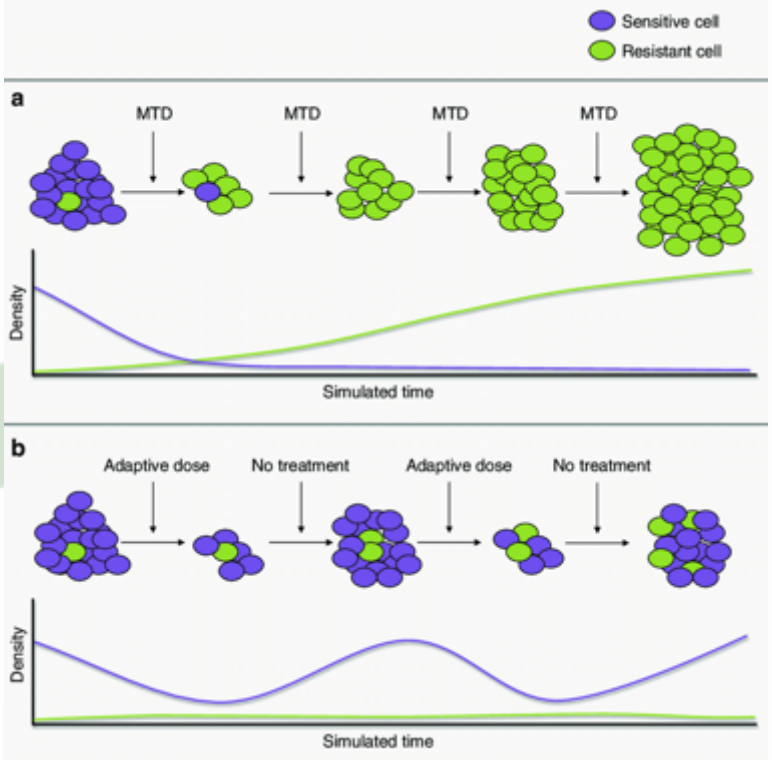
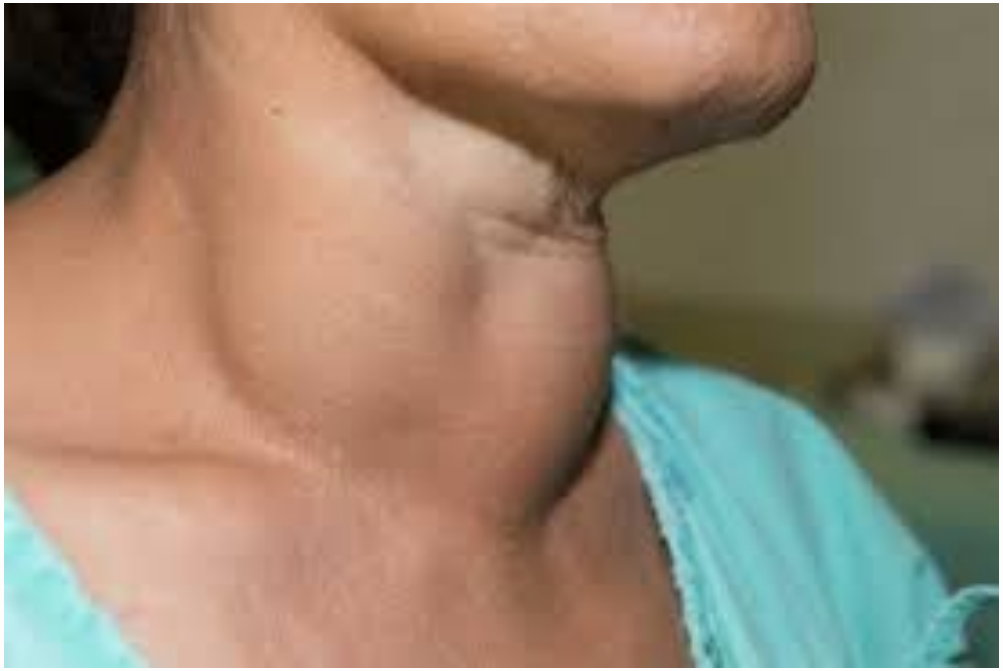
Designing and evaluating evolutionary therapies for advanced progressive thyroid cancer





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Primary Question: What is the potential for adaptive therapies to significantly improve progression free survival in metastatic thyroid cancer

We're Team GREEN

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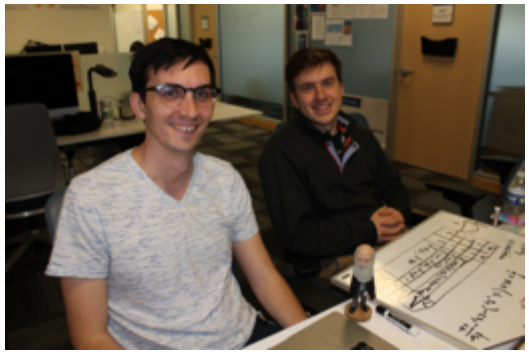
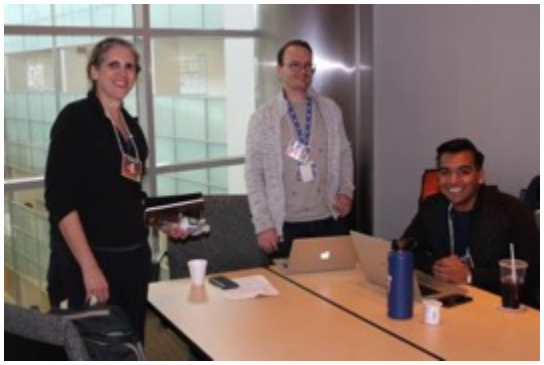
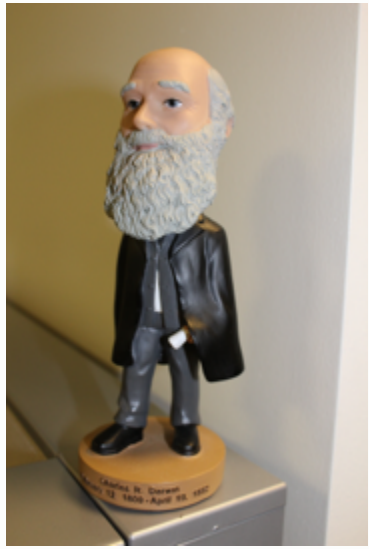


The modelers

The Reason



The Data Wranglers



The inspiration

The one who can make it happen!!

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Evolutionary Therapy?

- What is it?
- Cancer is more than a disease of the genes, a disease of unregulated proliferation
- Anticipate and Steer the ecological and evolutionary dynamics of the cancer
- For the patient – prolonging life, improving quality of life

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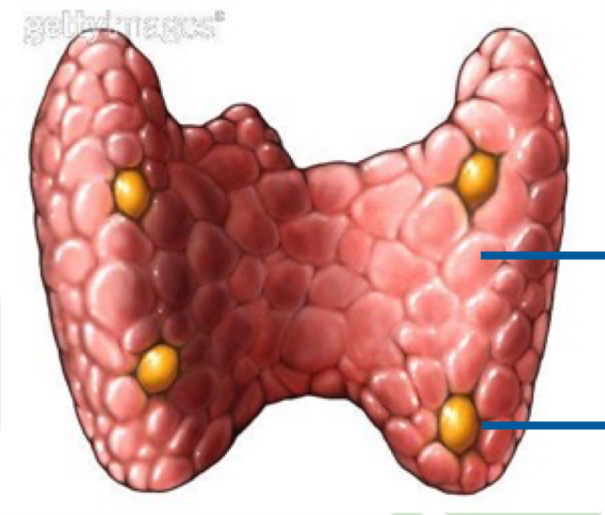
Evolutionary Therapy

- Cancer is the most intimate experience that patients will have with evolution by natural selection
- Cancer cells can only respond, physicians can plan with for-thought
- The goal is to integrate modelling, cancer biology and clinical data/application
- Ultimate Goal: Patient specific resistance management plans

Advanced Progressive Thyroid Cancer

DTC: Thyroglobulin



Follicular cells

Differentiated

Papillary

Follicular

Anaplastic

Parafollicular cells

Medullary

Sporadic

Familial

MTC: Calcitonin & CEA

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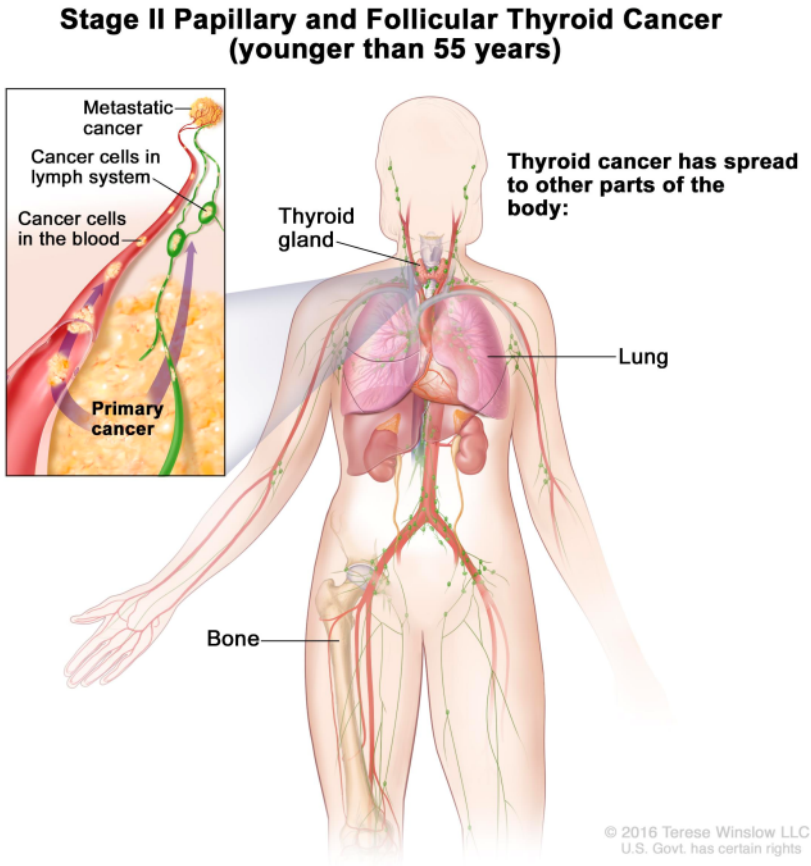
Advanced Progressive Thyroid Cancer

- 5-year survival of metastatic disease is 56%
- Standard of therapy
  - Tyrosine kinase inhibitor (TKI)
  - Median time to progression is 18-20 months
- Orphan Disease



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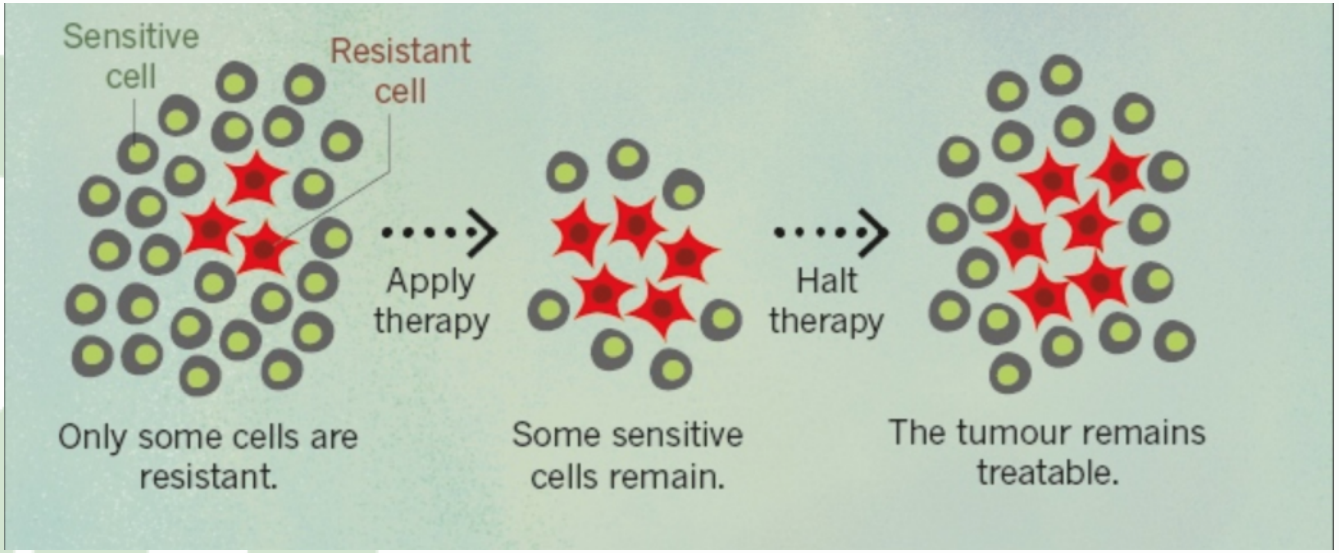
Adaptive TKI therapy

