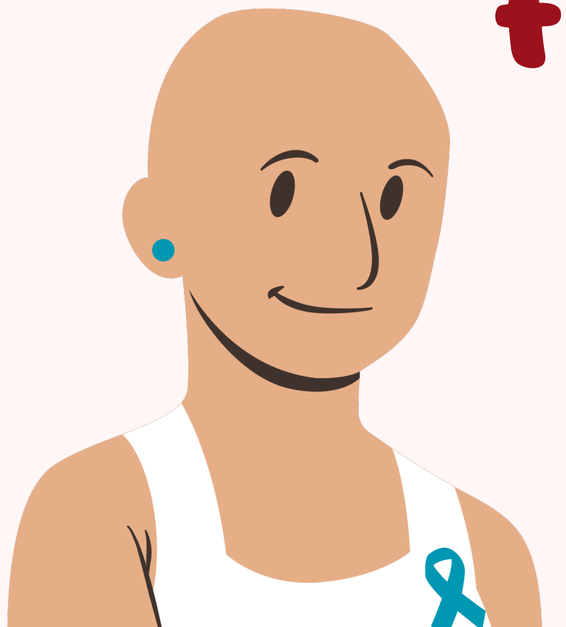
Controlling treatment toxicity in ovarian cancer to prime the patient for tumor extinction therapy



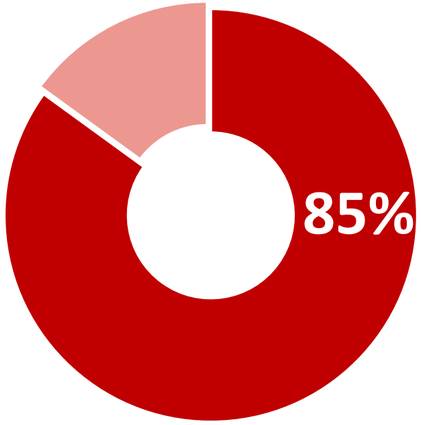
Team Ruby

1 IN 75 WOMEN

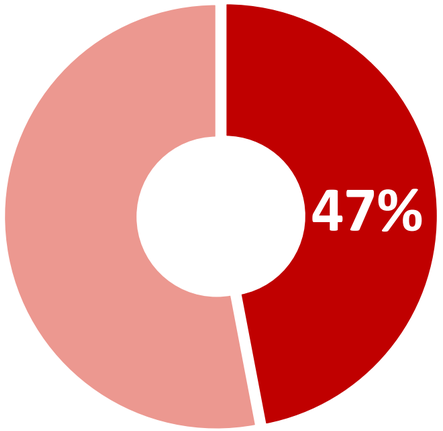
will be diagnosed with ovarian cancer during her lifetime

6TH

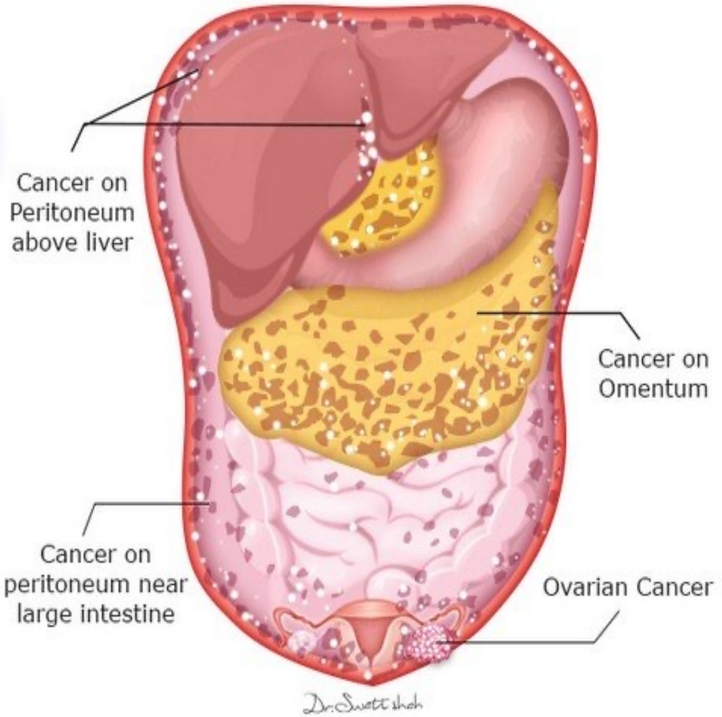
leading cause of cancer-related death among women



