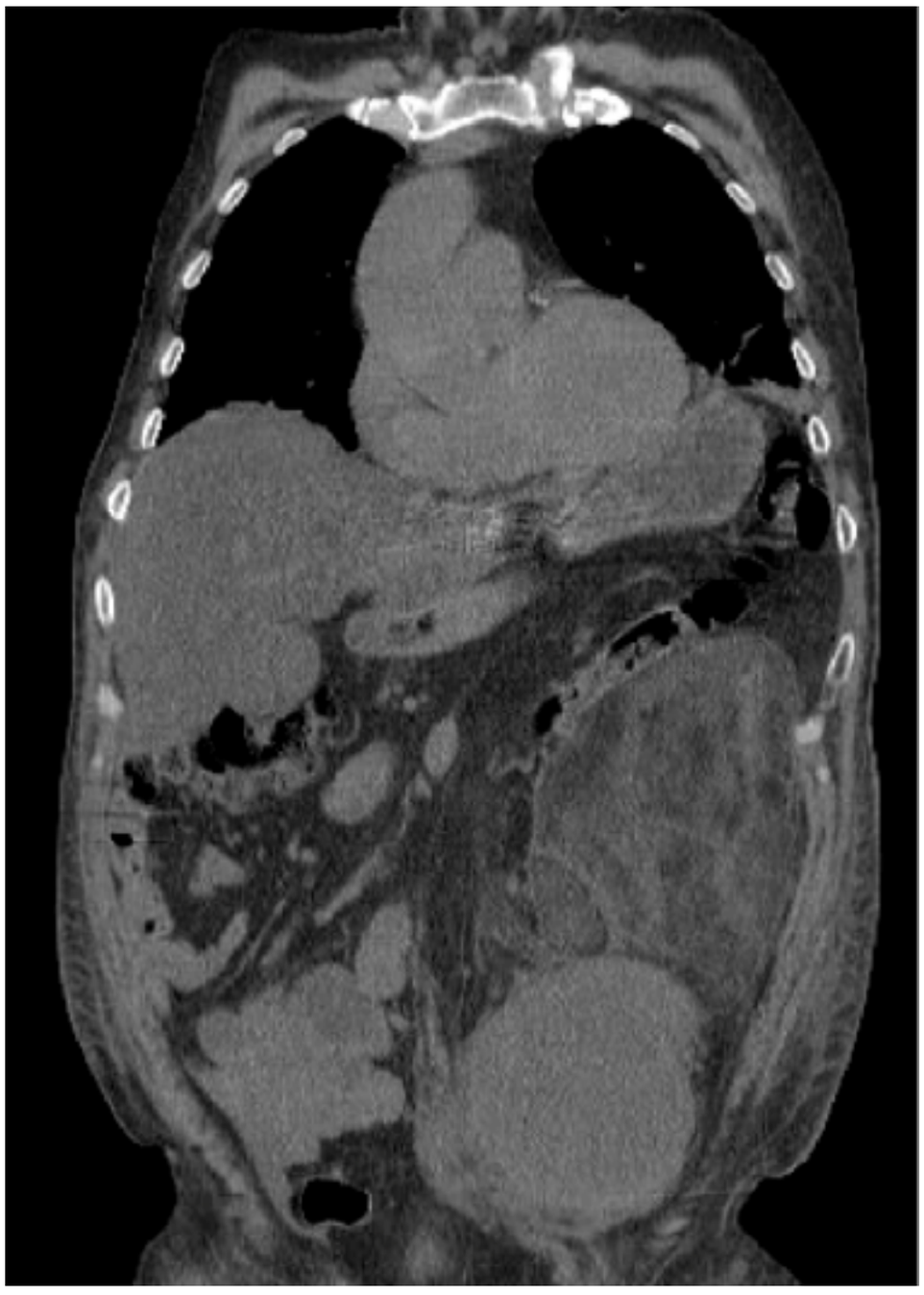
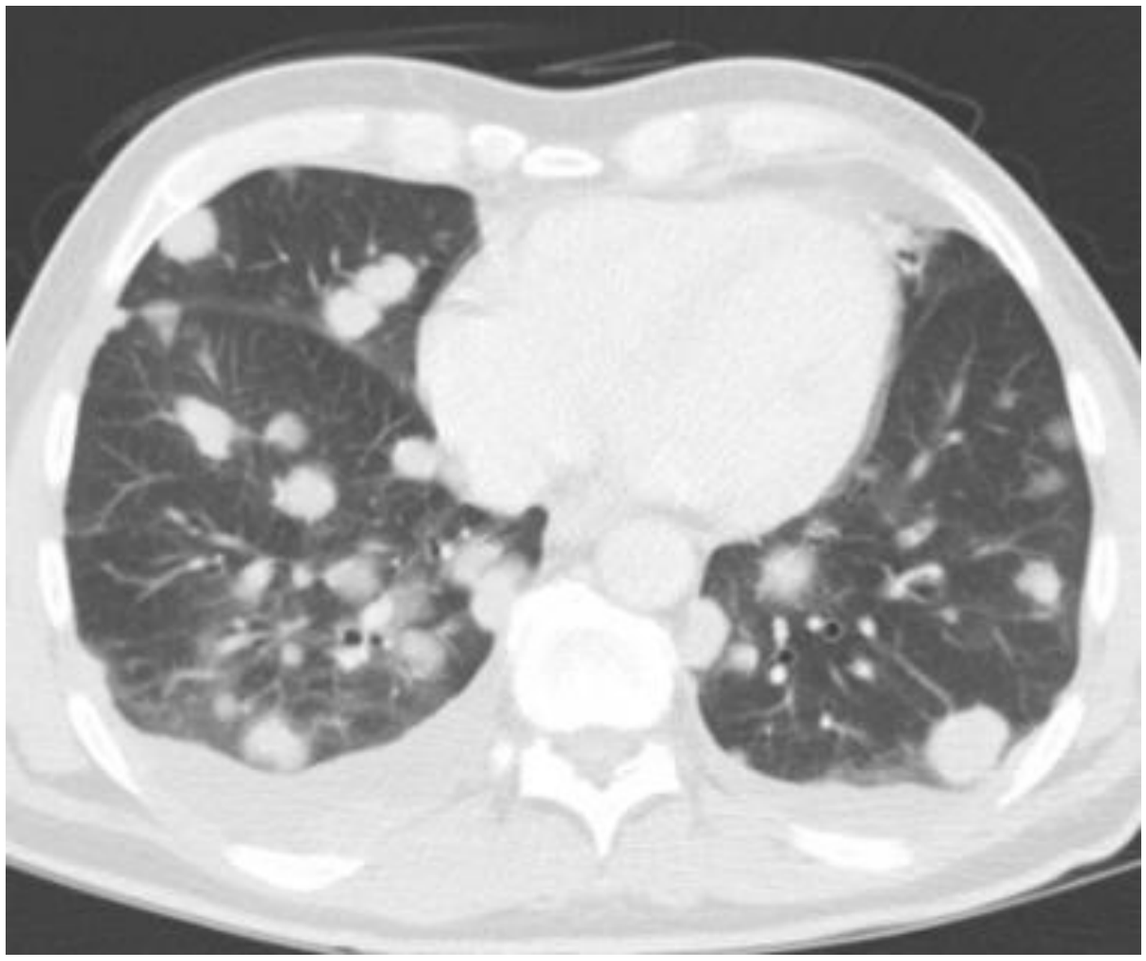
HARNESSING THE LYMPHOCYTE META-PHENOTYPE TO OPTIMIZE ADOPTIVE CELL THERAPY

Sarcoma ~~is a heterogeneous group of cancers arising from connective tissue~~ SUCKS

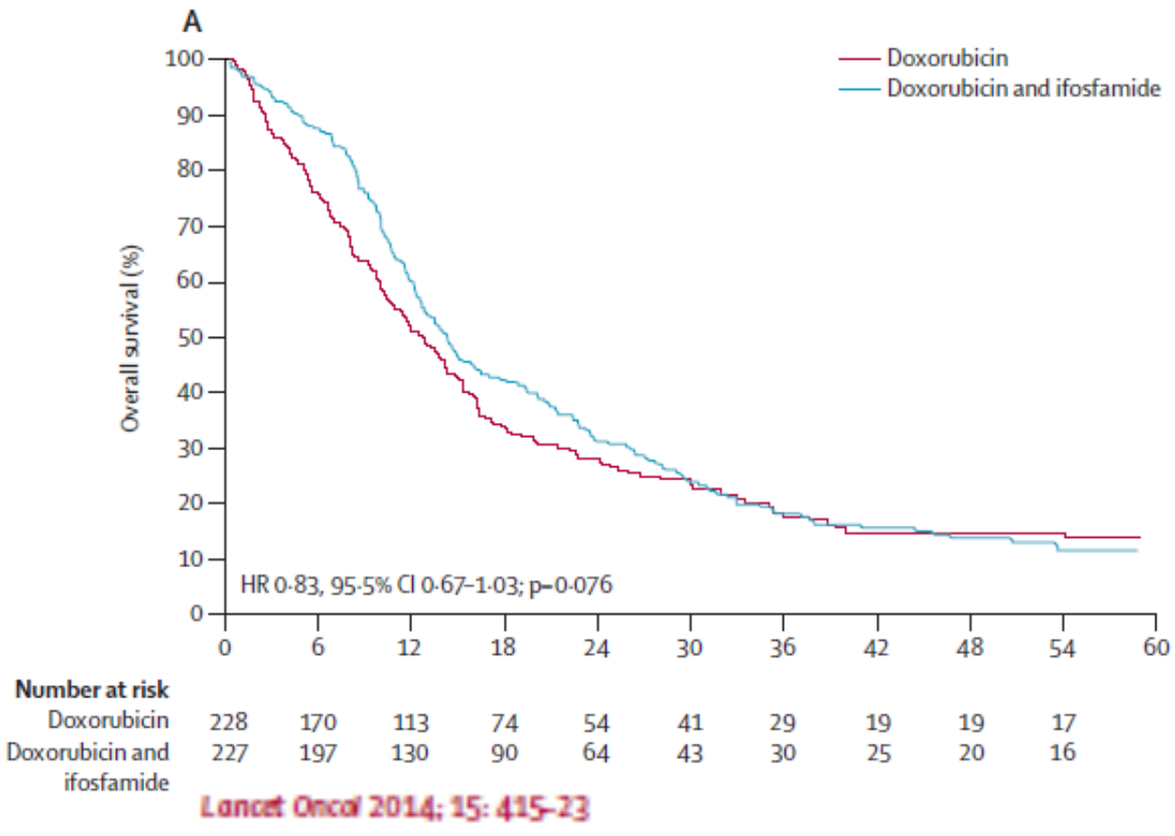
We can cure localized disease with surgery and radiation

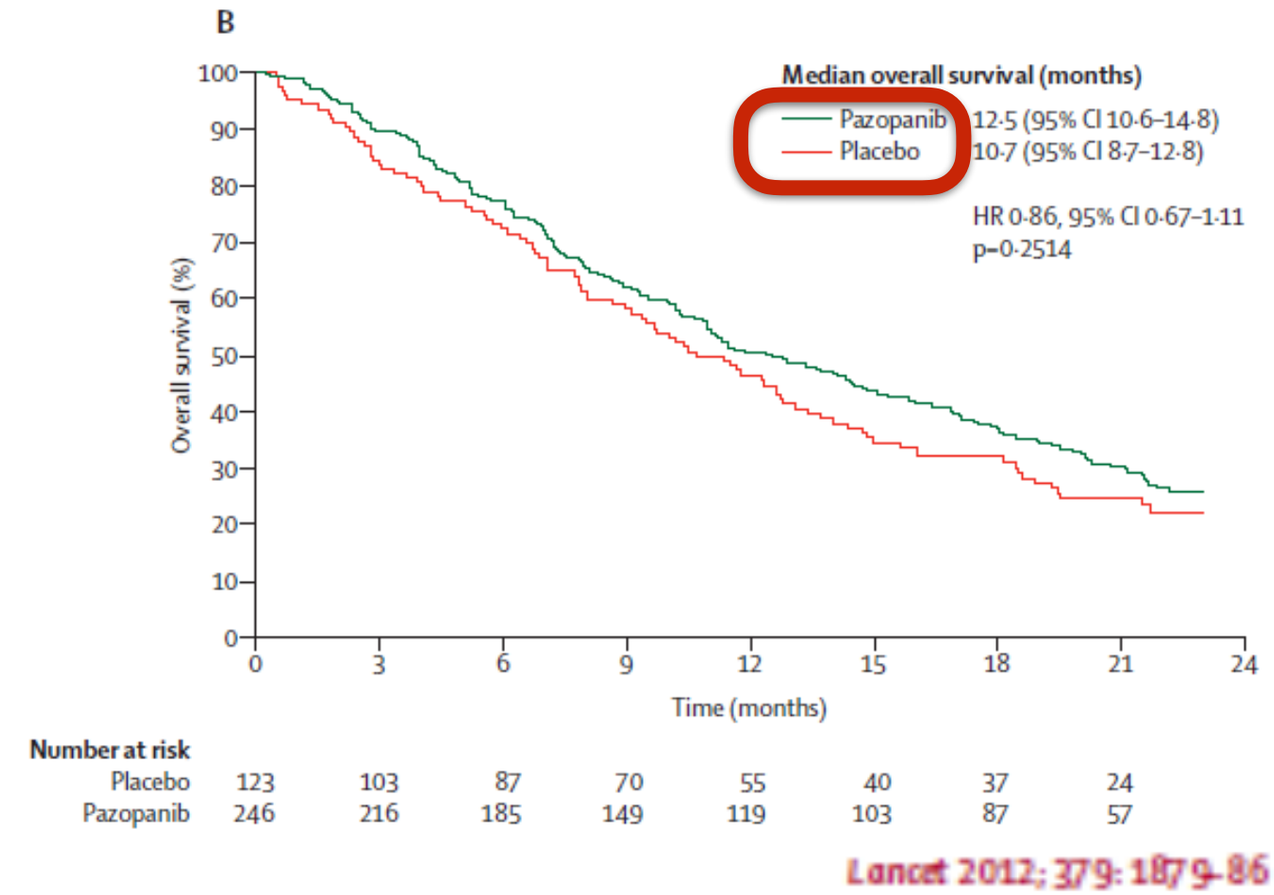




We can NOT cure metastatic disease by any means

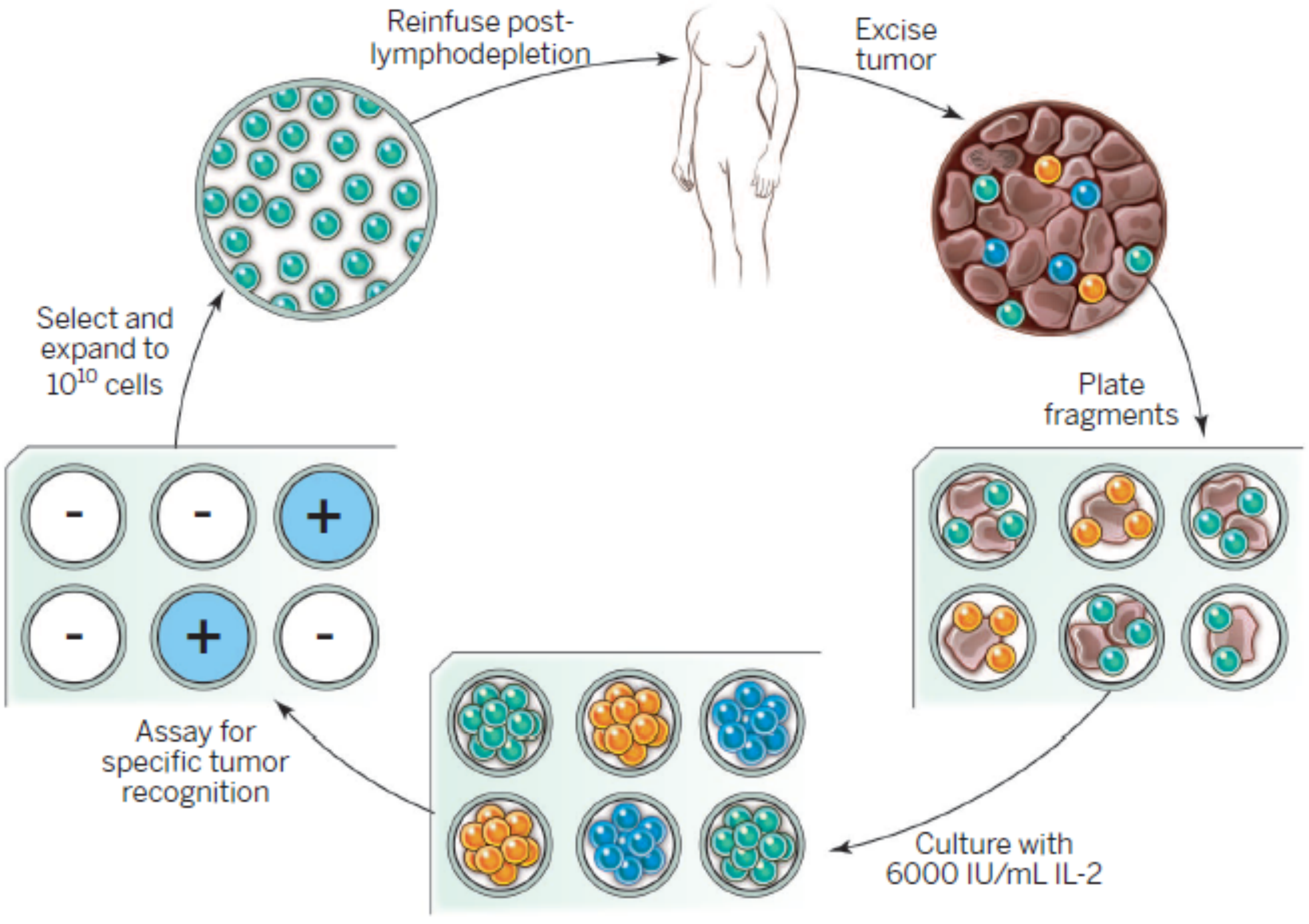
Formally: Standard therapy in metastatic soft tissue sarcoma is minimally effective and highly toxic





