Russell C. Rockne Ph.D.

@RRockne

- Assistant professor
- Director, Division of Mathematical Oncology

- Ph.D. Applied Mathematics,
  University of Washington, Seattle

- Mathematical Modeling of:
  - Cancer progression, response to therapy
  - Medical imaging (MRI, PET)
  - Radiation therapy

- Focus: translation of mathematics into the clinic

City of Hope

City of Hope

Optimizing treatment with radionuclide therapy and immunotherapy

Russell C. Rockne

Asst. Professor, Director, Division of Mathematical Oncology

Department of Computational and Quantitative Medicine

Beckman Research Institute, City of Hope

OUTLINE

- What is radioimmuno therapy (RIT)
- What is CAR T-cell immunotherapy

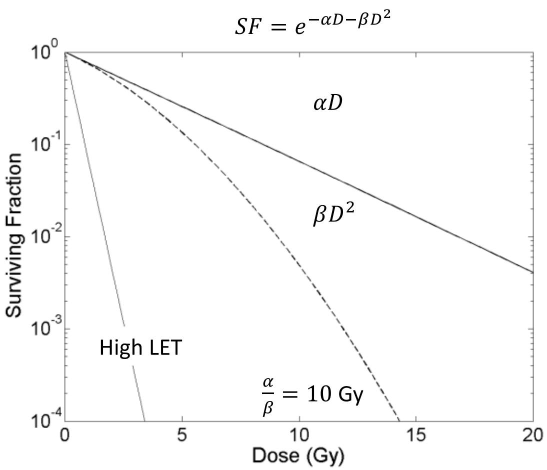
- Combination therapies and challenges of RIT + CAR T-cell immunotherapy

- Mathematical modeling to address challenges of combo therapy
  - Mathematical models can incorporate:
    - RIT decay, dose, tumor response, toxicity constraints
    - CAR T cell effect, proliferation, exhaustion
    - Provide a framework to optimize: dose, sequence, timing
    - Make **predictions** and give **dynamic quantifications** of response

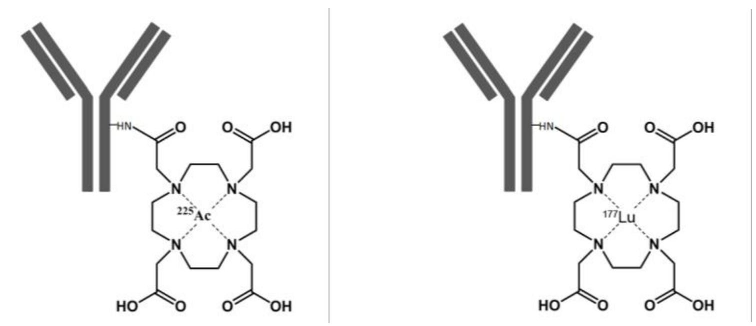
- Examples of mathematical modeling and analysis of:
  - ^{225}Ac, ^{177}Lu RIT + CAR T cells in preclinical multiple myeloma model

Radio-immunotherapy (RIT)

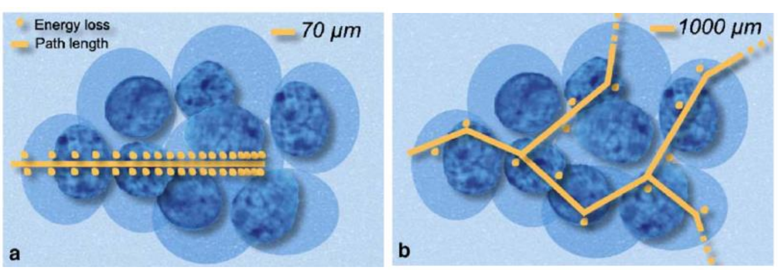
- Targeted Radionuclide therapy with antibodies (Ab)
- Renewed interest in alpha emitters in RIT (αRIT), ex. ^{225}Ac
- αRIT is high LET radiation