Delaying the evolution of resistant clones and decreasing the toxicity profile of TKIs should improve progressive free survival (PFS) and quality of life (QOL)



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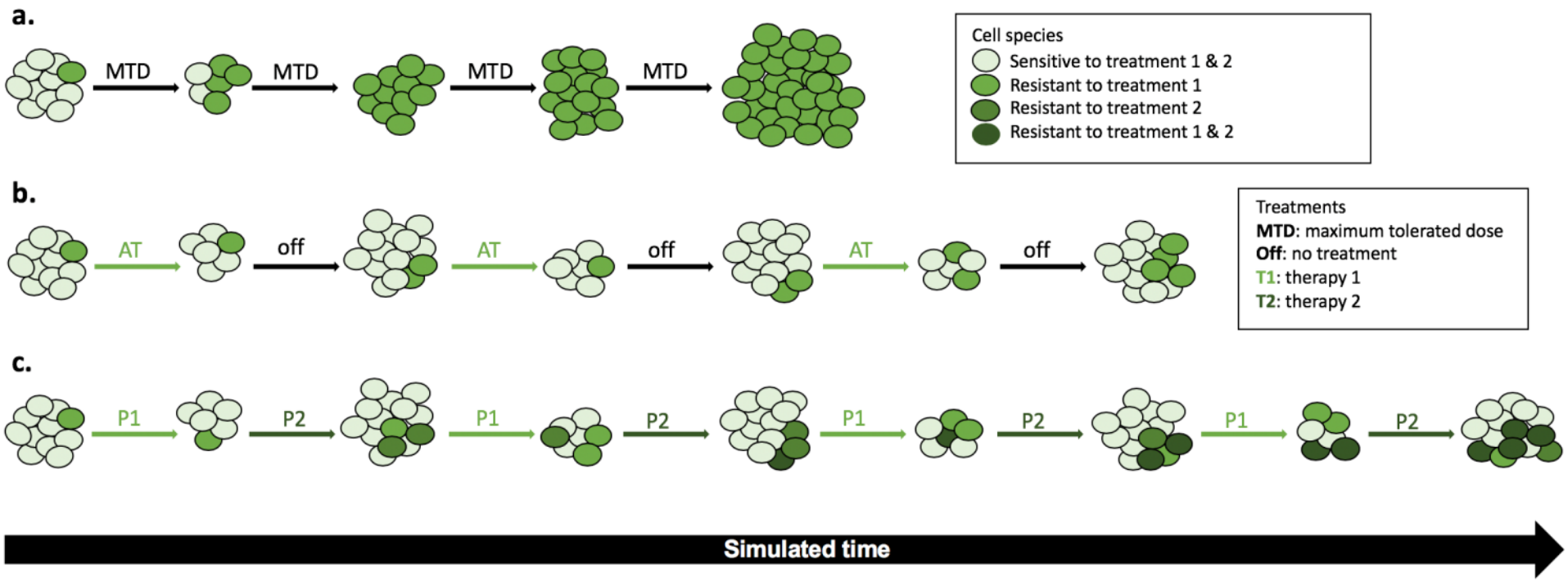
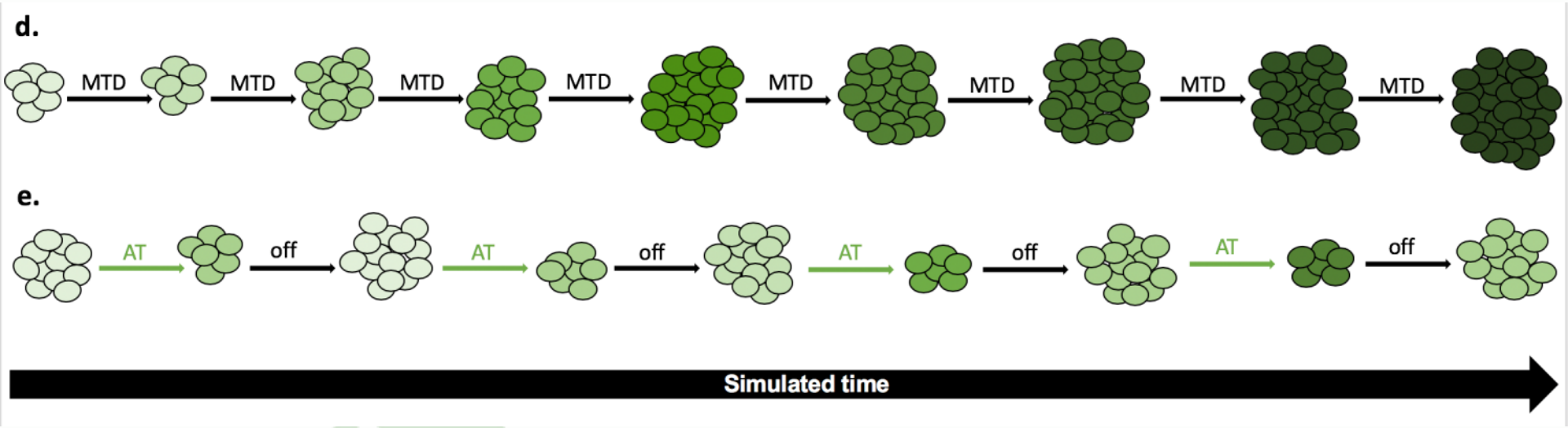
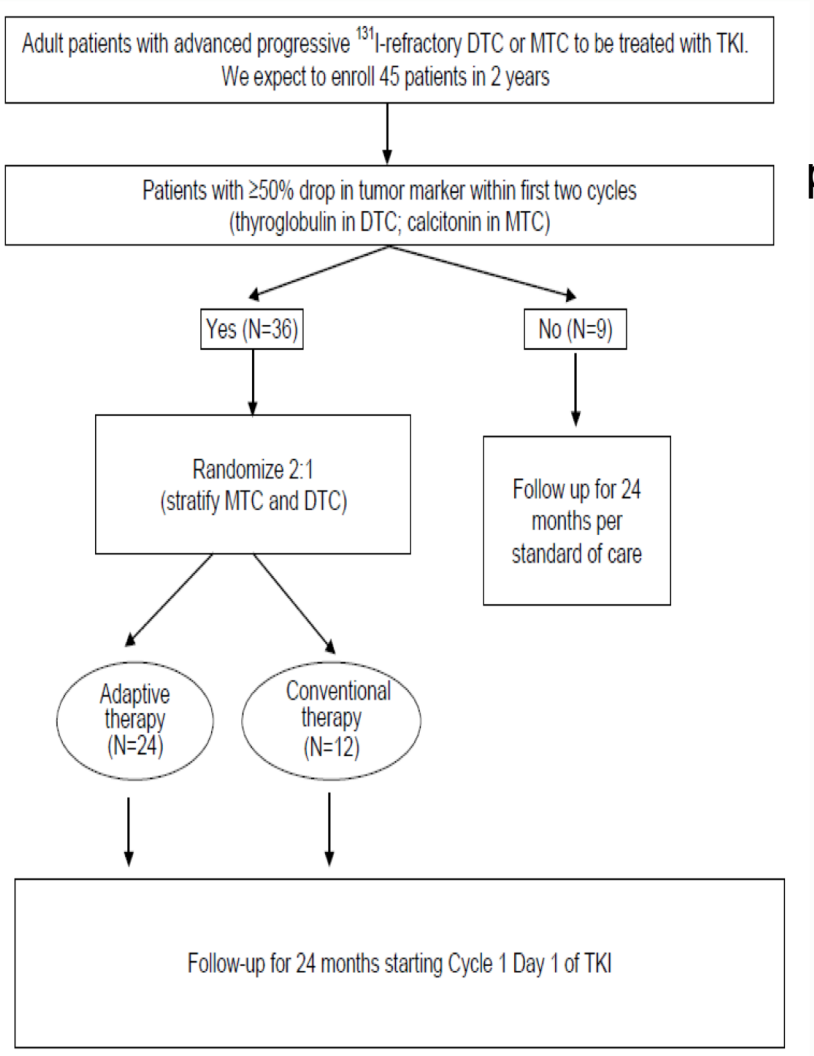
Sensitive-Resistant Release Adaptive Therapy



Quantitative Resistance and Evolutionary Therapy



Aim 1: To develop a core mathematical model of tumor progression and therapeutic response in advanced stage DTC and MTC



Adaptive tyrosine kinase inhibitor therapy in patients with advanced progressive thyroid cancer (PI: Chung)

<u>Biomarkers</u>

- Differentiated Thyroid Cancer (DTC)
  - Thyroglobulin
- Medullary Thyroid Cancer (MTC)
  - Calcitonin
  - Carcinoembryonic Antigen (CEA)

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One TKI, Separate Populations of Resistant and Sensitive Cells

Parameter	Description
x_S	Sensitive population
x_r	Resistant population
$u \in [0,1]$	Resistance rate
r	Growth rate
r_{max}	Maximal growth rate
K	Carrying capacity
$m \in [0,1]$	Treatment dose
k	Innate resistance
b	Rate of acquired resistance

Population dynamics:

$$\dot{x}_s = r\left(1 - \frac{x_s + x_r}{K}\right) - \frac{m}{k} - d$$

$$\dot{x}_r = r\left(1 - \frac{x_s + x_r}{K}\right) - \frac{m}{k + bu} - d$$

Cost of resistance realized as a decrease in growth rate

$$r = r_{max}(1 - u)$$

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One TKI, Quantitative Trait, Evolving Resistance

Parameter	Explanation
x	Population
$u \in [0,1]$	Resistance rate
r	Growth rate
r_{max}	Maximal growth rate
K	Carrying capacity
K_{max}	Maximal carrying capacity
$m \in [0,1]$	Treatment dose
k	Innate resistance
b	Rate of acquired resistance

Population dynamics:

$$\dot{x} = \frac{dx}{dt} = xG(u,x,m)$$

Evolution of resistance:

$$\dot{u} = \sigma \frac{\partial G(u,x,m)}{\partial u}$$

Per capita growth rate:

$$G(u,x,m) = r\left(1 - \frac{x}{K}\right) - \frac{m}{k+bu} - d$$

Cost of resistance realized as a decrease in growth rate

$$r = r_{max}(1-u)$$

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Generating virtual patient data from real data

Beautiful, but not real!!

Karras et al. 2017
(NVIDIA)

- Generative deep learning replicates and generates samples from a data distribution
- Using this technique with differential privacy, we use data from ongoing phase 2 and phase 3 drug trials to synthesize cohorts of virtual patients

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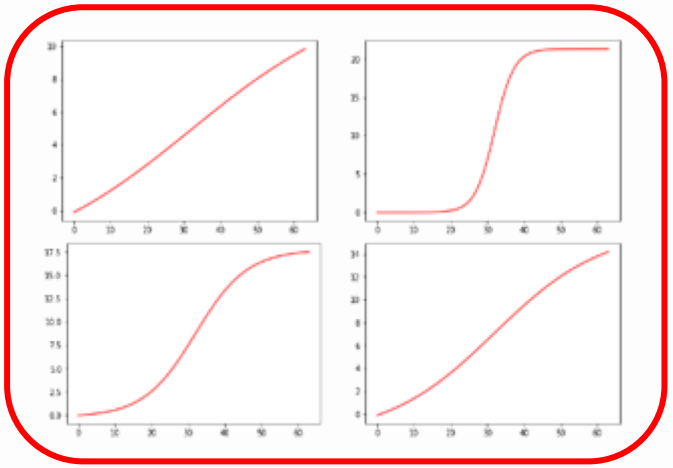
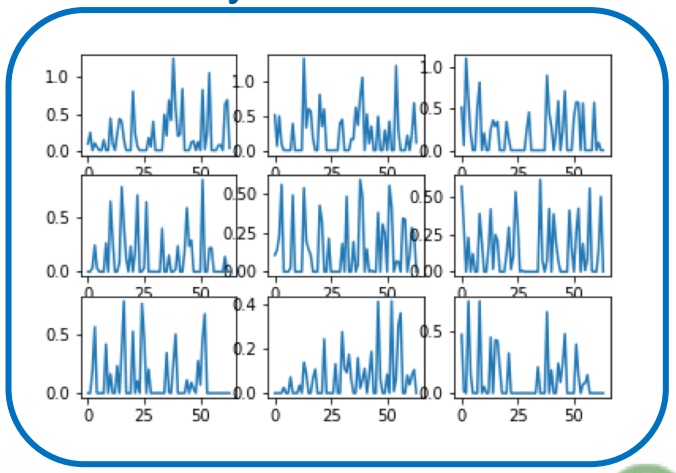
Adapting GANs to Medical Data

Motivated by recent successes in replicating ICU patient data, we can apply deep learning to generate tumor-treatment dynamics without the need of a model-based augmentation approach that could contaminate future fits.