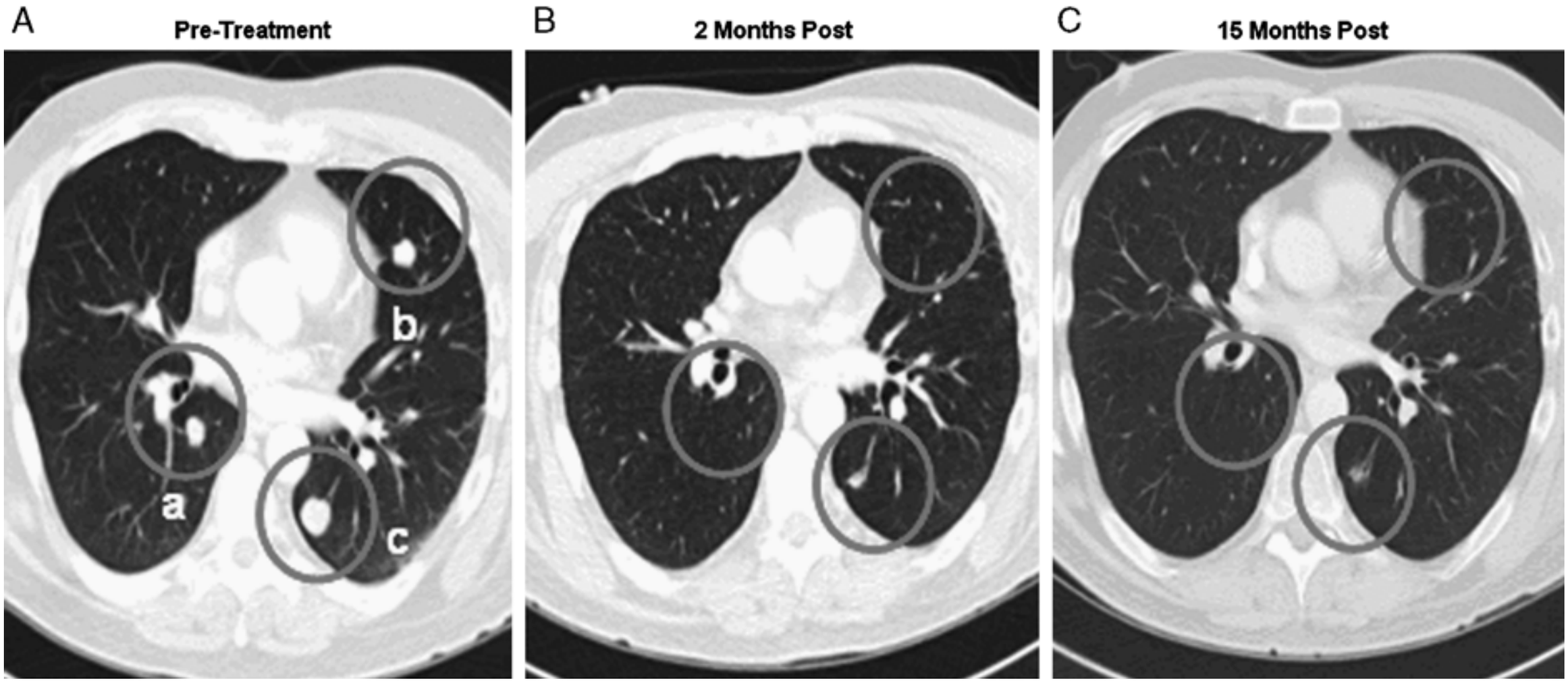
The best targeted agent was compared to PLACEBO as recently as 2012 and only won by 3 months in OS

Adoptive Cell Therapy with Tumor Infiltrating Lymphocytes



Rosenberg & Restifo, Science, 2015

TIL therapy works in melanoma

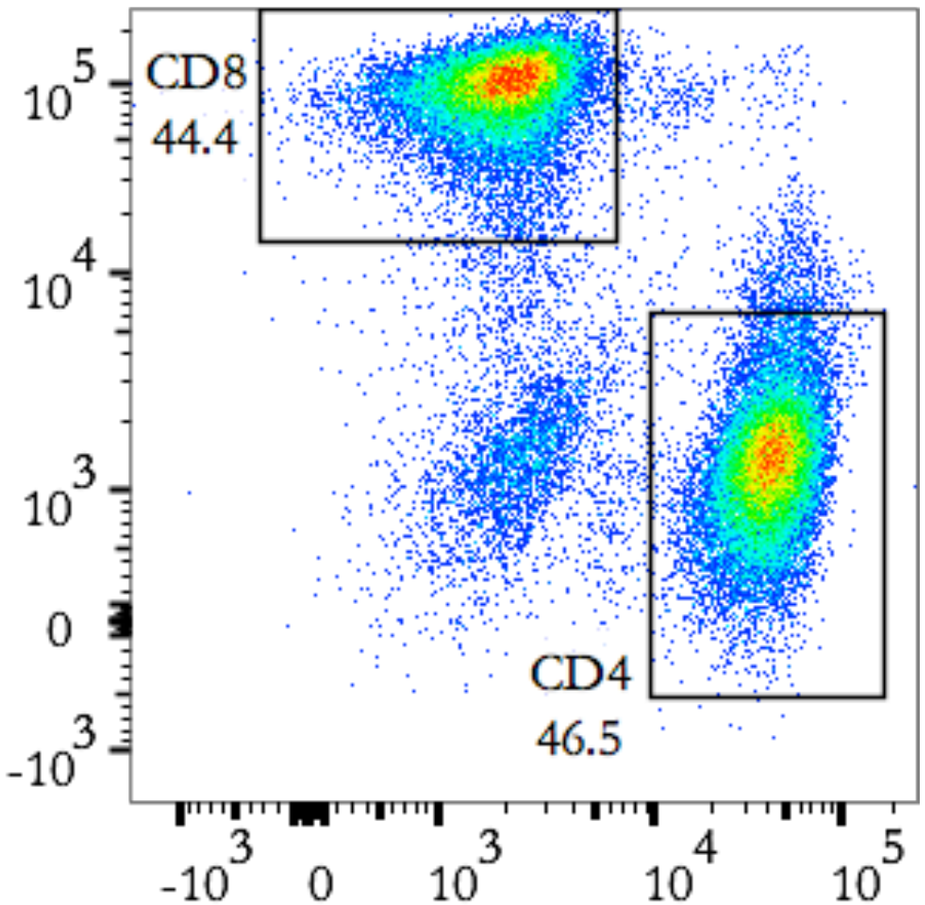


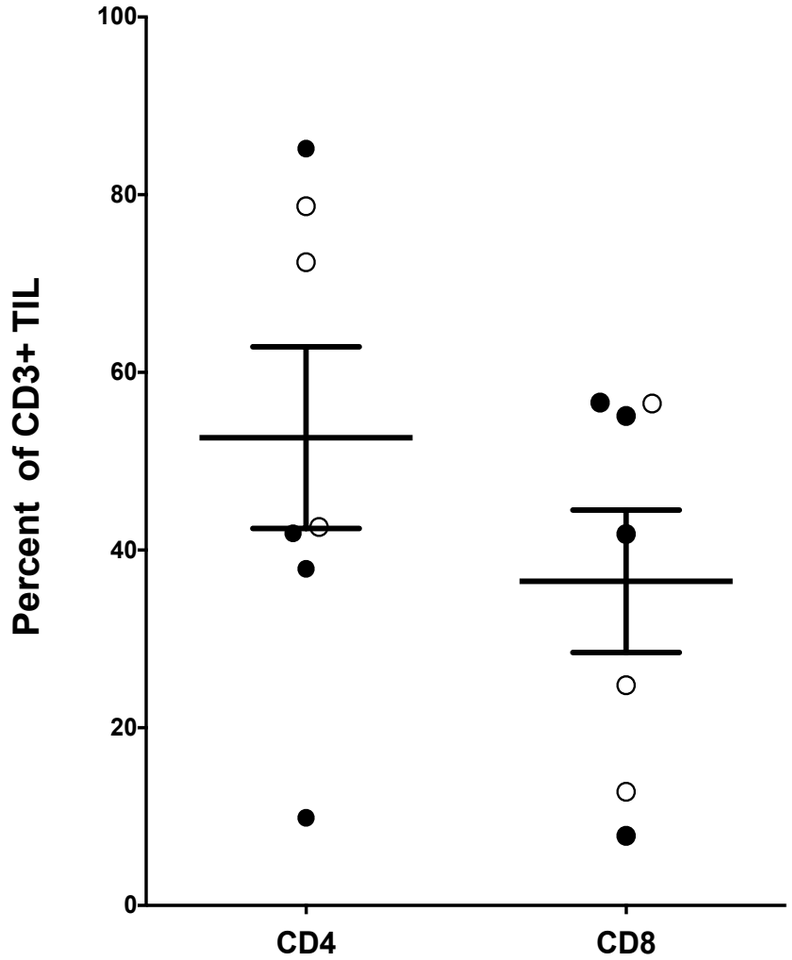
Of initial 36 consecutive patients treated on trial at MCC:

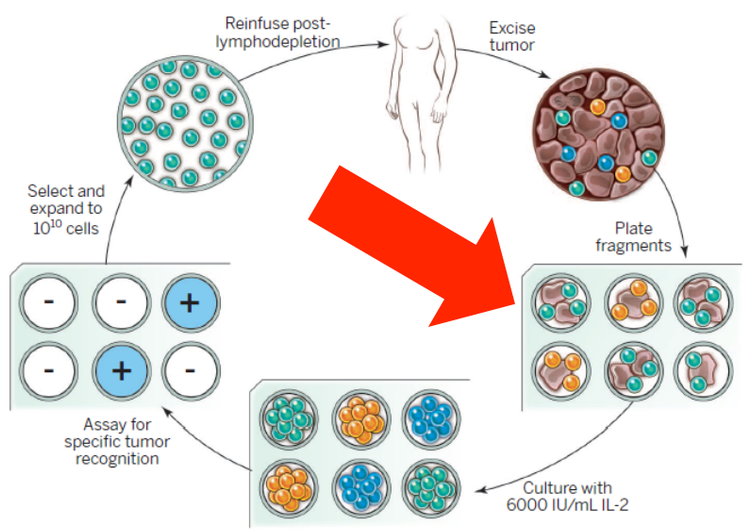
- 95% success rate for growth (>2e7) by patient
- 34% success rate for growth by fragment
- ~50% response rate in those treated

Pilon-Thomas et al, J Immunother, 2012

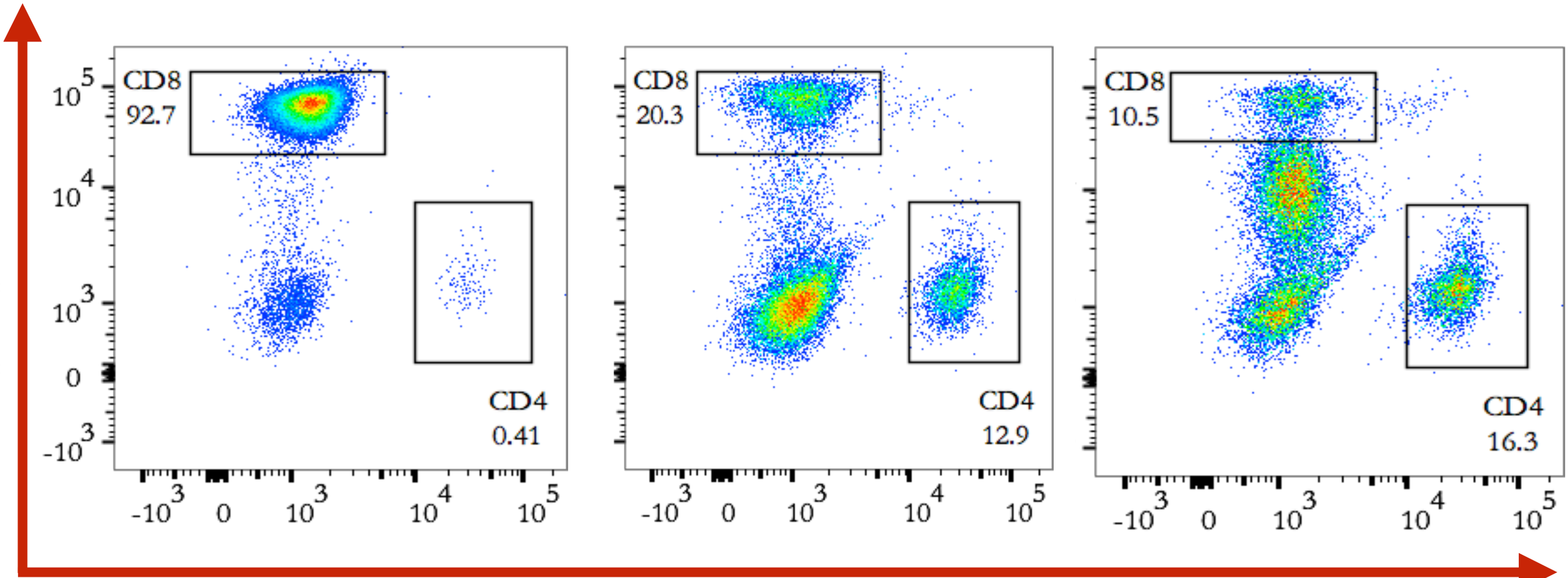
Sarcoma samples contain cytotoxic T lymphocytes

