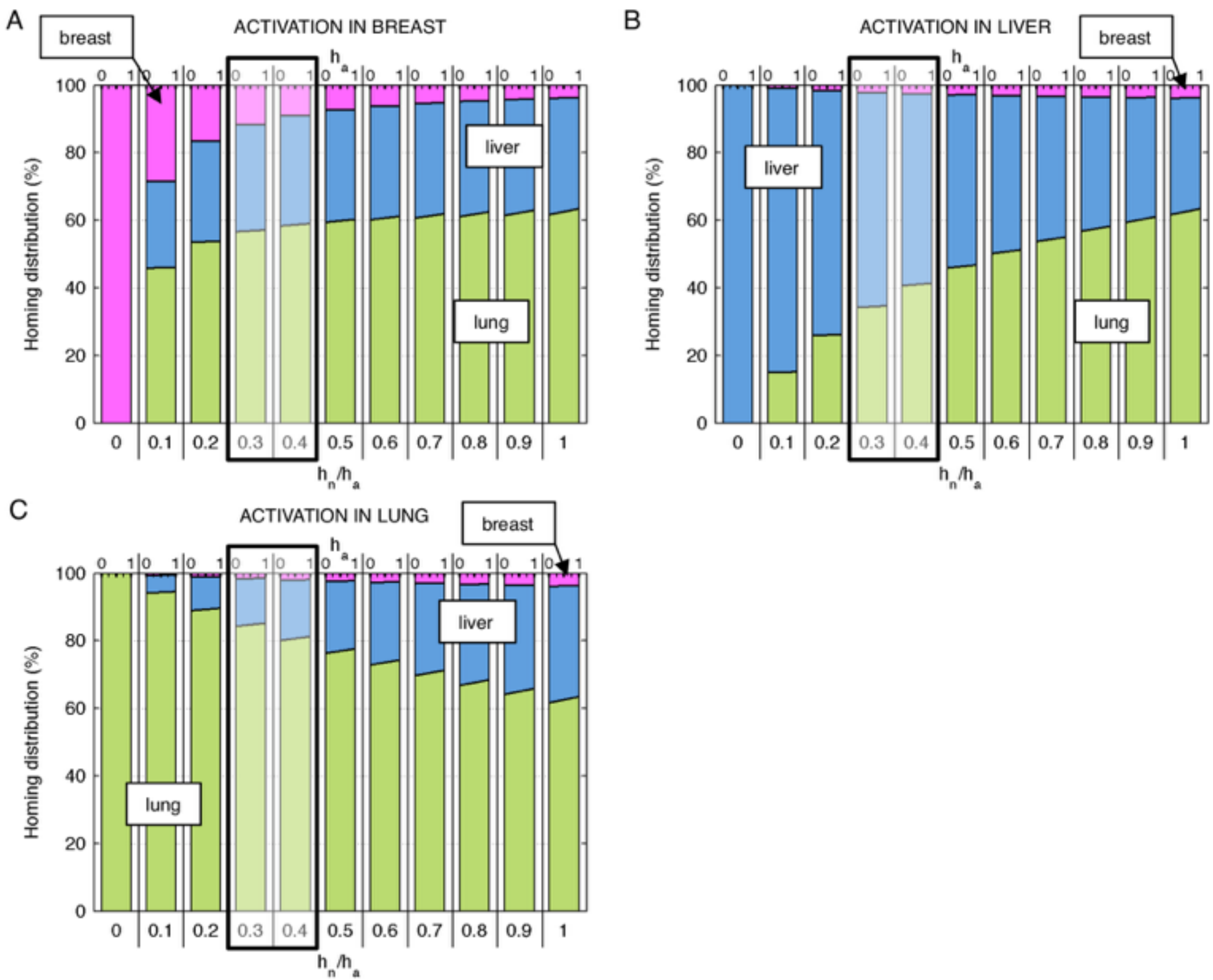
Trafficking of antigen-specific CD4+ T cells activated by lung DCs or other sites DCs in response to inhaled antigen (OVA, ovalbumin)