^{225}Ac-DOTA-Ab ^{177}Lu-DOTA-Ab



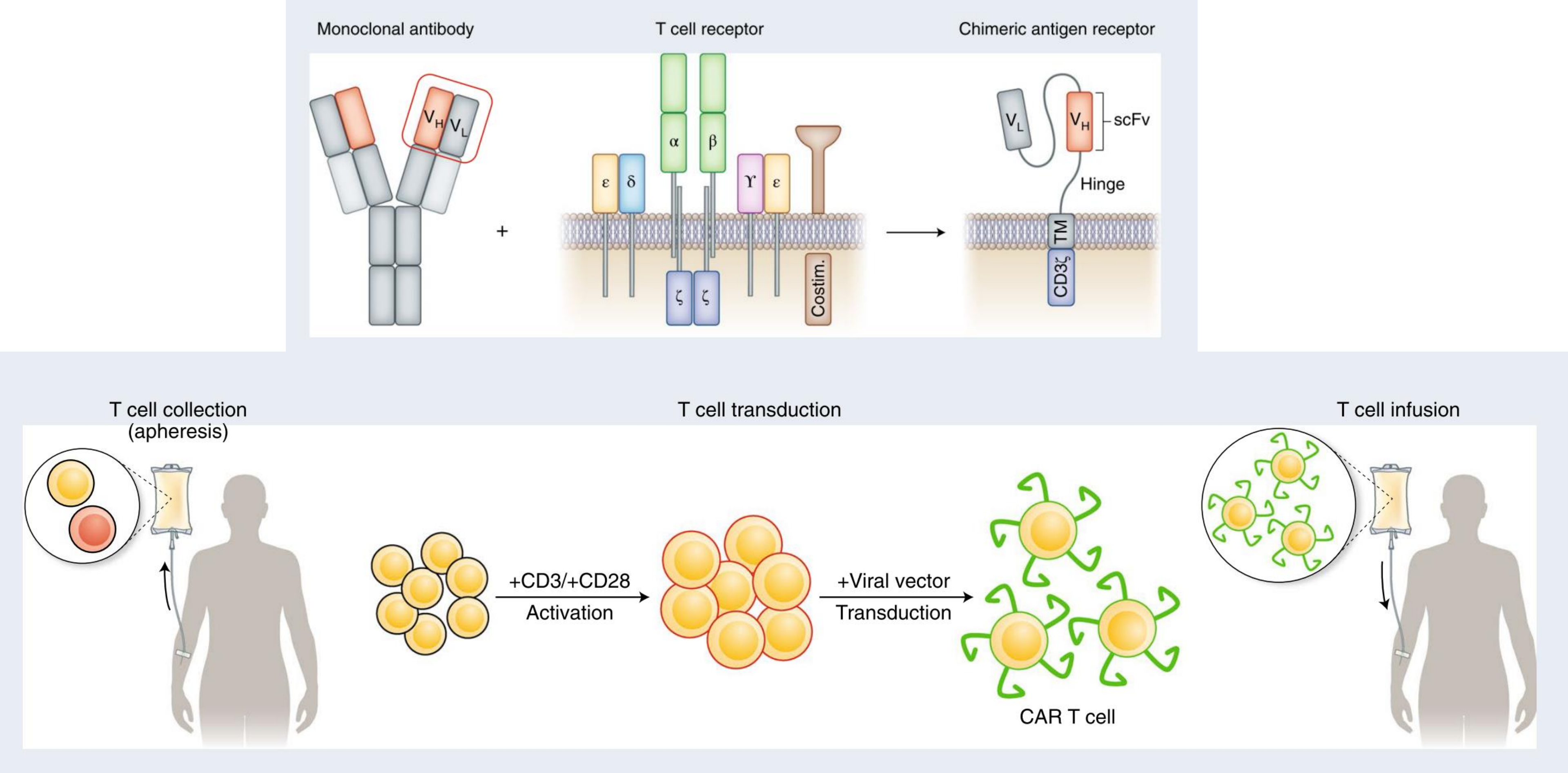
α-particles β-particles



High LET Low LET

1. Couturier et al. Cancer radioimmunotherapy with alpha-emitting nuclides. *Eur J Nucl Med Mol Imaging*. 2005;32(5):601–14.
2. Agrawal S. The role of 225Ac-PSMA-617 in chemotherapy-naive patients with advanced prostate cancer: Is it the new beginning. *Indian journal of urology : IJU*, 2020;*36*(1), 69–70.
3. Bal et al. Safety and Therapeutic Efficacy of 225Ac-DOTATATE Targeted Alpha Therapy in Metastatic Gastroenteropancreatic Neuroendocrine Tumors Stable or Refractory to 177Lu-DOTATATE PRRT. J Nucl Med. 2020 May 1;61(supplement 1):416.

Chimeric Antigen Receptor (CAR) T-cell Therapy



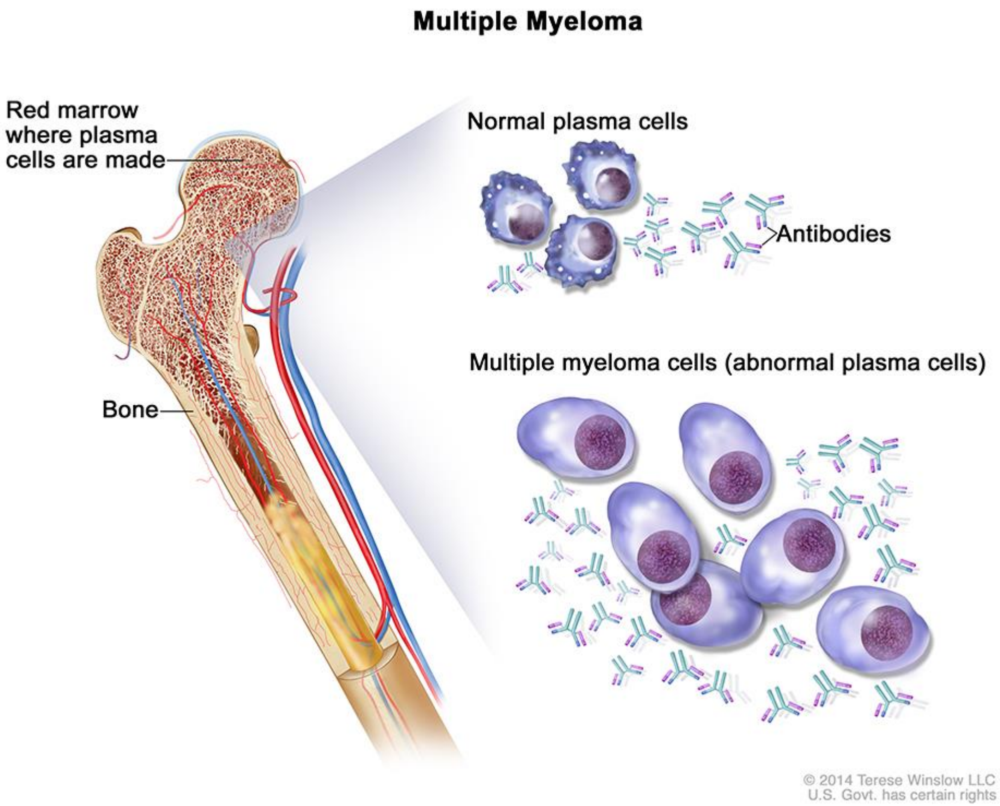
1. Majzner RG, Mackall CL. Clinical lessons learned from the first leg of the CAR T cell journey. Nat Med. 2019;25(9):1341–55.

City of Hope

Combination therapies in cancer

- Combination therapy approaches are challenging:
  - How to determine Dose, timing, sequence of therapies is not clear
- RIT and CAR Ts are a new, potentially important combo therapy, however this presents unique challenges:
  - αRIT – radiobiology, toxicity
  - CAR Ts – nonstandard PK/PD, living therapy with cell dynamics and kinetics
- **Mathematical modeling can help address these challenges**

Multiple Myeloma

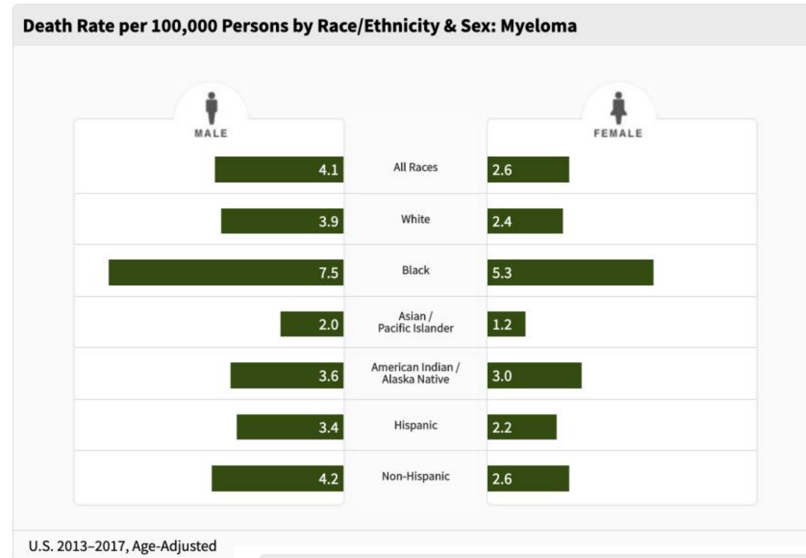


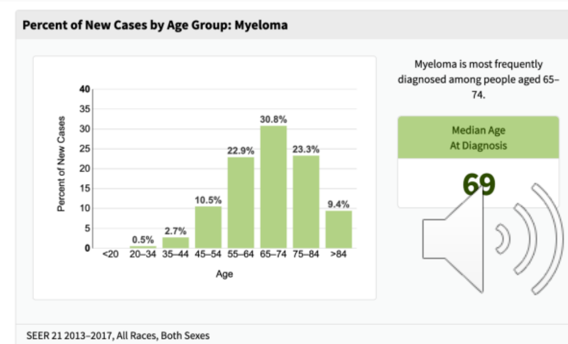
At a Glance

Estimated New Cases in 2020	32,270
% of All New Cancer Cases	1.8%

Estimated Deaths in 2020	12,830
% of All Cancer Deaths	2.1%

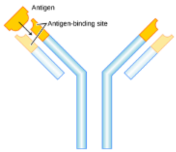
5-Year Relative Survival
53.9%
2010–2016





http://seer.cancer.gov

Daratumumab (Darzalex, Dara)



- CD38 is a multifunctional ectoenzyme which is essential for the regulation of intracellular Ca^{2+} and subsequent signal transduction.