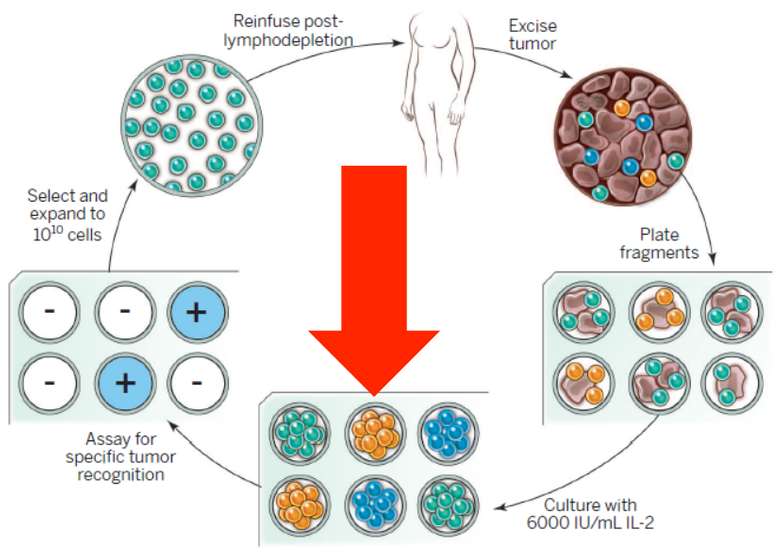




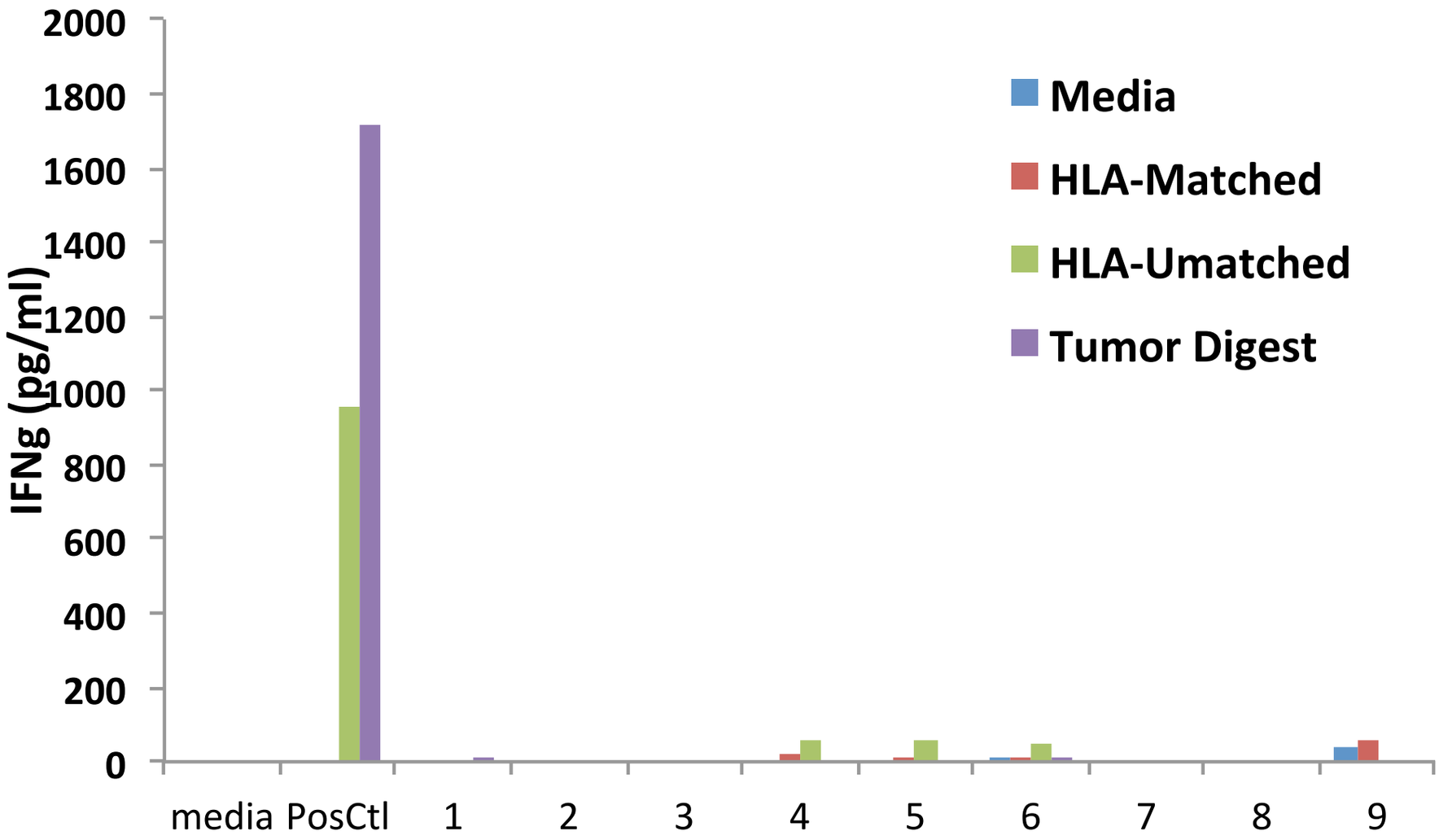


T-cell repertoire following TIL culture is heterogeneous

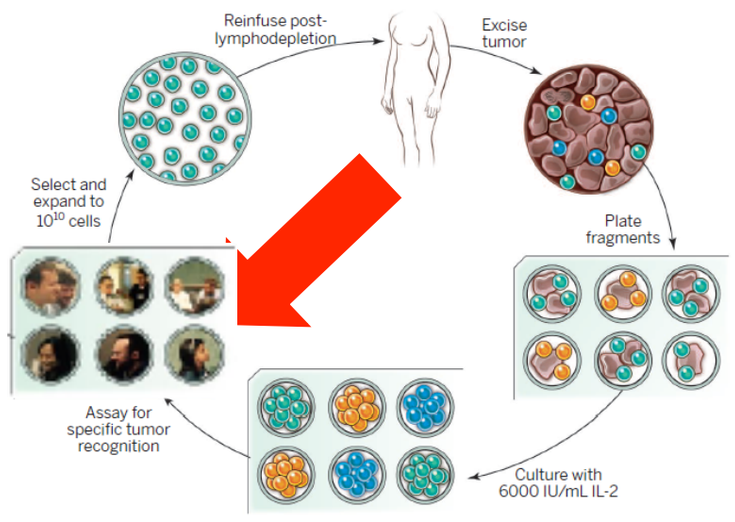




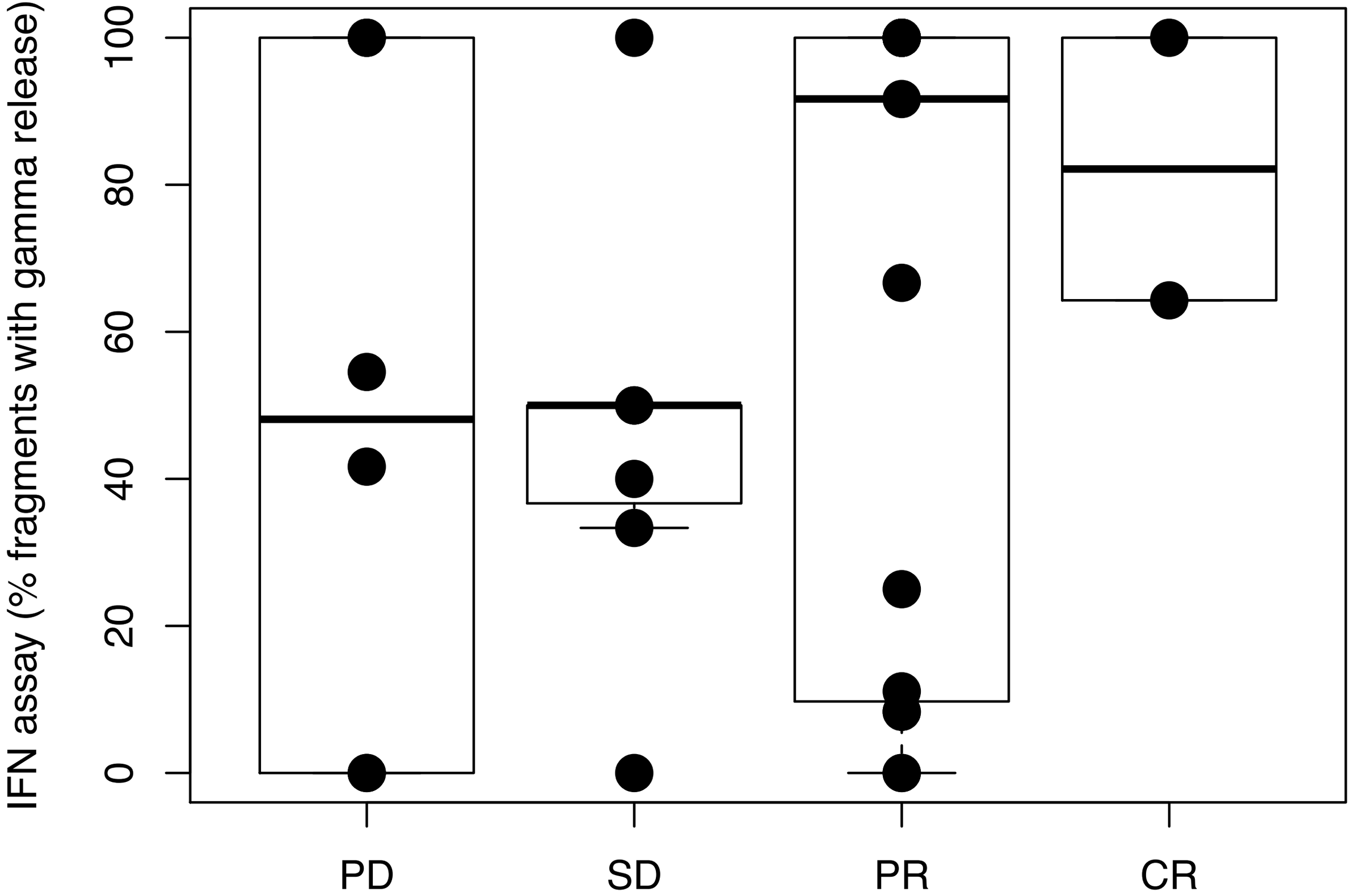
TIL reactivity is generally poor in sarcoma



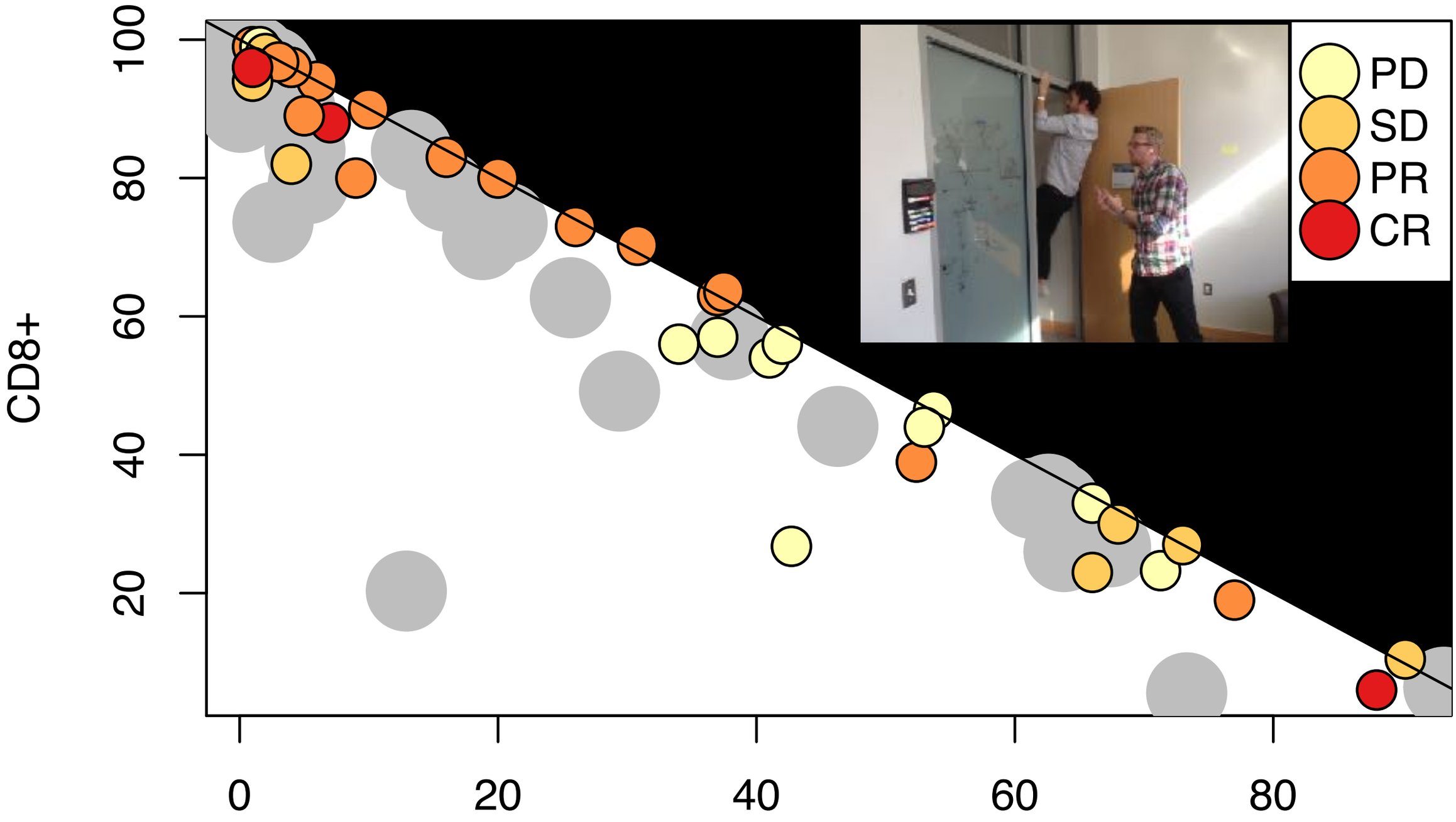
TIL population from separate tumor fragments



Result 1: IFN gamma reactivity assay does not correlate with outcome



Result 2: Sarcoma TIL are more heterogeneous than melanoma TIL



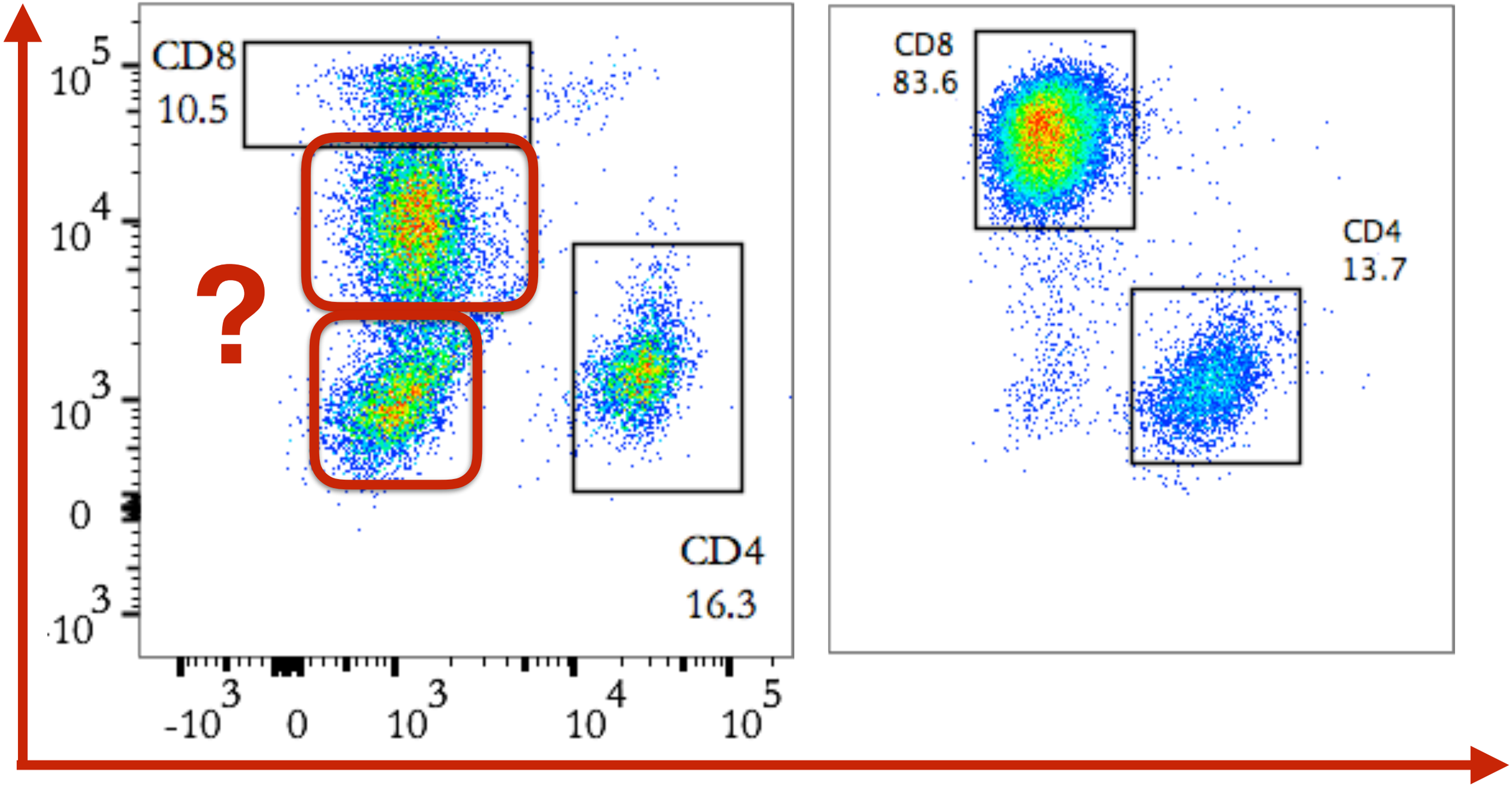
Colored dots: melanoma patients treated on trial

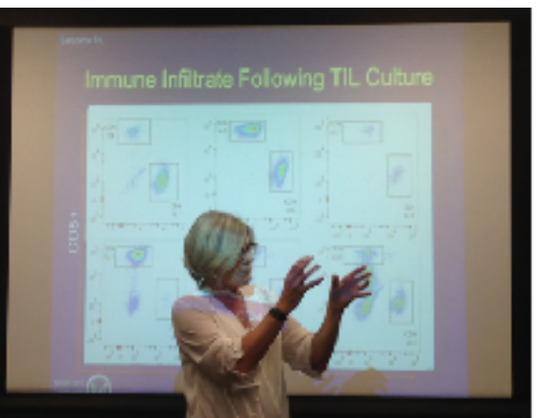
Grey dots: TIL derived from fragments of resected sarcomas

In contrast to melanoma, sarcoma TILs are diverse

sarcoma

melanoma





How does the TIL meta-P

map to

Outcome for

Meta-phenotype: The emergent charac

of a population consisting

from the interactions be

the constituent subtypes

How does the TCR

map to

immunotherapeutic outcome

-phenotype:

emergent

population

the interacti

constituent

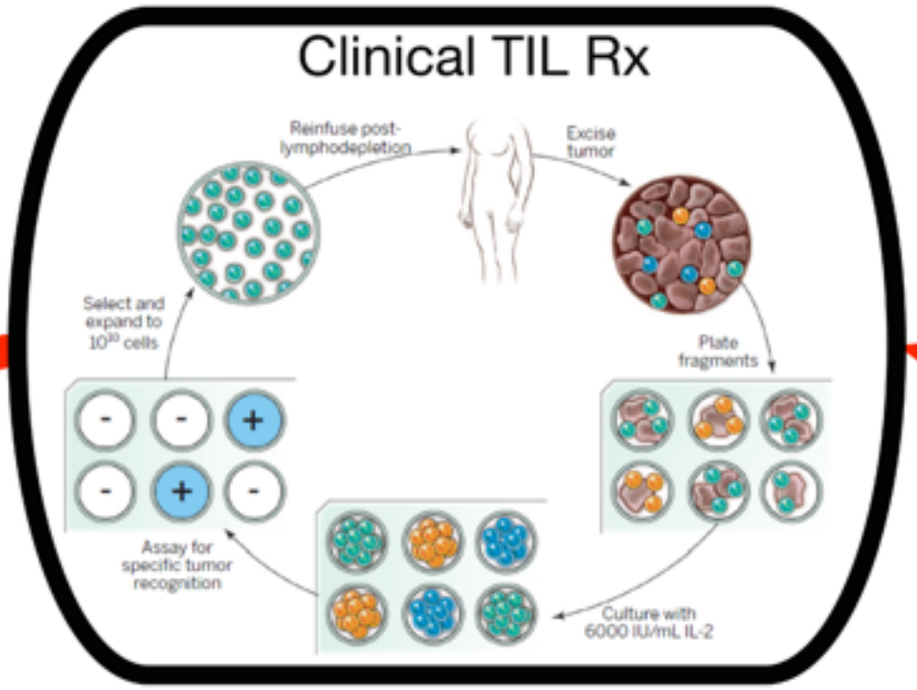
Team Blue Question:

How does the TIL meta-phenotype map to immunotherapeutic outcome for Sarcoma?