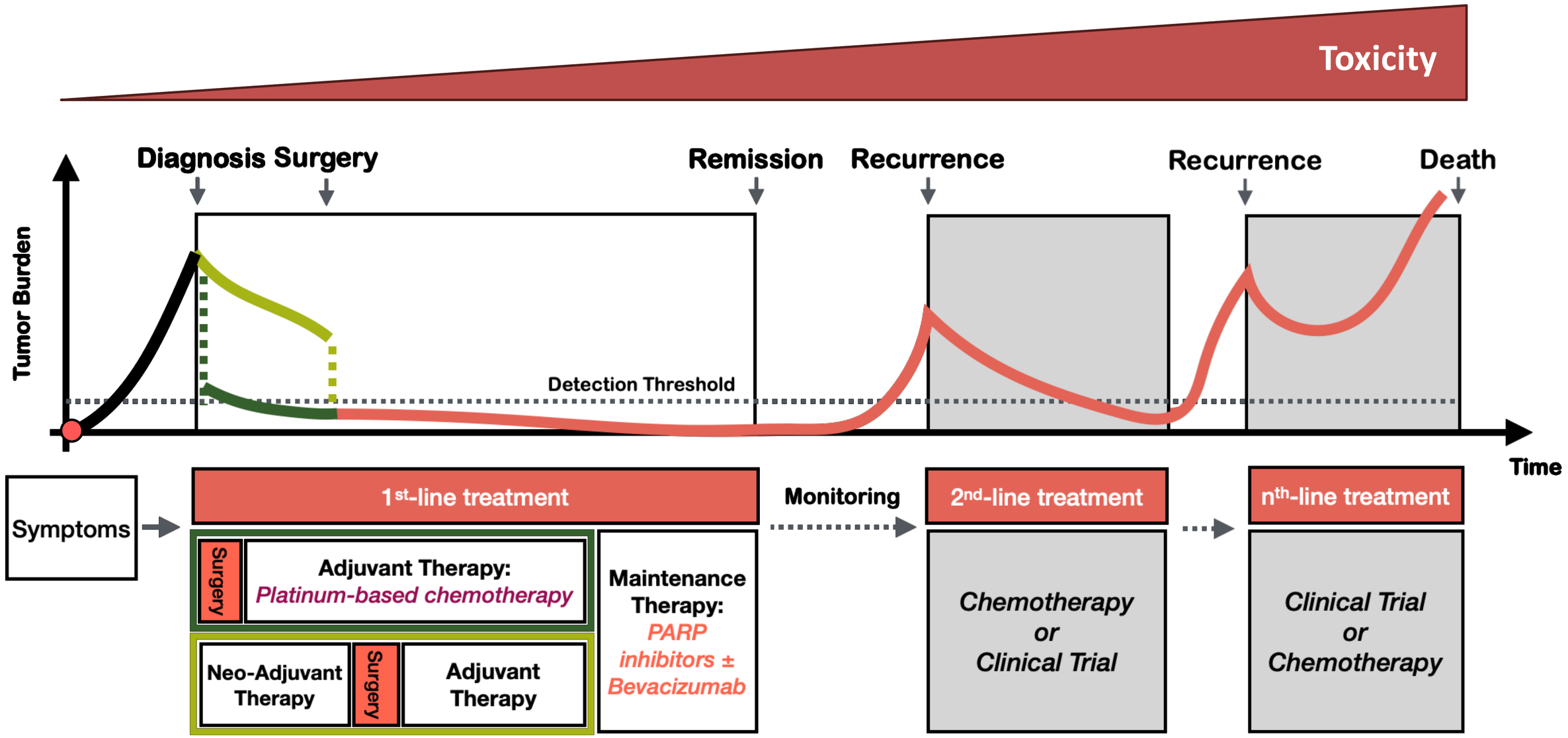
Recurrence:
Resistance to Treatment



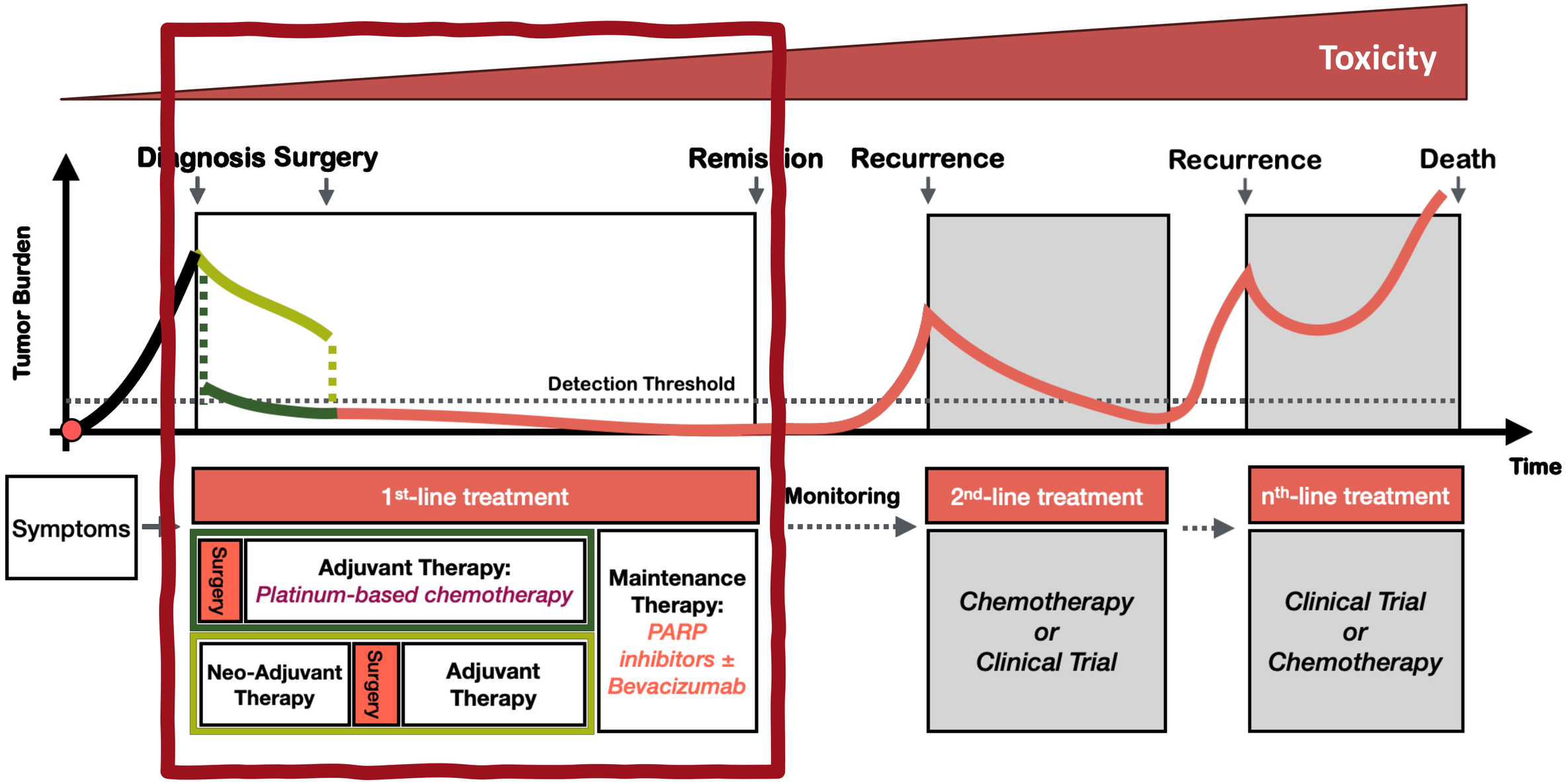
HR Proficient:
Limited Treatment Options



Ovarian Cancer with spread to Peritoneum


Toxicity
Diagnosis Surgery
Remission
Recurrence
Recurrence
Death
Tumor Burden
Detection Threshold
Time
Symptoms
1st-line treatment
Surgery
Adjuvant Therapy:
Platinum-based chemotherapy
Neo-Adjuvant Therapy
Surgery
Adjuvant Therapy
Maintenance Therapy:
PARP inhibitors ± Bevacizumab
Monitoring
2nd-line treatment
Chemotherapy or Clinical Trial
nth-line treatment
Clinical Trial or Chemotherapy

