Multiscale Models for Predicting Optimum Immune and Targeted Therapy Schedules

Goals

- We are combining multiscale mathematical approaches with novel cellular quantification experimental technologies in order to:
  - To gain a deeper, more robust understanding of tumor-immune dynamics
  - To optimize combination immunotherapy and receptor kinase targeted therapy
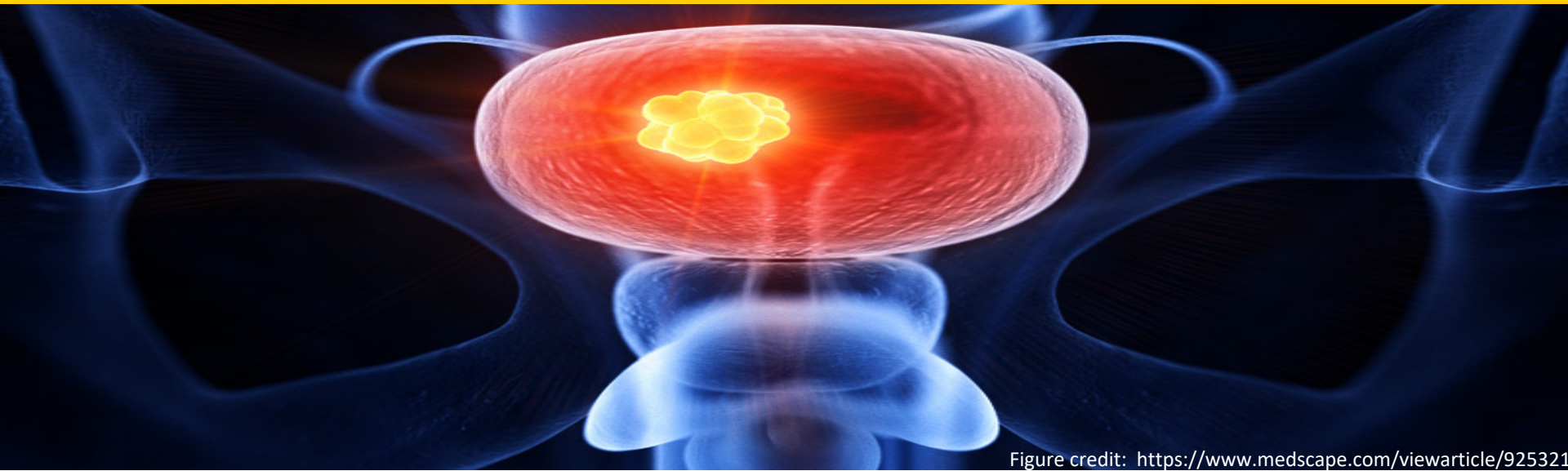
Aggressive Bladder Cancer Mutations

Figure credit: https://www.medscape.com/viewarticle/925321

- Genomic analysis of bladder cancer has identified frequent alterations of FGFRs, including mutations of *FGFR3* that activate the receptor via ligand-independent dimerization → increased cell proliferation and survival.

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Targeted Therapy

- Clinical trials using SMIs of FGFR3 are leading to promising clinical responses for patients with FGFR3 mutations.

- Last year, the FDA approved the first FGFR3 targeted therapy for bladder cancer.