Meta-phenotype: The emergent characteristics of a population arising from the interactions between the constituent subtypes

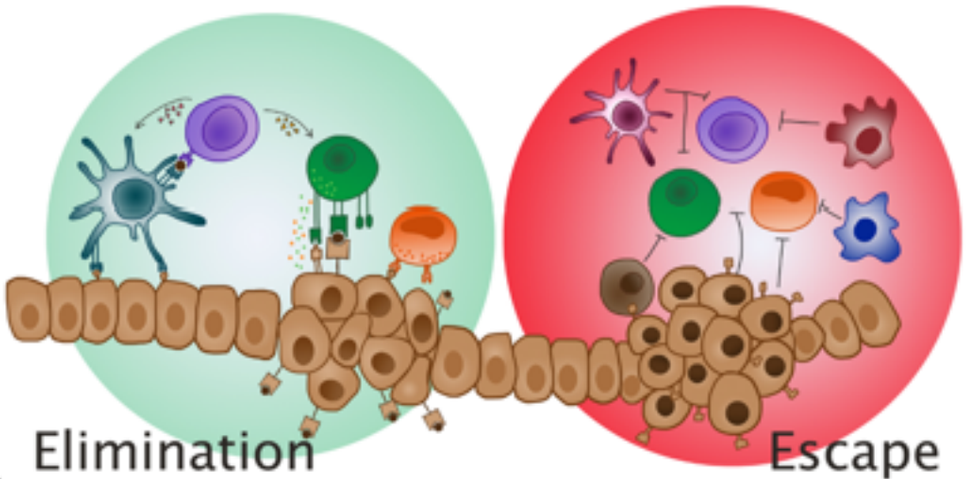
Problem and patient data

Clinical TIL Rx

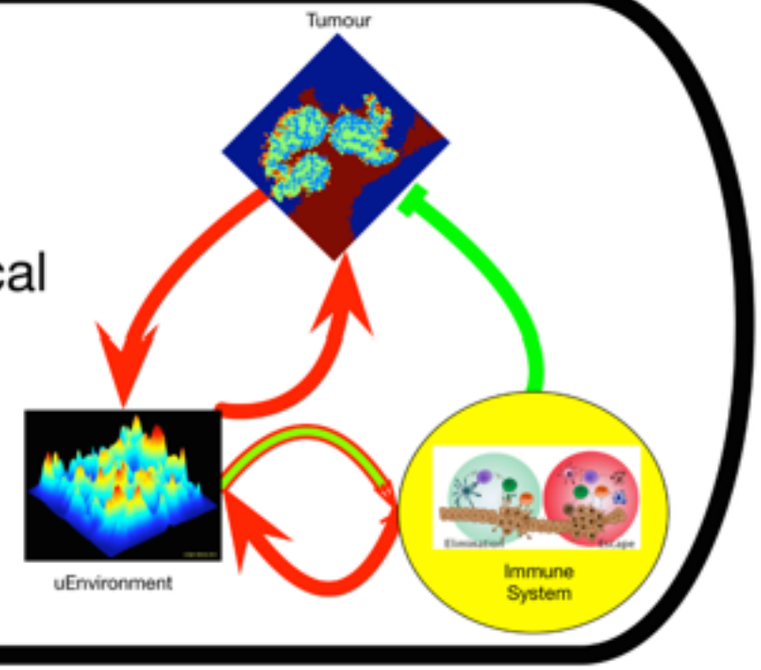


Synthesis and personalization

Immuno-Biology

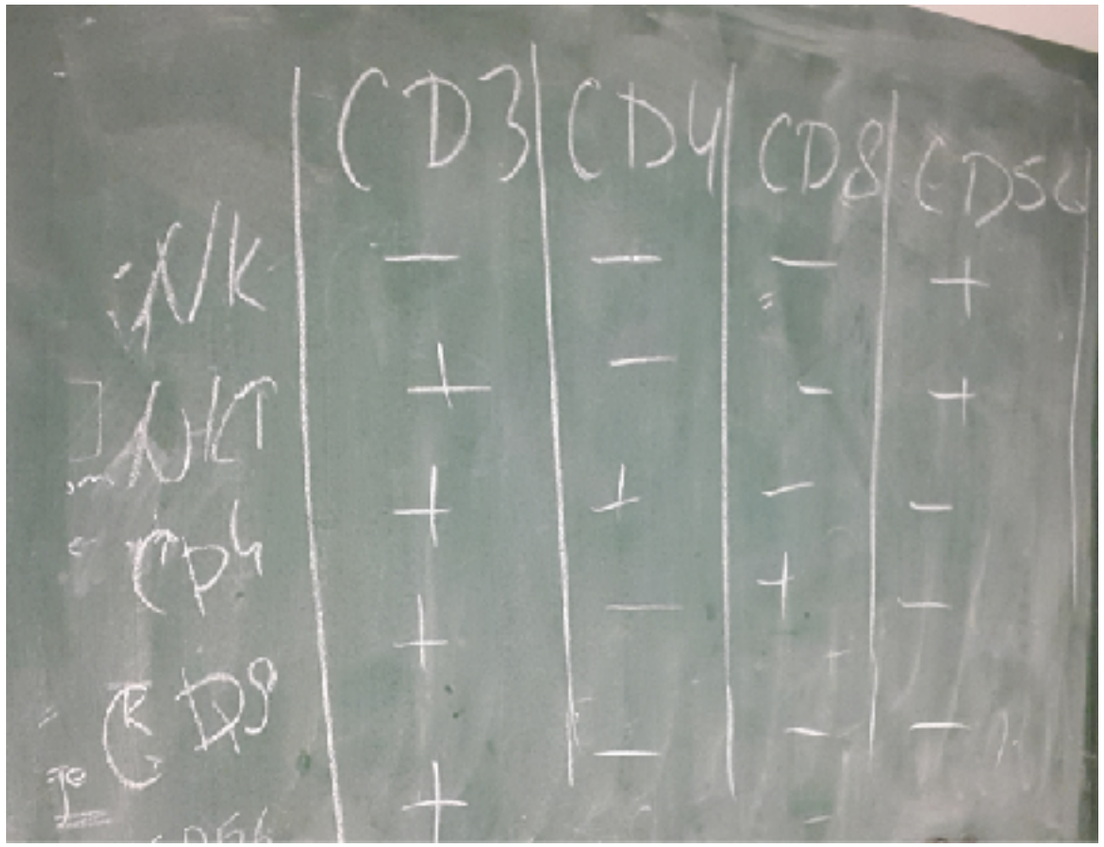


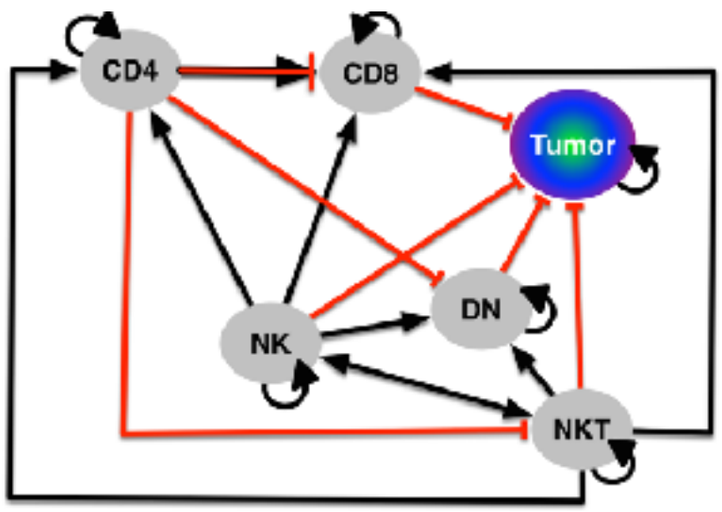
Suite of Mathematical Models

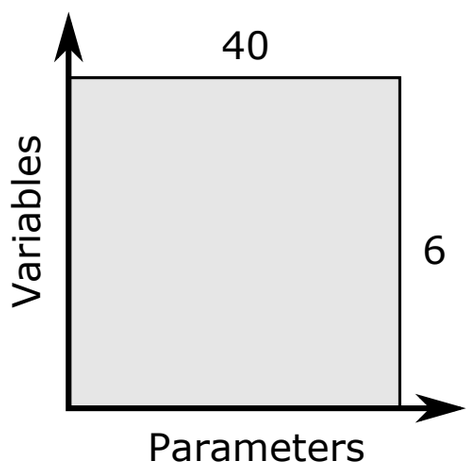


Understanding and parameterization

Modeling tumor-immune interactions is complex…
too complex!

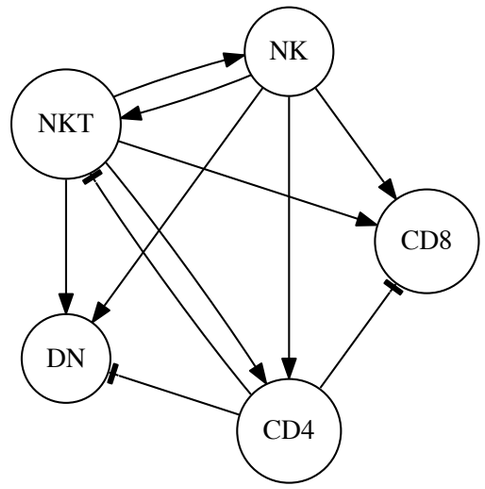






A Boolean network approach to reduce regulatory complexity

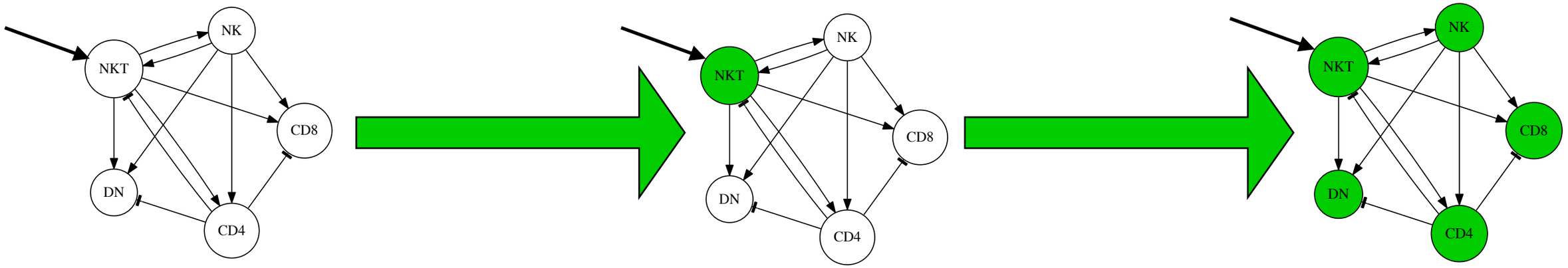
$$M = \begin{pmatrix} 0 & -1 & -1 & 0 & -1 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 1 & 0 & 1 \\ 1 & 1 & 1 & 1 & 0 \end{pmatrix} \equiv$$



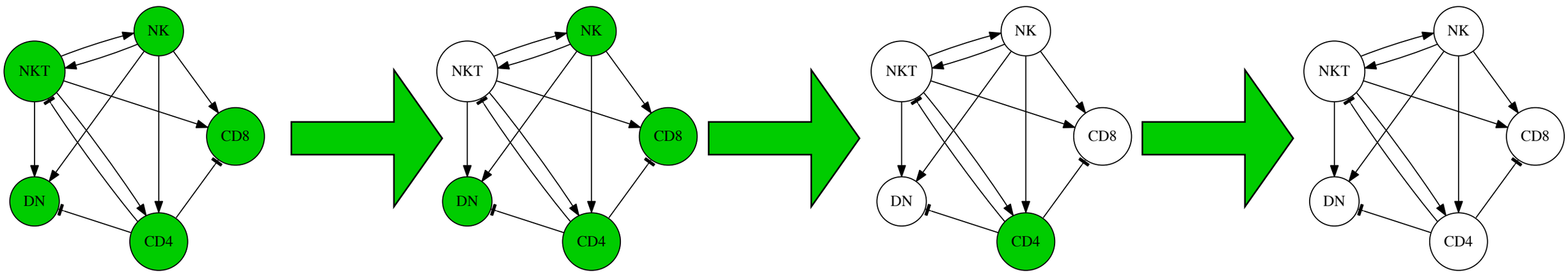
Update:

$$N_j(t+1) = \chi_{>0}\left(\sum_i M_{i,j} N_i(t)\right)$$

Response to stimulation:

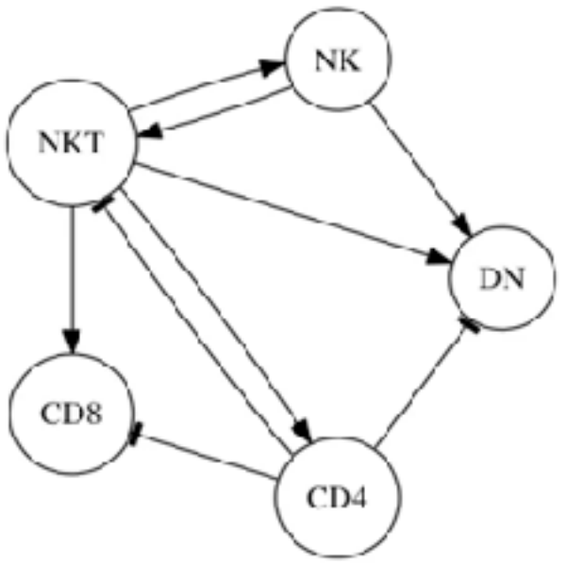


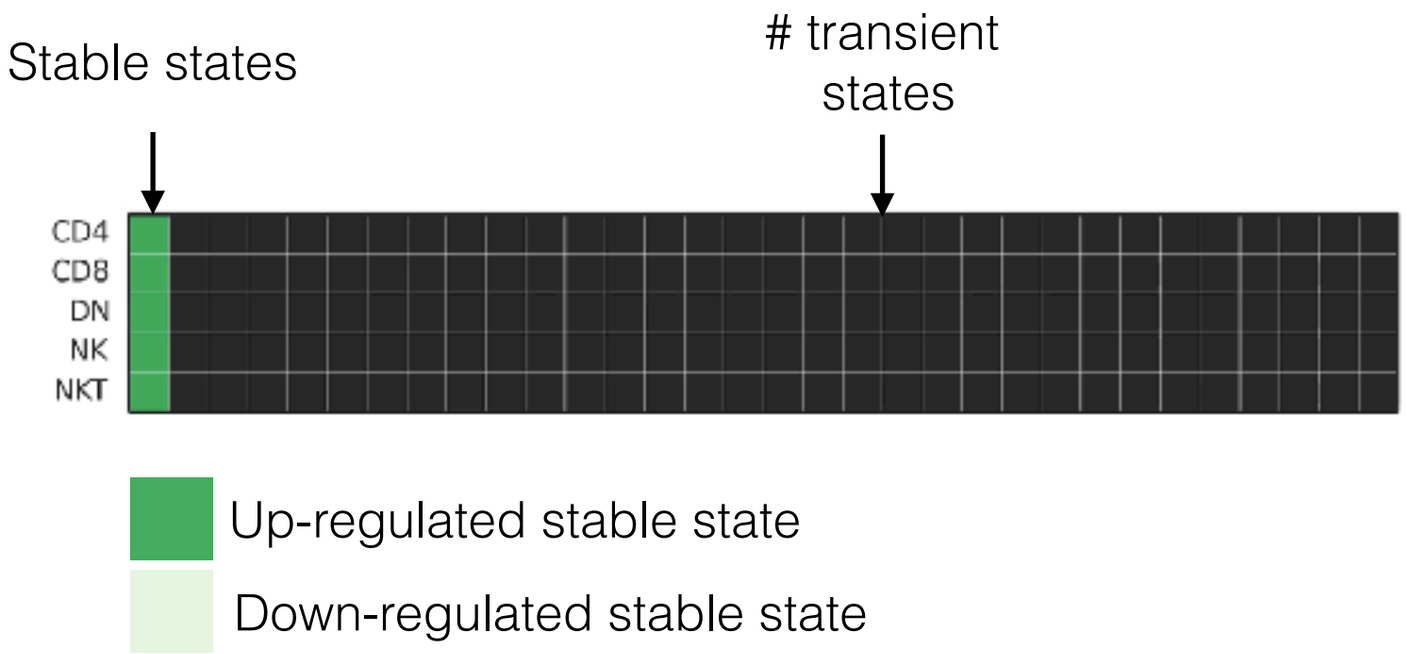
Return to homeostasis:



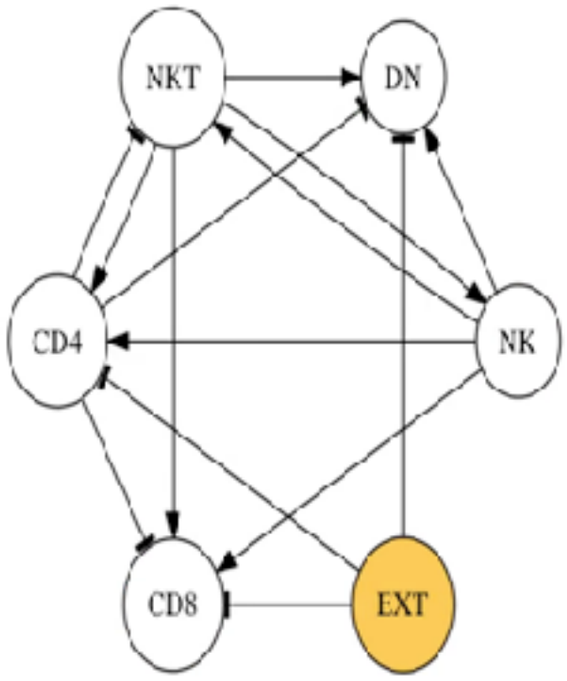
Analysis of network perturbations

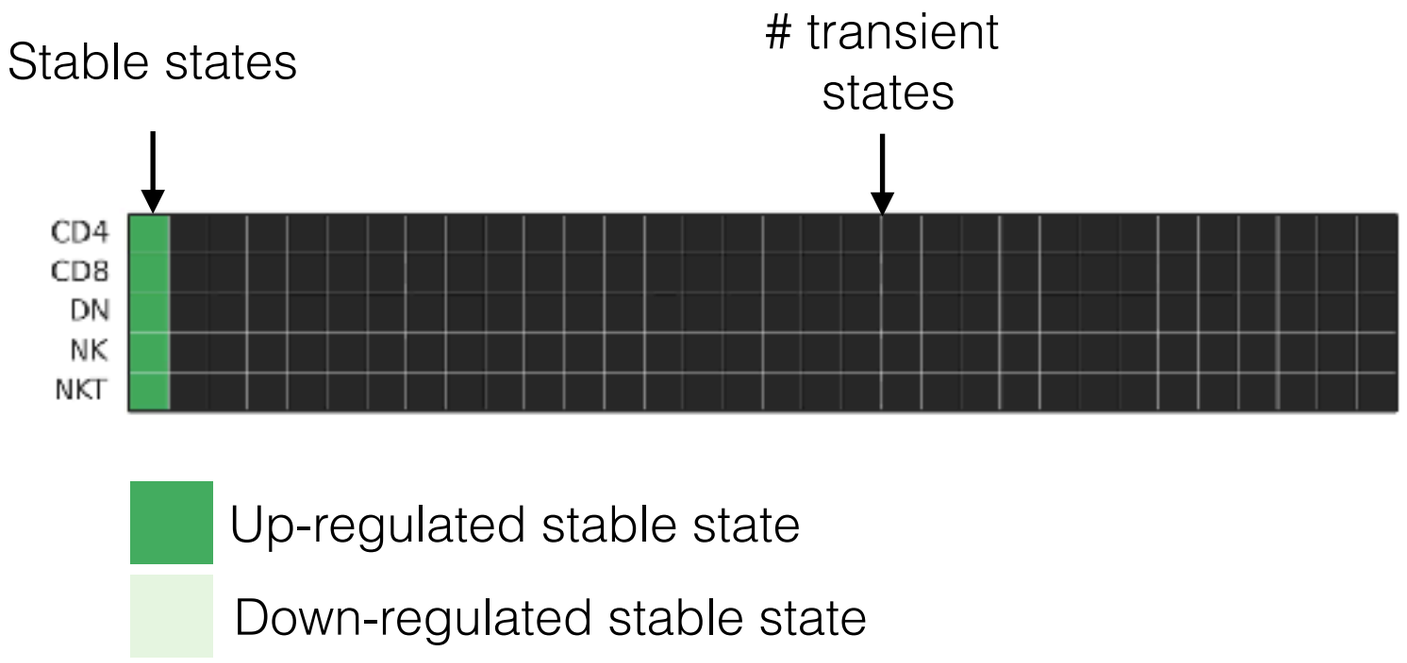
Internal perturbations:



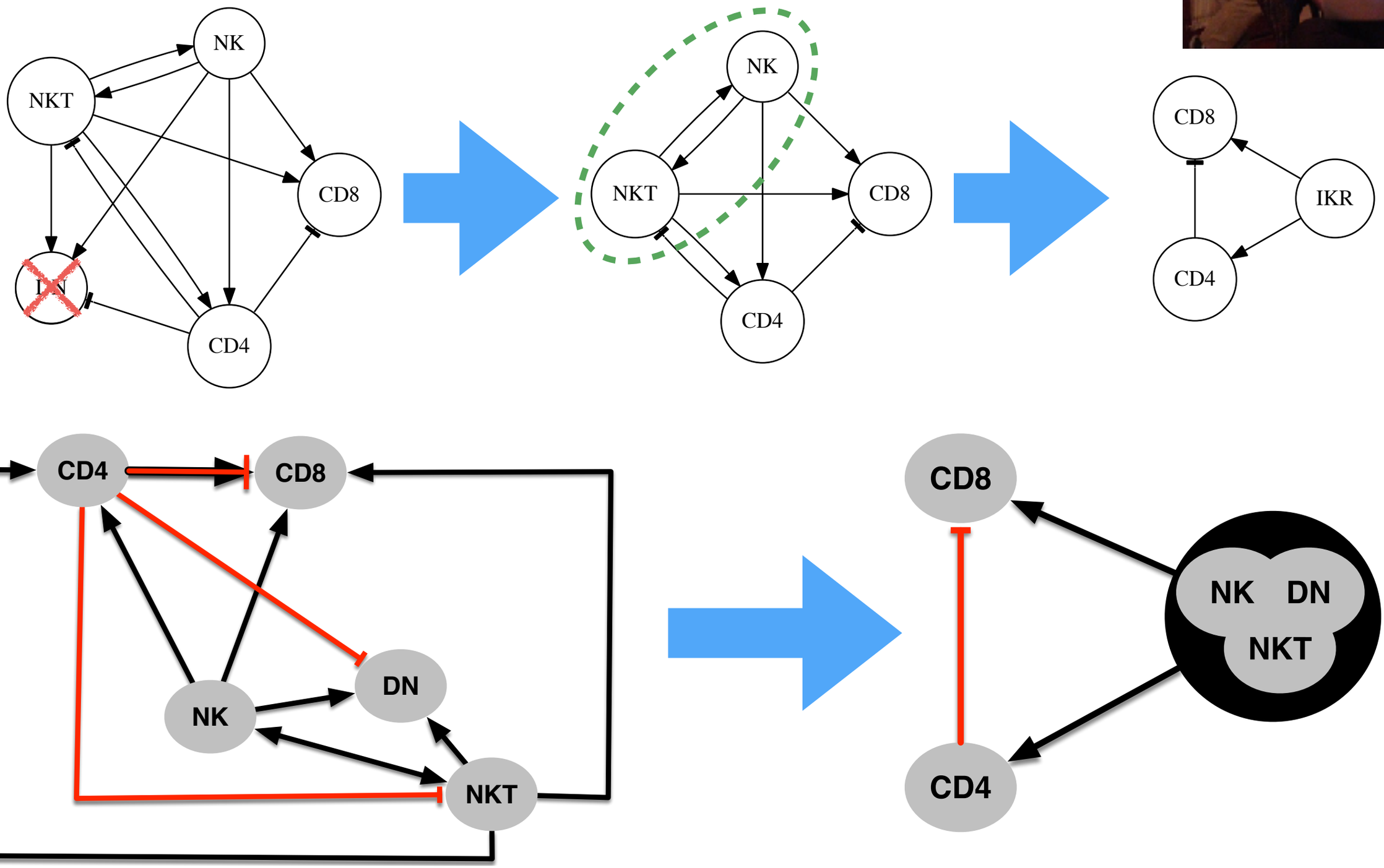


External regulation:

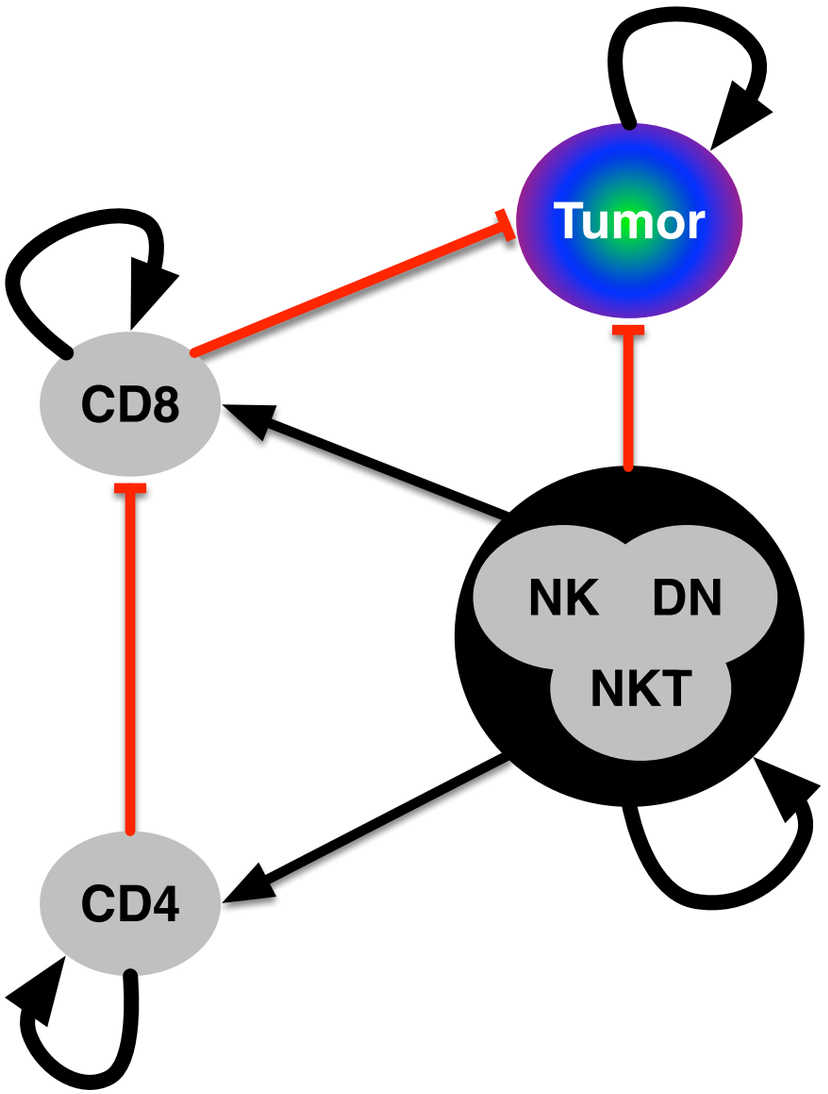




Result 3: A simplified model captures the essential regulatory dynamics



Understanding tumor-immune dynamics with an ODE model



Tumor

$$\dot{V}(t) = \overbrace{r_V V}^{\text{growth}} - \overbrace{(f_N(N) + f_E(E))V}^{\text{death by innate killers and CD8+}}$$

NK DN NKT

$$\dot{N}(t) = \overbrace{\sigma_N}^{\text{growth}} \overbrace{-\delta_N N}^{\text{natural death}} + \overbrace{h_N(V)N}^{\text{interaction with tumor cells}}$$

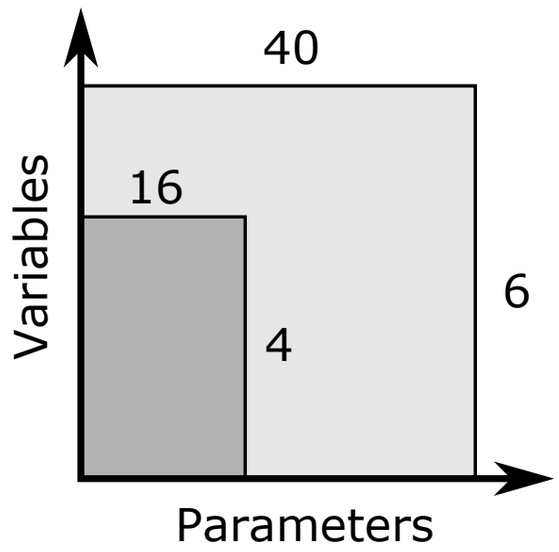
CD8

$$\dot{E}(t) = \overbrace{\sigma_E}^{\text{growth}} + \overbrace{g_N(N)E}^{\text{stimulation by innate killers}} + \overbrace{g_V(V)E}^{\text{interaction with tumor}} - \overbrace{g_L(R)E}^{\text{inhibition by CD4}}$$

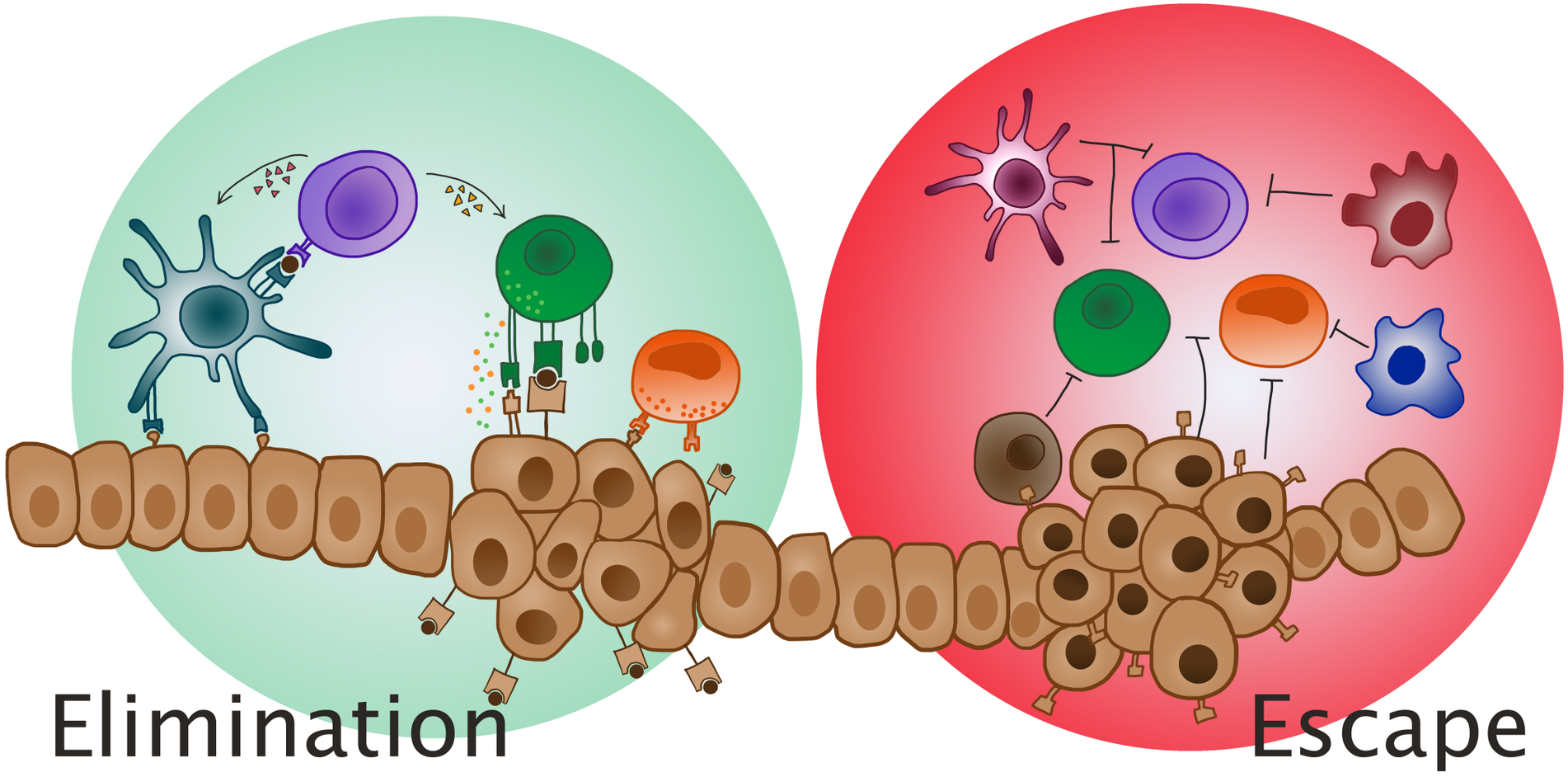
CD4

$$\dot{R}(t) = \overbrace{\sigma_R}^{\text{growth}} \overbrace{-\delta_L R}^{\text{natural decay}} + \overbrace{l_N(V)R}^{\text{stimulation by innate killers}}$$

$$V(0) = V_0, N(0) = N_0, E(0) = E_0, R(0) = R_0$$

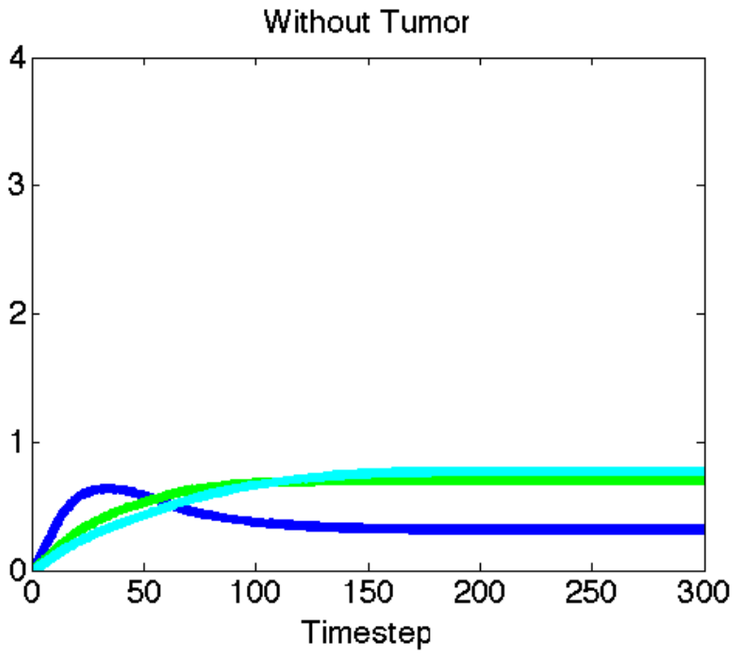


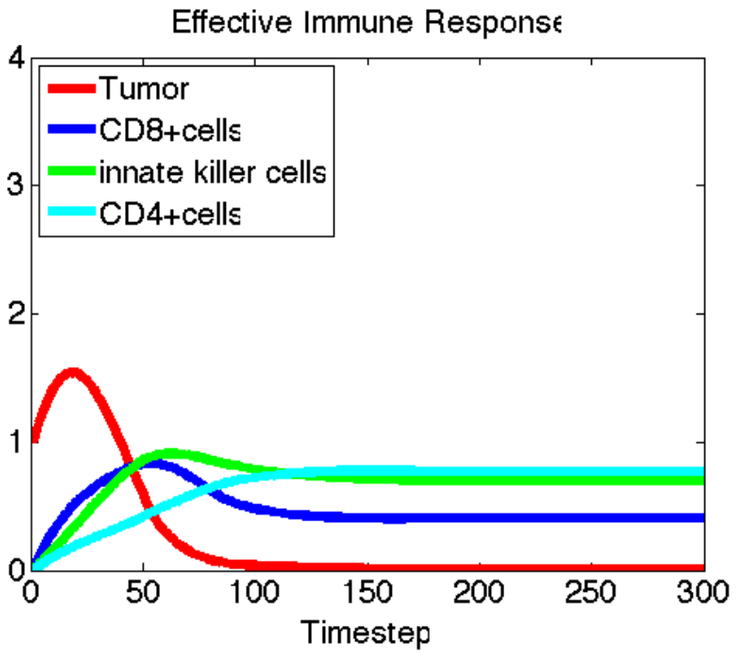
Recapitulating homeostasis, successful immune surveillance and tumor immune evasion