- How do we take control of treatment toxicity in HR proficient ovarian cancer to prime the patient for tumor extinction therapy?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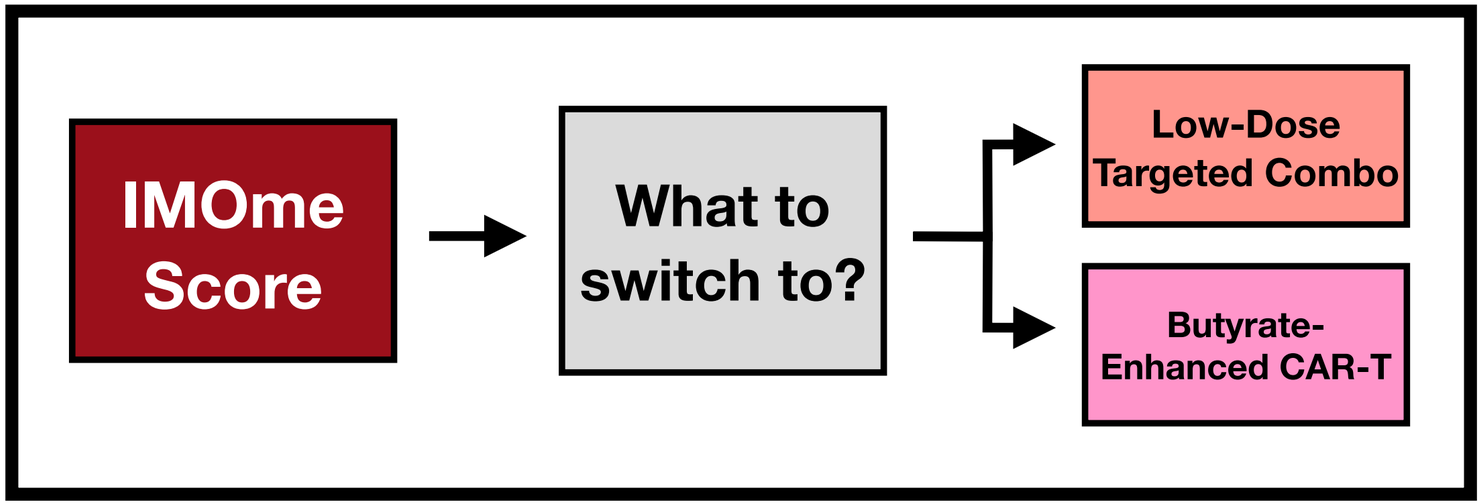
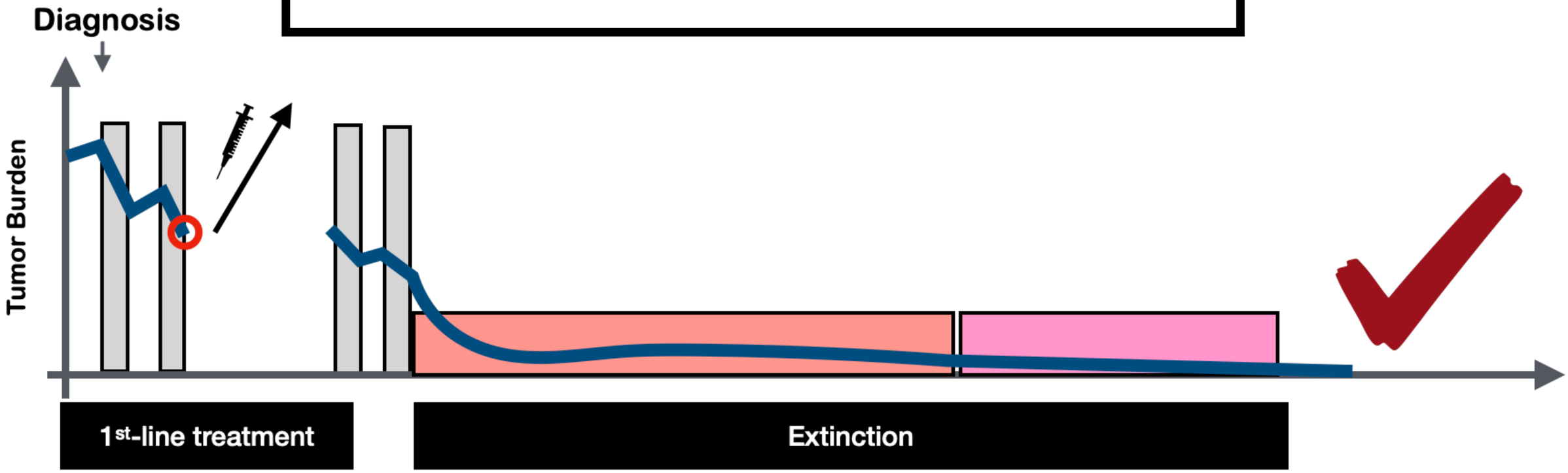
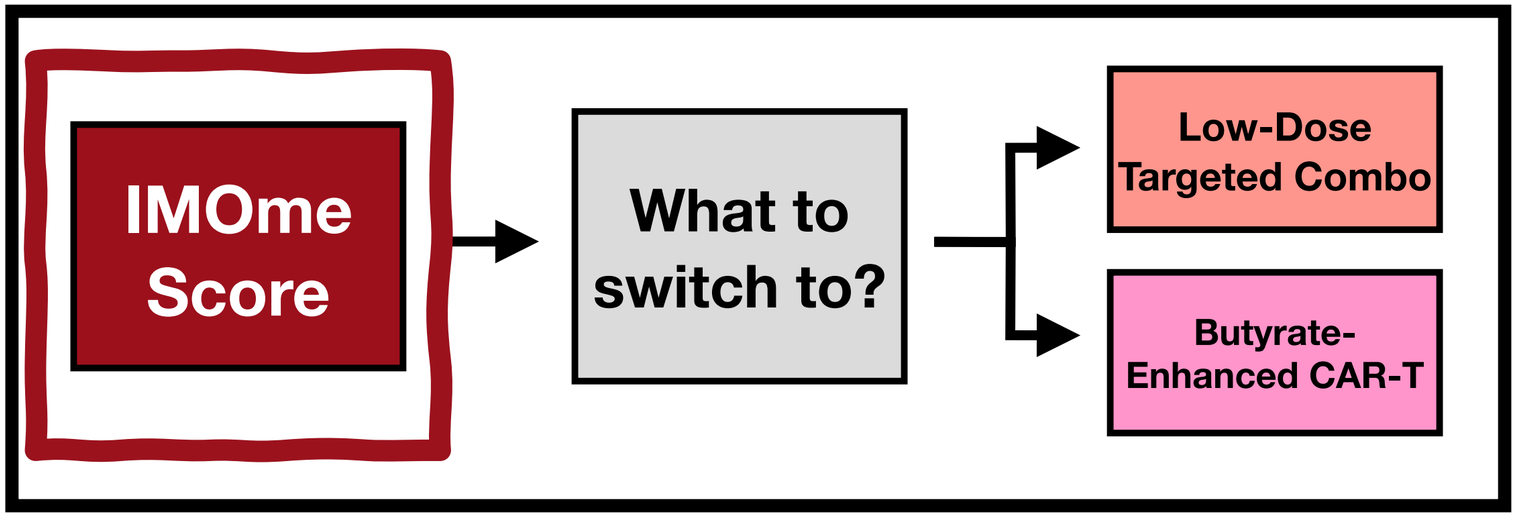
2nd-line treatment
Chemotherapy or Clinical Trial
nth-line treatment
Clinical Trial or Chemotherapy