Figure credit: https://www.medscape.com/viewarticle/925321

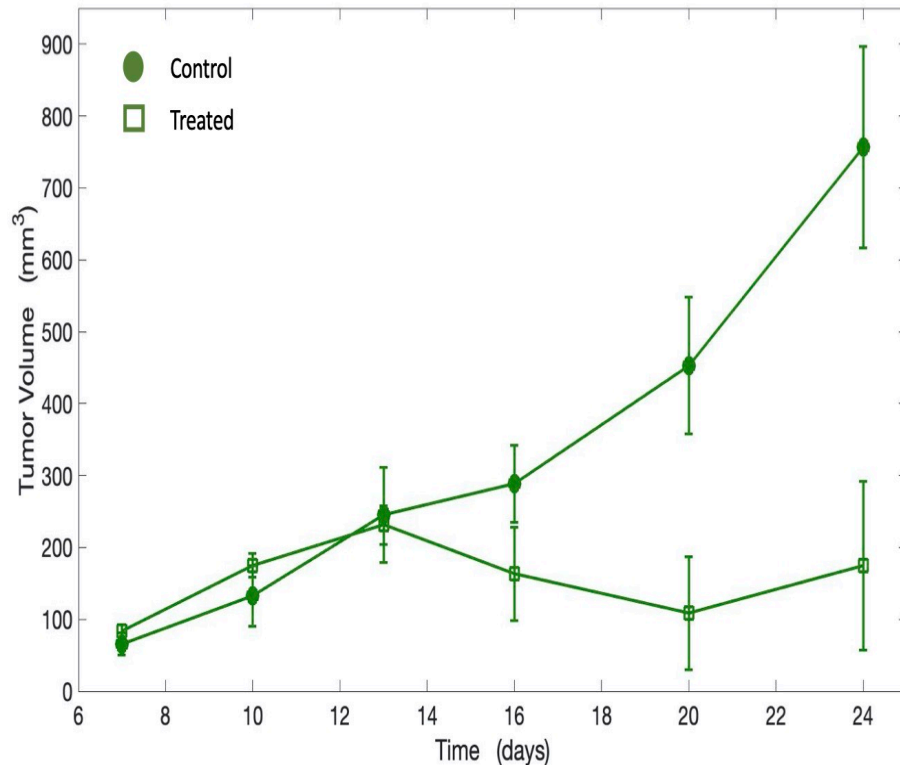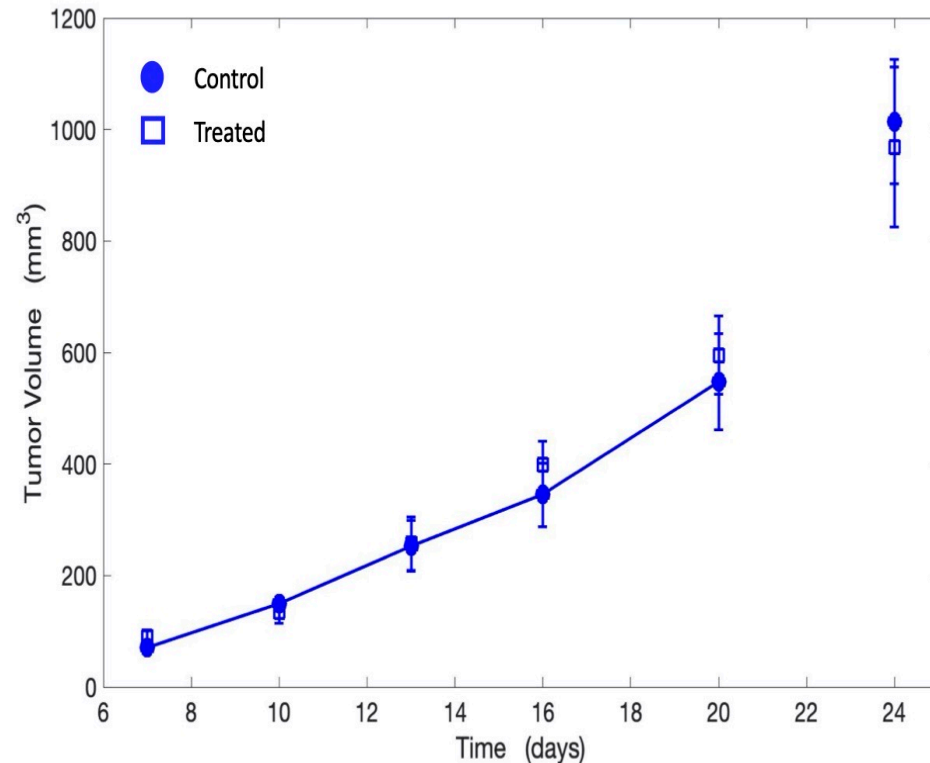LSA MATHEMATICS
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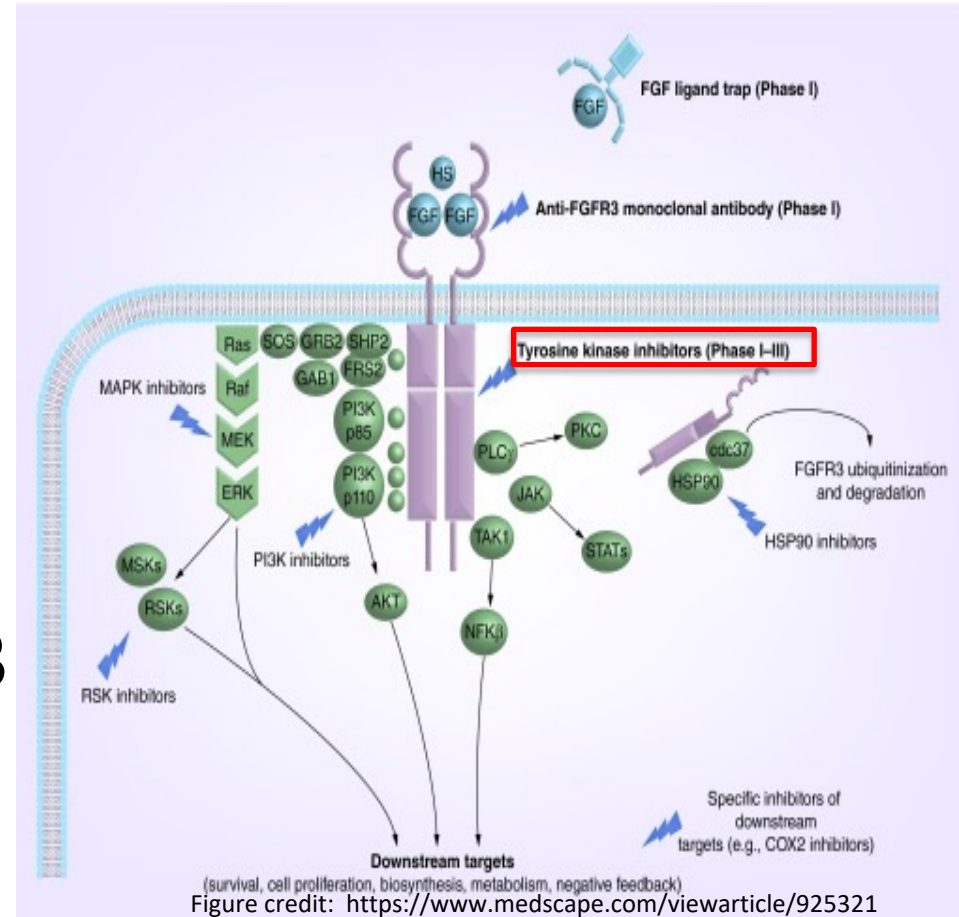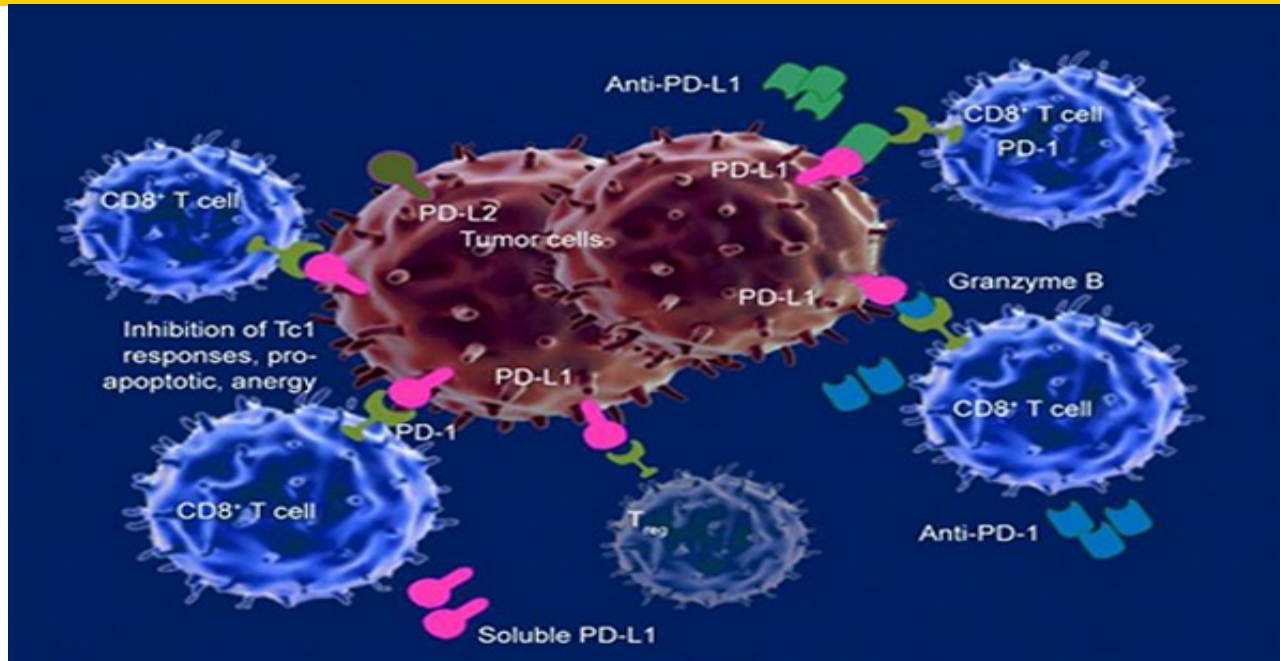
Immunotherapy

- MAbs targeting the PD-1/PD-L1 pathway have resulted in favorable outcomes in advanced bladder cancer.
- Despite the activity of these drugs in some patients, the objective response rate remains less than 25%.