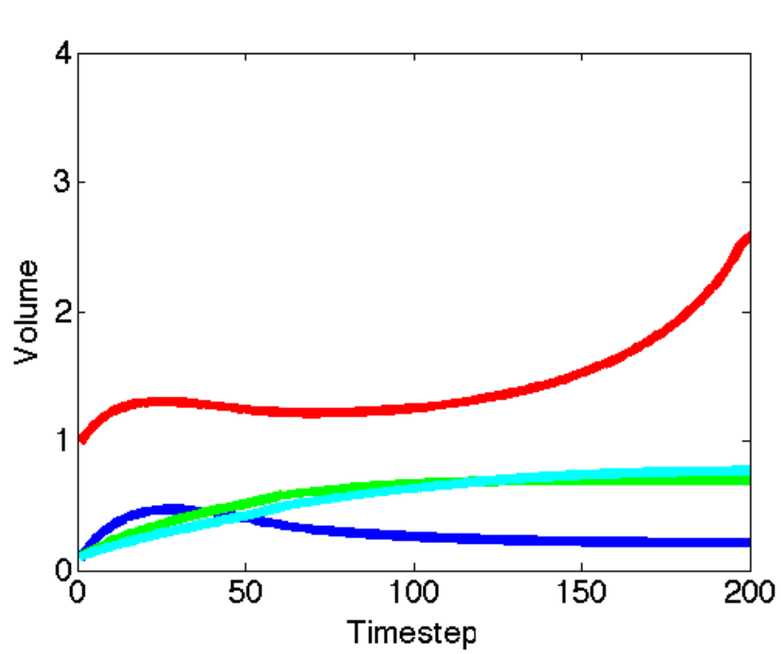


Elimination

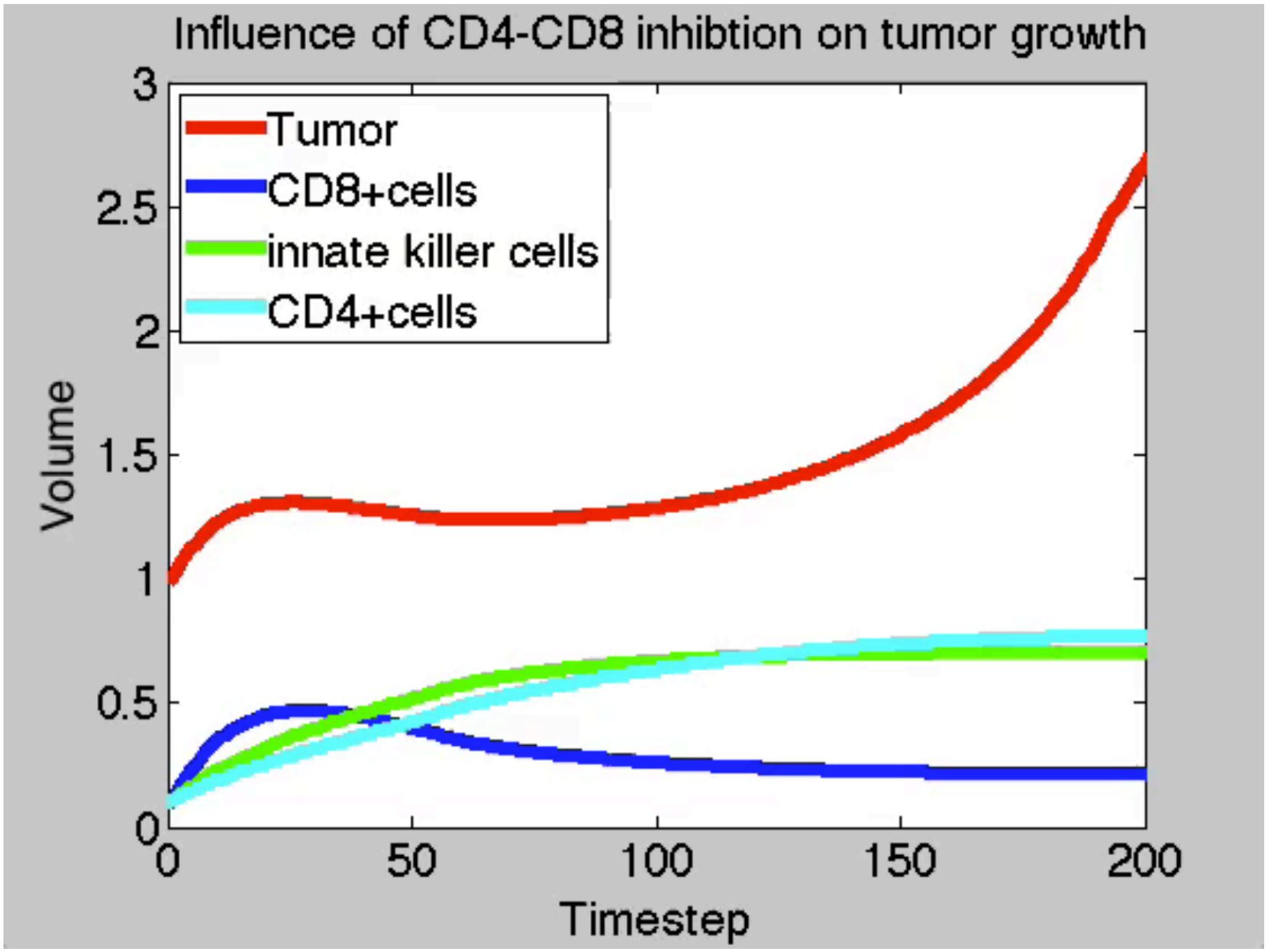
Escape

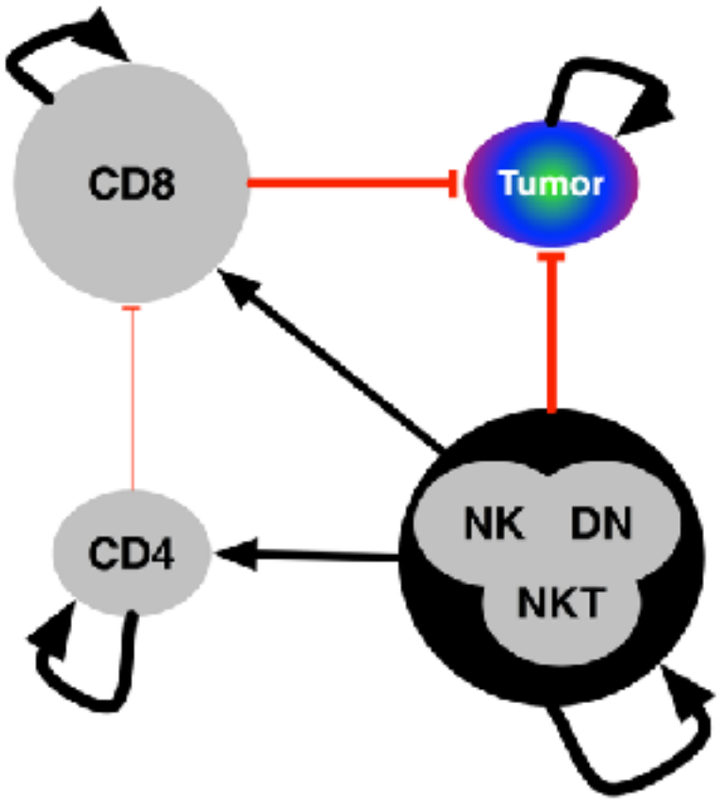






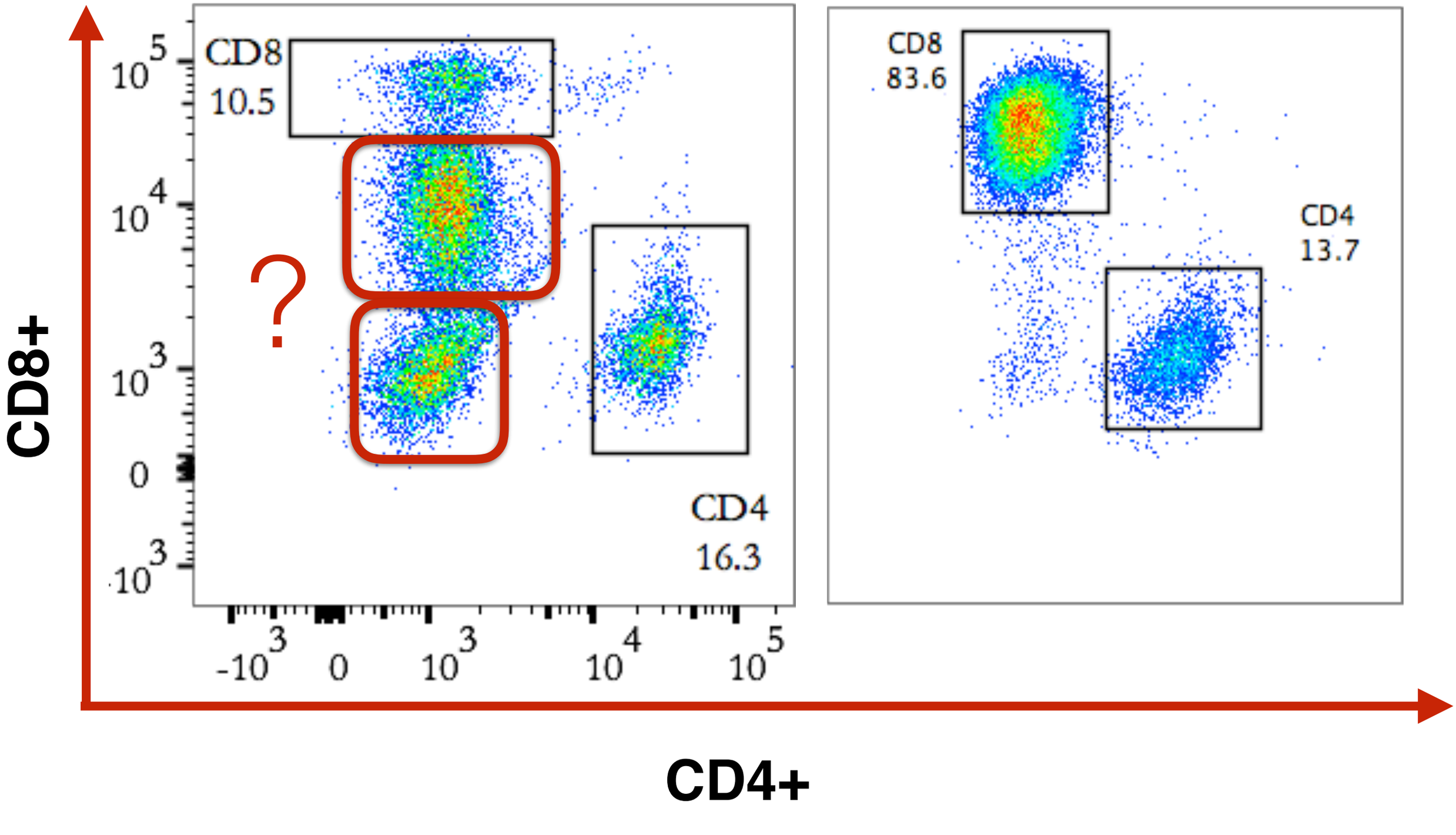
modulating immune response 1: checkpoint inhibitors



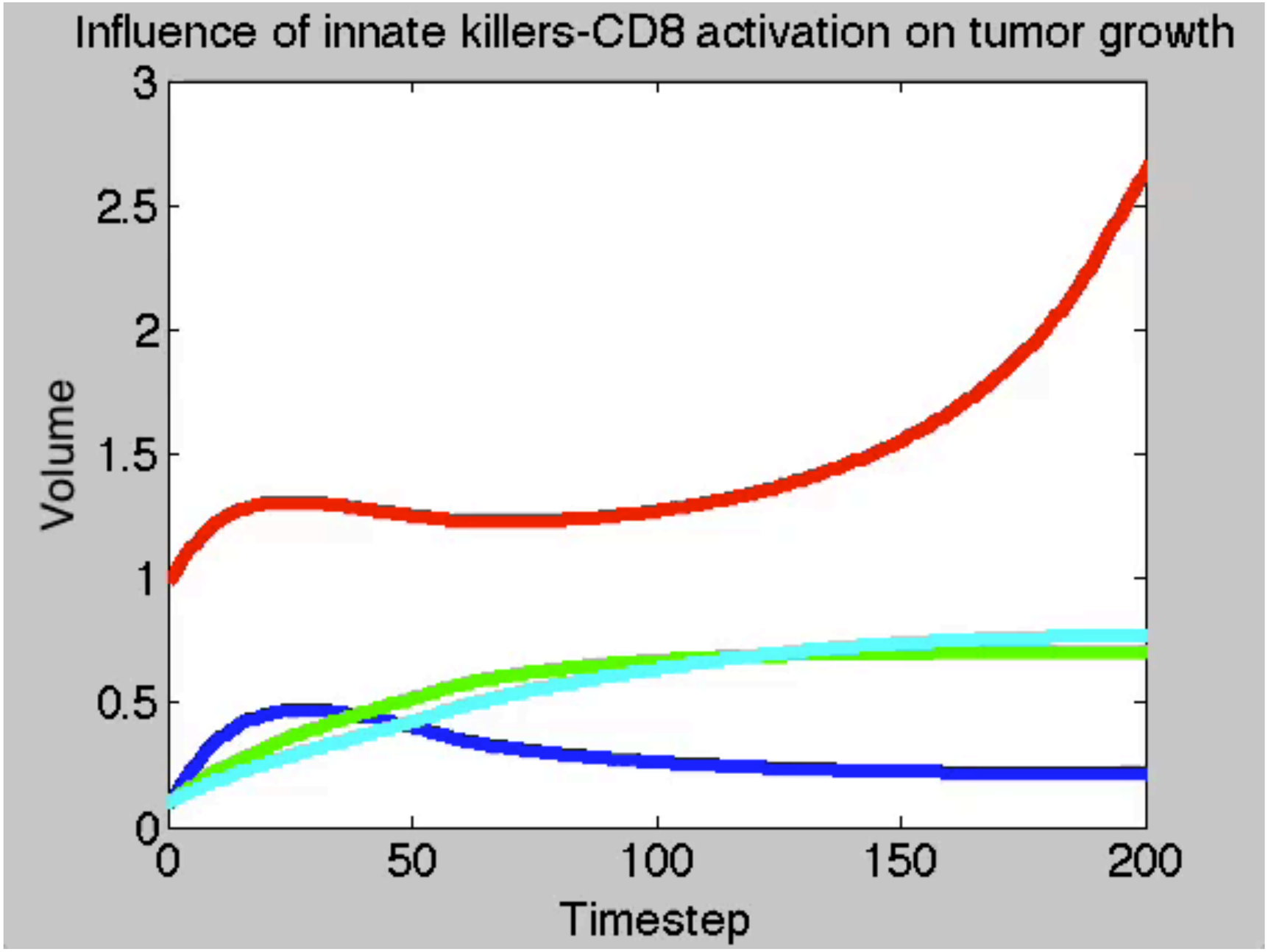


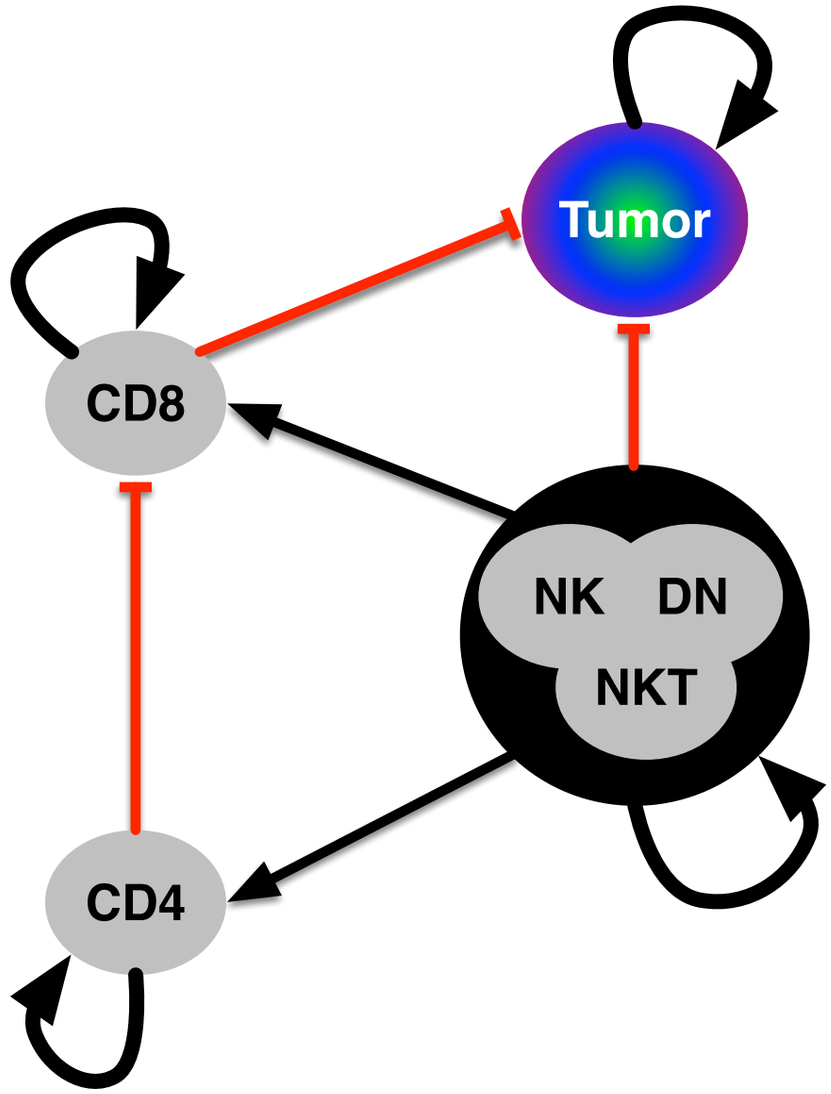
Sarcoma

Melanoma

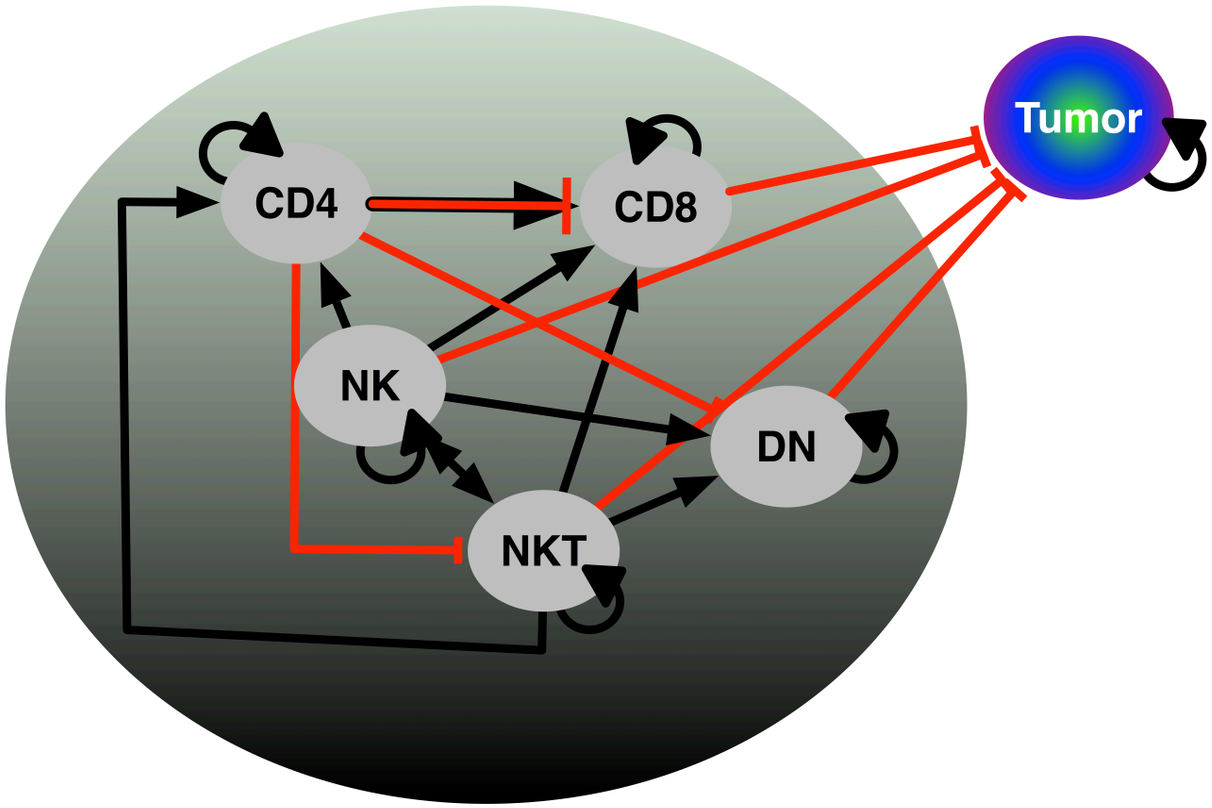


Result 4: Shifting the balance of innate and adaptive immune interactions can change tumor fate