Answer

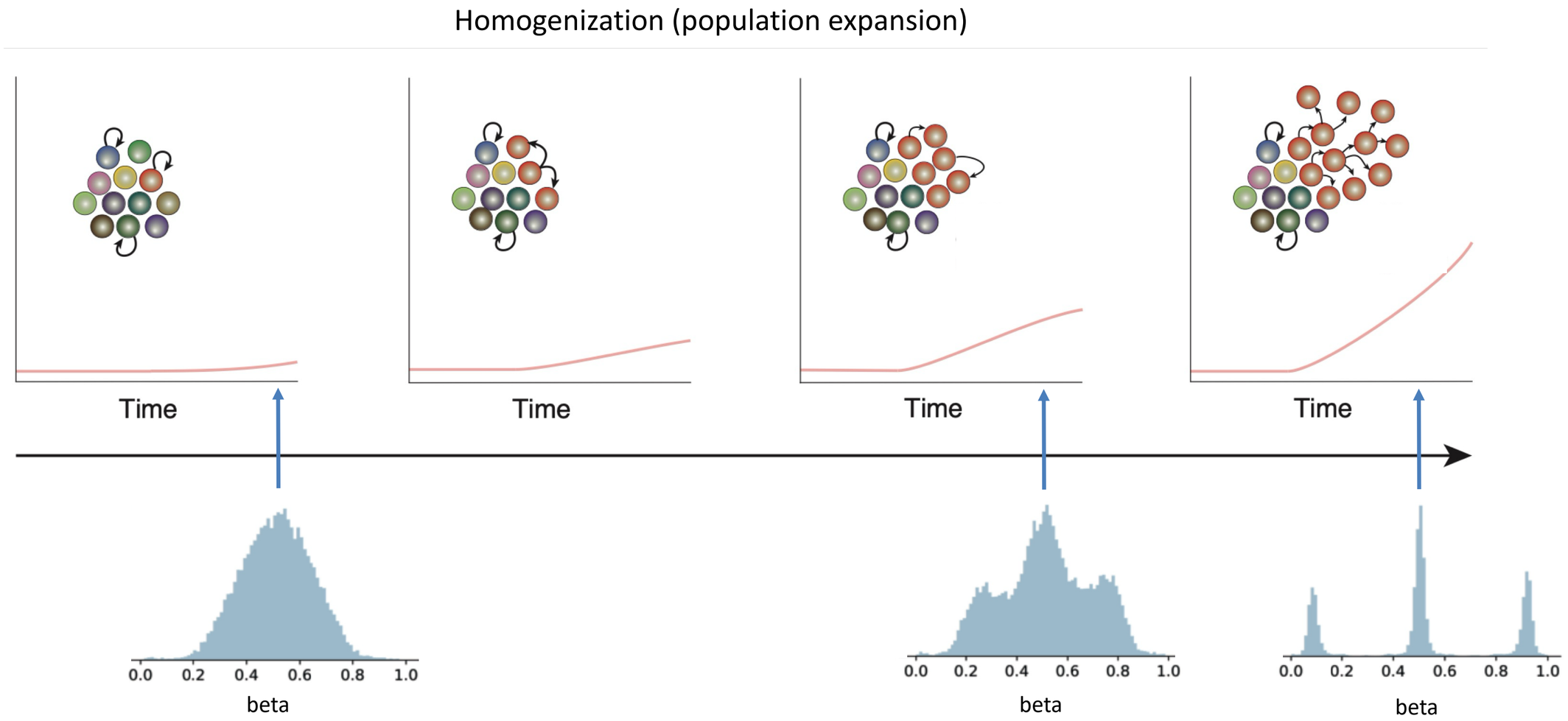

IMOme Score
What to switch to?
Low-Dose Targeted Combo
Butyrate-Enhanced CAR-T


Diagnosis
Tumor Burden
1st-line treatment
Extinction

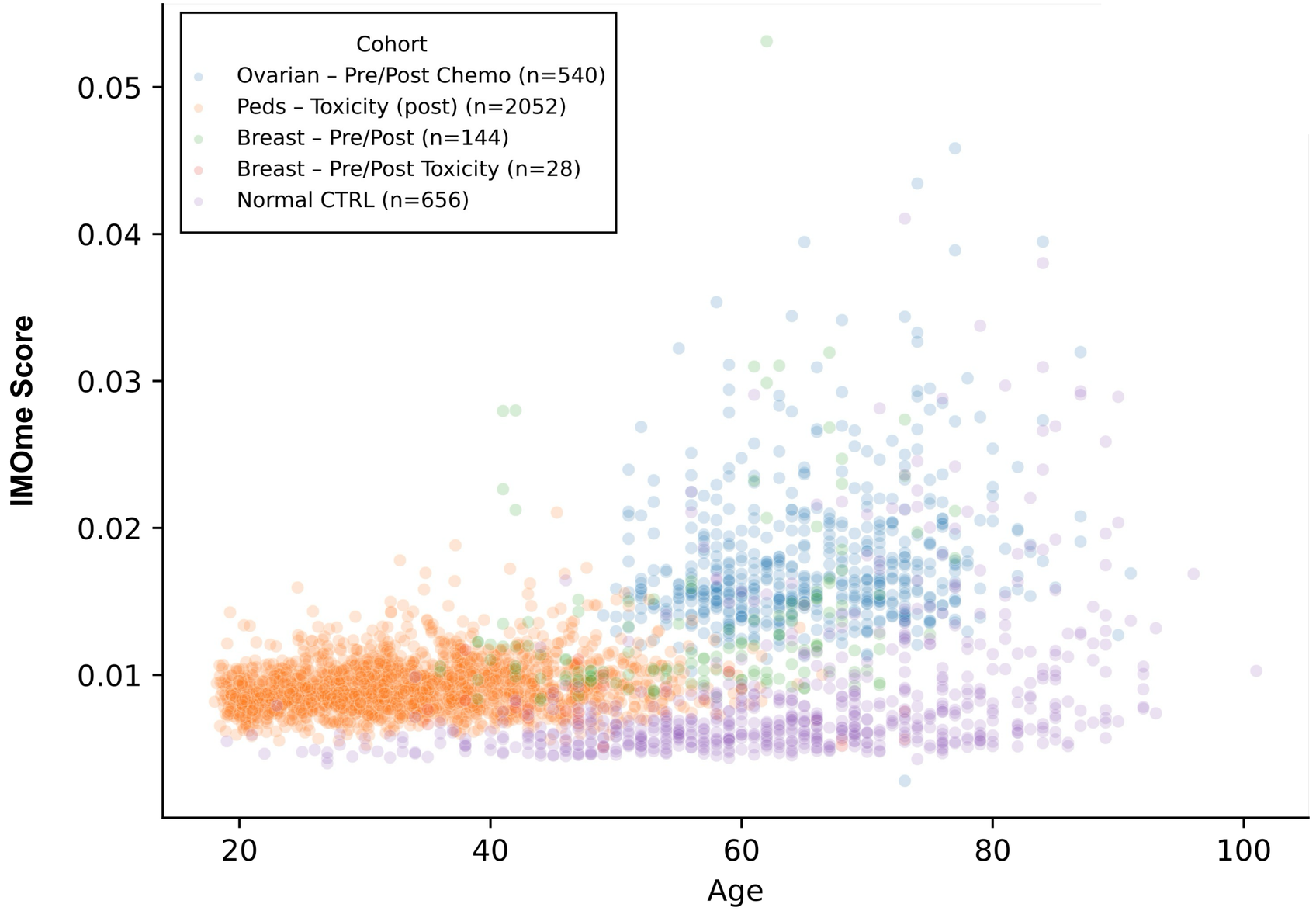
Aim 1: Anticipate and pre-empt treatment-related toxicity risk using PBMC fluctuating methylation clocks