- Daratumumab (Dara), is a human anti-CD38 IgG_1 (κ subclass) antibody against the receptor CD38, is now considered the last FDA approved treatment option for MM patients at relapse.

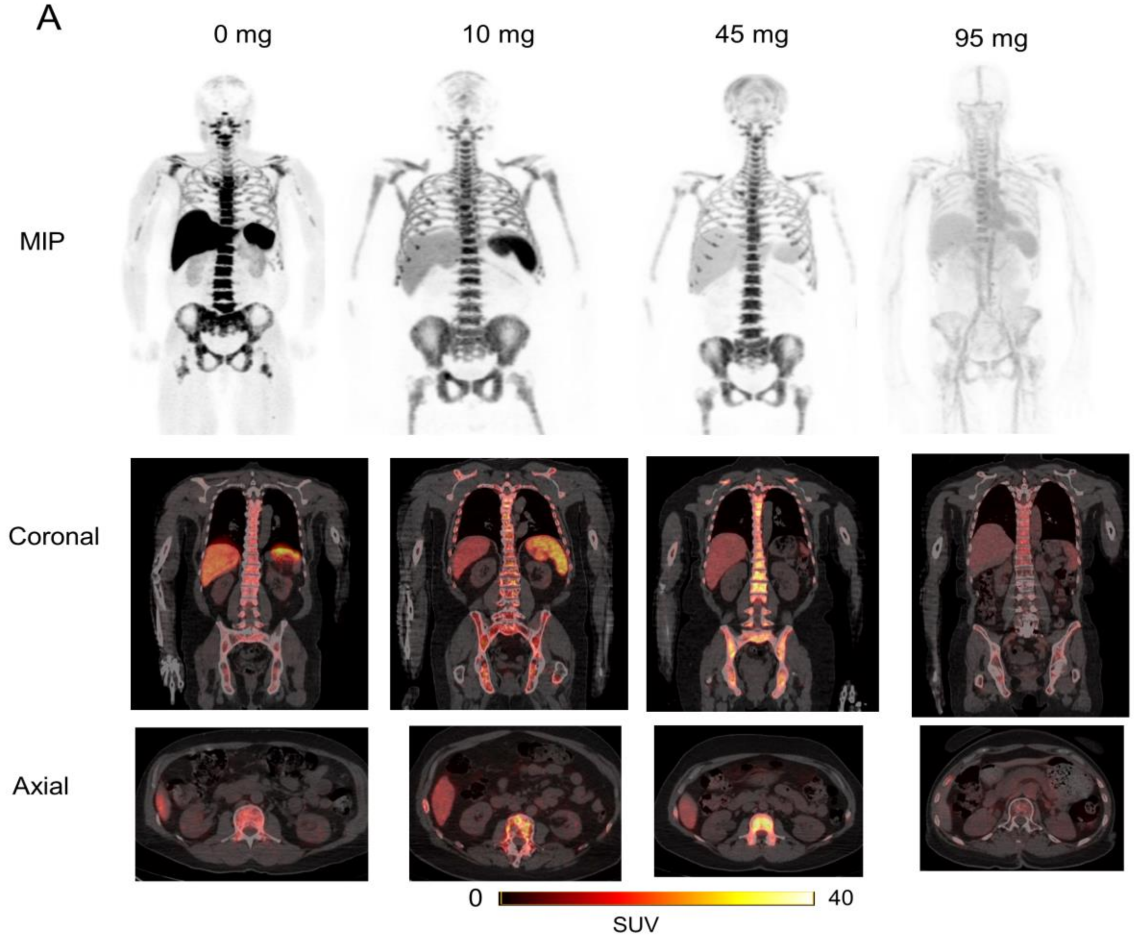
- Since CD38 is a highly expressed surface protein on PCs, the main anti-MM effect of Dara has been attributed to its associated antibody-dependent cellular cytotoxicity (ADCC), complement dependent cellular cytotoxicity (CDC), and antibody-dependent cellular phagocytosis activities (Phipps *et al*., 2015).

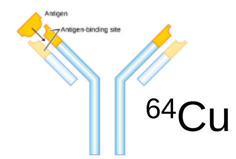
- Clinical results obtained with Dara have been impressive (Dimopoulos, 2016), but unfortunately most MM patients relapse.

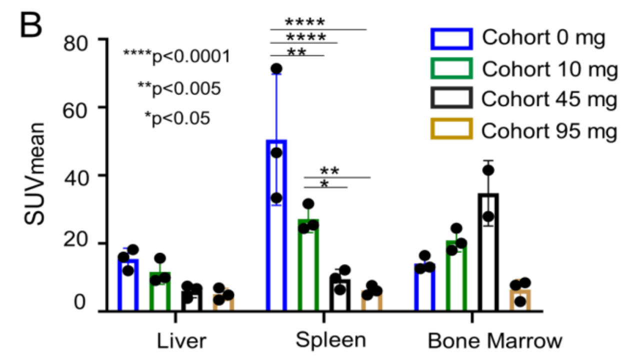
1. Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2016;375(14):1319–31.
2. Phipps C, Chen Y, Gopalakrishnan S, Tan D. Daratumumab and its potential in the treatment of multiple myeloma: Overview of the preclinical and clinical development. Ther Adv Hematol. 2015;6(3):120–7.

Multiple Myeloma is a disseminated disease

^{64}Cu-DOTA-Daratumumab PET/CT



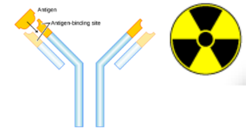




1. Adhikarla V, Chaudhry A, Krishnan A, Rockne R, Palmer J, Poku E, et al. Evaluation of a novel radiotracer targeting CD38 receptor expression for imaging multiple myeloma:64Cu-DOTA-Daratumumab. J Nucl Med. 2020 May 1;61(supplement 1):168.