Real Data



Synthetic Data



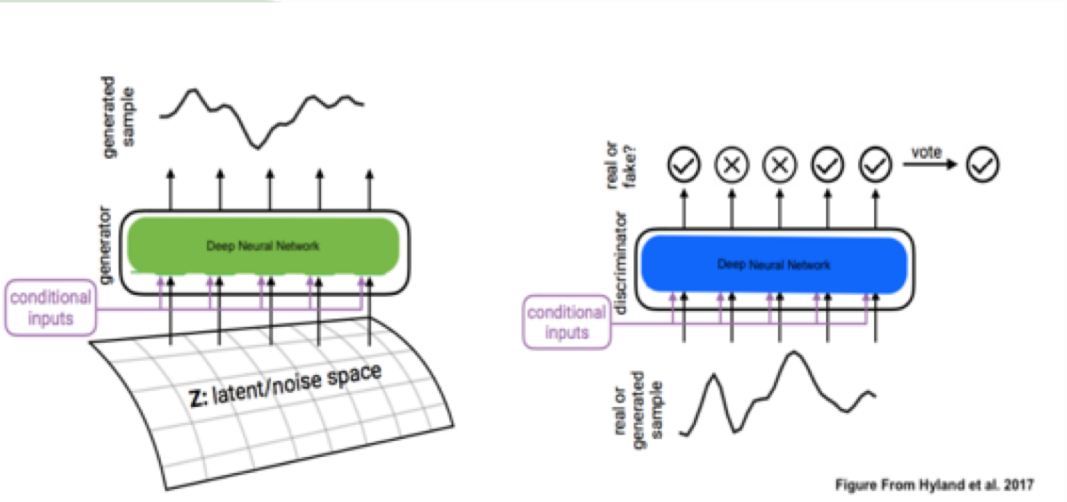


Figure From Hyland et al. 2017

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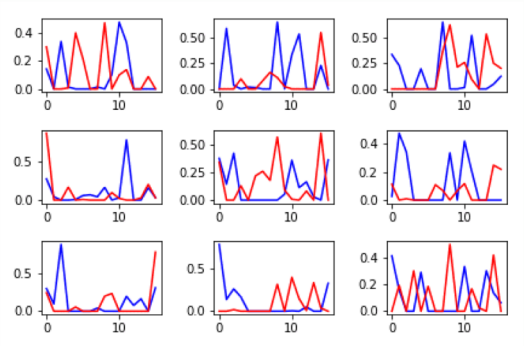
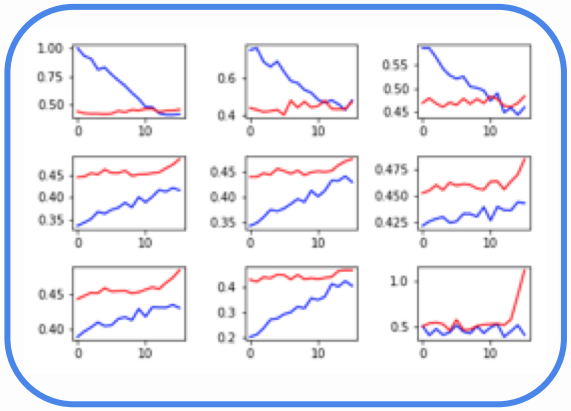
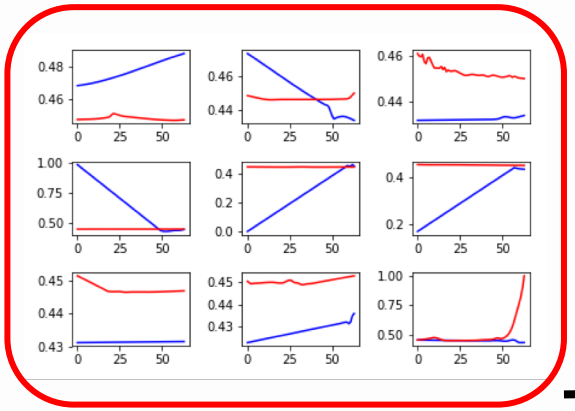
Bringing this to Thyroid Cancer Patients

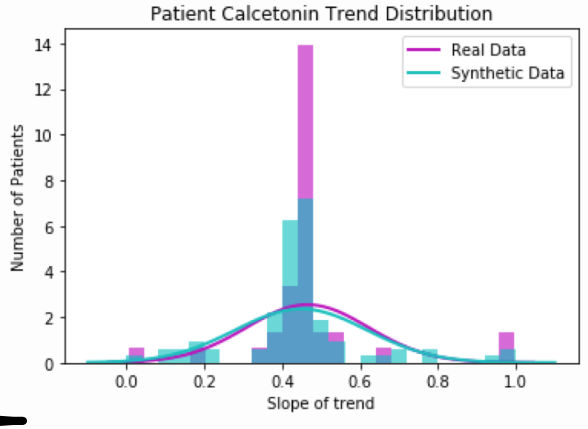


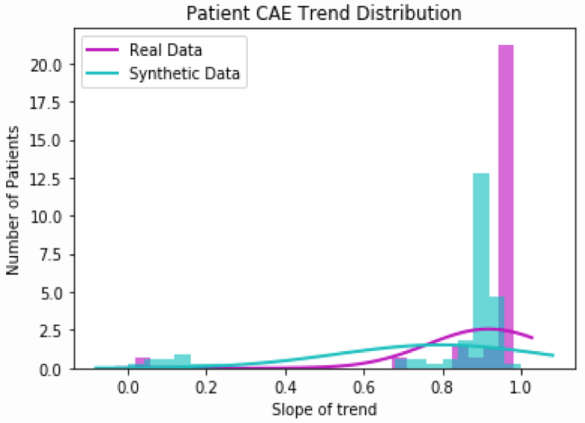
Synthetic Data





Real Data





From a set of 78 real patient records, we are able to train a GAN that reliably mimics the data distribution.

With more data, we will be able to enhance our model with a wide variety of synthetic cohorts

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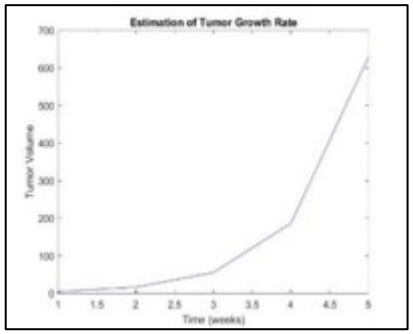
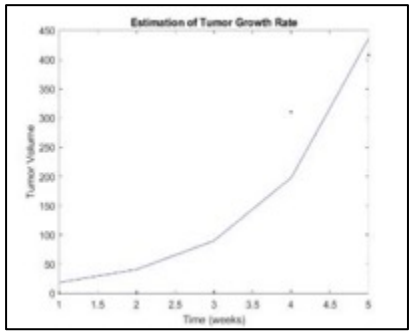
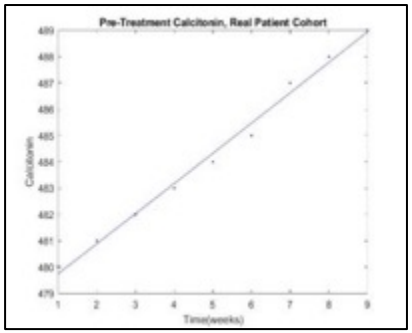
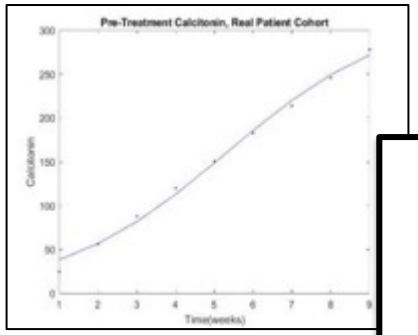
Obtaining Parameters from Real and Virtual Patients

Pre-Treatment Data Informs Tumor Growth Parameters









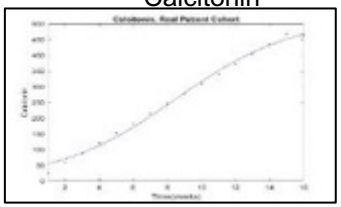
Treated Data Sets

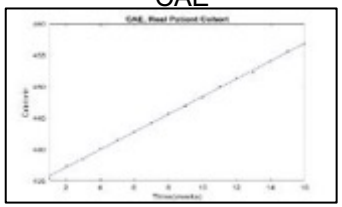
Real Patients

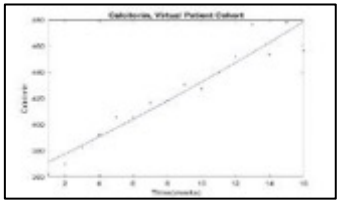
Virtual Patients

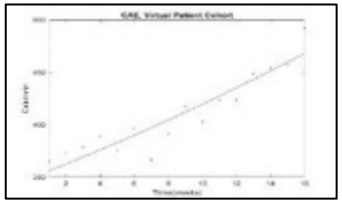
Calcitonin

CAE









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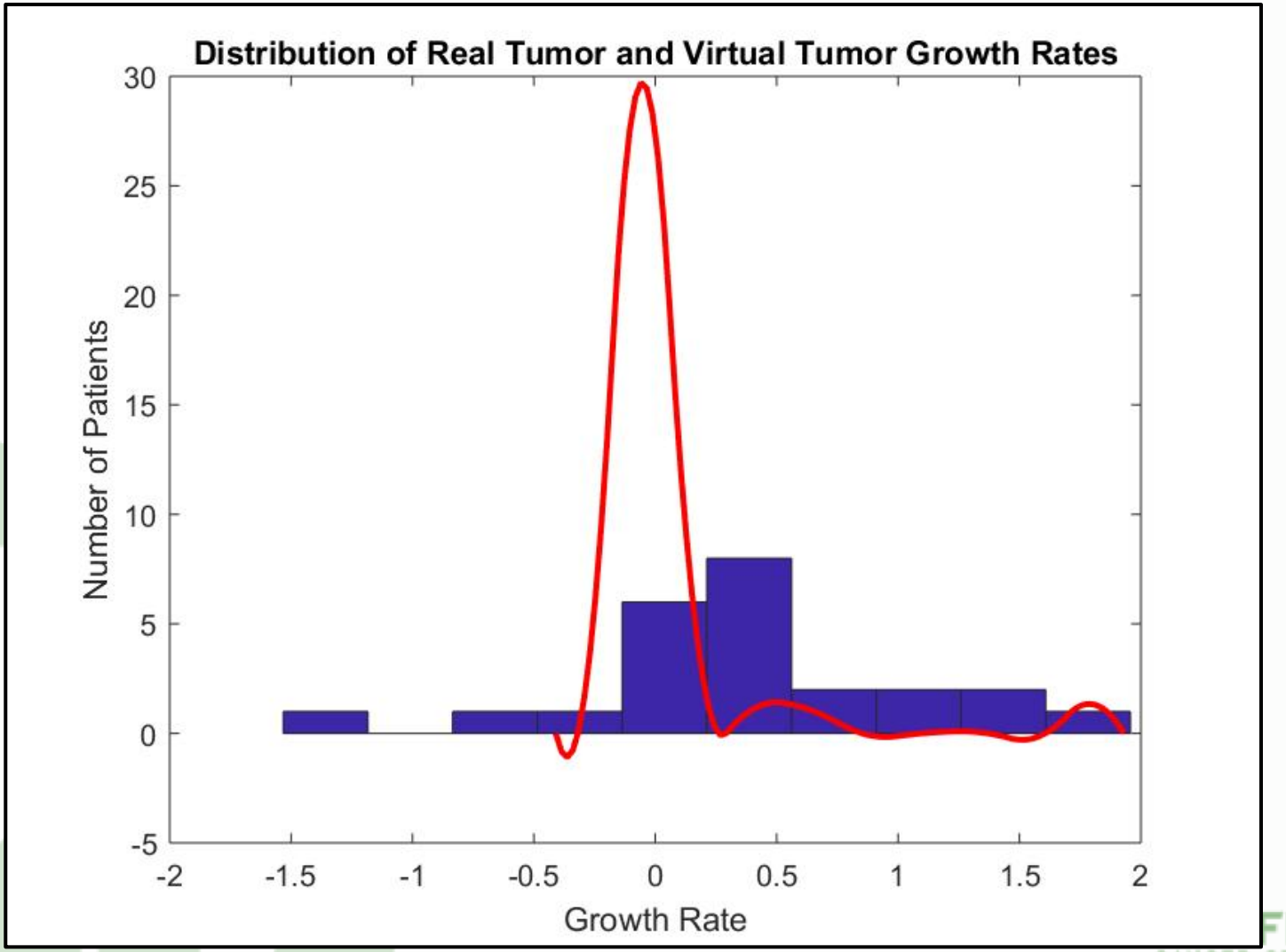
Obtaining Parameters from Real and Virtual Patients