I. Integrated Monitoring of Oscillatory methylation-clocks (IMOme)

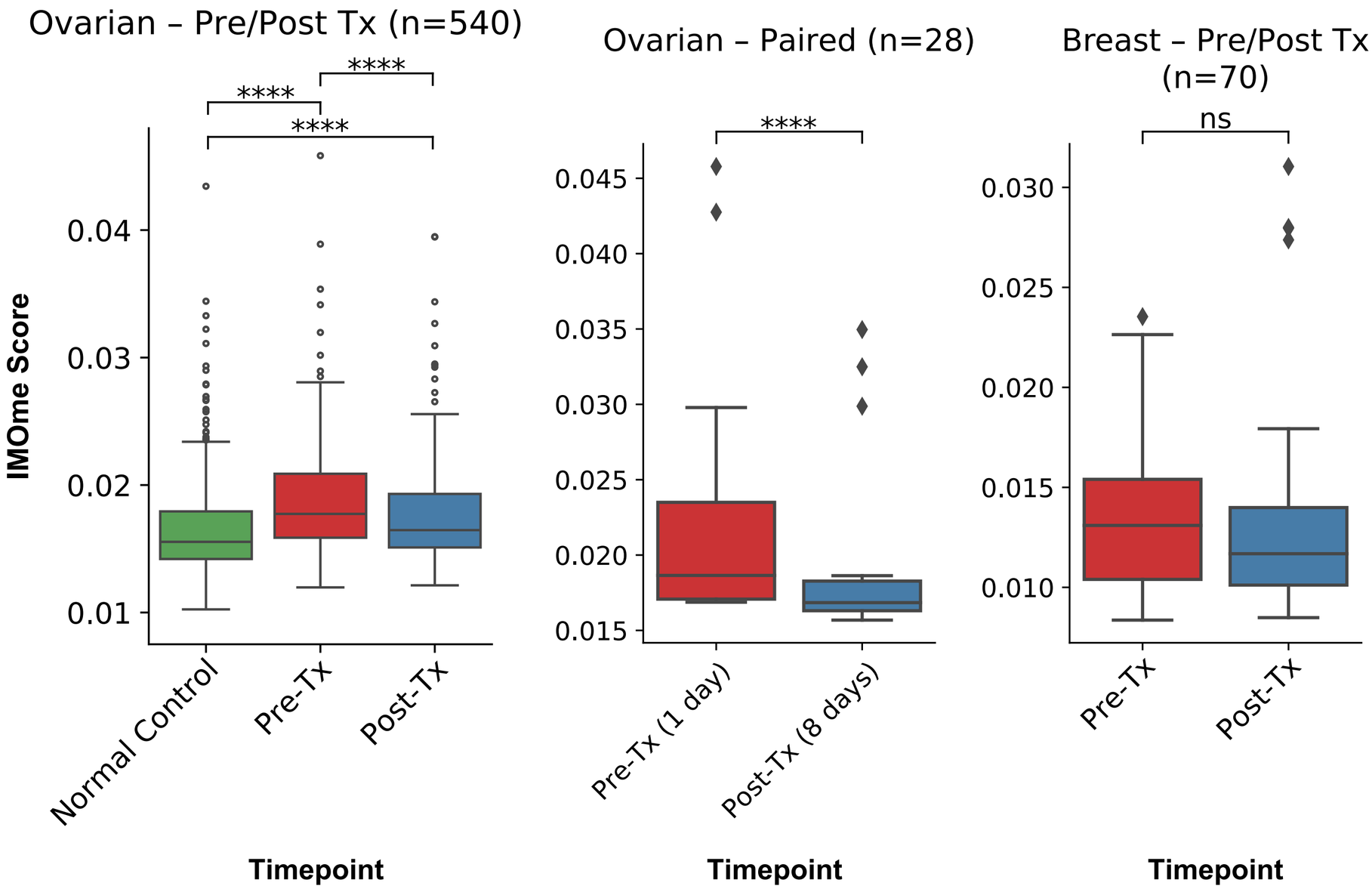


I. IMOme scores from 3,420 peripheral blood samples



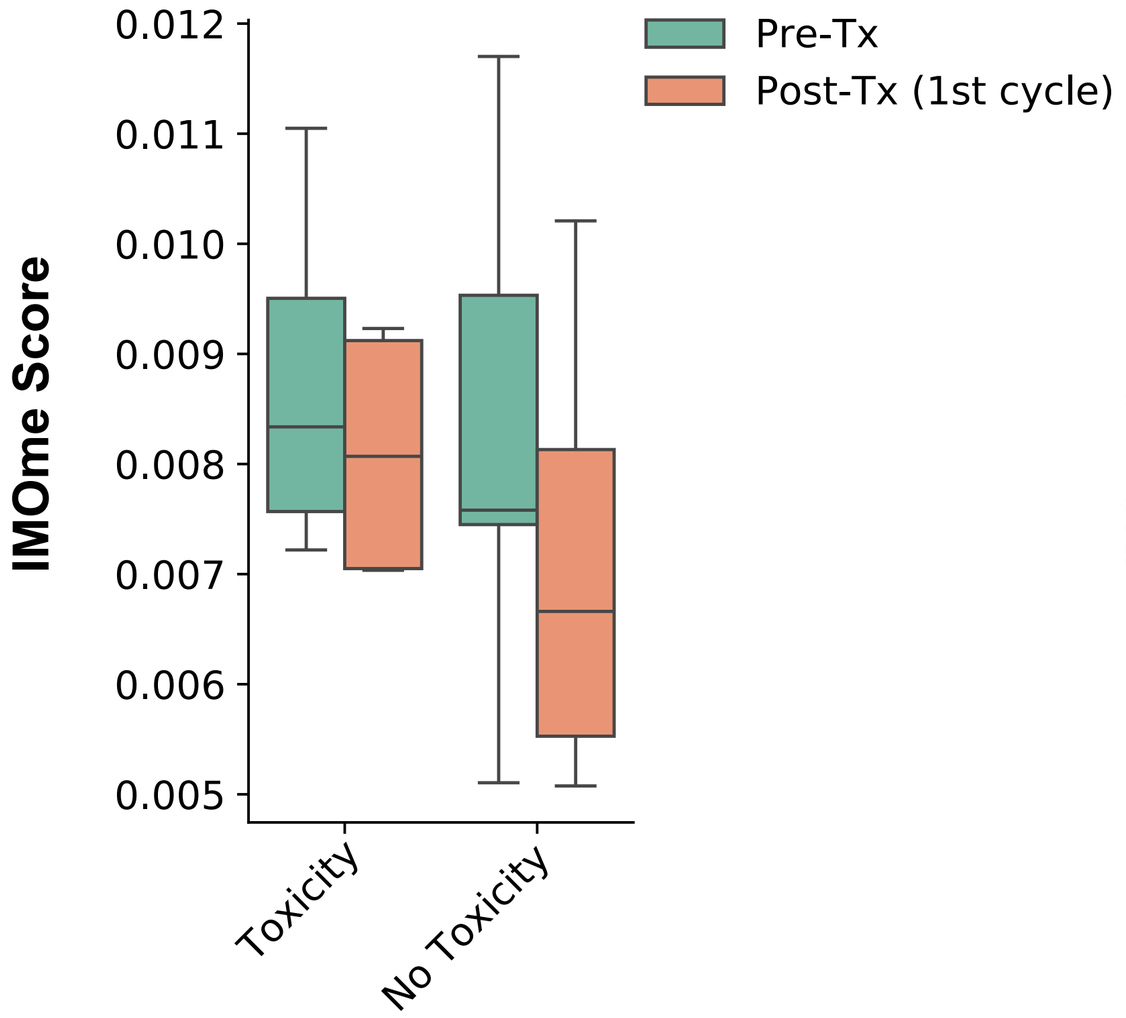
I. IMOme trends are consistent between cancer types

- **IMOme score** reflects systemic changes in PBMC's upon treatment.
  - This is consistent across different timescales and cancer type.