City of Hope

Mathematical modeling: RIT



We want the model to capture

- **Effect of cell kill of radiation**
- **Decay of radionuclide**
- Proliferation of tumor cells
- Clearance of dead cells from system

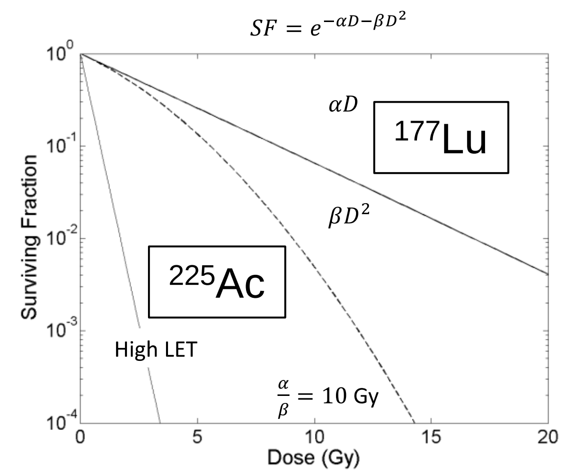
Consider the hazard function

$$\frac{dSF}{dt} = -h(t)SF(D(t))$$

Lea-Catcheside Dose protraction factor

$$h(t) = \alpha R_0 e^{-\lambda_p t} + \frac{2\beta R_0^2}{\gamma - \lambda_p}\left(e^{-2\lambda_p t} - e^{-(\lambda_p+\gamma)t}\right)$$

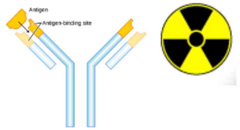
Good ‘Old Linear-Quadratic (LQ)



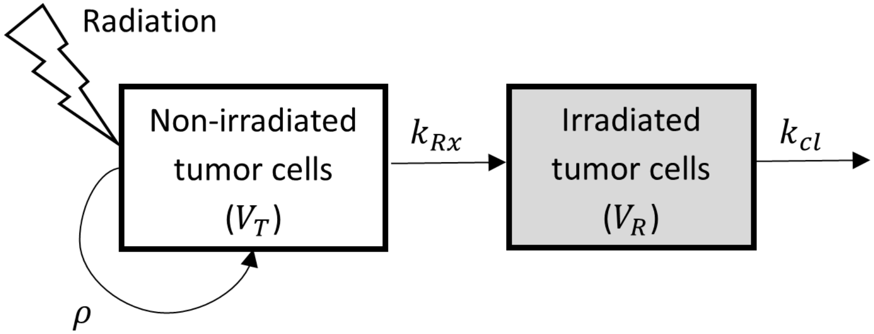
parameter	description	unit
α	Linear Quadradic parameter	Gy^{-1}
β	Linear Quadradic parameter	Gy^{-2}
R_0	Initial dose rate	Gy $time^{-1}$
λ_p	Radionuclide decay constant	$time^{-1}$
γ	Cell repair rate constant	$time^{-1}$

1. Gong J, Dos Santos MM, Finlay C, Hillen T. Are more complicated tumour control probability models better? Math Med Biol. 2013;30:1–19.

Mathematical modeling: RIT



We want the model to capture
- Effect of cell kill of radiation
- Decay of radionuclide
- **Proliferation of tumor cells**
- **Clearance of dead cells from system**



$$\frac{dV_T}{dt} = \rho V_T - k_{Rx} V_t$$

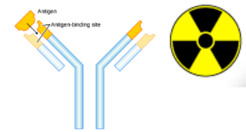
$$k_{Rx} = \alpha R_0 e^{-\lambda_p t} + \frac{2\beta R_0^2}{(\gamma - \lambda_p)} \left(e^{-2\lambda_p + \gamma)t}\right) \gamma \lambda_p$$

$$\frac{dV_R}{dt} = k_{Rx} V_T - k_{cl} V_R$$

parameter	description	unit
ρ	Tumor cell proliferation rate	time^{-1}
k_{Rx}	Rate of tumor cells being irradiated	time^{-1}
k_{cl}	Clearance rate of irradiated tumor cells	time^{-1}

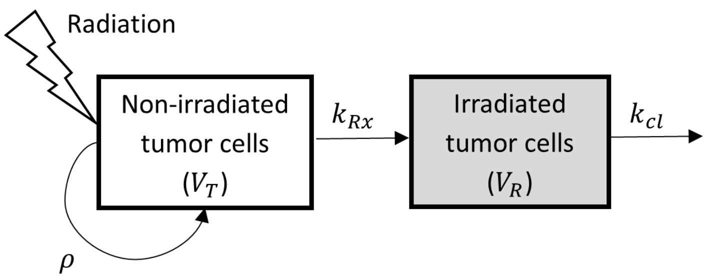
1. Karimian A, Ji NT, Song H, Sgouros G. Mathematical modeling of preclinical alpha-emitter radiopharmaceutical therapy. Cancer Res. 2020;80(4):868–76.

Mathematical modeling: RIT



We want the model to capture

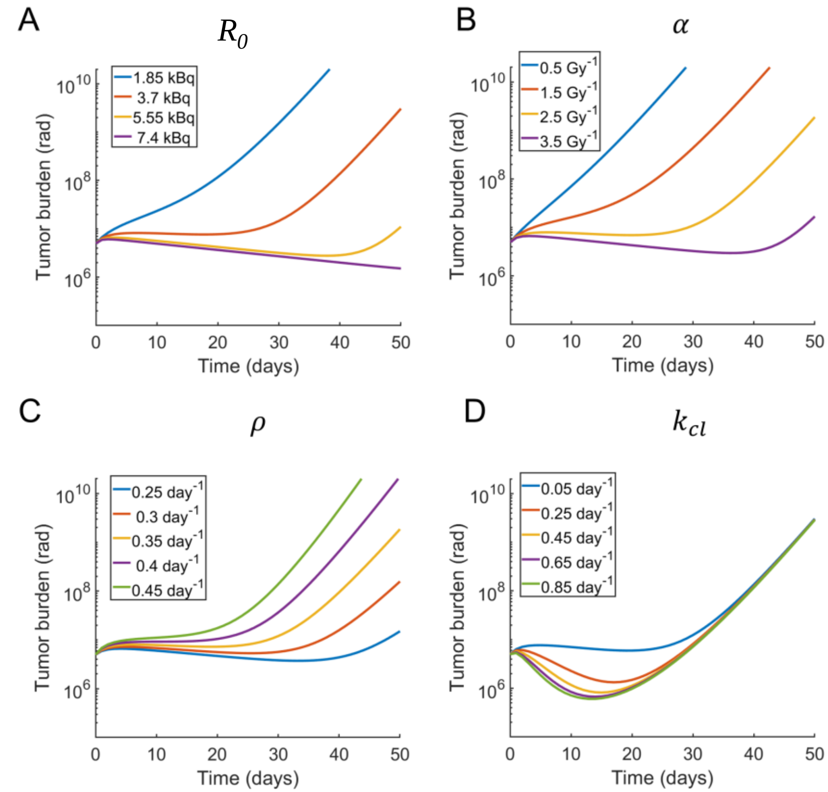
- Effect of cell kill of radiation
- Decay of radionuclide
- Proliferation of tumor cells
- Clearance of dead cells from system



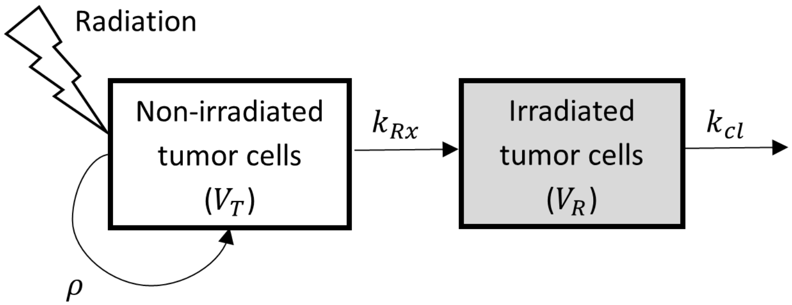
$$\frac{dV_T}{dt} = \rho V_T - k_{Rx} V_t$$