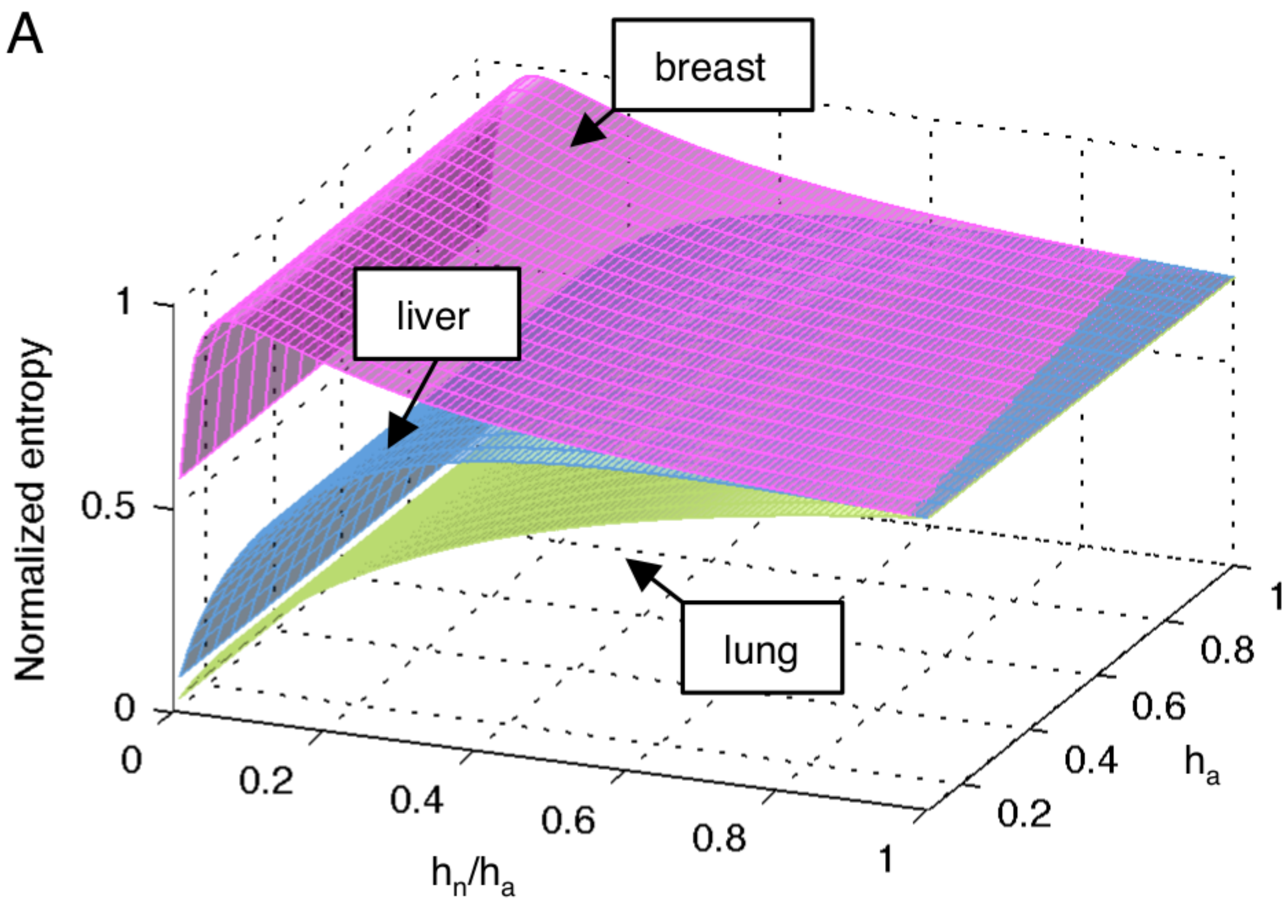
$h_n/h_a \sim 1/3$

Mikhak et al, J Exp Med, 2013

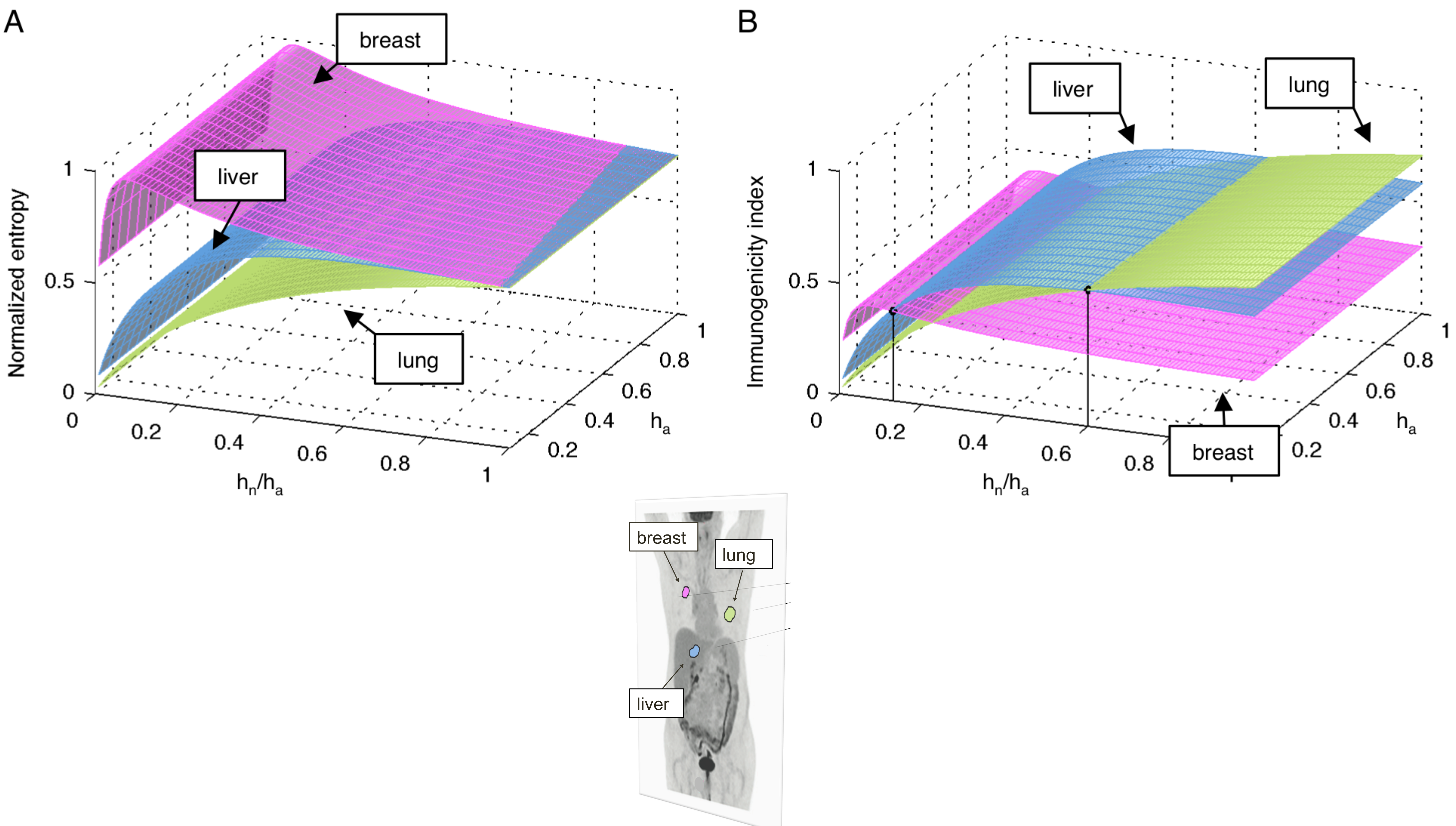
Case study


A
ACTIVATION IN BREAST
breast
liver
lung
Homing distribution (%)
h_a
h_n/h_a
0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1
B
ACTIVATION IN LIVER
breast
liver
lung
Homing distribution (%)
h_a
h_n/h_a
C
ACTIVATION IN LUNG
breast
liver
lung
Homing distribution (%)
h_a
h_n/h_a

Case study


A
breast
liver
lung
Normalized entropy
1
0.5
0
0
0.2
0.4
0.6
0.8
1
h_n/h_a
0.2
0.4
0.6
0.8
1
h_a

Case study



A
breast
liver
lung
Normalized entropy
1
0.5
0
0
0.2
0.4
0.6
0.8
1
h_n/h_a
0.2
0.4
0.6
0.8
1
h_a
B
liver
lung
breast
Immunogenicity index
1
0.5
0
0
0.2
0.4
0.6
0.8
h_n/h_a
0.2
0.4
0.6
0.8
1
h_a
breast
lung
liver