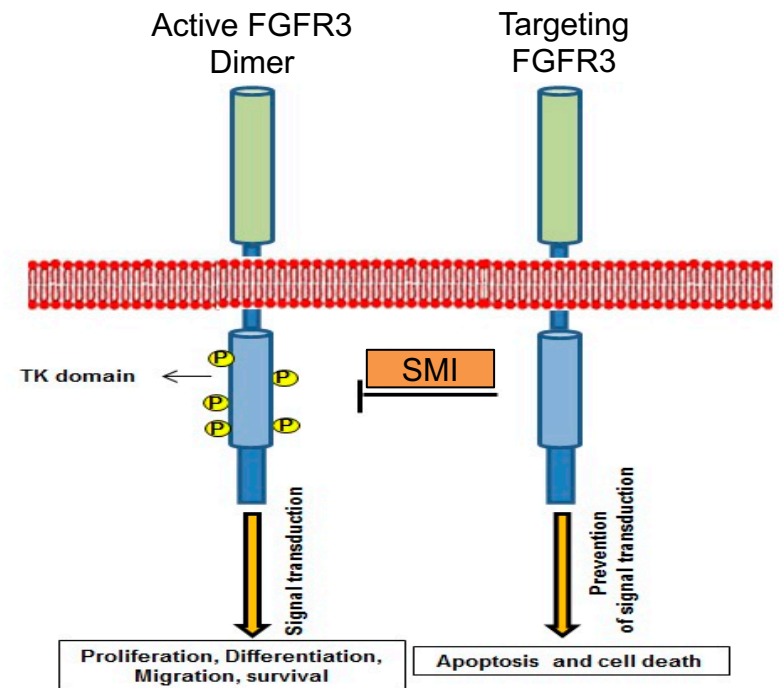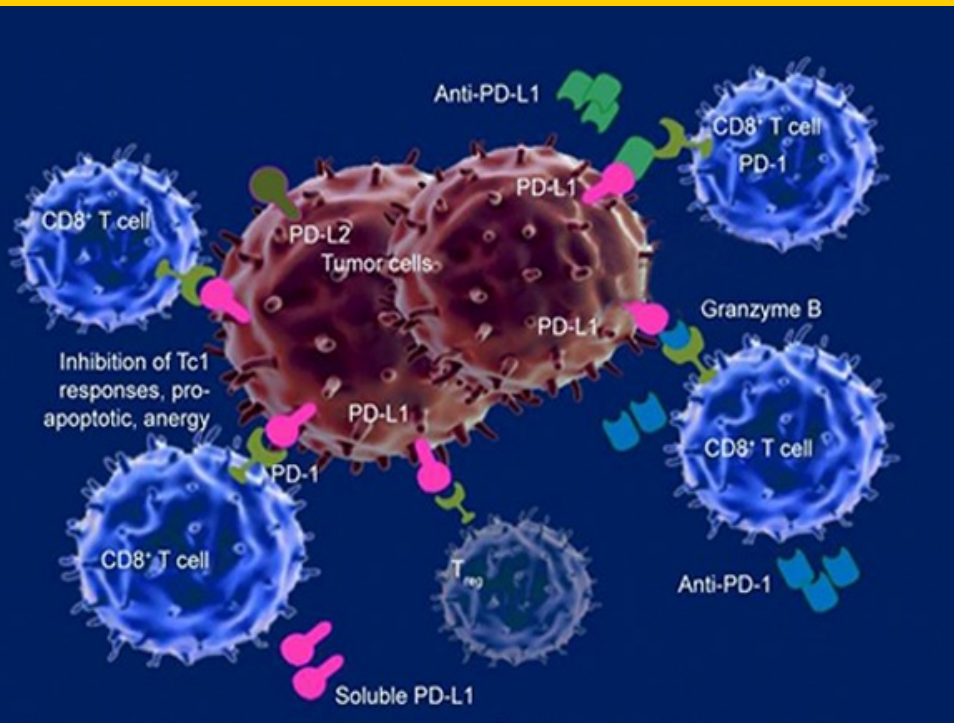# Mutations Hinder Immunotherapy