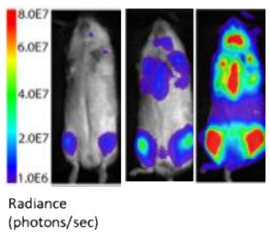
$$k_{Rx} = \alpha R_0 e^{-\lambda_p t} + \frac{2\beta R_0^2}{(\gamma - \lambda_p)} \left(e^{-2\lambda_p + \gamma) t}\right) \gamma \lambda_p$$

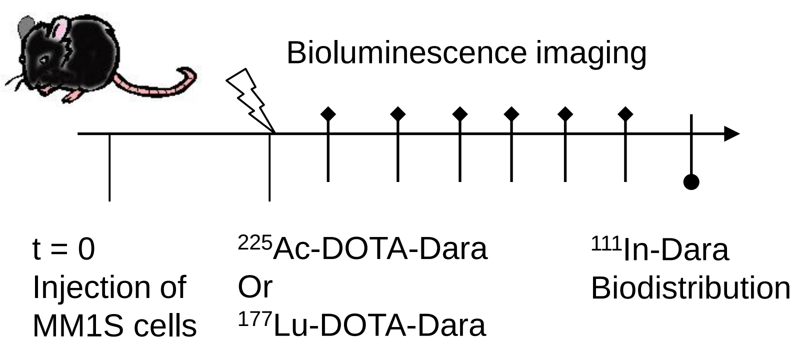
$$\frac{dV_R}{dt} = k_{Rx} V_T - k_{cl} V_R$$