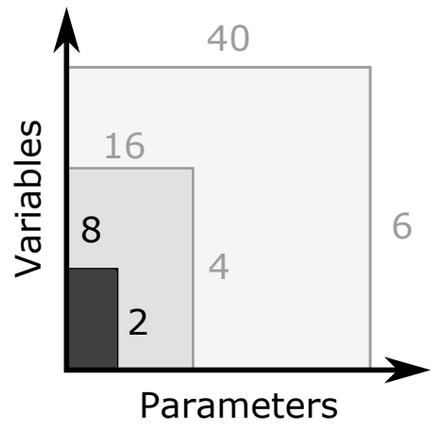


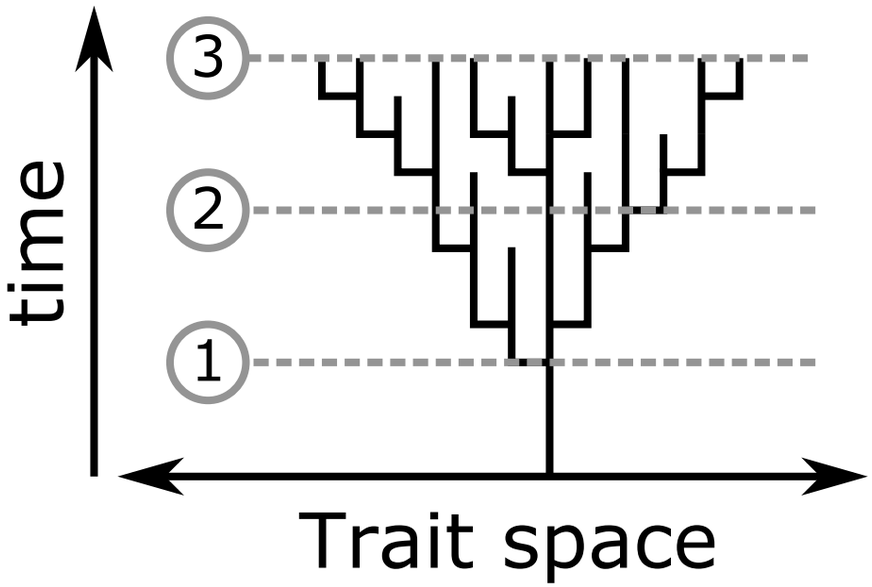
Incorporating tumor/immune co-evolution: effects of heterogeneity on therapeutic response

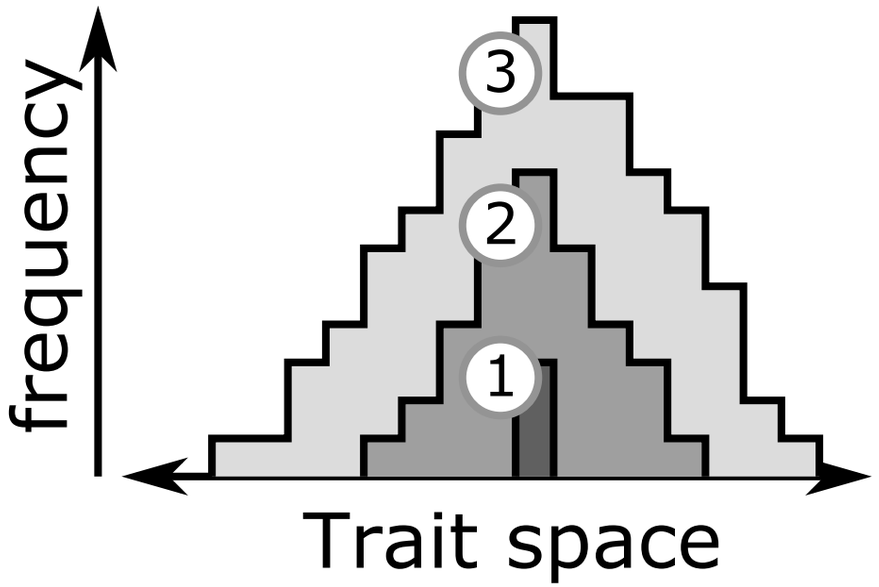


$$\frac{\partial C(x,t)}{\partial t} = \overbrace{f(C,x)}^{\text{Proliferation}} + \overbrace{D\frac{\partial^2 C}{\partial x^2}}^{\text{Mutation}} - \overbrace{h(T,C,x)}^{\text{T-cell killing}} - \overbrace{\delta C}^{\text{Innate killing}}$$

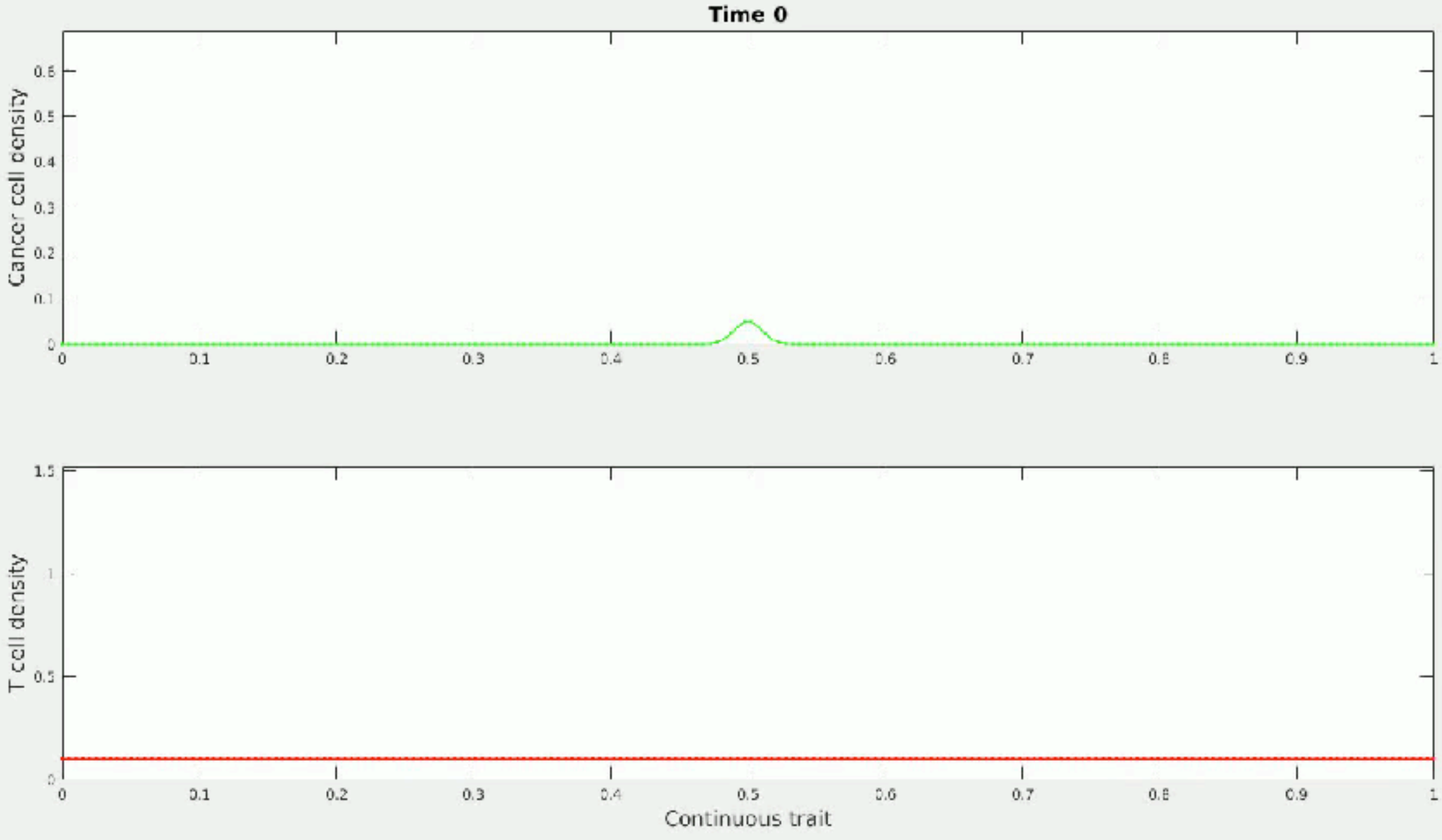
$$\frac{\partial T(x,t)}{\partial t} = \overbrace{g(C,T)}^{\text{T-cell response}} - \overbrace{\delta_T T}^{\text{Turnover}}$$