Wild Type Cells

Mutant Cells

Combination Therapy

Co-acting combination of potent immune checkpoint inhibitors and specific FGFR3 inhibitors potentially offers an advance in targeted therapeutics for cancer.
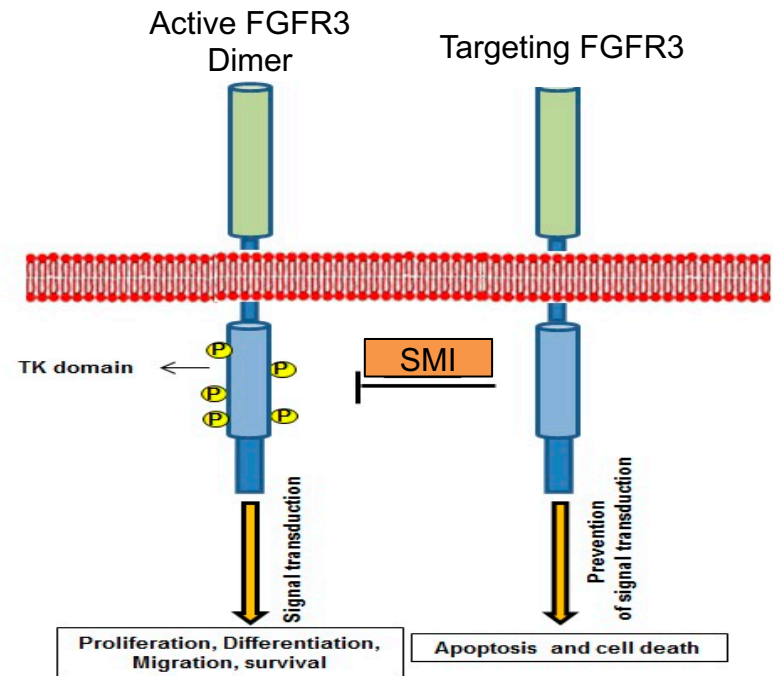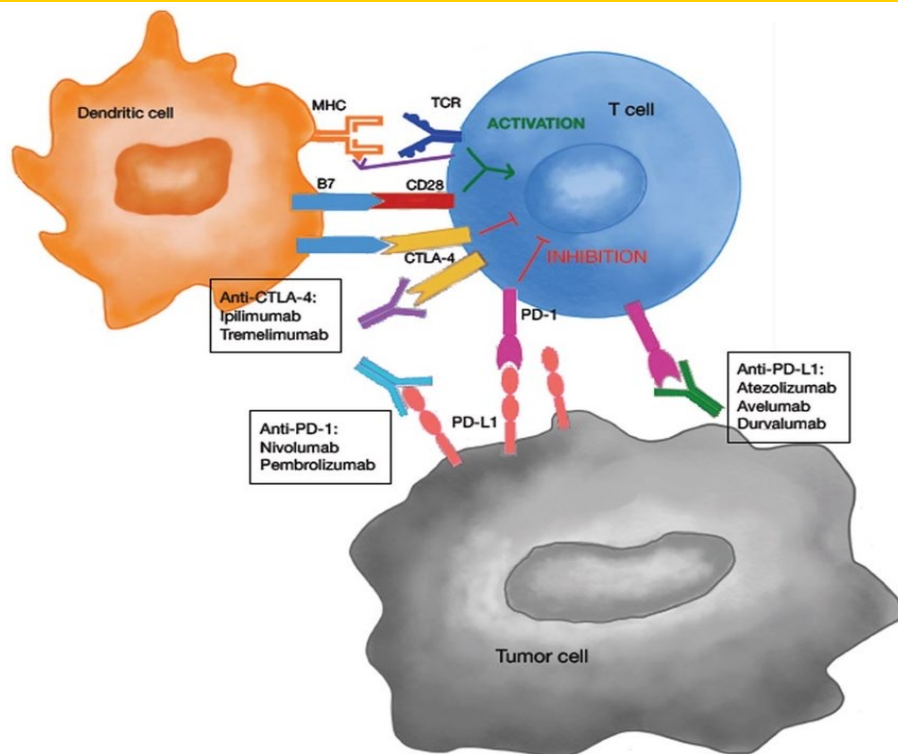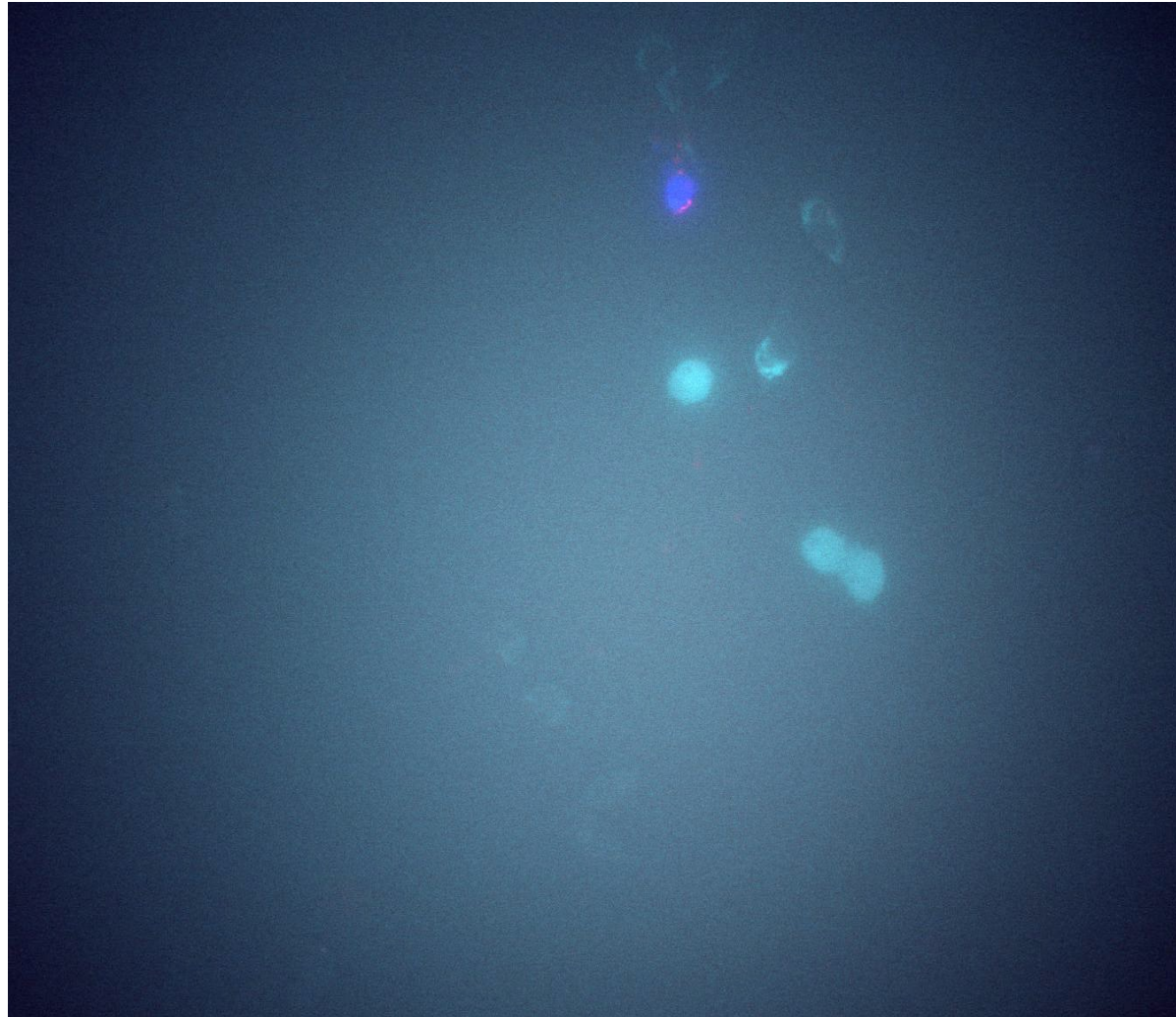
Optimizing Combination Therapy