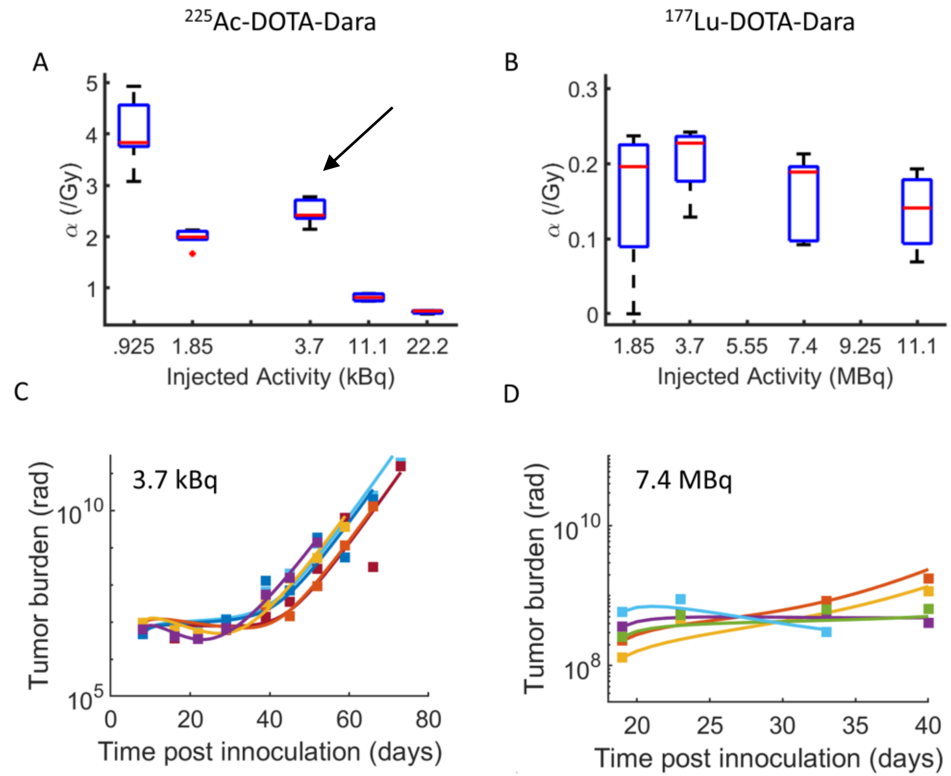


^{225}Ac-DOTA vs ^{177}Lu-DOTA-Daratumumab



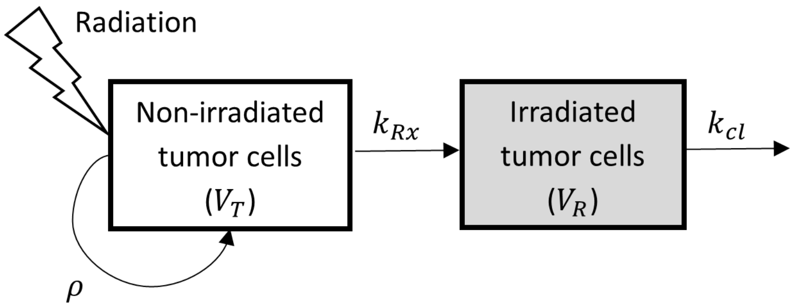


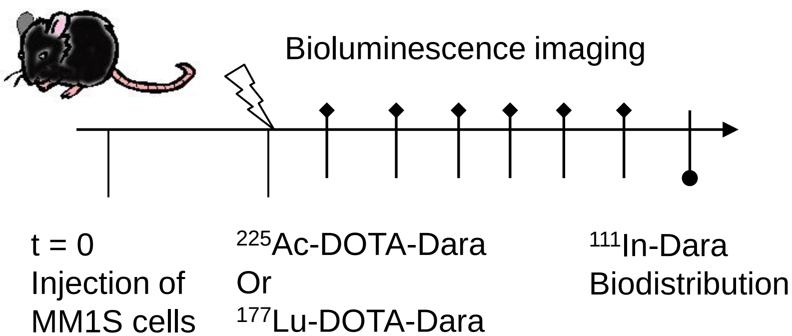


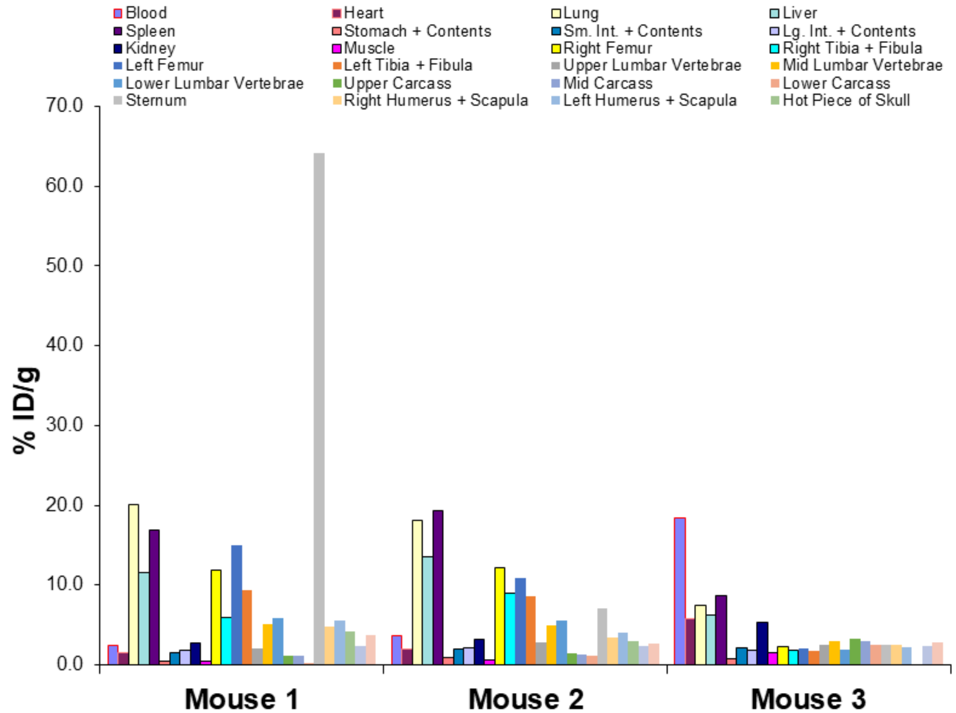


1. Minnix M, Adhikarla V, Caserta E, Poku E, Rockne R, Shively J, Pichiorri F. Comparison of CD38 targeted alpha- vs beta-radionuclide therapy of disseminated multiple myeloma in an animal model. 2020

^{225}Ac-DOTA vs ^{177}Lu-DOTA-Daratumumab







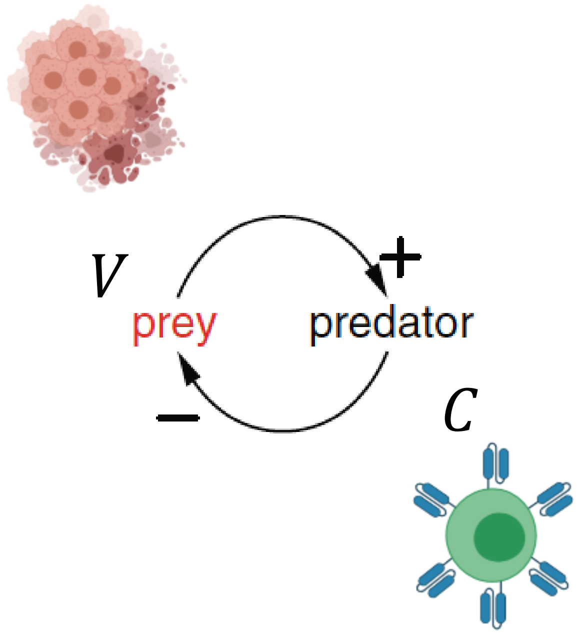
1. Minnix M, Adhikarla V, Caserta E, Poku E, Rockne R, Shively J, Pichiorri F. Comparison of CD38 targeted alpha- vs beta-radionuclide therapy of disseminated multiple myeloma in an animal model. 2020

CAR T-cell Predator-Prey Mathematical Model

$$\frac{dV}{dt} = \rho V\left(1 - \frac{V}{K}\right) - \kappa_1 V C$$

$$\frac{dC}{dt} = \kappa_2 V C - \theta C$$

$V(t)$: tumor cells
$C(t)$: CAR T−cells

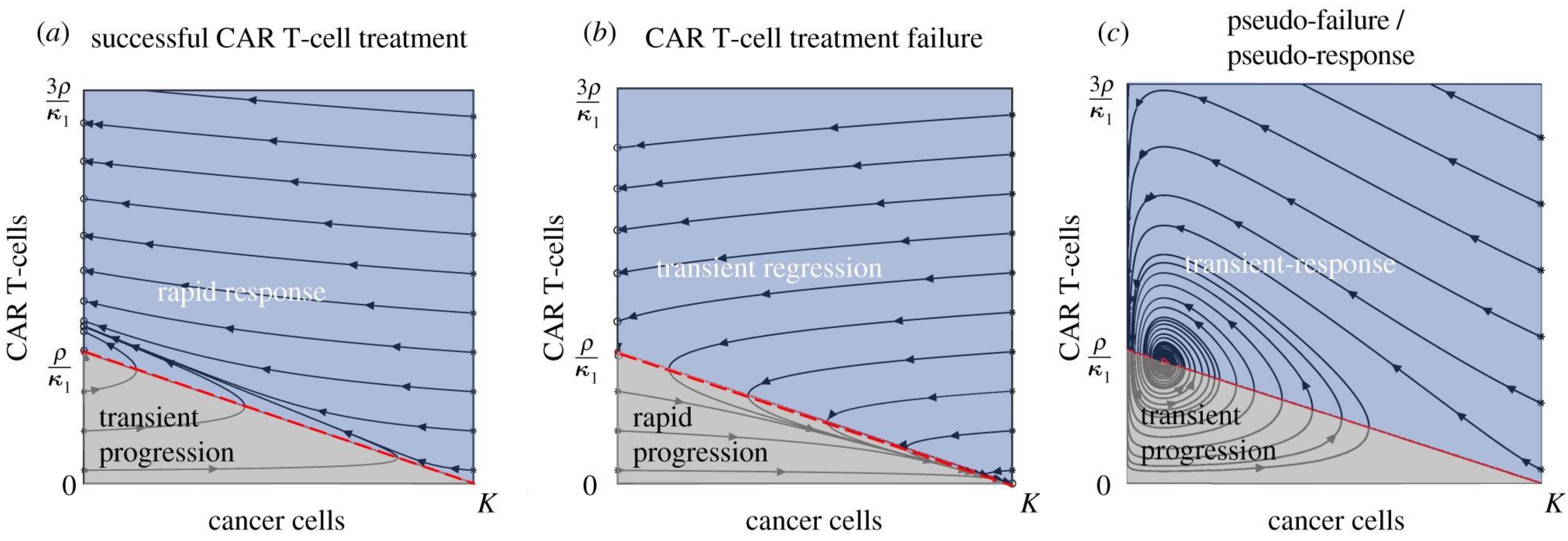


Biorender.com

parameter	description	unit
ρ	cancer cell net growth rate	day^{-1}
K	carrying capacity	cell
κ_1	CAR T-cell killing rate	day^{-1} cell^{-1}
κ_2	net rate of proliferation and exhaustion of CAR T-cells when stimulated by cancer cells	day^{-1} cell^{-1}
θ	CAR T-cell death rate (persistence)	day^{-1}

1. Sahoo P, Yang X, Abler D, Maestrini D, Adhikarla V, Frankhouser D, et al. Mathematical deconvolution of CAR T-cell proliferation and exhaustion from real-time killing assay data. J R Soc Interface. 2020;17(20190734).