Tumor **dynamics** and treatment response

Distributed tumor - immune system interaction model

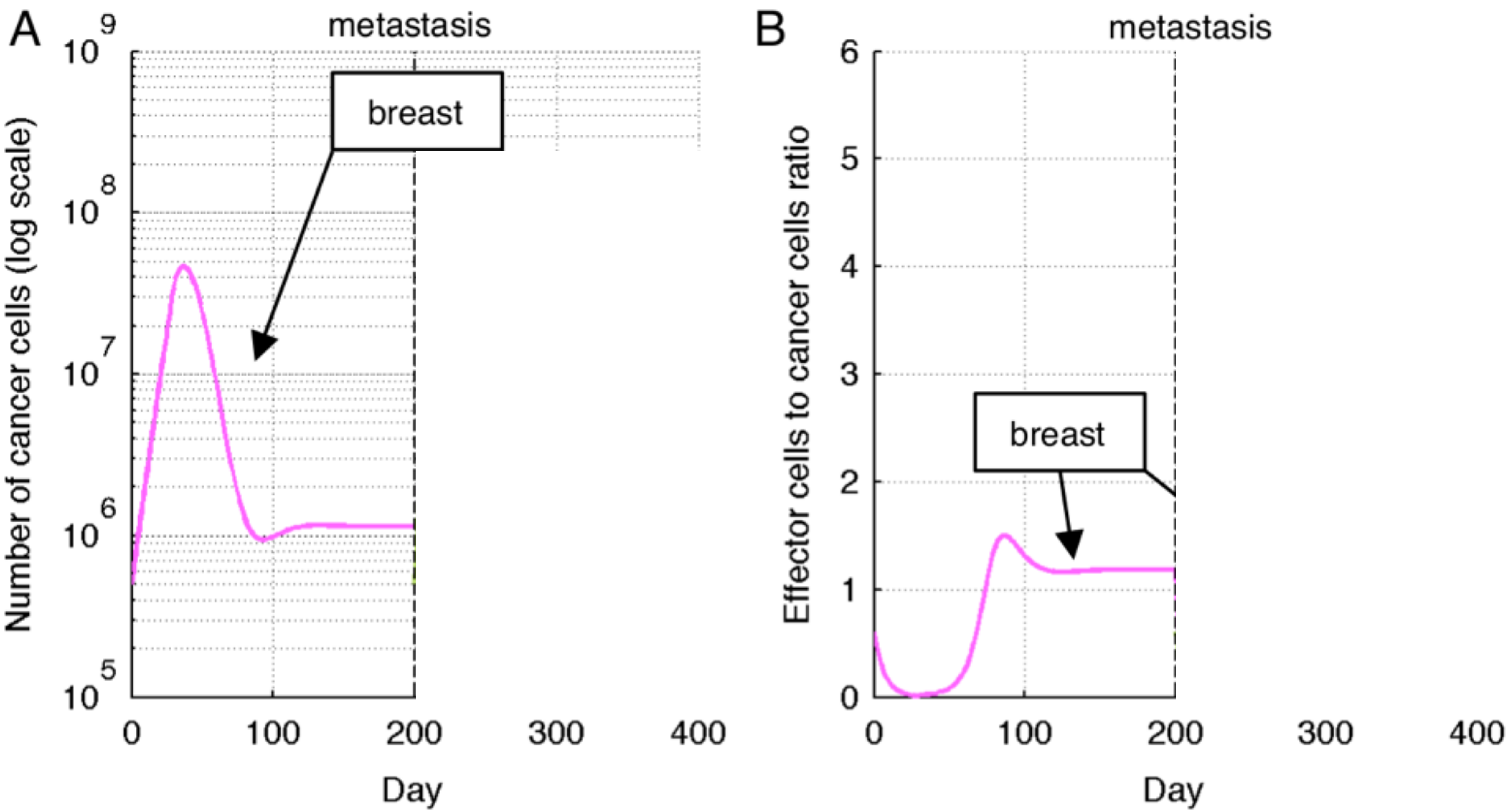
Logistic tumor growth

CTLs target tumor cells

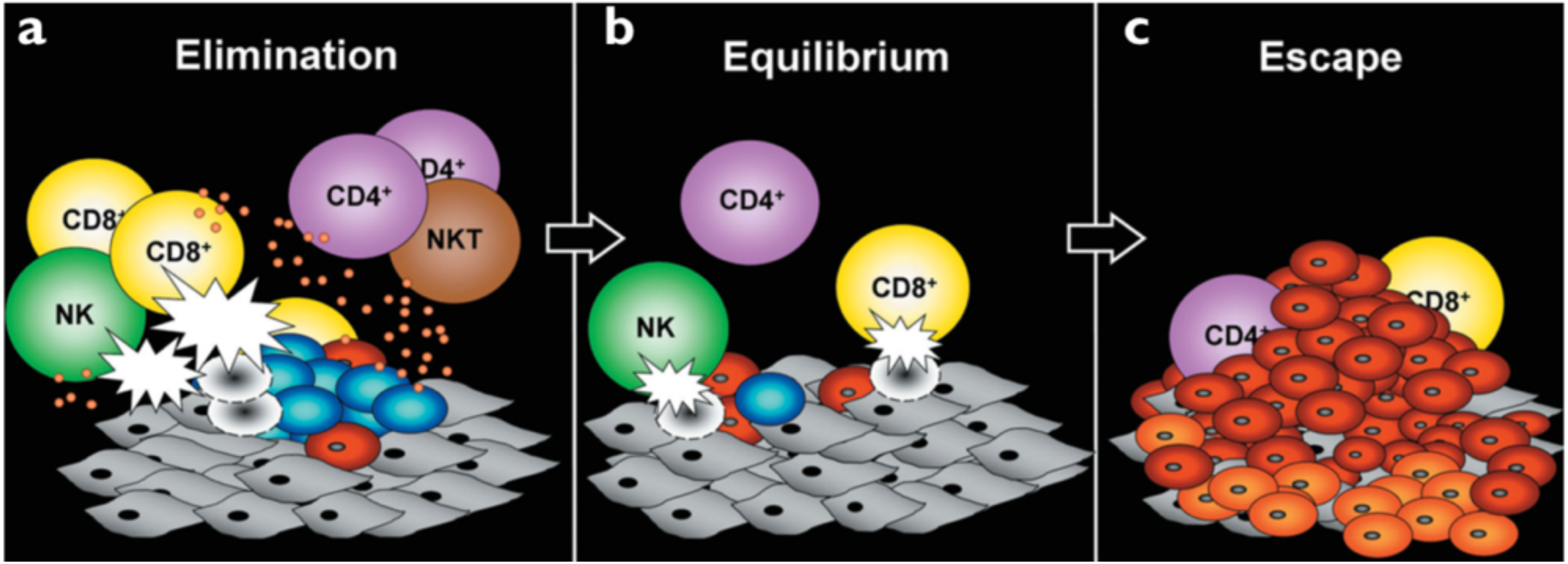
$$\begin{cases} \dot{T}_i = rT_i\left(1 - \dfrac{T_i}{K}\right) - \mu T_i E_i, \\ \dot{E}_i = -dE_i + \sum_{j=1}^{n} \omega_{ij}(T)\dfrac{g_j E_j T_j}{h + T_j} \end{cases}$$

CTLs decay

CTLs recruitment through the network


A
metastasis
breast
Number of cancer cells (log scale)
10^9
10^8
10^7
10^6
10^5
0
100
200
300
400
Day
B
metastasis
breast
Effector cells to cancer cells ratio
6
5
4
3
2
1
0
0
100
200
300
400
Day