Figure Credit: Durvalumab in NSCLC: latest evidence and clinical potential. *Ther Adv Med Oncol*. 2018
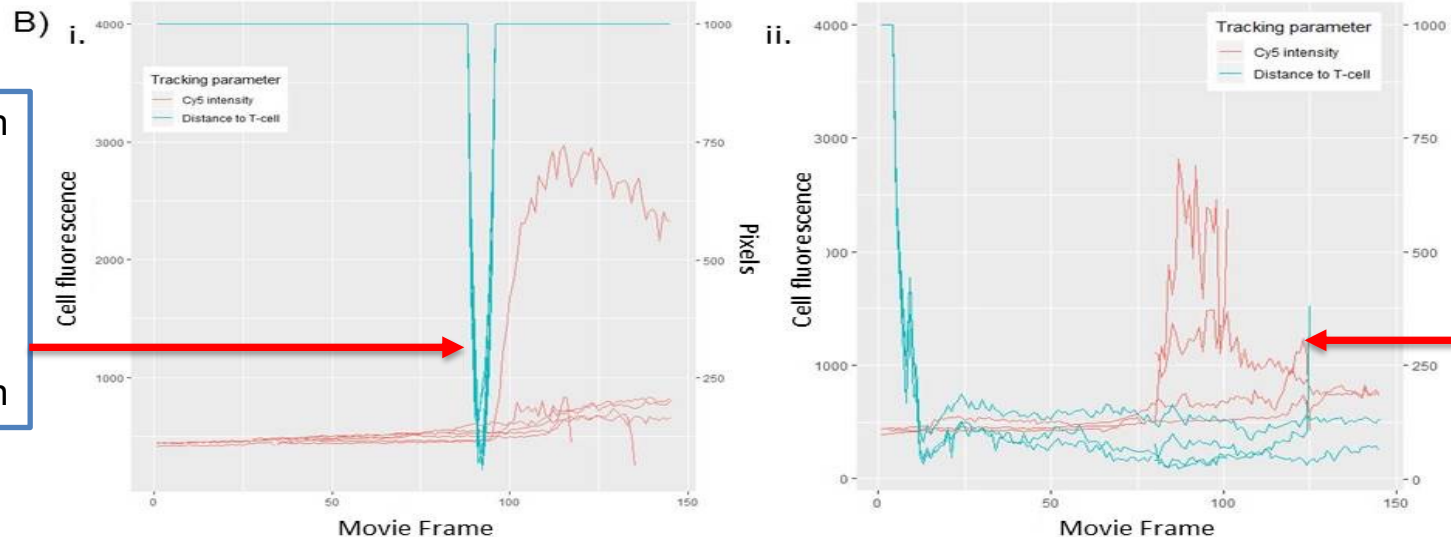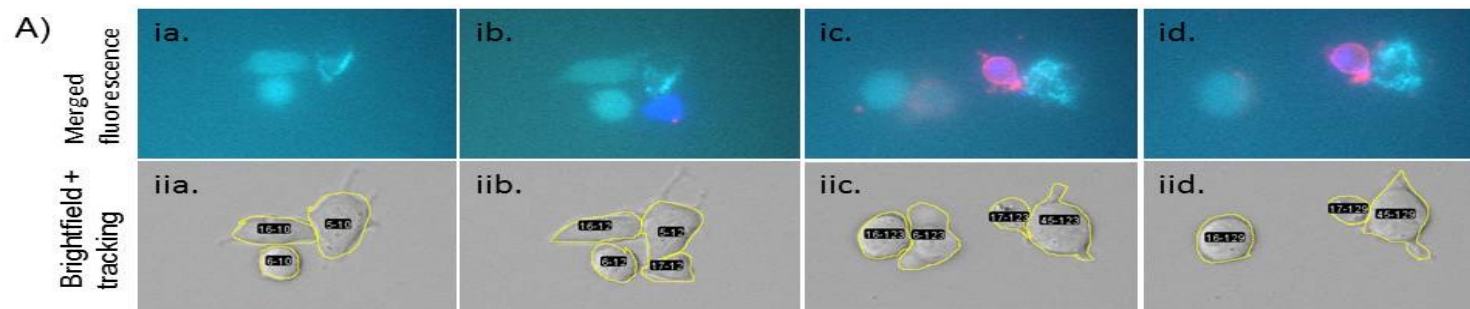
A powerful and practical way to optimize novel drug combinations for clinical cancer treatment is to use data-driven computational models.