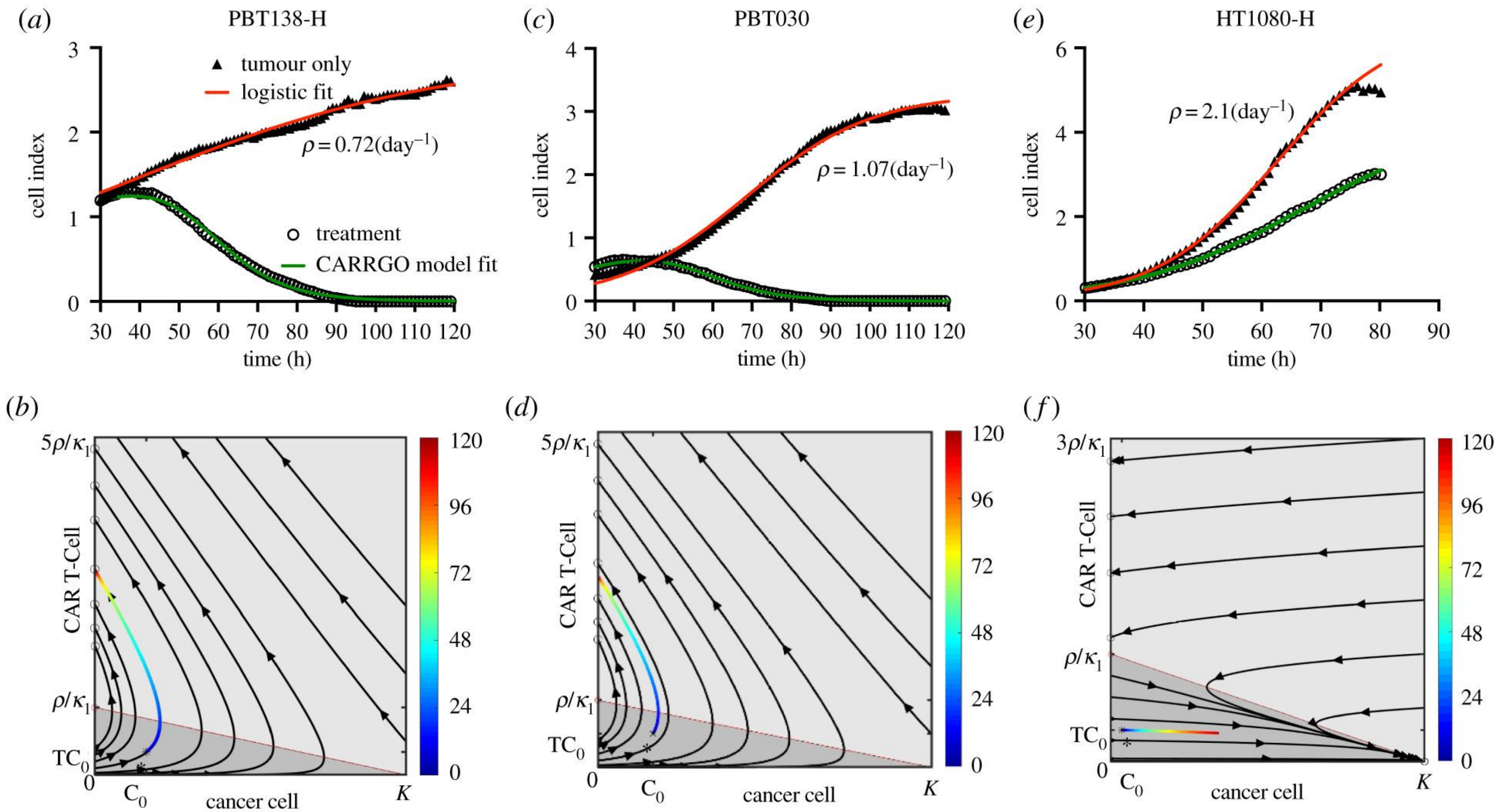
CAR T-cell model potential PK/PD



1. Sahoo P, Yang X, Abler D, Maestrini D, Adhikarla V, Frankhouser D, et al. Mathematical deconvolution of CAR T-cell proliferation and exhaustion from real-time killing assay data. J R Soc Interface. 2020;17(20190734).

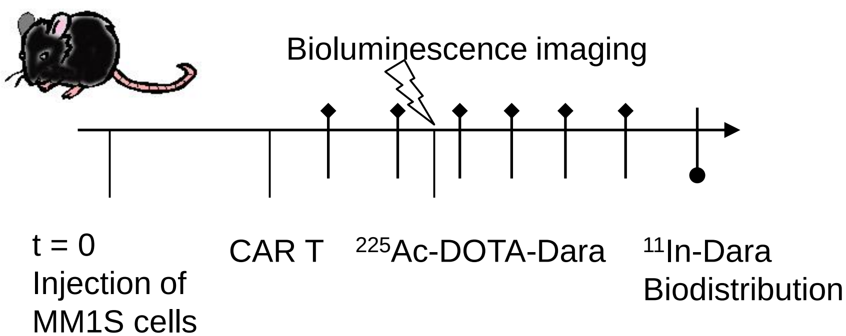
City of Hope

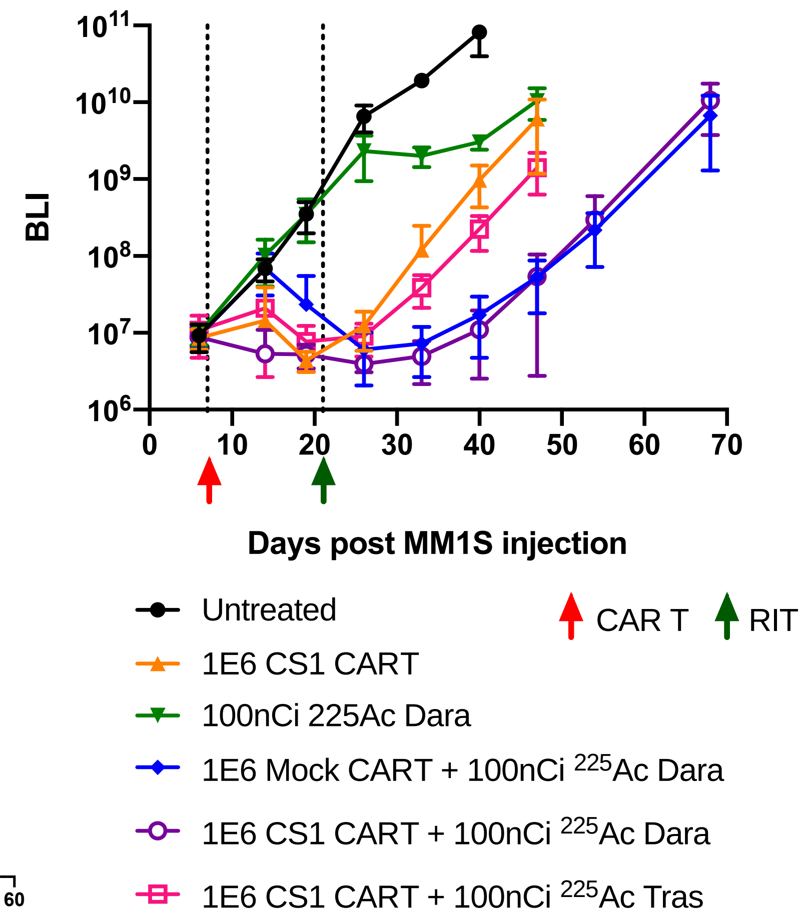
CAR T-cell killing dynamics



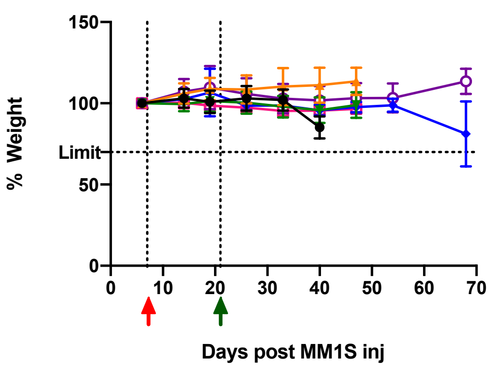
1. Sahoo P, Yang X, Abler D, Maestrini D, Adhikarla V, Frankhouser D, et al. Mathematical deconvolution of CAR T-cell proliferation and exhaustion from real-time killing assay data. J R Soc Interface. 2020;17(20190734).