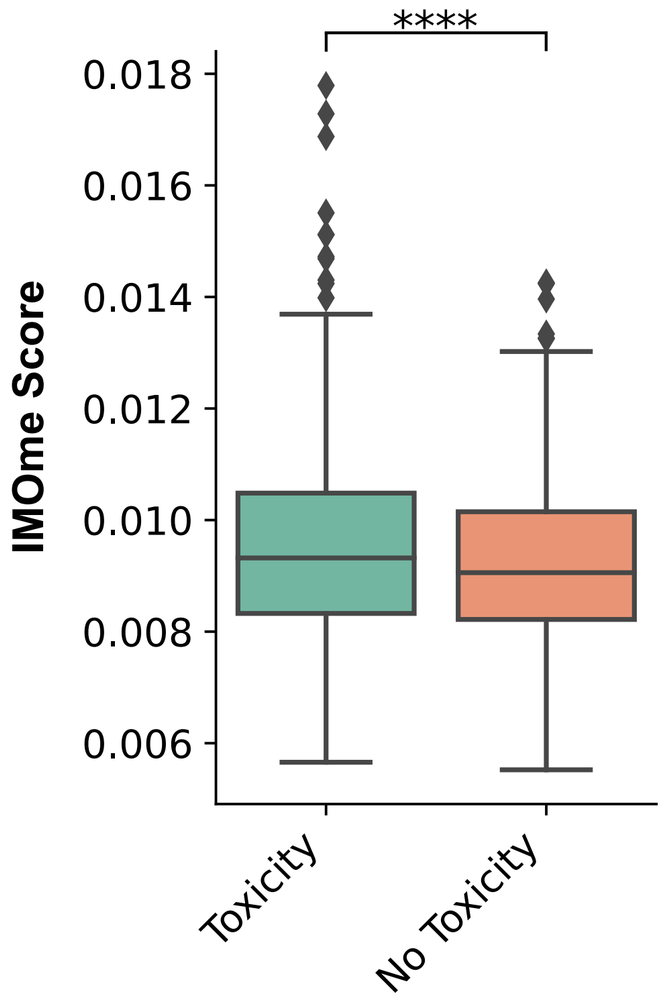


I. Differences in IMOme score pre/post Tx predictive of toxicity?

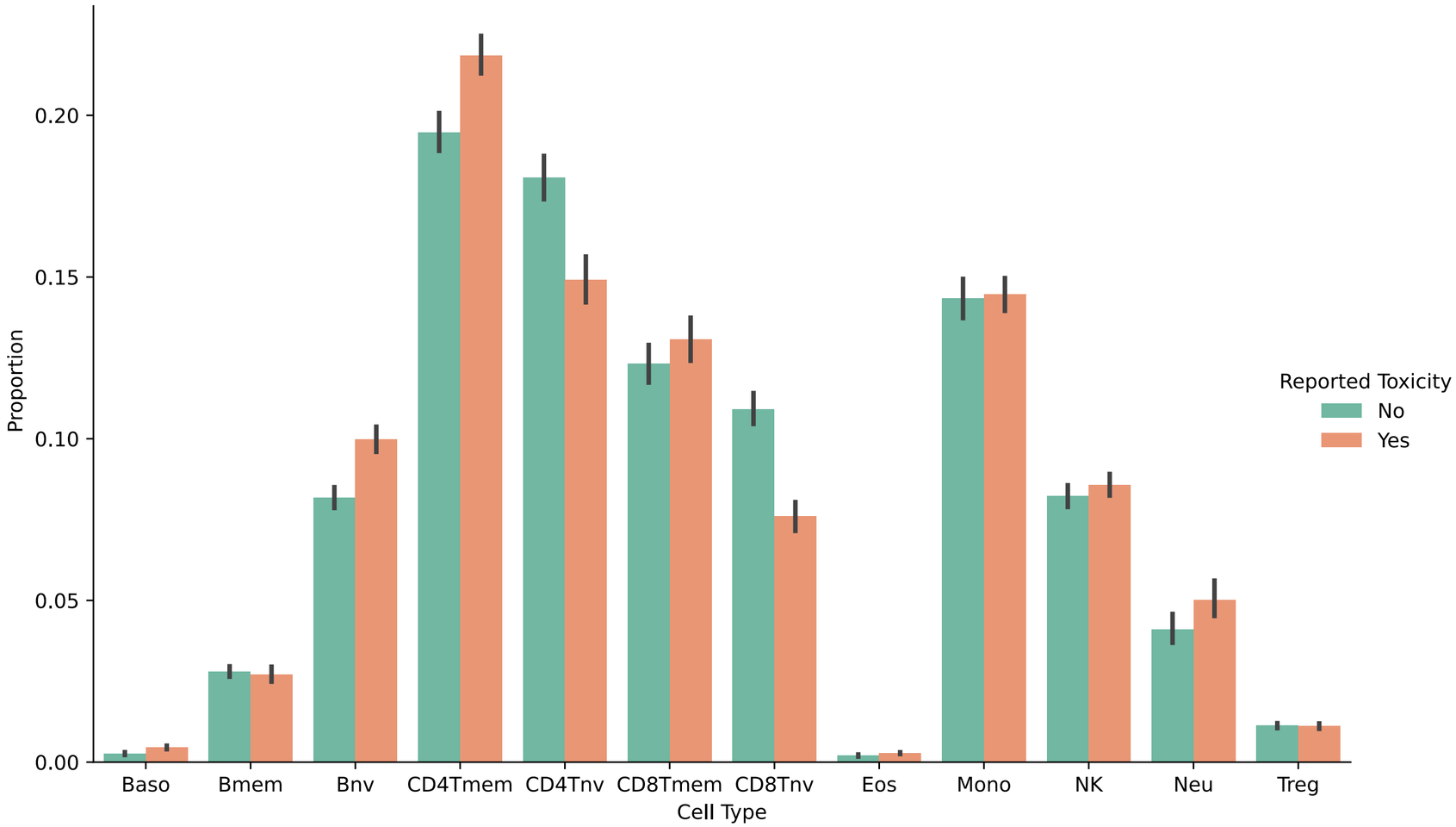
- Paired breast cancer dataset of patients with and without toxicity.



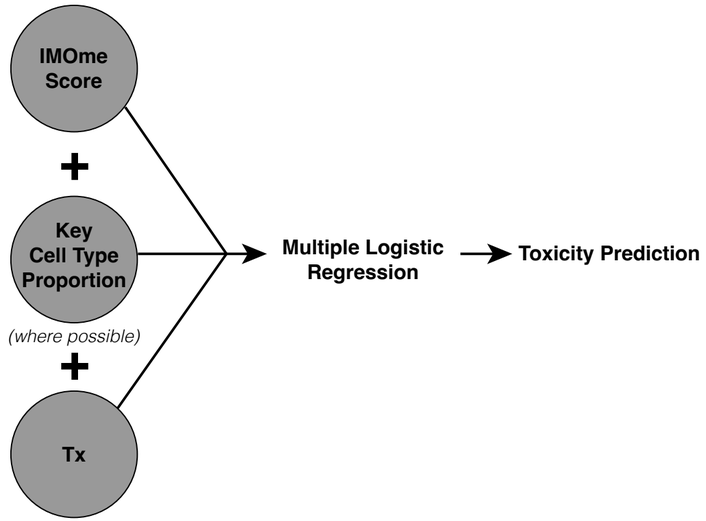
Peds – Post Tx (n=968)

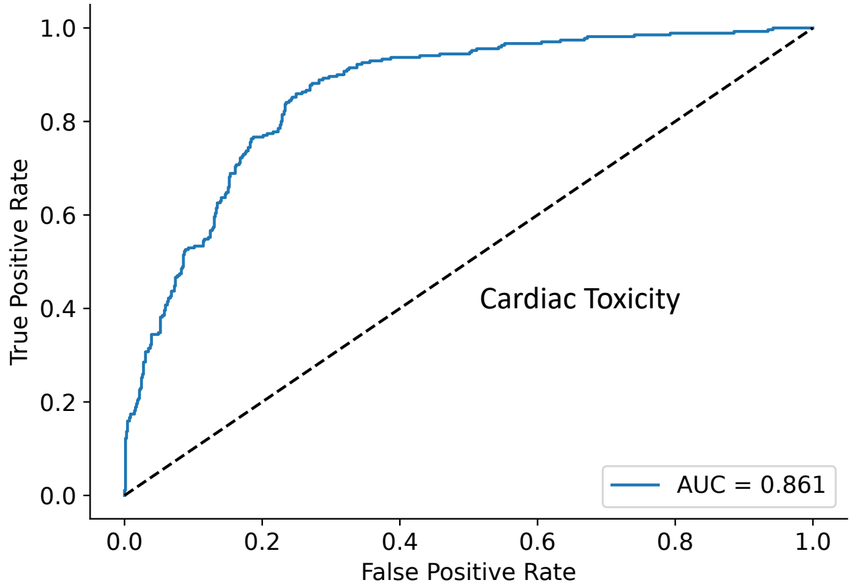


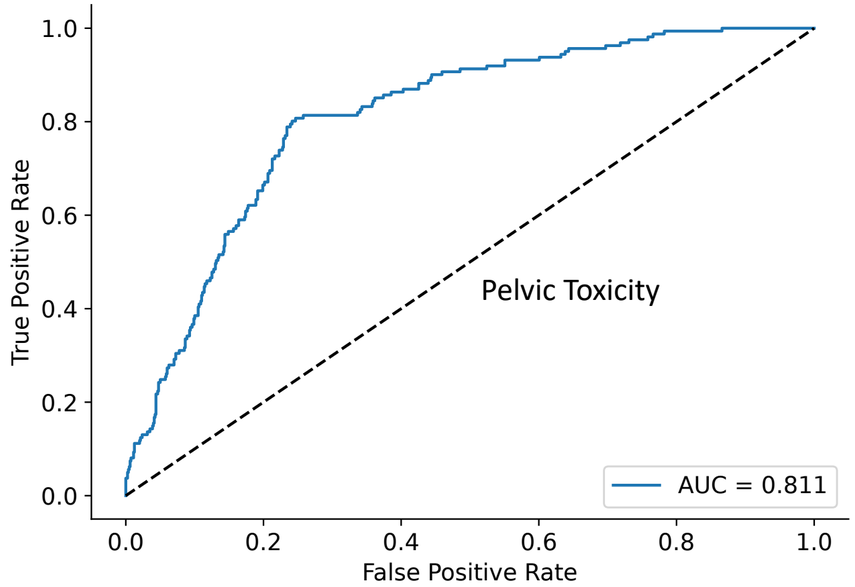
I. Immune cell distribution varies with toxicity outcomes