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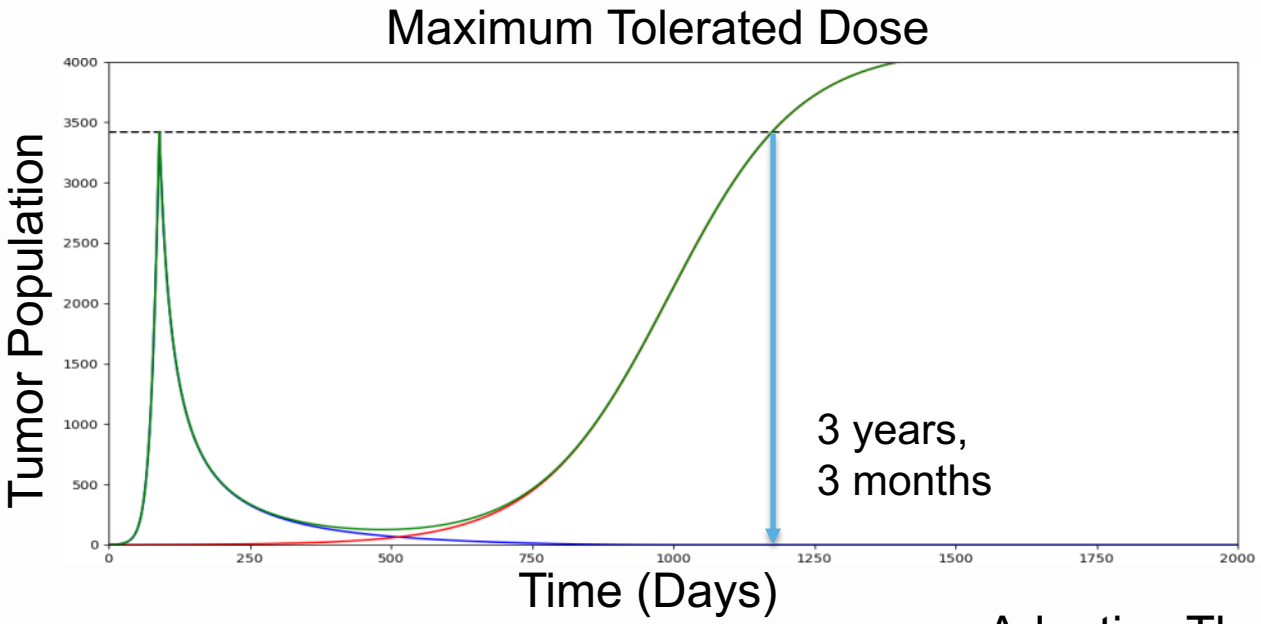
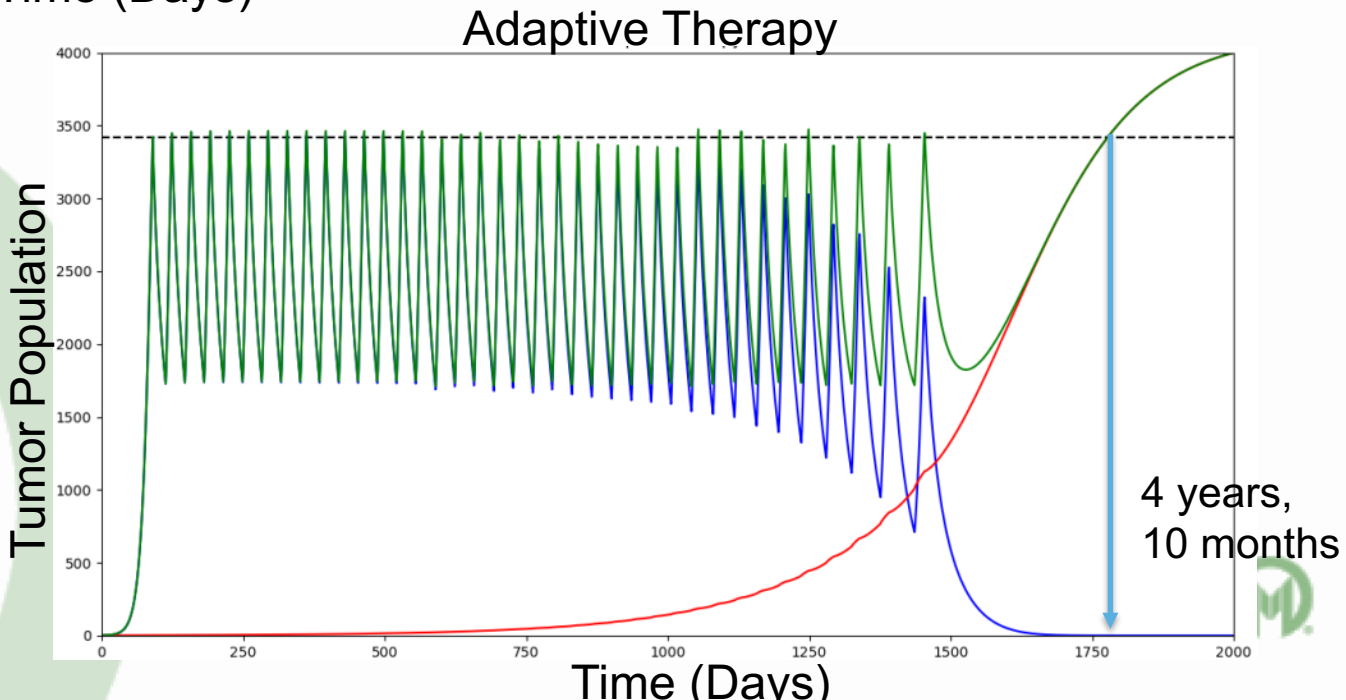
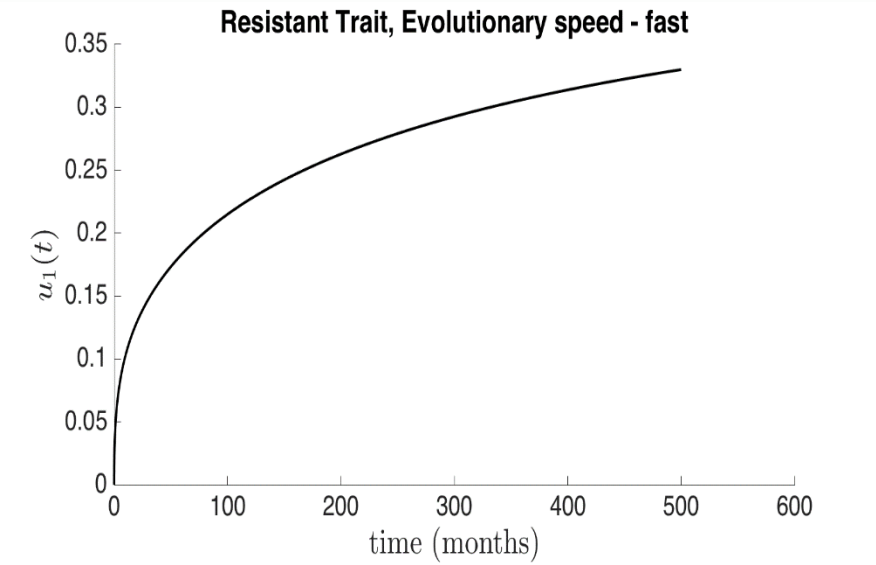
Max Tolerated Dose vs Adaptive Therapy





In the quantitative trait model, resistance can be parameterized to evolve quickly or slowly

Fast speed of resistance



Slow speed of resistance

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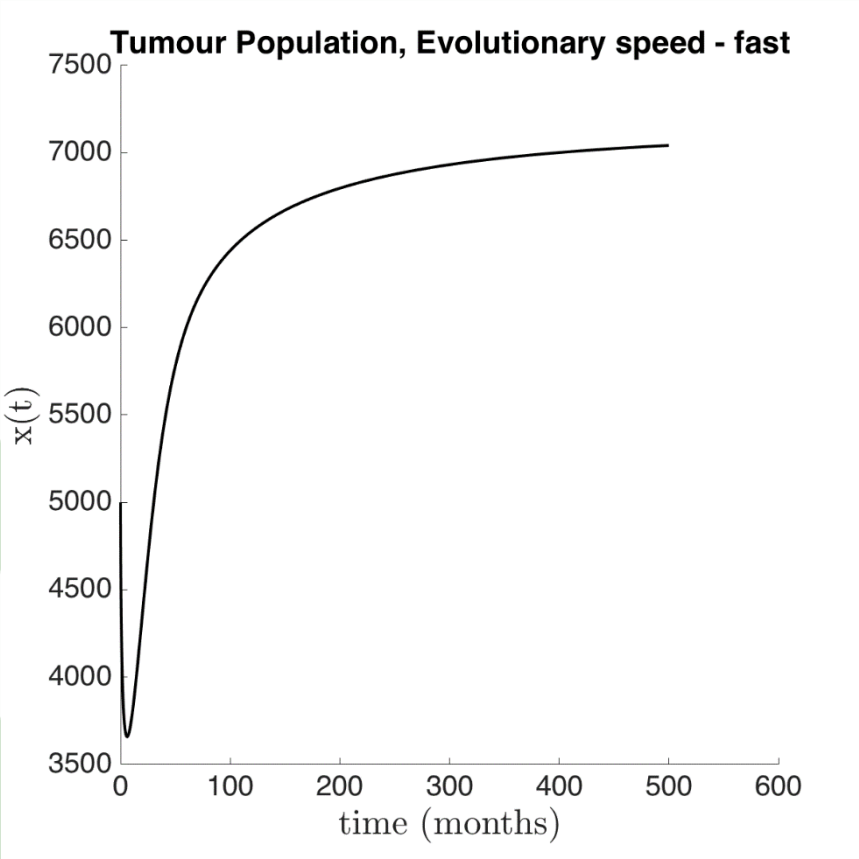
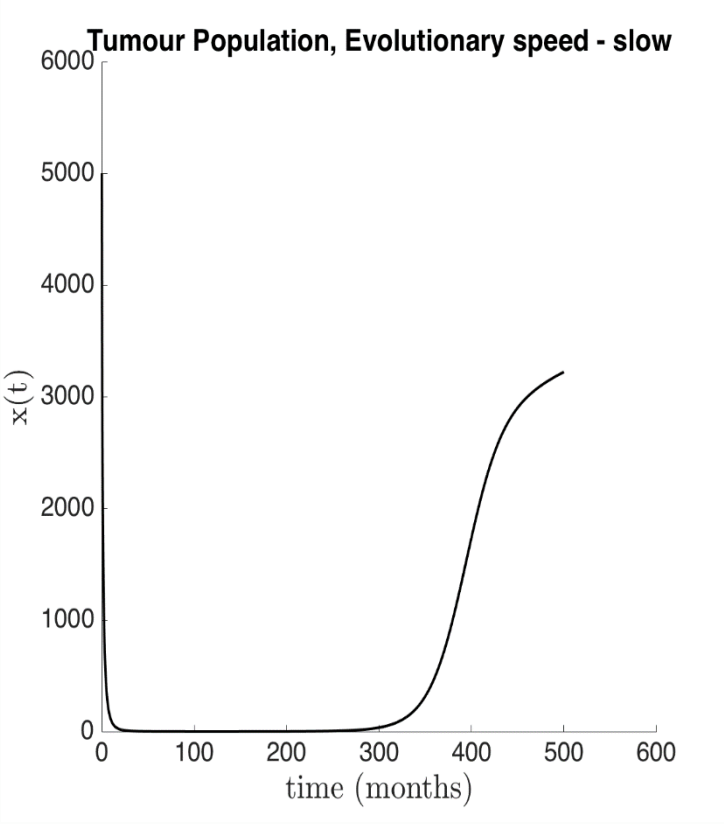
Tumor growth rate compared between models with fast vs. slow evolution of resistance