CAR T-cell + αRIT Combination therapy in MM

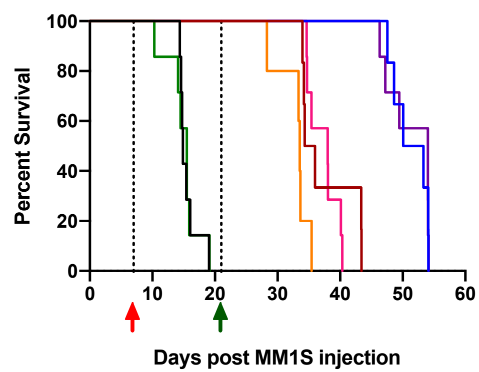




Whole body Toxicity

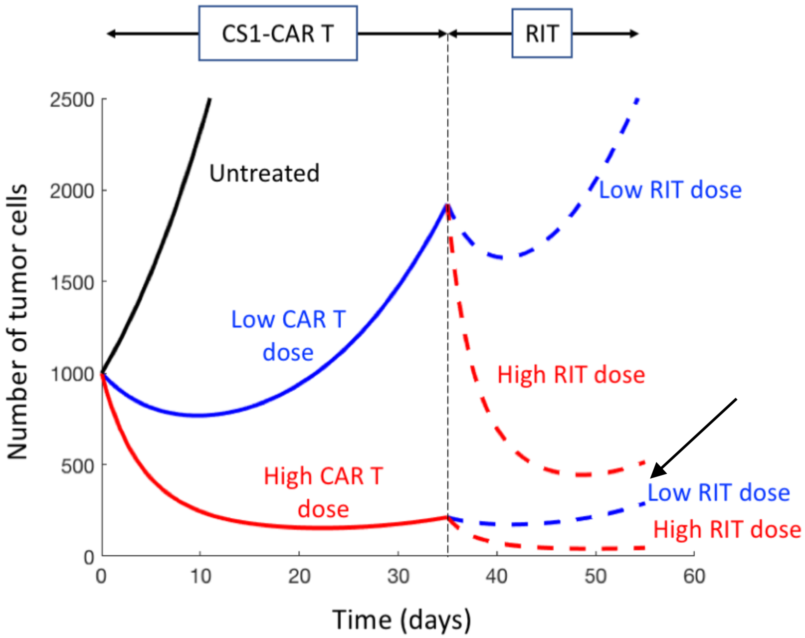


Survival



1. Unpublished data.

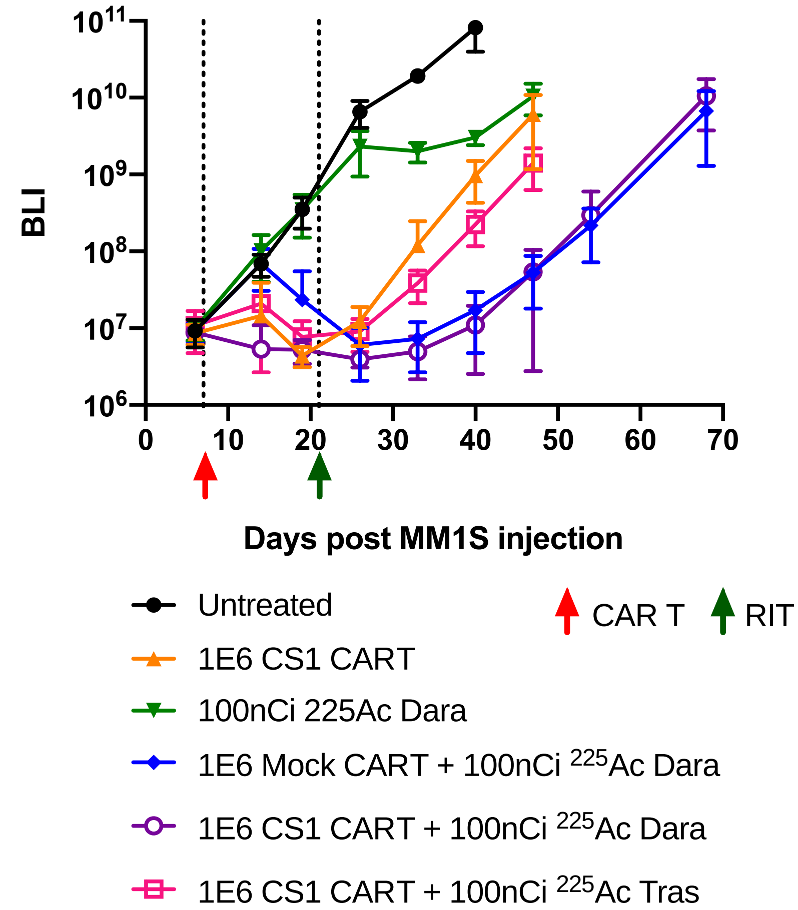
CAR T-cell + αRIT Combination therapy in MM



$$\frac{dV_T}{dt} = \rho V_T - \delta(t-\tau_{Rx})k_{Rx}V_R - \delta(t-\tau_C)\kappa_1 V_T C$$

$$\frac{dV_R}{dt} = \delta(t-\tau_{Rx})(k_{Rx}V_R - k_{cl}V_R) - \delta(t-\tau_C)\kappa_1 V_R C$$

$$\frac{dC}{dt} = \kappa_2(V_T + V_R)C - \theta C$$



Summary

- Combination therapies and challenges of RIT + CAR T-cell immunotherapy

- Mathematical modeling to address challenges of combo therapy
  - Mathematical models can incorporate:
  - RIT decay, dose, tumor response, toxicity constraints
  - CAR T cell effect, proliferation, exhaustion
  - Provide a framework to optimize: dose, sequence, timing
  - Make predictions and give dynamic quantifications of response

Thank you

@RRockne

Flavia Pichiorri, John Shively
Megan Minnix, Amrita Krishnan
Joycelynne Palmer, Vikram Adhikarla

Christine Brown, Behnam Badie
Russell Rockne, Michael Barish
Prativa Sahoo, Xin (Cindy) Yang

HORIZON 2020

NCCN National Comprehensive Cancer Network®

YOUNG INNOVATORS FUND

NATIONAL CANCER INSTITUTE®

CANCER SYSTEMS BIOLOGY CONSORTIUM

PHYSICAL SCIENCES in ONCOLOGY

City of Hope™