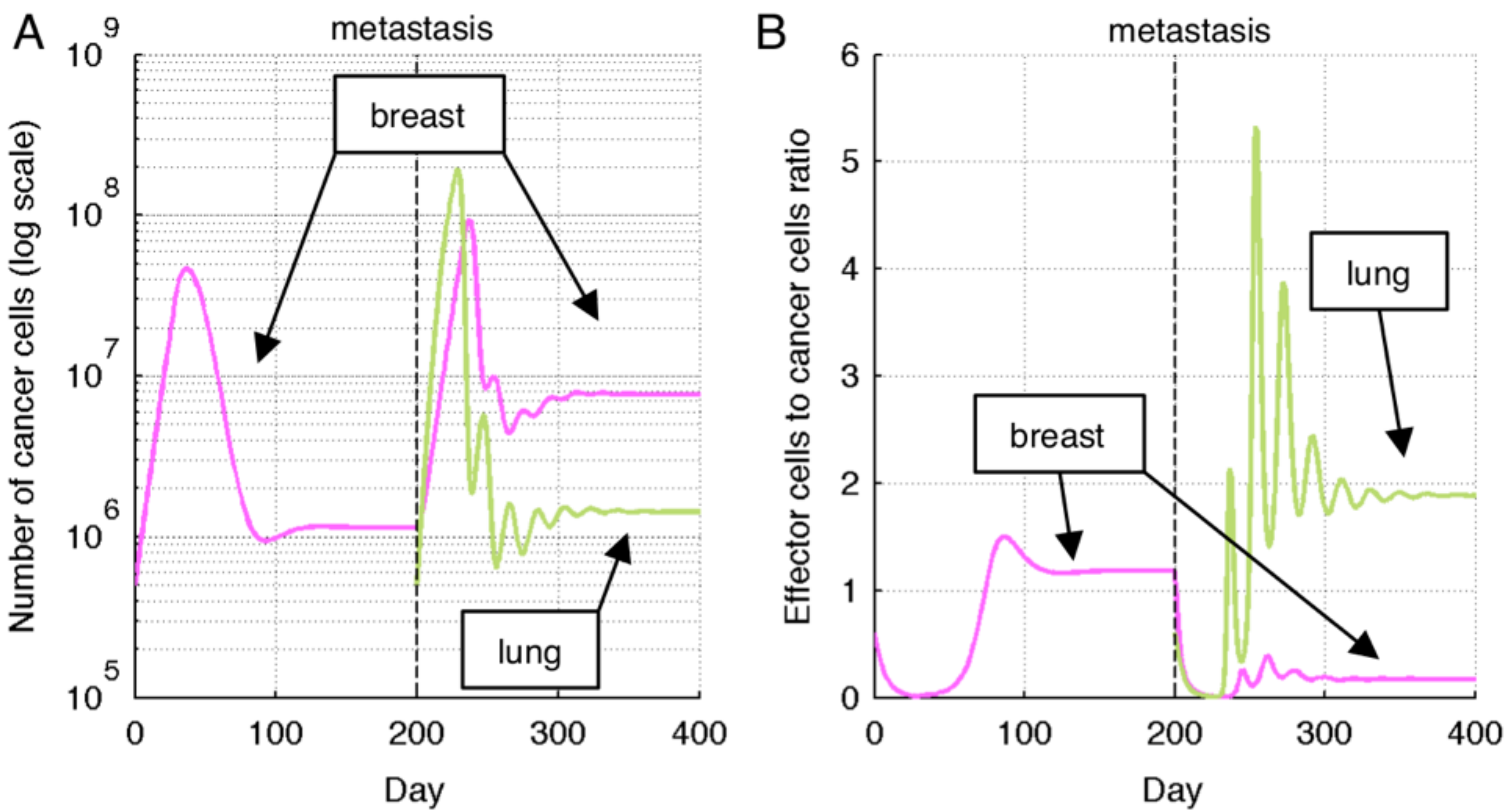
Immune-mediated dormancy



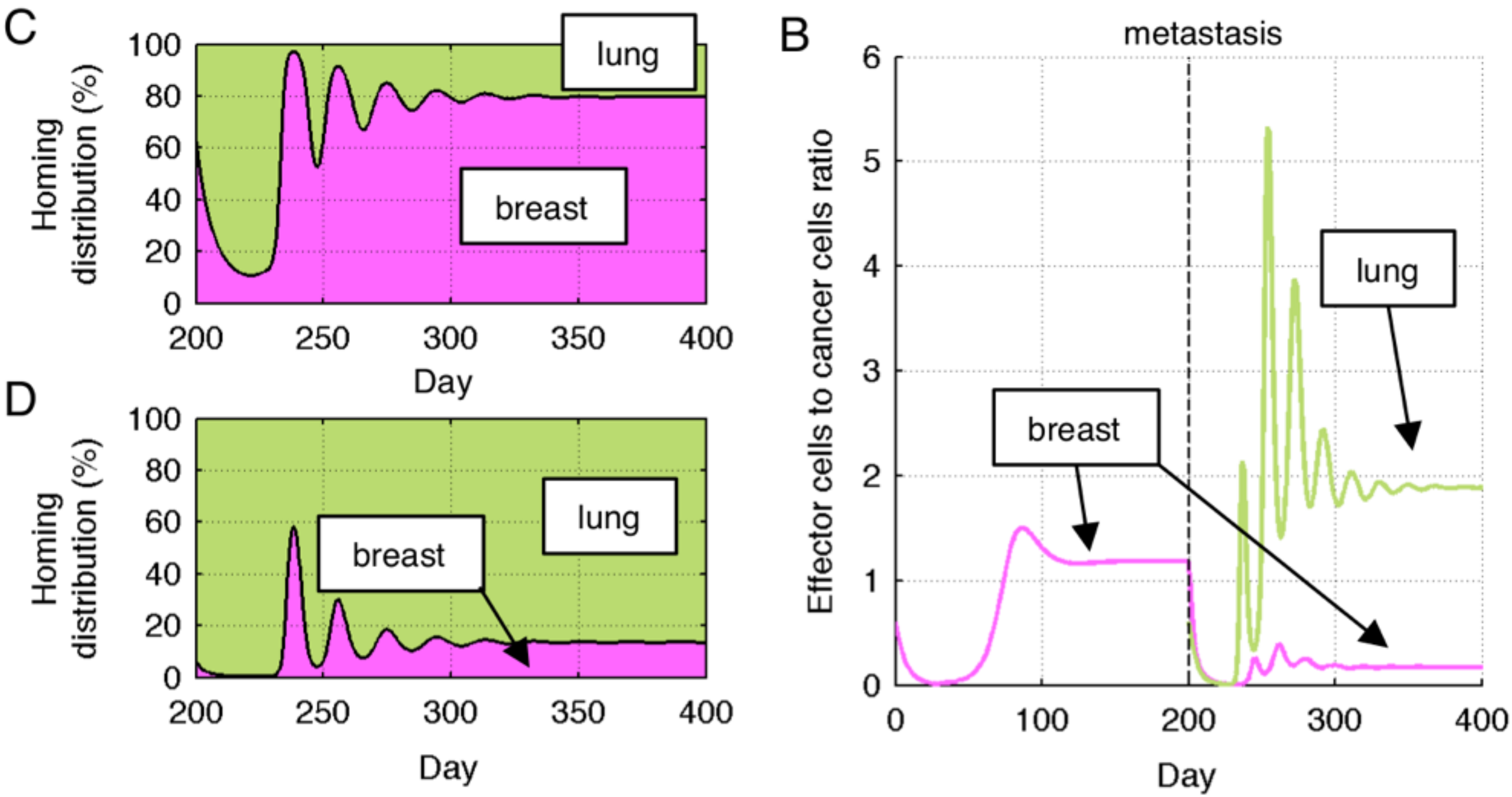
Dunn et al., Nat Immunol, 2002

72

Metastases enable transient escape from tumor dormancy



Metastases enable transient escape from tumor dormancy



Concomitant Immunity

[CANCER RESEARCH 43, 138–145, January 1983]
0008-5472/83/0043-0000$02.00

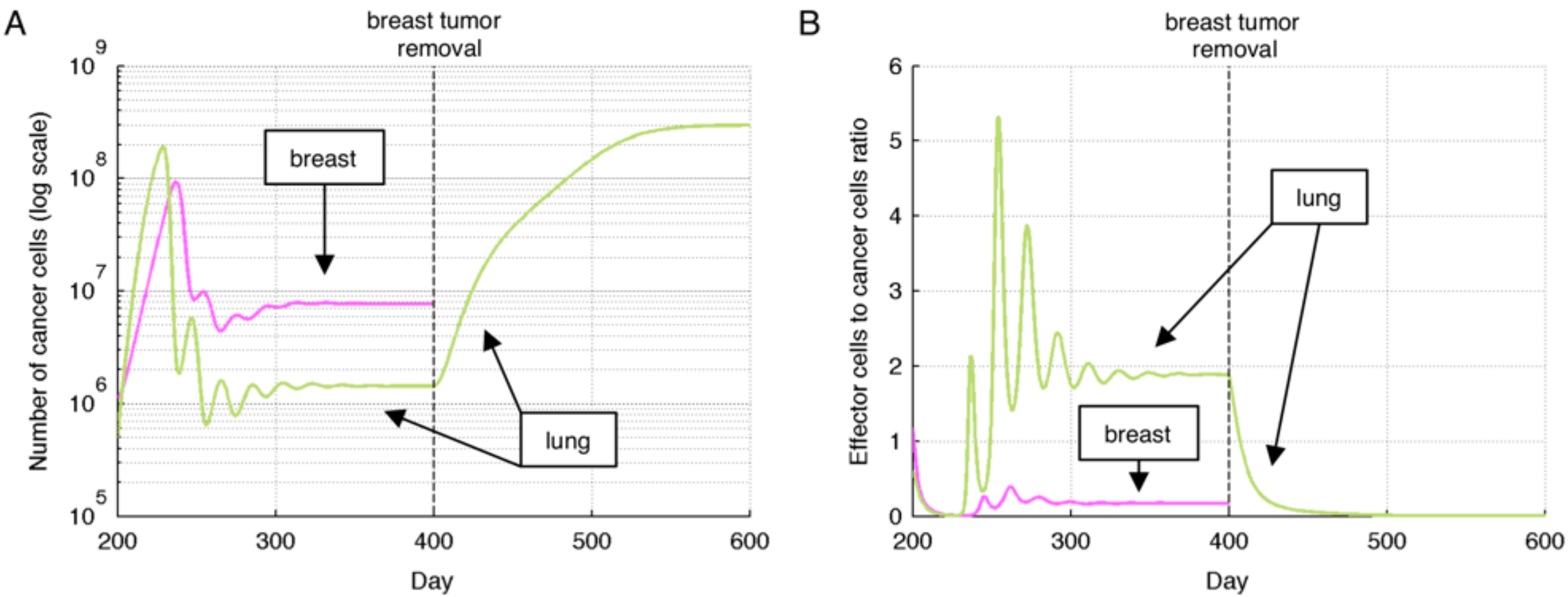
Resistance of Tumor-bearing Mice to a Second Tumor Challenge

Elieser Gorelik[1]

Laboratory of Immunodiagnosis, National Cancer Institute, NIH, Bethesda, Maryland 20205

The inhibition of growth of a second tumor graft in mice bearing the original tumor was described by Ehrlich (6) in 1906. This phenomenon was later attributed to the antitumor immunological response and termed concomitant tumor immunity (2).