Fast speed of resistance



Slow speed of resistance



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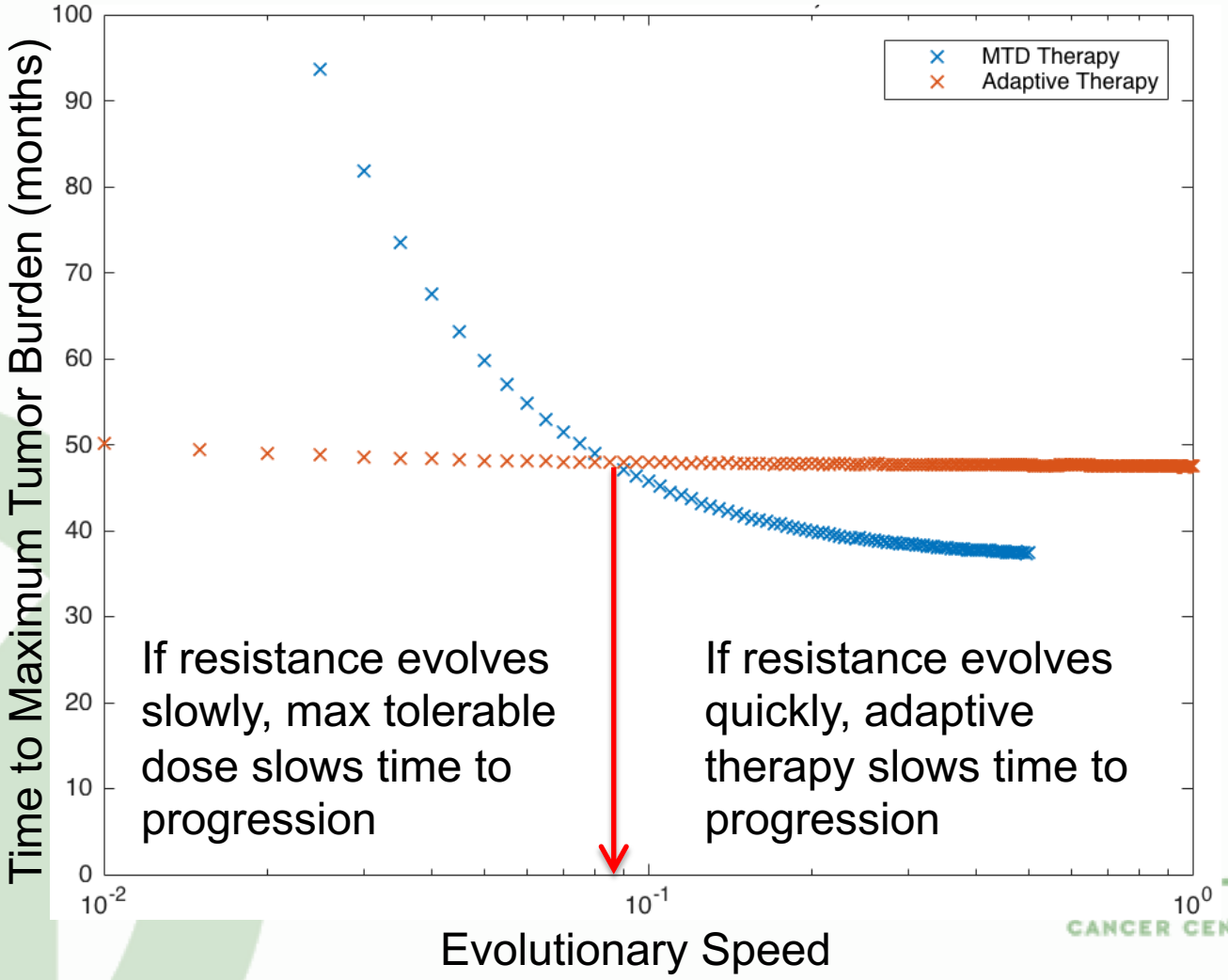
Evolutionary resistance speed dictates whether adaptive therapy makes sense



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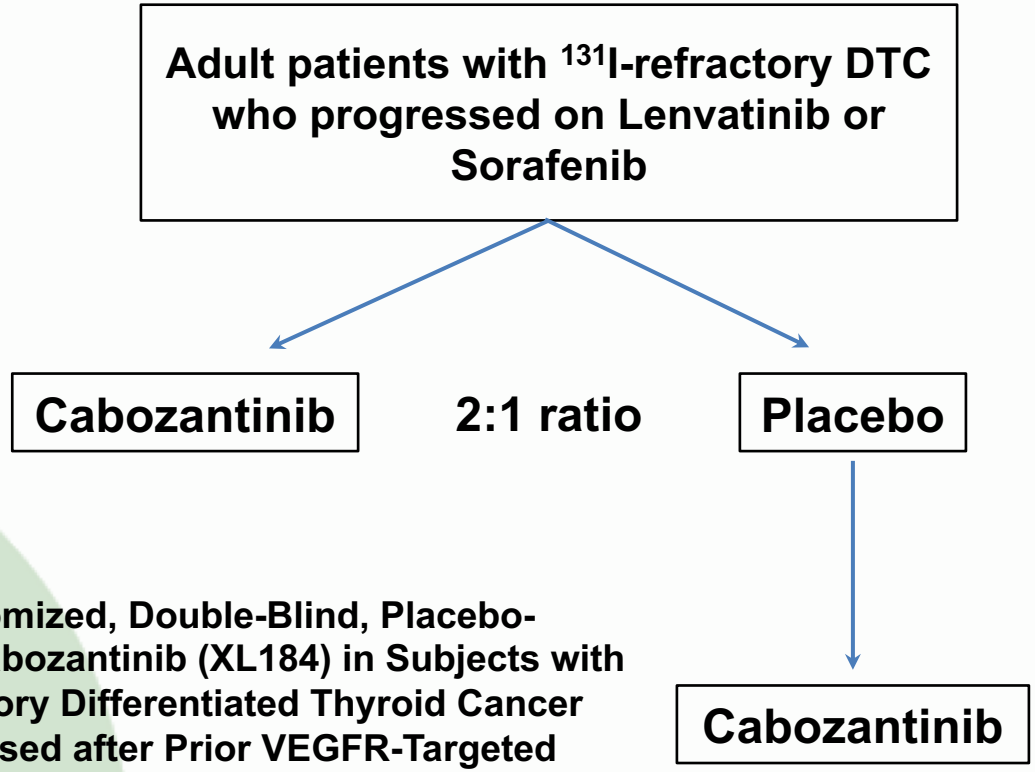
Aim 2: To develop a core mathematical model of tumor progression and therapeutic response given a sequential therapy using two different TKIs.



A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Cabozantinib (XL184) in Subjects with Radioiodine Refractory Differentiated Thyroid Cancer Who Have Progressed after Prior VEGFR-Targeted Therapy (PI- Tarasova)

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Sequential use of 2 TKIs, quantitative trait, evolving resistance

Parameter	Description
x	Population
$u_1 \in [0,1]$	Resistance rate to drug 1
$u_2 \in [0,1]$	Resistance rate to drug 2
$u_3 \in [0,1]$	Resistance rate to both drugs
$m \in [0,1]$	Treatment dose

Population dynamics: $\dot{x} = \frac{dx}{dt} = xG(u_1, u_2, u_3, x, m)$

Resistance evolution: $\dot{u}_i = \sigma_i \frac{\partial G(u_1,u_2,u_3,x,m)}{\partial u_i}$

G-function: $G(u_1, u_2, u_3, x, m) = r\left(1 - \frac{x}{K}\right) - \frac{m}{k_1+b_1u_1+\beta_1u_3} - \frac{m}{k_2+b_2u_2+\beta_2u_3} - d$

Cost of resistance realized as a decrease in growth rate

$$r = r_{max}(1 - u_1)(1 - u_2)(1 - u_3)$$

Assumptions: $\beta_1 > b_1, \beta_2 > b_2$

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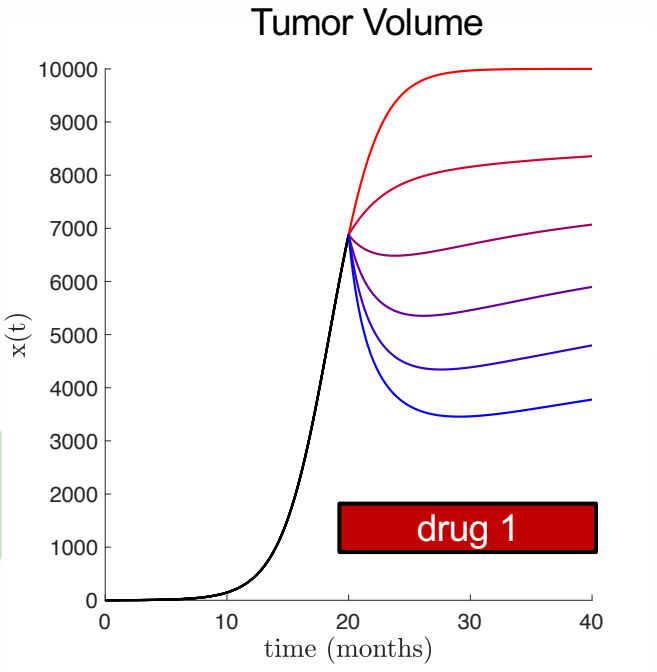
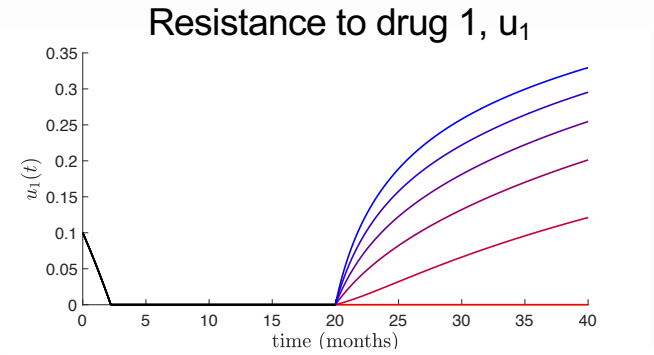
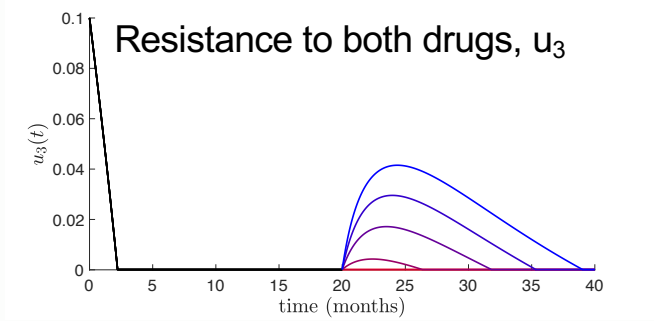
Higher drug dose reduces tumor growth but hastens resist







Drug 1 kill rate, m

$m_1 = 0$ $m_1 = 0.05$

Parameters
(unless otherwise noted)