Preliminary Data: Live Cell Tracking

- My collaborators developed a novel pipeline to track and quantify the interactions of living tumor cells and immune cells, including cell death.
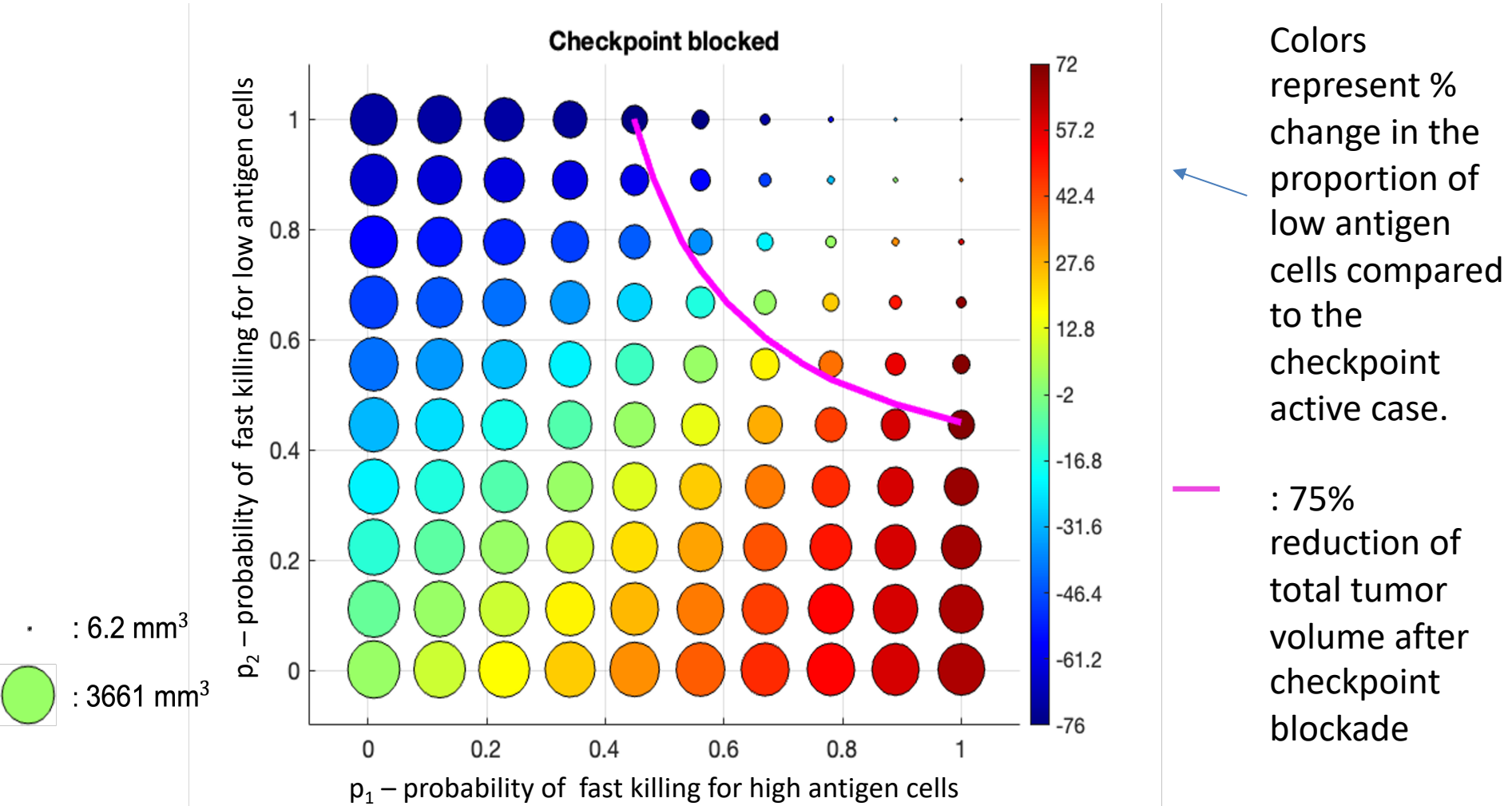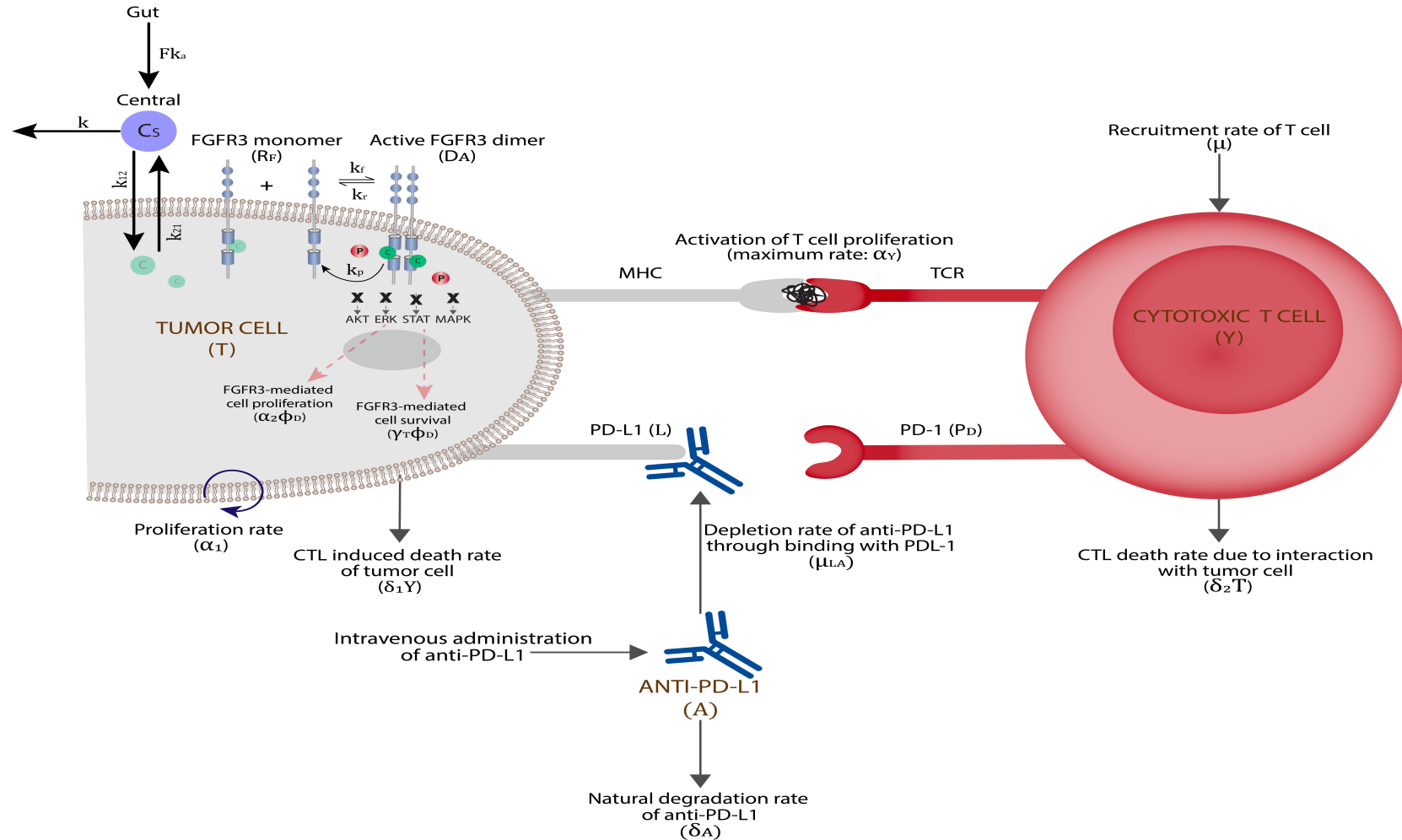
- Evidence of both rapid and slow killing during tumor-immune interactions.
- The proportion of slow and rapid killing within a solid tumor could have significant impact on immune mediated anti-cancer effects.

Impact of Fast/Slow Killing Probabilities

Checkpoint blocked

- p_2 – probability of fast killing for low antigen cells (y-axis)
- p_1 – probability of fast killing for high antigen cells (x-axis)

Colorbar: 72, 57.2, 42.4, 27.6, 12.8, -2, -16.8, -31.6, -46.4, -61.2, -76

Legend:
- : 6.2 mm^3
- : 3661 mm^3

Colors represent % change in the proportion of low antigen cells compared to the checkpoint active case.