Surgical removal of primary facilitates escape of distant metastases



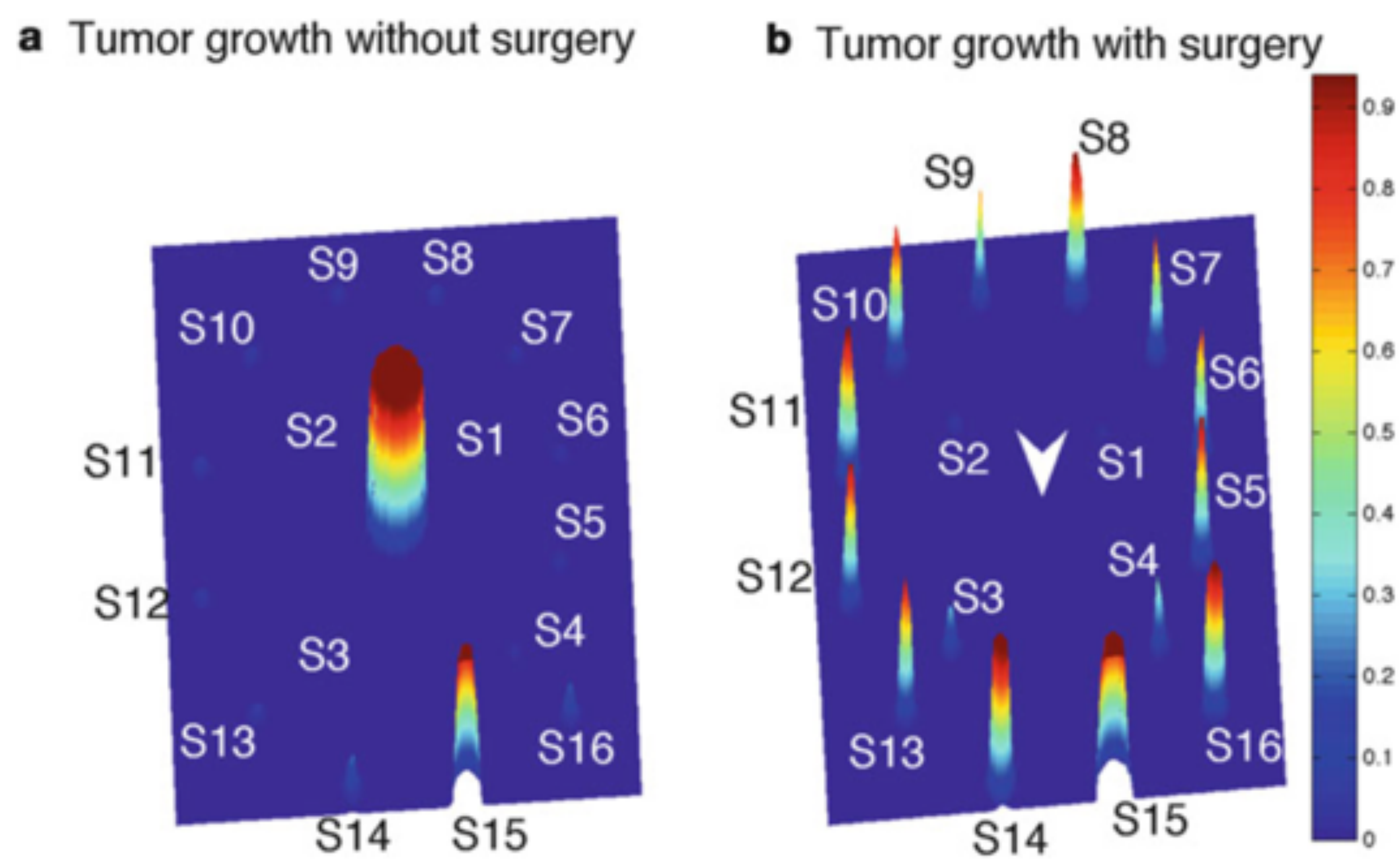
Surgical removal of primary facilitates escape of distant metastases

APMIS 116: 730–41, 2008

ISSN 0903-4641

Dormancy and surgery-driven escape from dormancy help explain some clinical features of breast cancer

M. W. RETSKY,[1] R. DEMICHELI,[2] W. J. M. HRUSHESKY,[3] M. BAUM[4] and I. D. GUKAS[5]



Kim & Boushaba, Systems Biology of Tumor Dormancy, Springer, 2013

Calibrate / Validate Math Model