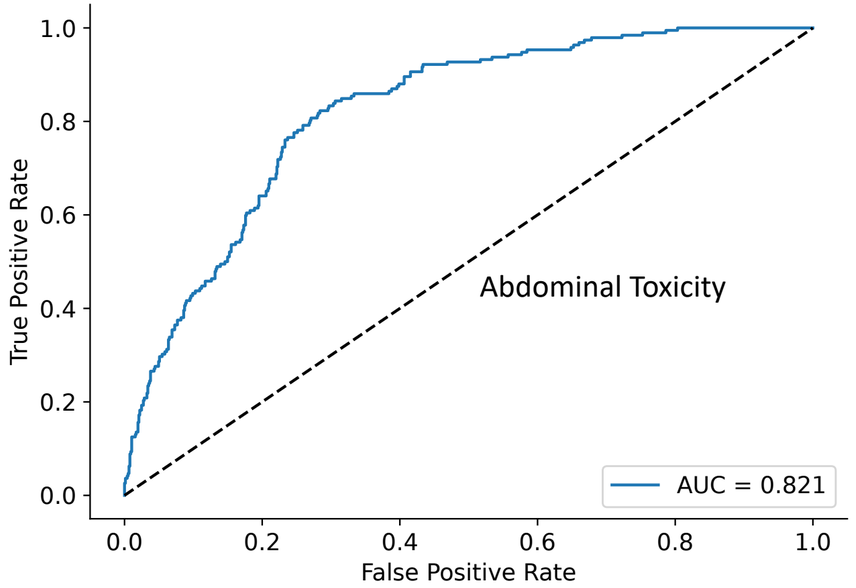


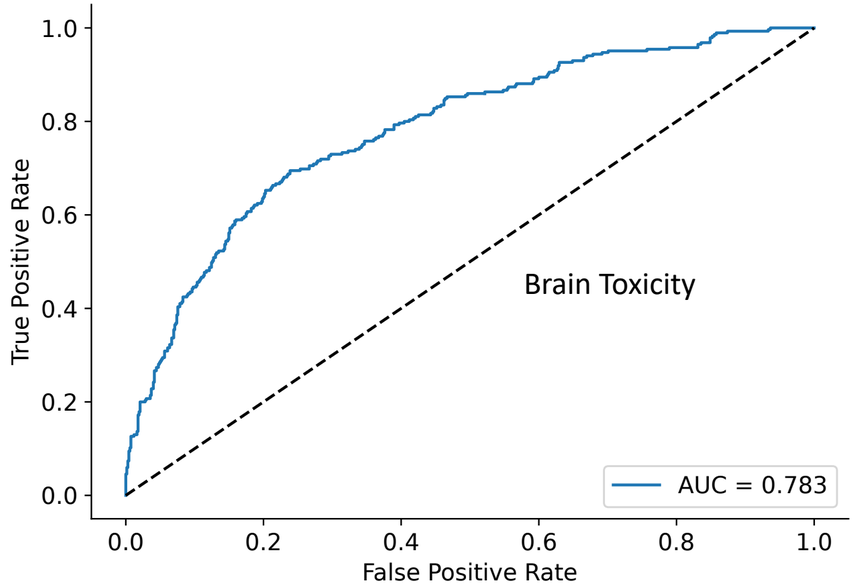
I. IMOme score is a valuable biomarker for toxicity prediction



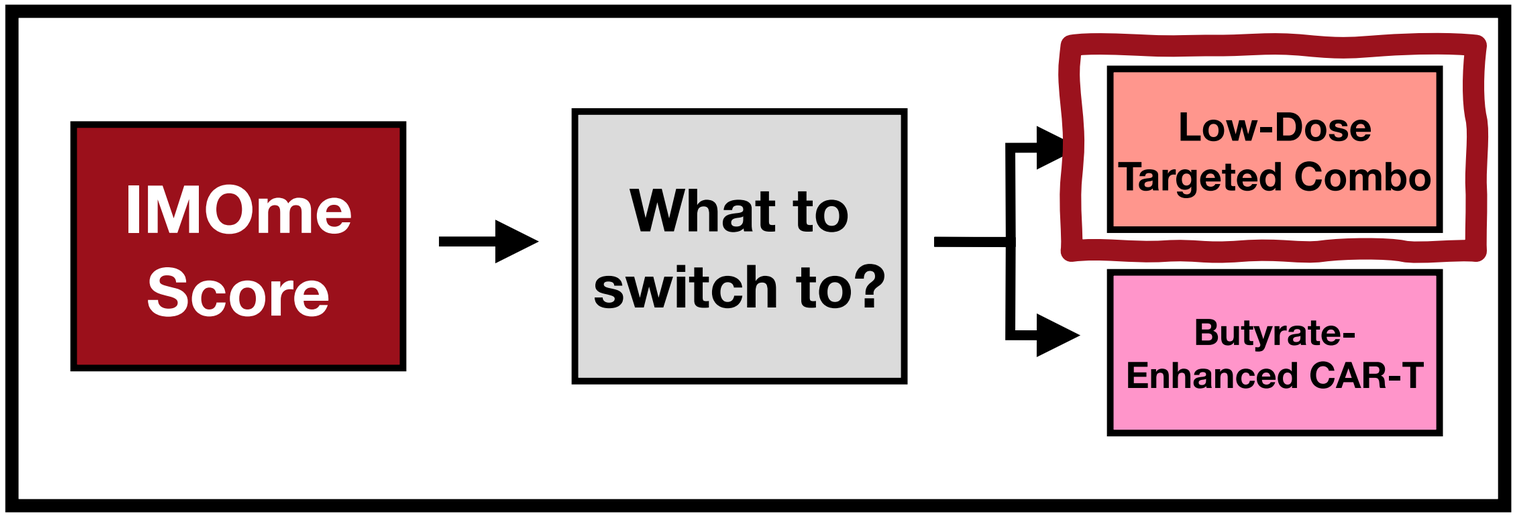








Aim 2: Buffer the direct toxicity of PARPi-targeted therapy combinations in HGSOC using dosing optimized via mathematical modelling.

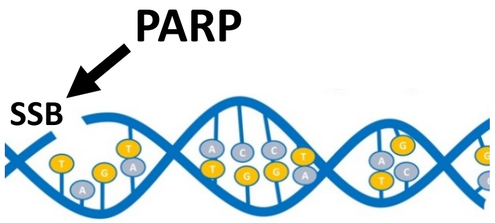


II. Cell Cycle – Combination Therapy

High Dose Monotherapy

Lower Dose Combo Therapy

DNA Damage Response



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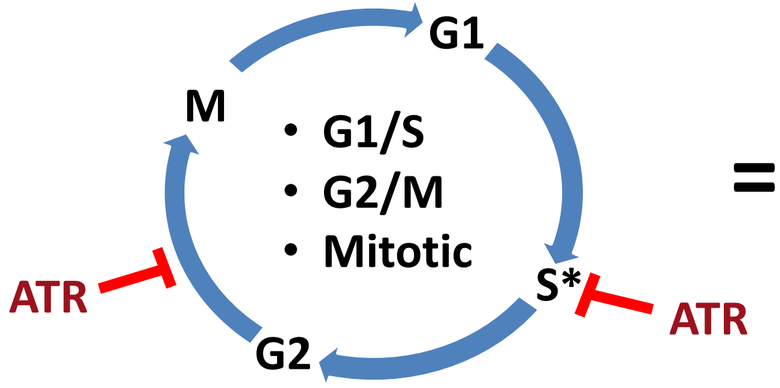