—— : 75% reduction of total tumor volume after checkpoint blockade

FGFR3 Mutation and Immune Dynamics

Model Predictions: Monotherapies

- We can predict when targeted therapy outperforms the immune therapy.
- The heatmap shows the difference between the immune and targeted therapies on day 25 as the impact of the mutation on proliferation and survival varies.
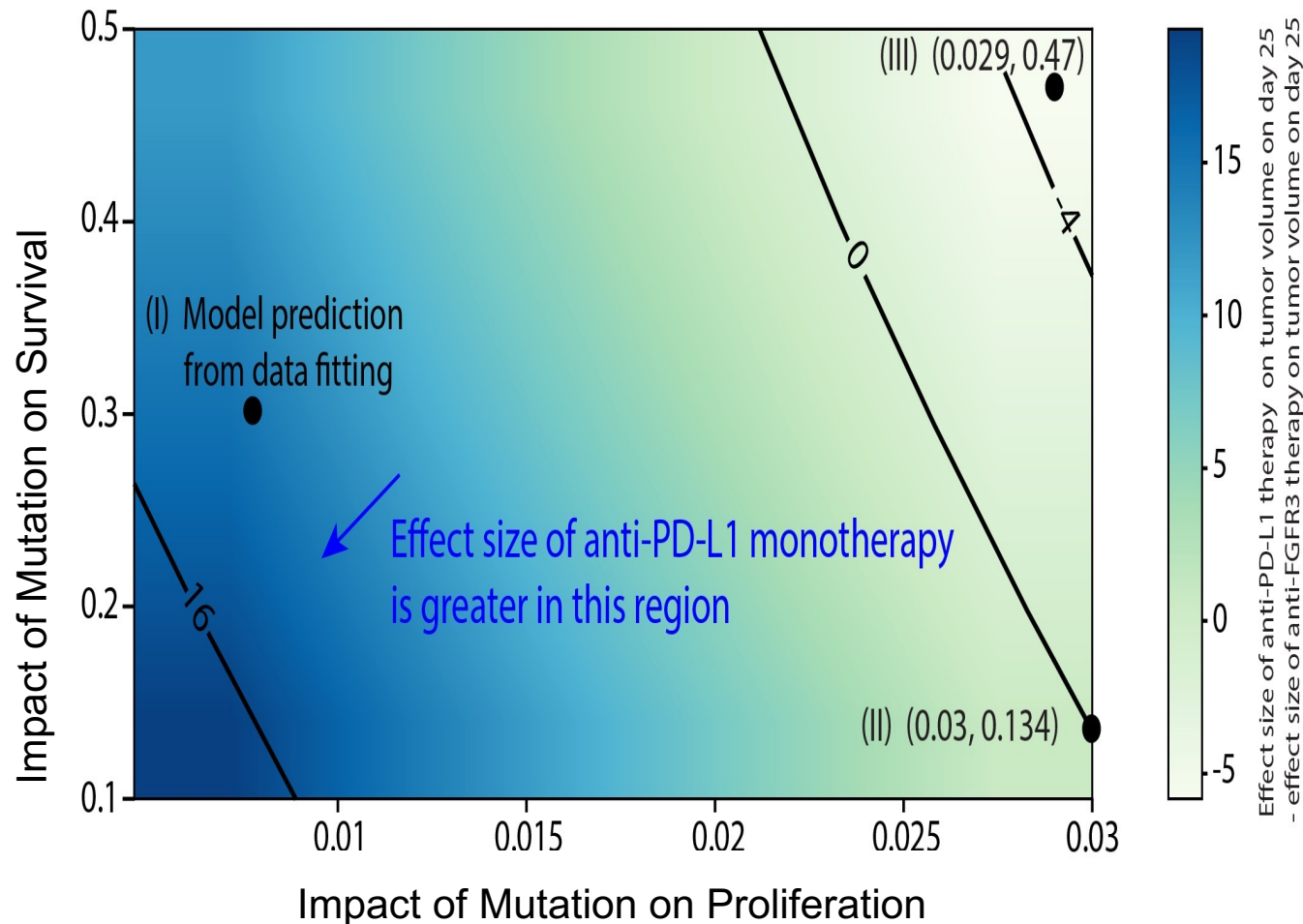
Model Predictions - Combo Therapy

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Anti-FGFR3							▦	▦	▦	▦	▦			▦	▦	▦	▦	▦			▦	▦	▦	▦	▦
Anti-PDL1							■			■				■			■				■			■	
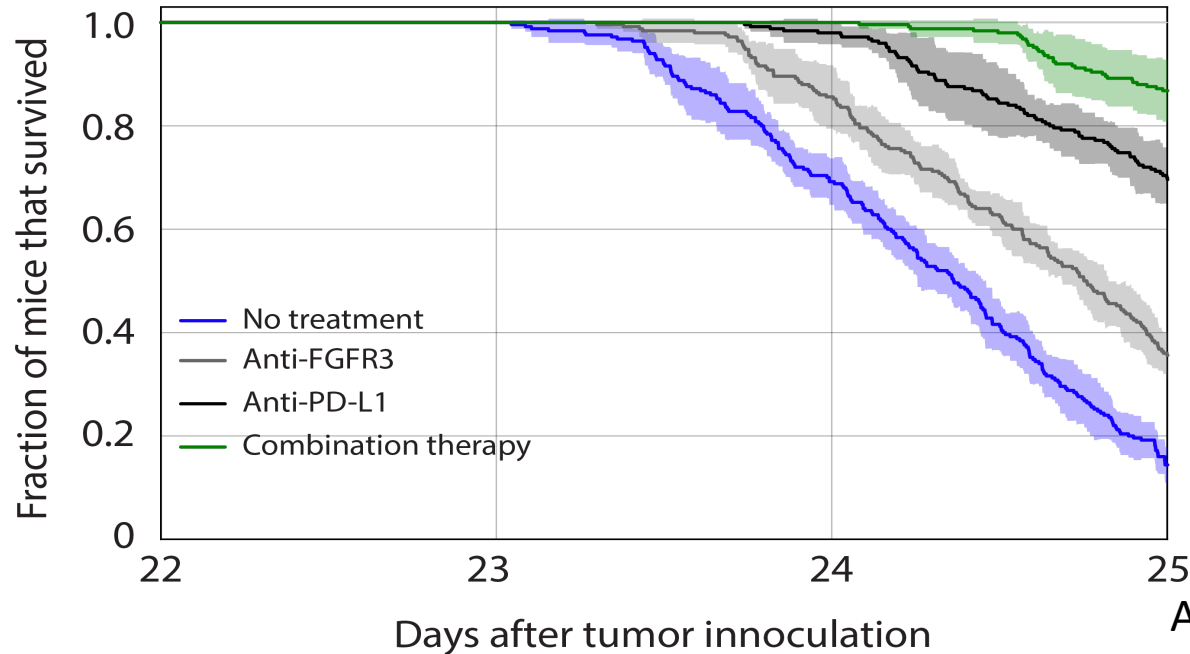
Mean number of mice at risk				Average % of mice that survived
No treatment	50	34	7	(14%)
Anti-FGFR3	50	42	18	(36%)
Anti-PD-L1	50	49	34	(70%)
Combination therapy	50	50	43	(86%)

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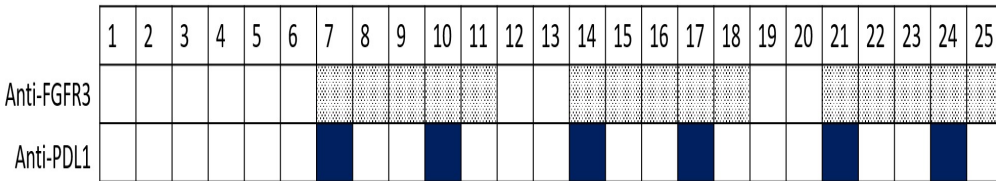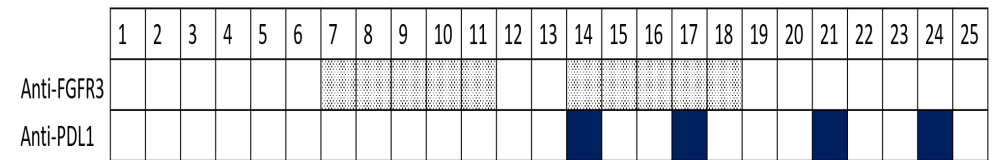
Comparing Dosing Strategies