$b_1 = b_2 = 0.1$

$\beta_1 = \beta_2 = 0.1$

$\gamma_1 = \gamma_2 = \gamma_3 = 1$

$r_{\max} = 0.5$

$\sigma = 0.1$

$k_1 = k_2 = k_3 = 0.1$

$m_1 = 0.05$

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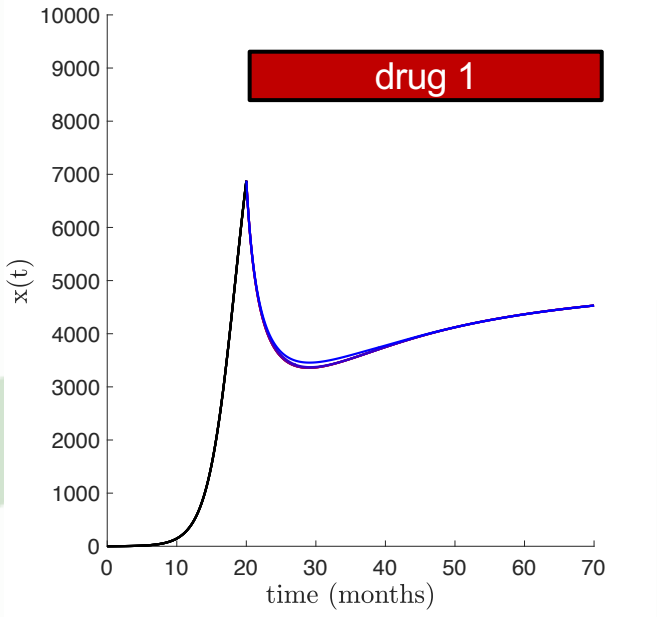
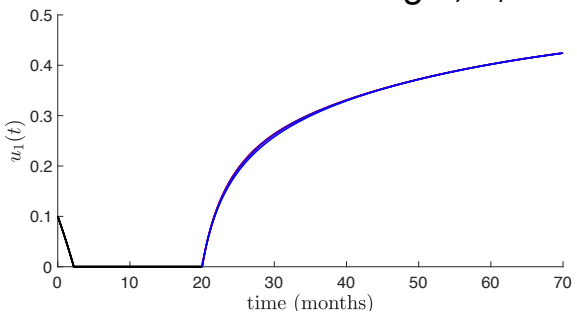
Consequence of increasing generic resistance

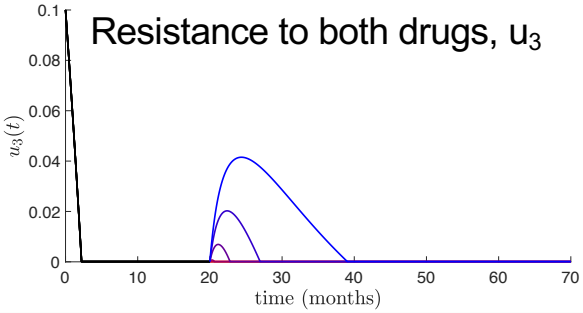
Tumor Volume



Resistance to drug 1, u_1



Resistance to both drugs, u_3



Trait 3 rate of evolution, β_1

$\beta_1 = 0$ $\beta_1 = b_1 = 0.2$

Parameters

$b_1 = b_2 = 0.2$

$\beta_1 = \beta_2 = 0.1$

$\gamma_1 = \gamma_2 = \gamma_3 = 1$

$r_{\max} = 0.5$

$\sigma = 0.1$

$k_1 = k_2 = k_3 = 0.1$

$m_1 = 0.05$

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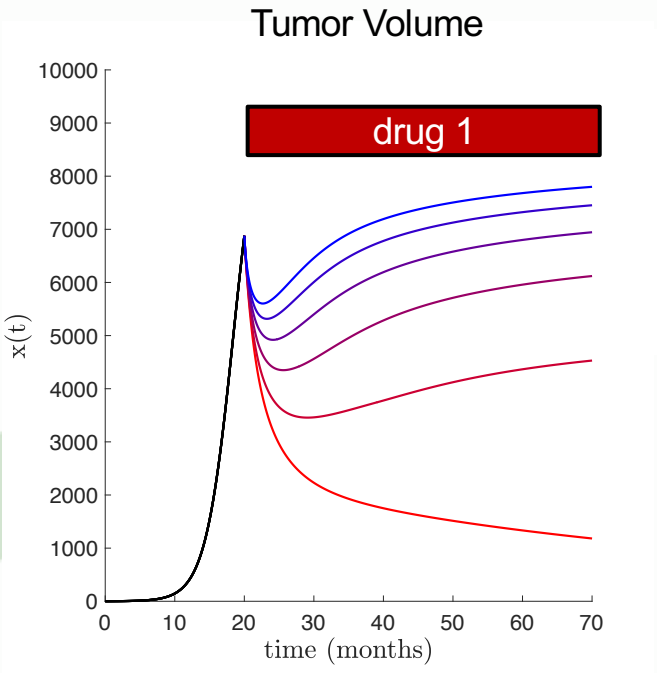
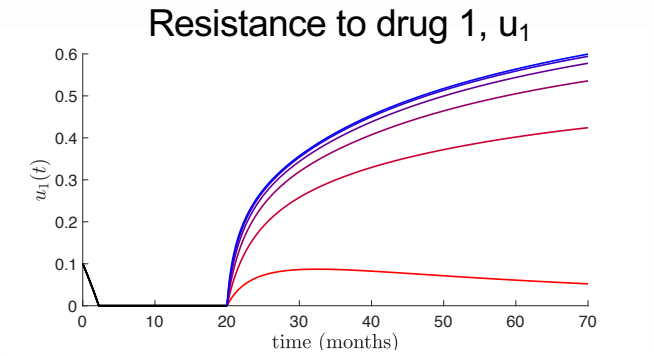
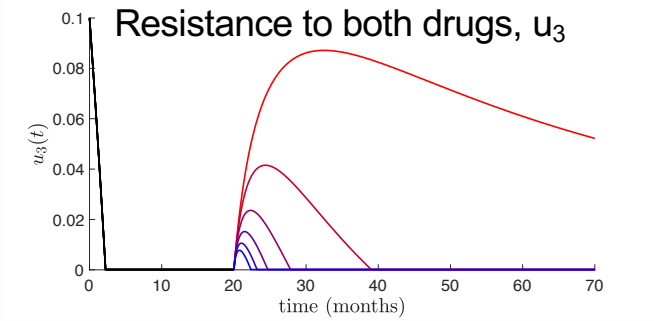
Consequence of increased specific resistance







Trait 3 rate of evolution, b_1

$b_1 = \beta_1 = 0.1$ $b_1 = 0.6$

Parameters

$b_1 = b_2 = 0.2$

$\beta_1 = \beta_2 = 0.1$

$\gamma_1 = \gamma_2 = \gamma_3 = 1$

$r_{max} = 0.5$

$\sigma = 0.1$

$k_1 = k_2 = k_3 = 0.1$

$m_1 = 0.05$

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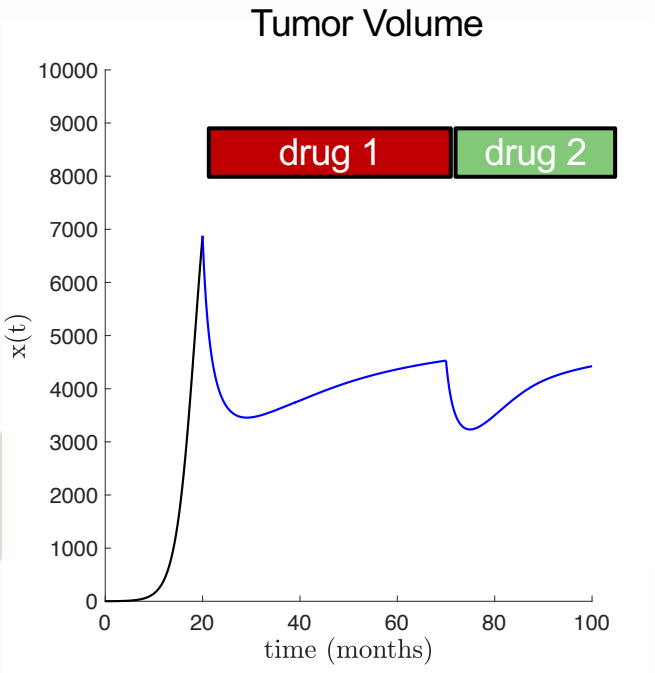
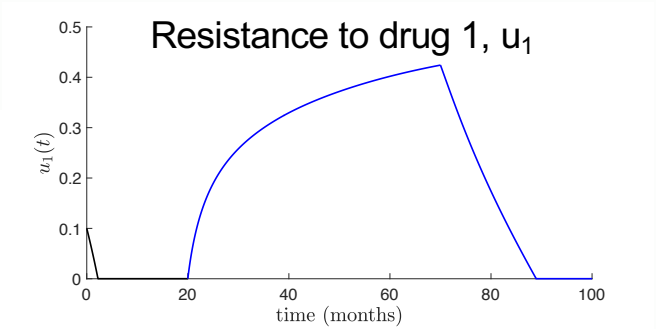
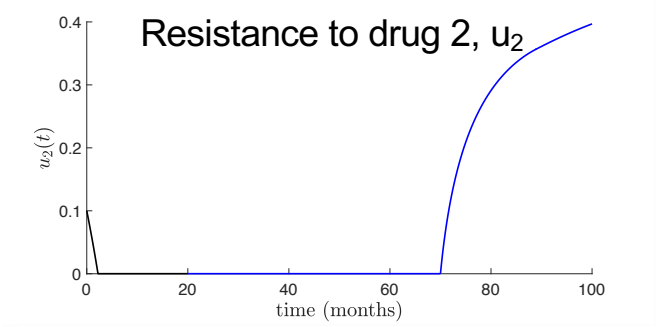
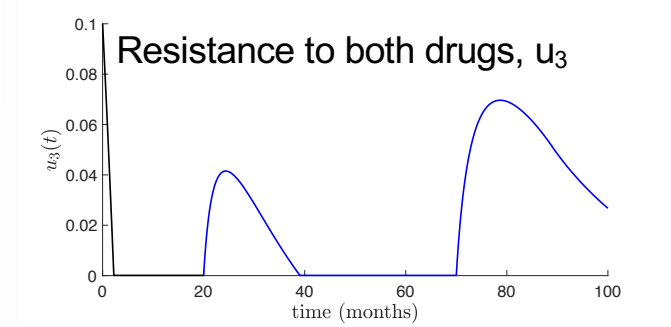
Effect of two TKI treatment on tumor growth and resistanc