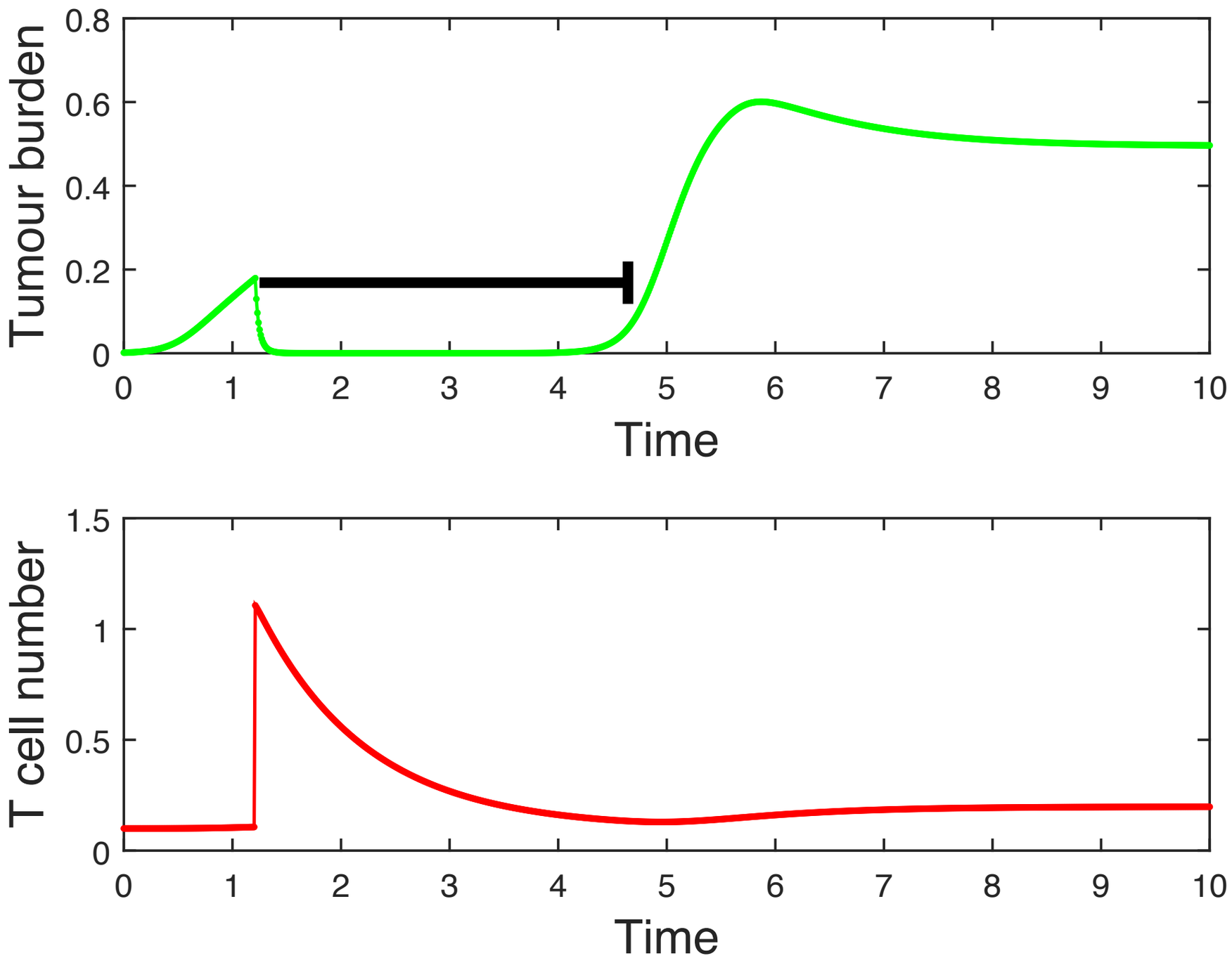




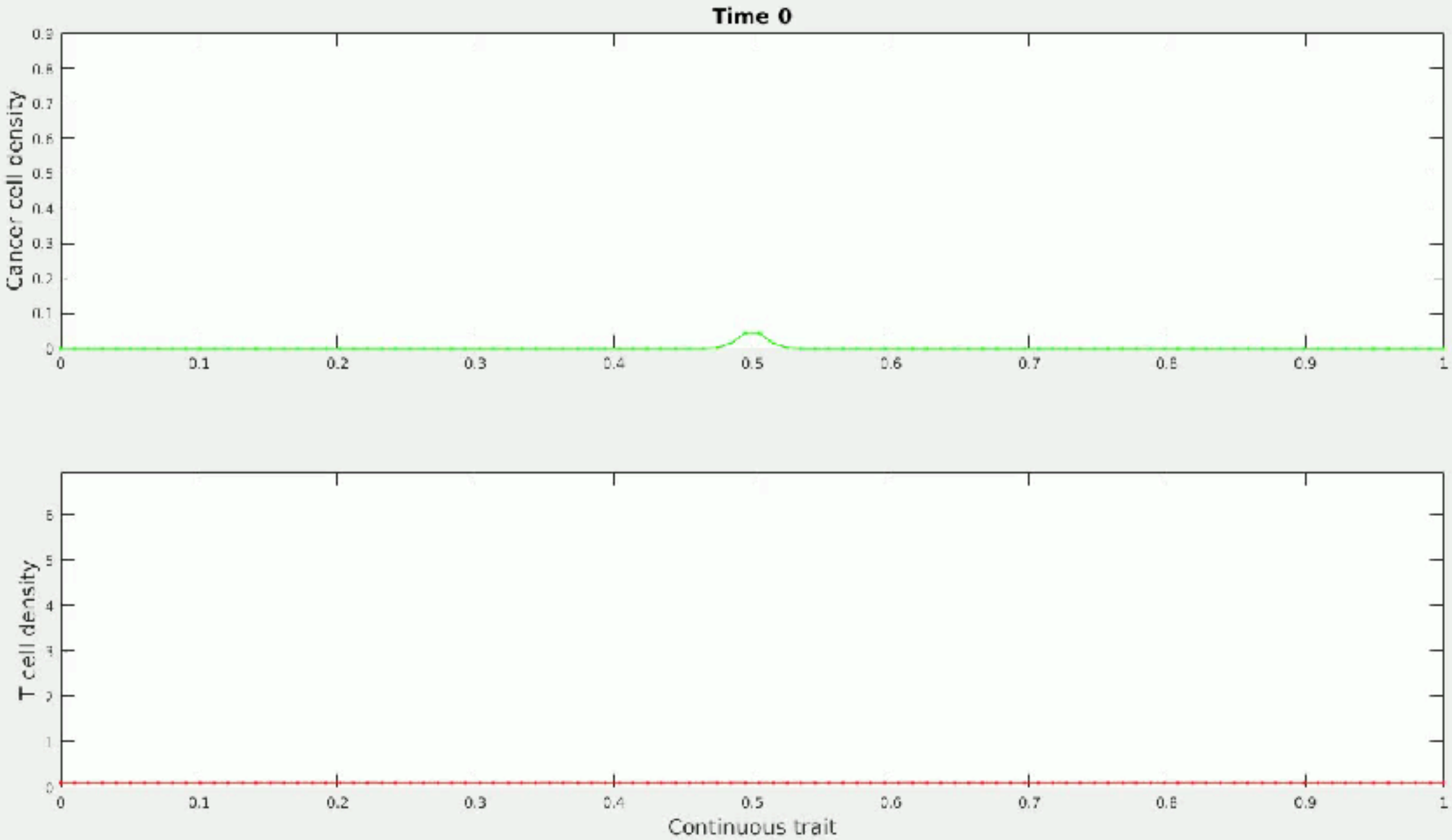
Treatment with all possible TIL clones



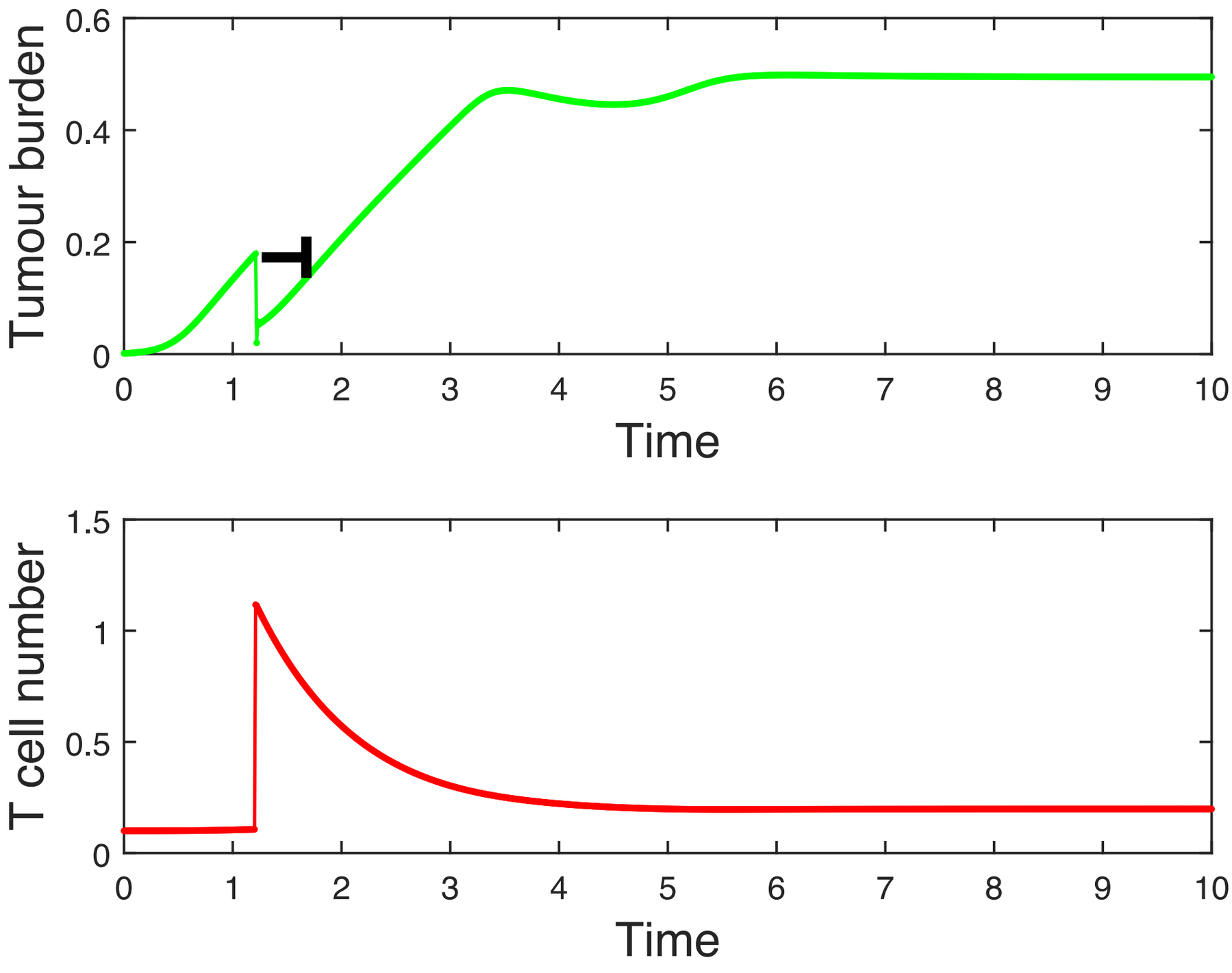
Disease free interval can be measured *in silico*



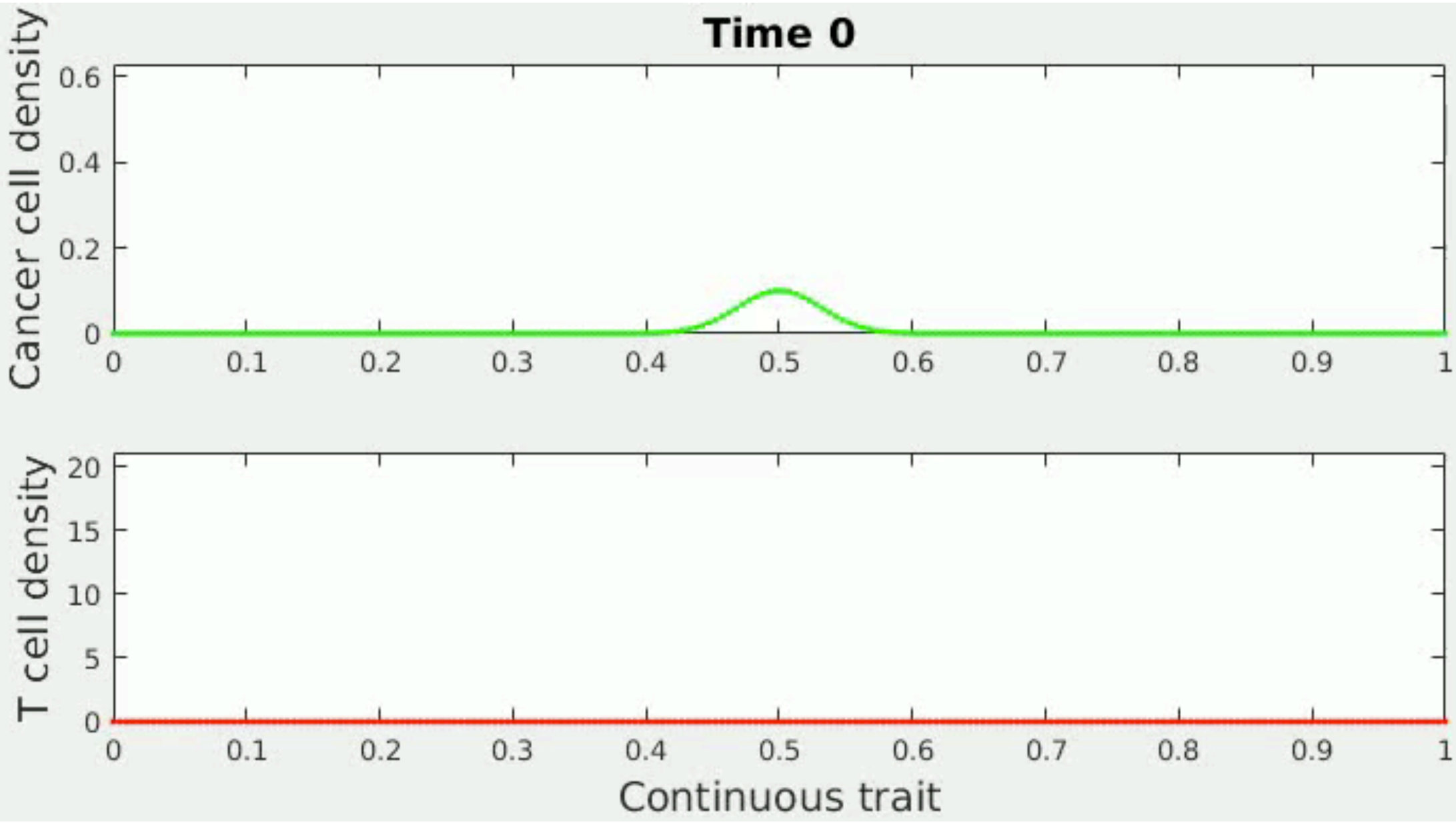
Treatment with near-clonal TIL (CAR T-cells?)

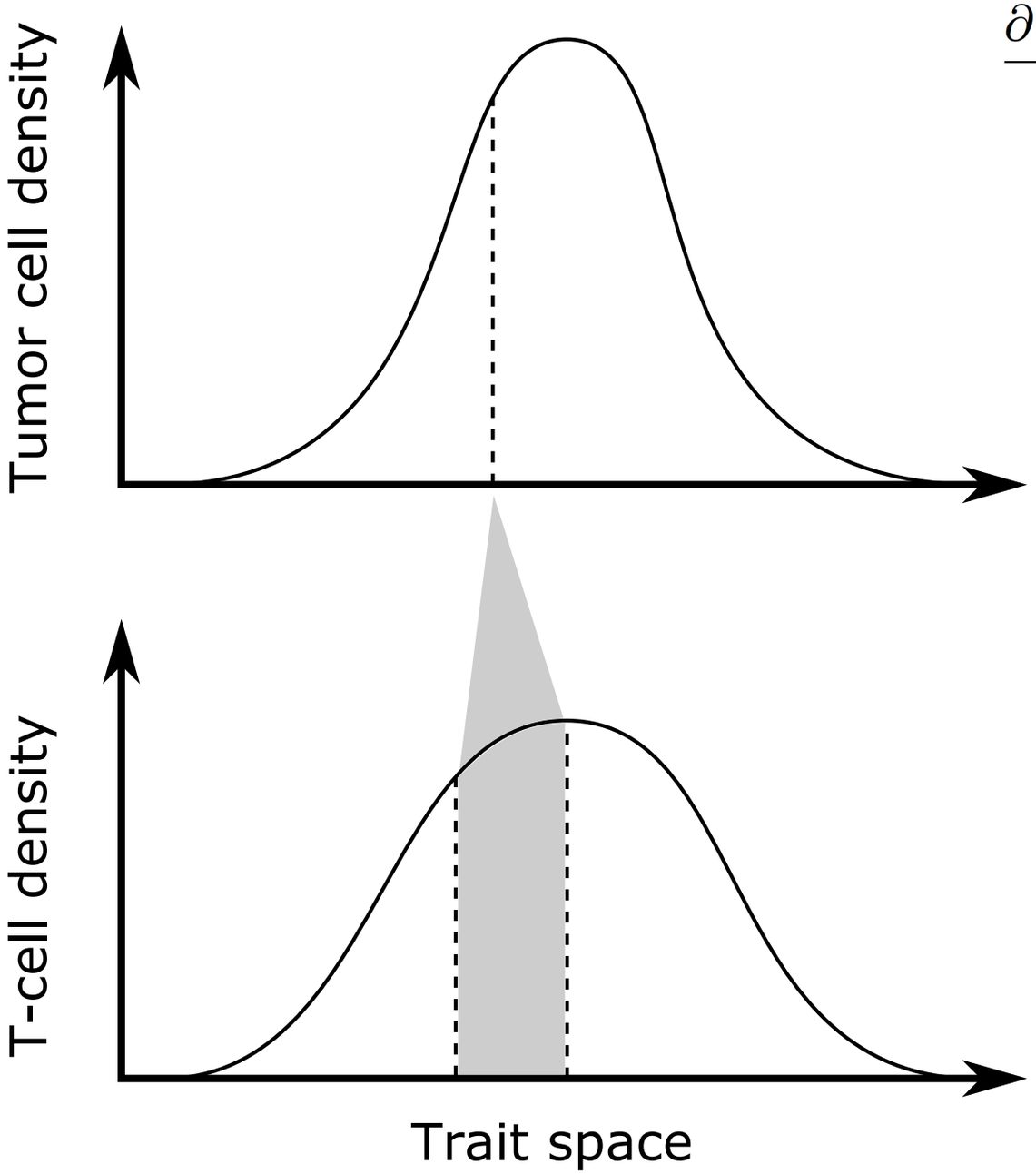


Result 5: Highly heterogeneous tumors are resistant to treatment with specific T-cell populations



What if we have a oligo-clonal tumor where one clone is amenable to targeted therapy?

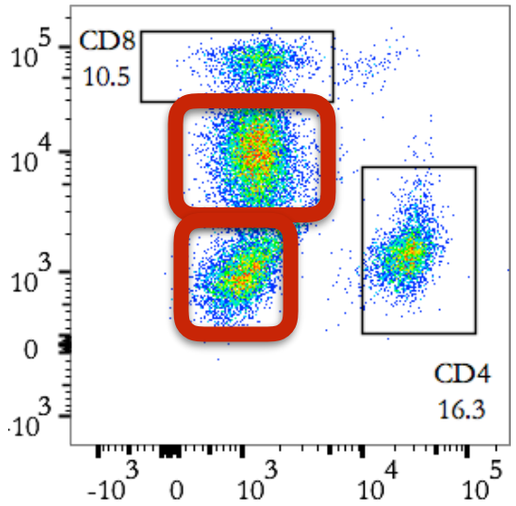




$$\frac{\partial C(x,t)}{\partial t} = f(C,x) + \cancel{D\frac{\partial^2 C}{\partial x^2}} - \cancel{h(T,C,x)} - \delta C$$

$$\int r(y)\, M(y,x)\, C(y,t)\, \mathrm{d}y$$

$$\int k(x,y)\; C(x,t)\; T(y,t) \mathrm{d}y$$



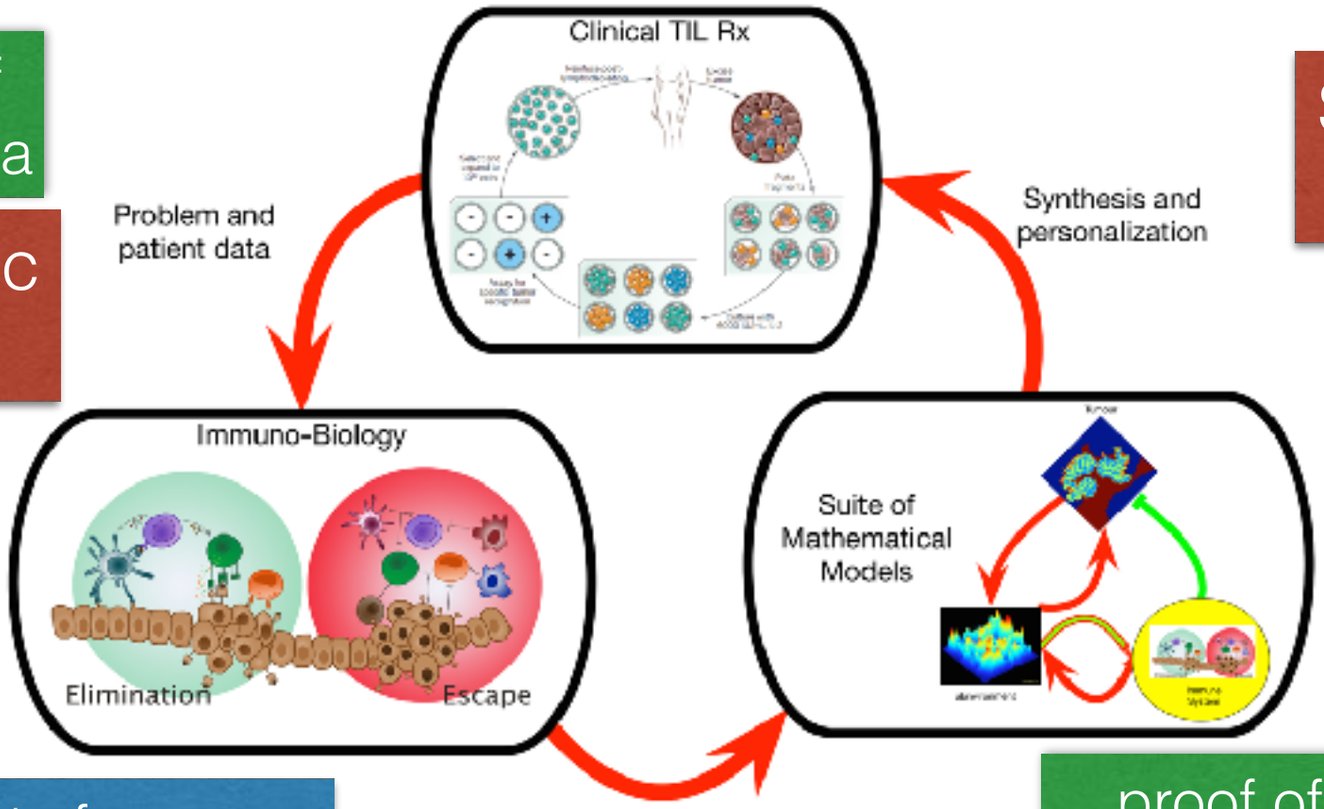
Result 1: Standard IFN gamma reactivity assay does not correlate with outcome
Result 2: Sarcoma TIL are more heterogeneous than melanoma TIL
Result 3: A simplified model captures the essential regulatory dynamics
Result 4: Shifting the balance of innate and adaptive immune interactions can change tumor fate
Result 5: Highly heterogeneous tumors are resistant to treatment with specific T-cell populations

Specific aim 1: *Identify phenotypic signatures of ex vivo sarcoma-derived TIL that predict ACT efficacy*
Specific aim 2: *Construct mathematical models to characterize the optimum patient-specific TIL meta-phenotype in metastatic sarcoma*

9 patients to date
+ 20 within 12 months

re-analysis of melanoma data

$20k postDoc —> SA1



$10k postDoc —> SA2

>20 fragments frozen CD3/4/8/56 phenotype data

$20k lab data acquisition

proof of principle to describe dynamics

Importance: Our approach will improve ACT for sarcoma, and is generalizable.
Originality: We are the world's leading group applying ACT to sarcoma. A hierarchy of mathematical models tackles the complexity of tumor-immune dynamics.
Feasibility: We are augmenting an on-going Moffitt clinical protocol in human subjects with sarcoma.


#TeamBlue #MoffittIMO