Model prediction of tumor volume on day 25
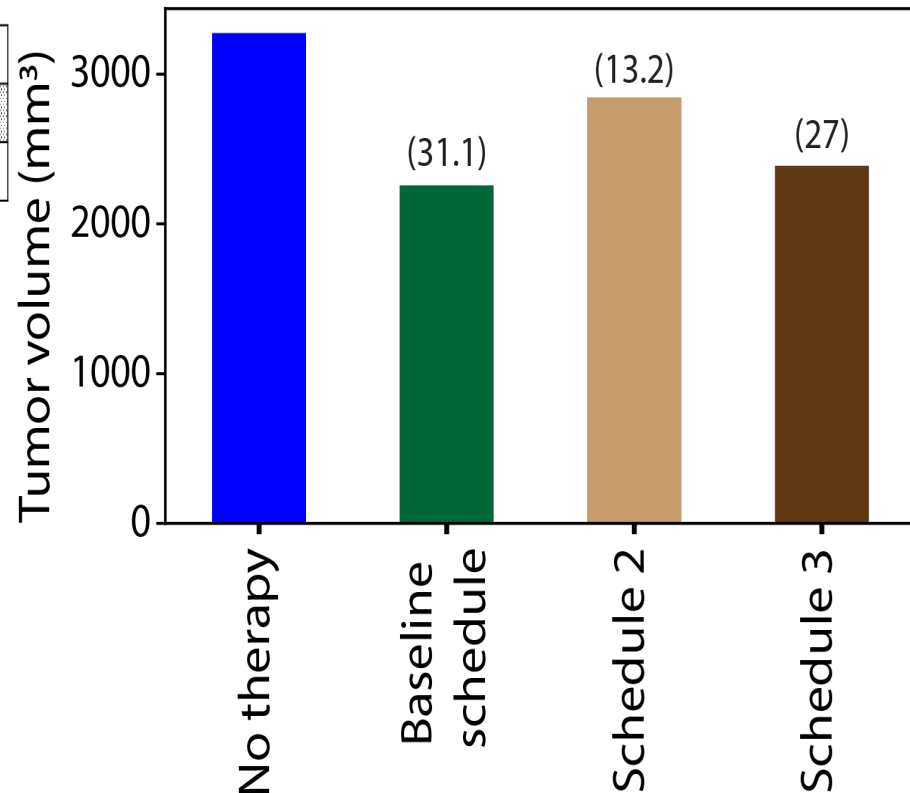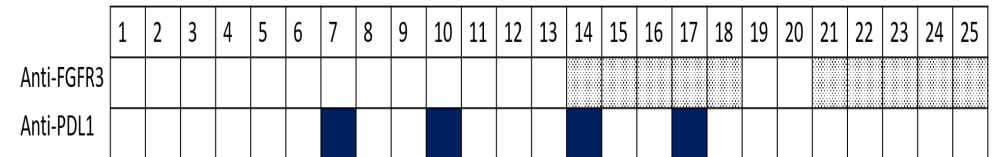(% reduction in tumor volume relative to no treatment)
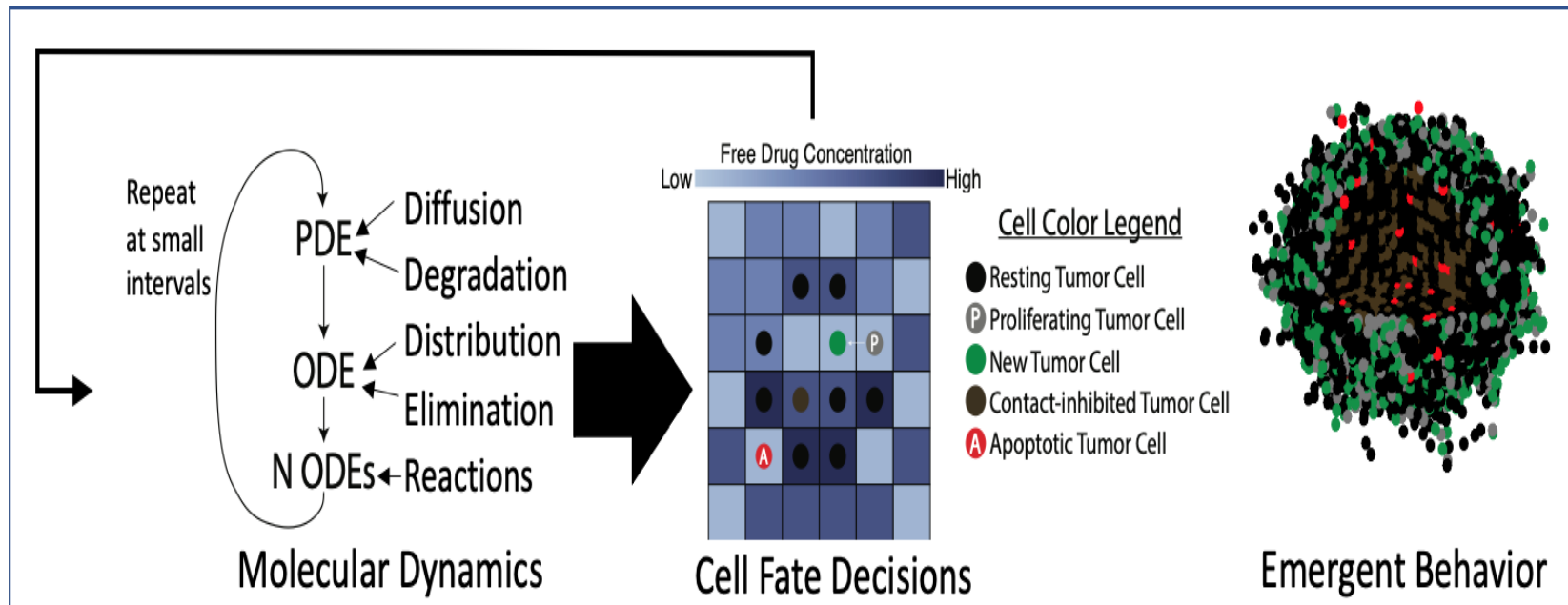
Baseline Schedule: Co-treatment

Schedule 2: Pretreatment with RTK Targeted Therapy

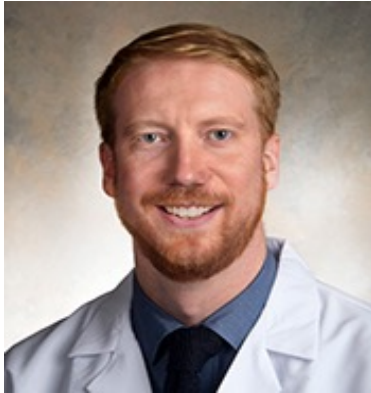**Schedule 3**: Pretreatment with Immune Checkpoint Therapy

Next Steps: Agent-based Modeling

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