Parameters

$b_1 = b_2 = 0.2$

$\beta_1 = \beta_2 = 0.1$

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$r_{\max} = 0.5$

$\sigma = 0.1$

$k_1 = k_2 = k_3 = 0.1$

$m_1 = 0.05$

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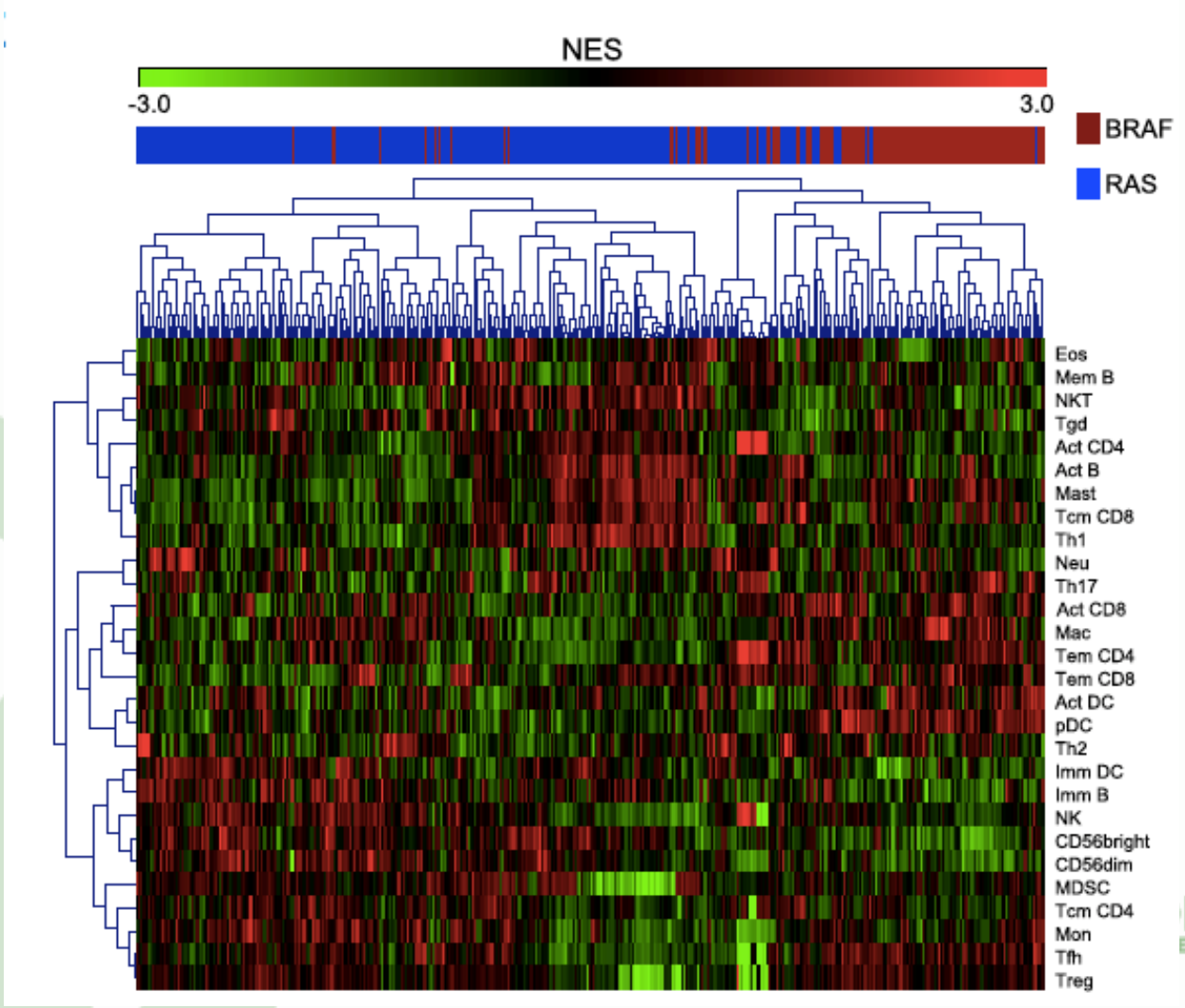
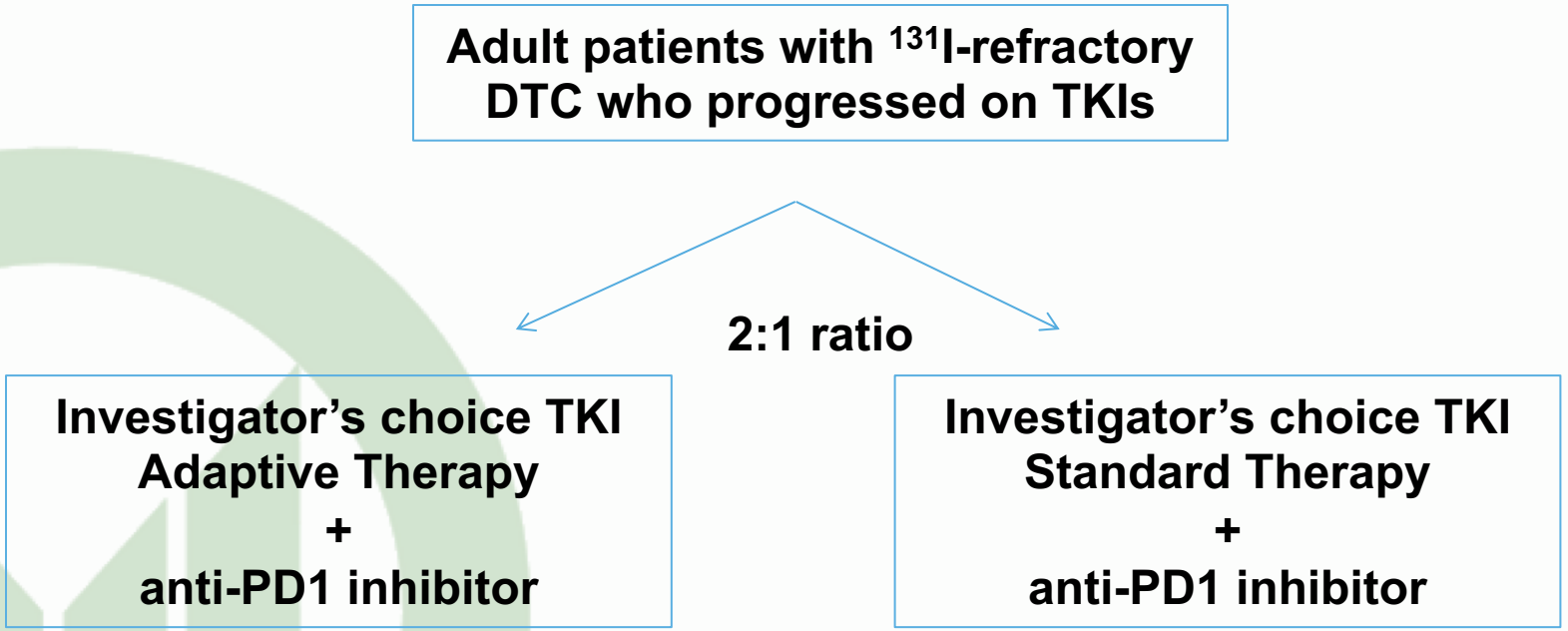
Potential for immunotherapy in Thyroid



Aim 3: To develop, validate and test a core mathematical model of therapeutic response and its effects in the tumor immune microenvironment.

Next trial concept: Combination of adaptive tyrosine kinase inhibitor and anti-PD1 therapy in patients with advanced progressive thyroid cancer



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S.I.M.P.L.E

Sequential Imunoperoxidase Labeling and Erasing

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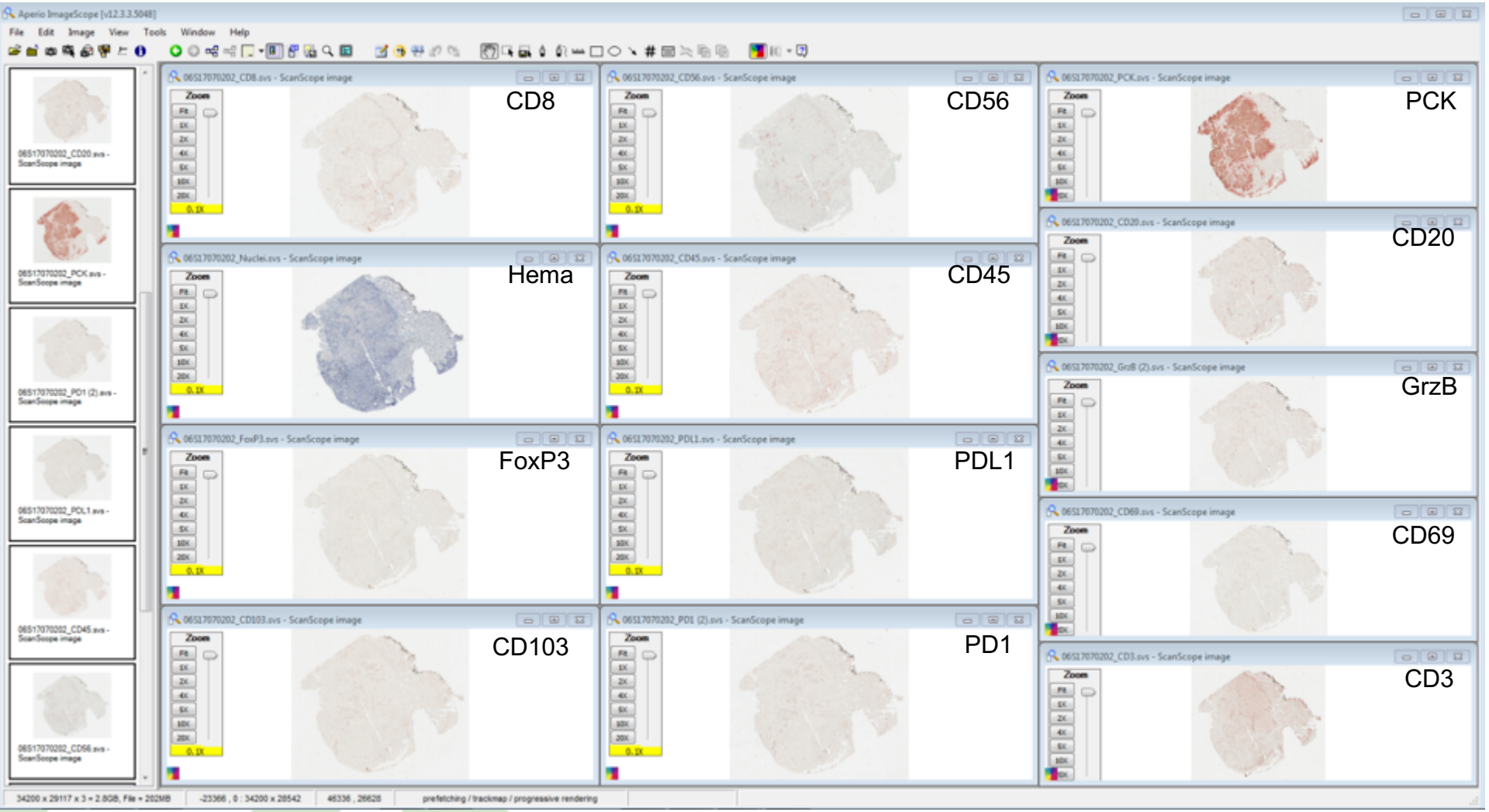


Lymphoid panel (n=15)

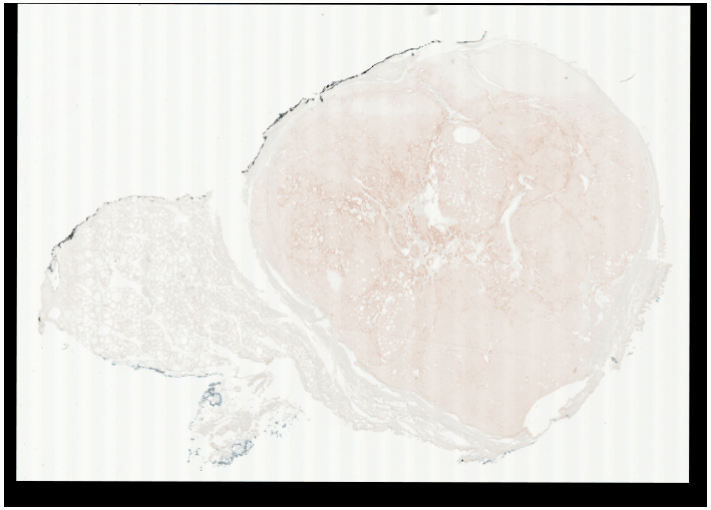
Marker name	Target
GrzB	NK and T-cells
PD1	Activated T- and B-cells
PD-L1	Activated T- and B-cells
FOXP3	T-reg cells
CD8	Cytotoxic T-cells
CD69	Activated leukocytes, NK, platelets, Langerhans cells, and activated macrophages
CD103	Intra-epithelial lymphocytes, E-Cadherin receptor
CD3	T-cells
CD4	T-helper cells
CD20	B-cells
CD45	Common lymphocyte marker
CD45	Common lymphocyte marker
Cytoketin 7	Epithelial cells
Thyroglobulin	Thyroid cells
BRAF V600E	Thyroid cells

Myeloid panel (n=17)

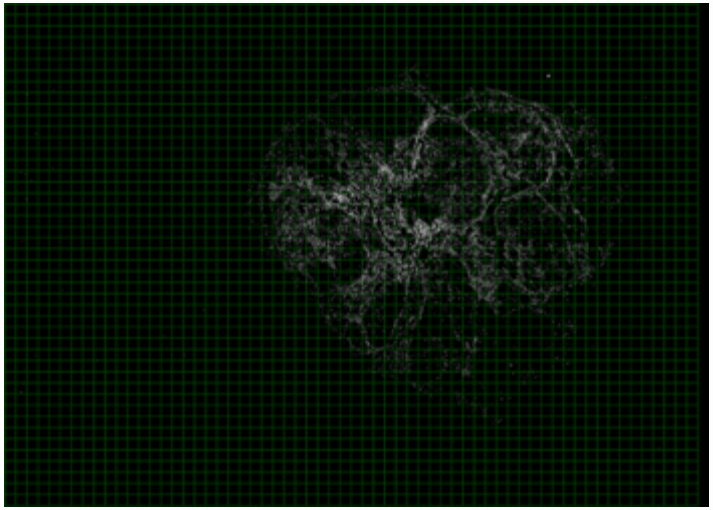
Marker name	Target
Ki67	Proliferation marker
CD66b	Neutrophils
MHC II	Antigen presenting cells
CD68	Macrophages
DC-SIGN	Dendritic cells
CD163	Macrophages (M2)
Tryptase	Mast cells
HLA-DR	Macrophages (M1)
CD14	Monocytes, macrophages, Langerhans cells and granulocytes
CD15	Granulocytes, monocytes, neutrophils, and eosinophils
CD33	Monocytes, granulocytes, and mast cells
CSF1R	Macrophages (TAM)
CD206	Macrophages (M2)
CD80	Macrophages (M1)
Cytoketin 7	Epithelial cells
Thyroglobulin	Thyroid cells
BRAF V600E	Thyroid cells

What Does The Tumor Immune Ecology Look Like?

Co-register Images

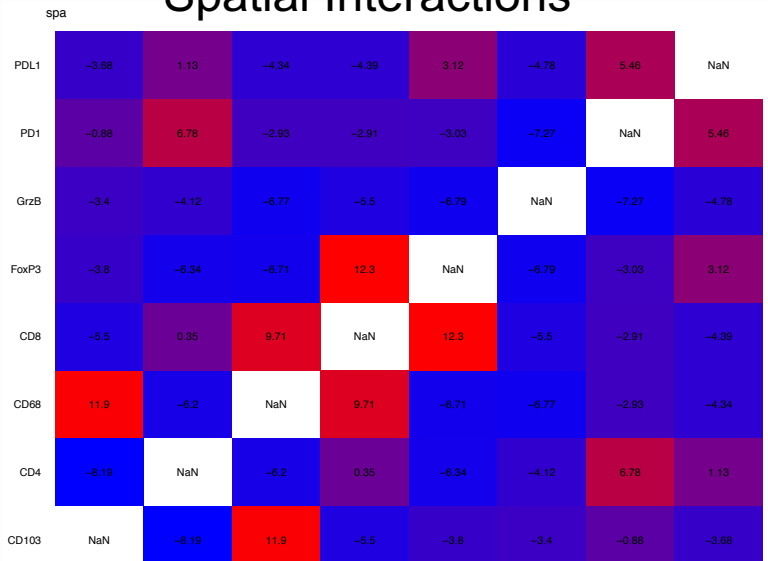


Slice into Quadrats & Count Stain Positivity

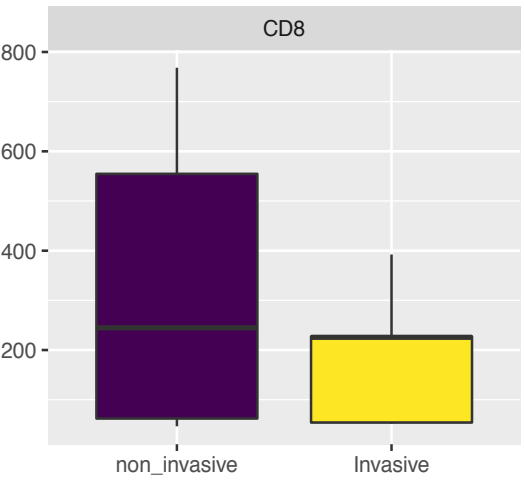


- The success of immunotherapy depends on the immune composition of the tumor
- Ecological methods can be used to describe the immune ecology using immunohistochemistry

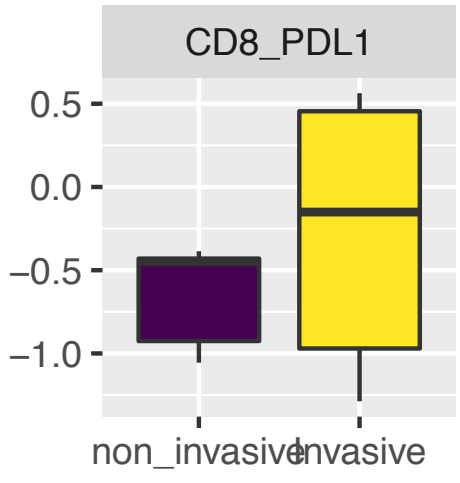
Quantify Cell Abundance and Spatial Interactions

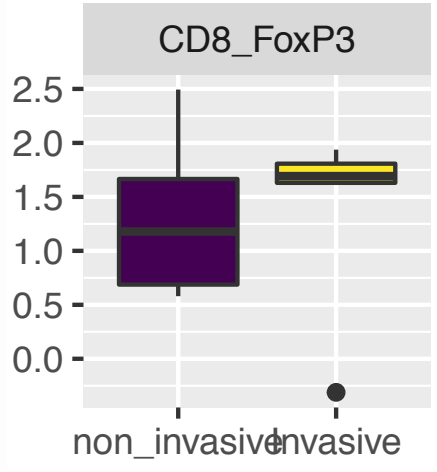


Combining TKIs and Immunotherapy May Re-awaken the Suppressed Immune Response

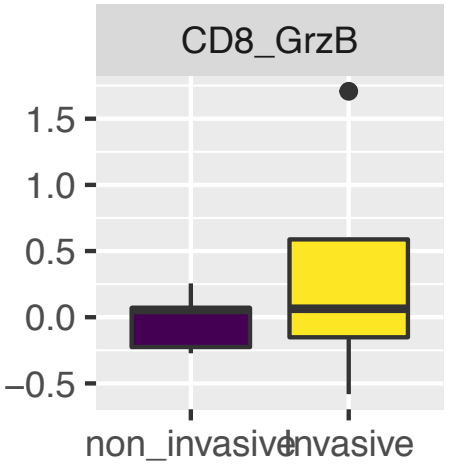


Decreased T-cell infiltration





Increased interactions between T-cells and immunosuppressive cells



Increased T-cell exhaustion

- See evidence of immune suppression in invasive tumors
- Immunotherapies can be used to “re-awaken” the immune system, allowing it to attack the tumor.
- Can model the combination to test prediction and determine most effective treatment strategies
- Will test verify in upcoming clinical trial, description of the immune ecology before and after treatment

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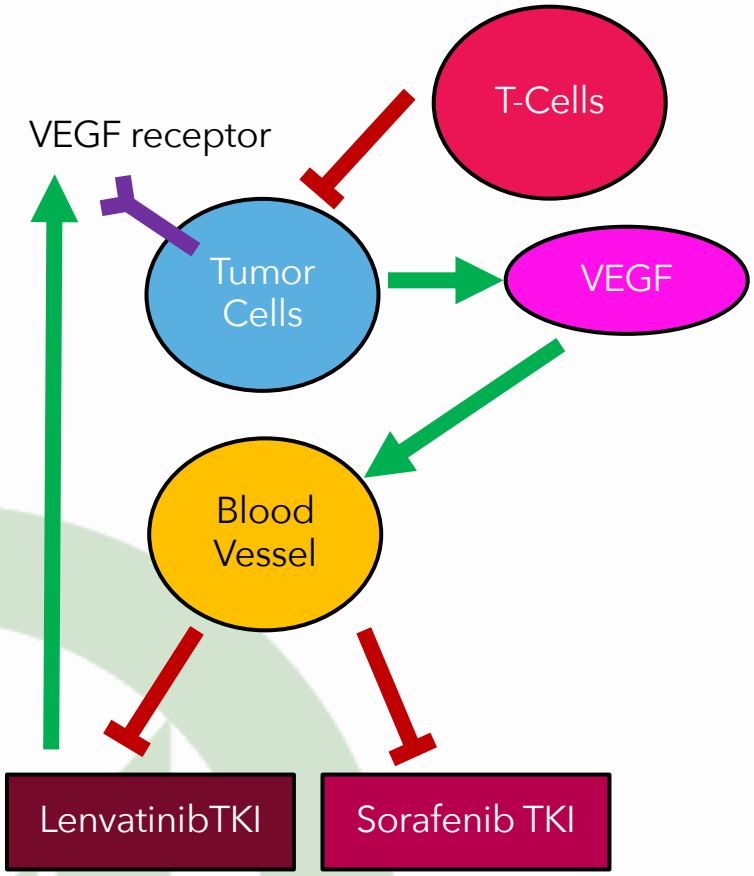
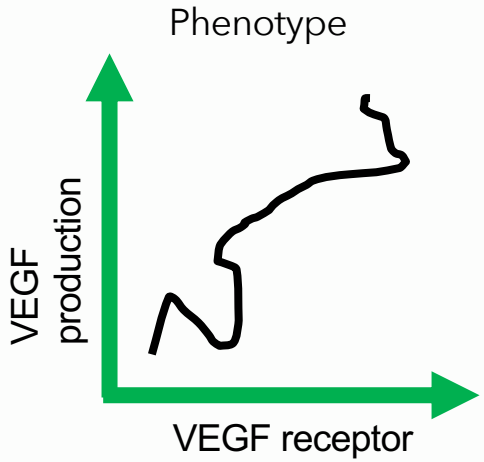
Modeling the Tumor Microenvironment





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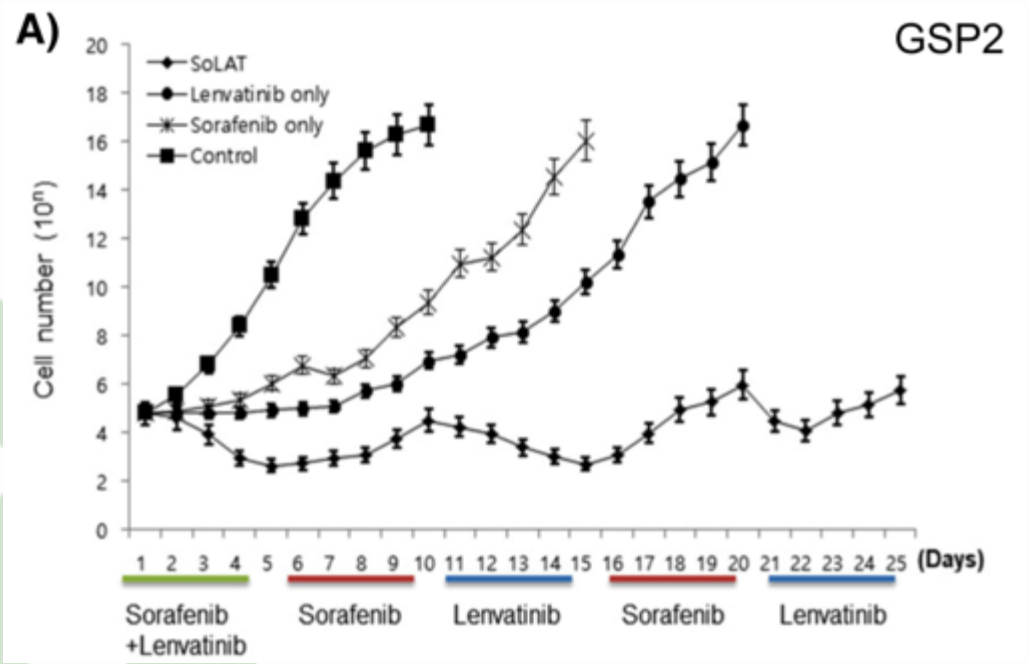
Patient-Derived Aggressive Papillary Thyroid Cancer (PTC) Cell Lines (RAI-refractory)



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Arig Ibrahim-Hashim
Jeffery West
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Minah Dinh
Gustavo DeLeon
Audrey Freischel
Matthew Wicker
Chandler Gatenbee

Thank you IMO, Danae, Melina, Sandy!!!

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Budget

- 20K for Post-doc to continue work with model
- 15K for technician to generate multiplex IHC of samples from pre- and post biospies. Can be used to validate model in clinical specimens
- 15K for mice xenograft model

Functional Eco-Evo Index Panel in Development

GrzB	CD34
Ki-67	CD31
Eomes	CAIX
LAG3	CAXII
TIM3	EGFR
CTLA4	VEGFR
CD39	FGFR
VISTA	c-MET
OX40	AKT
OX40L	MSH2
GITR	MSH6
4-1BB (CD137)	MLH1
IDO	PMS2
Tbet	

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