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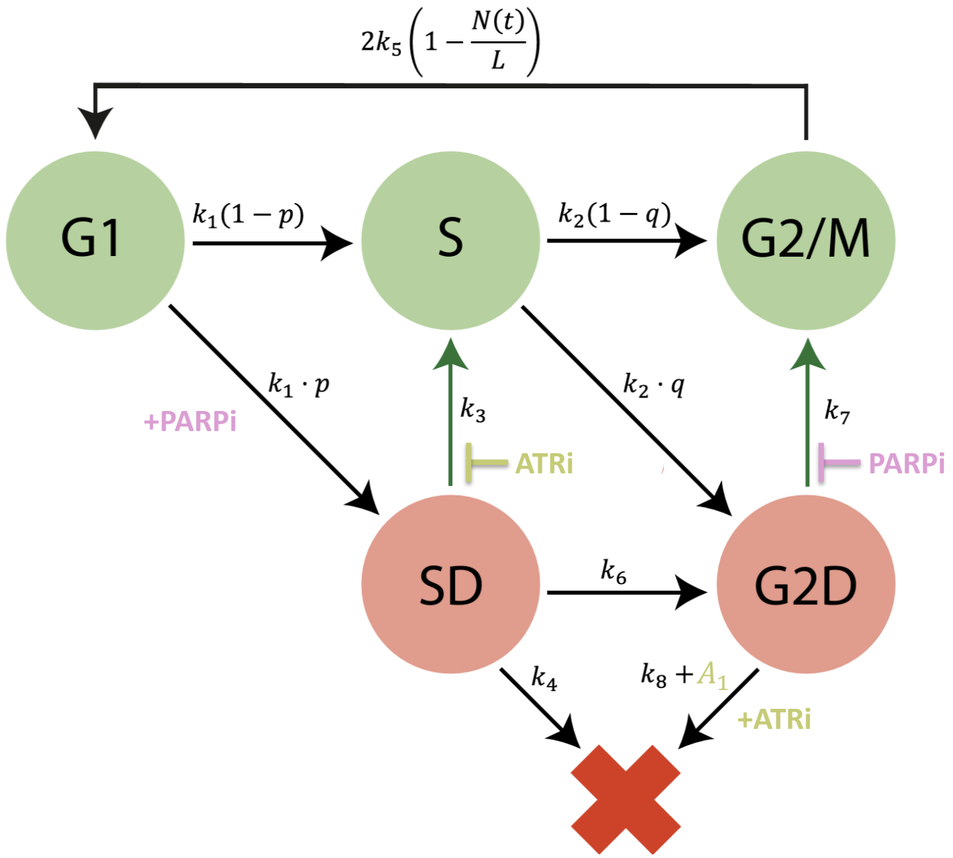
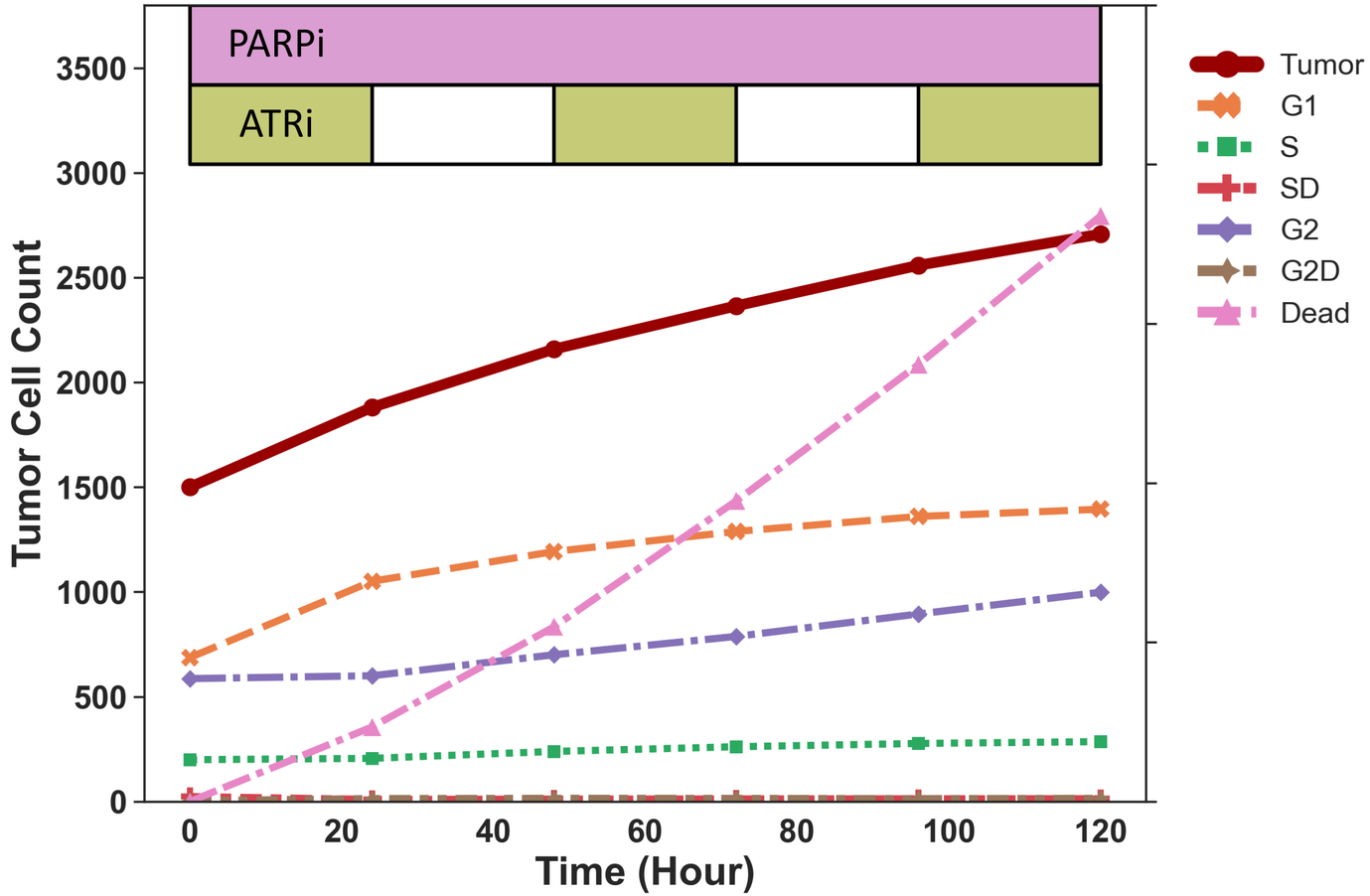
Cell Death & Lower Toxicity

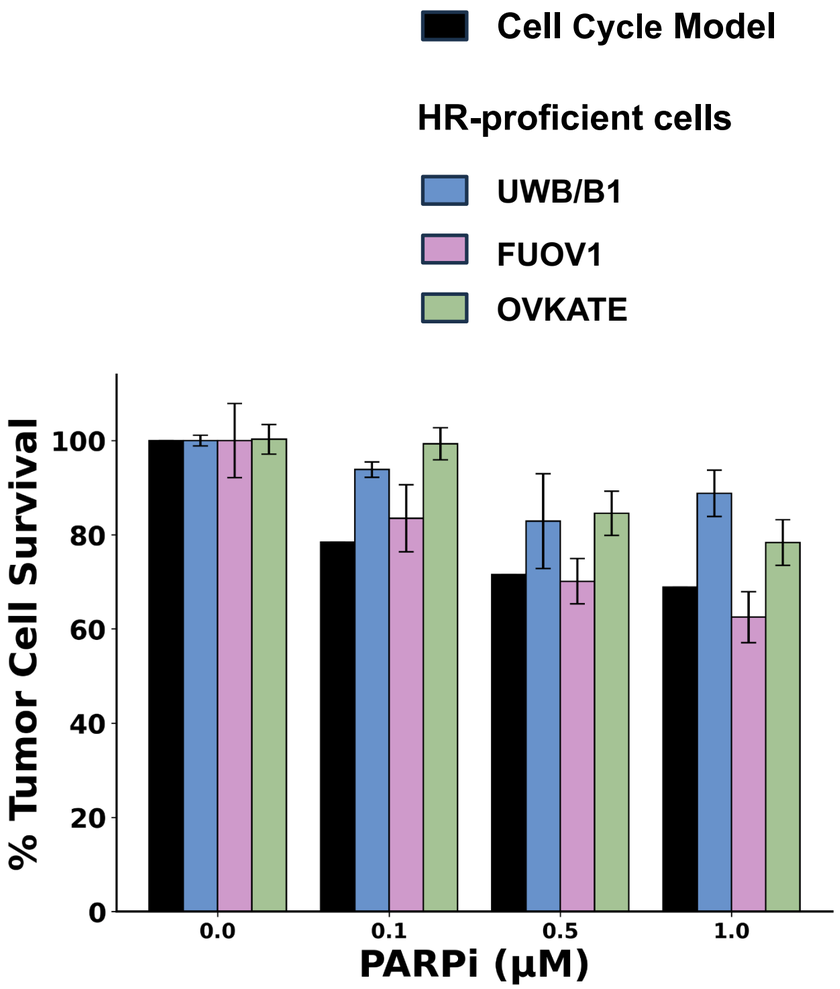
II. Cell Cycle Mathematical Model

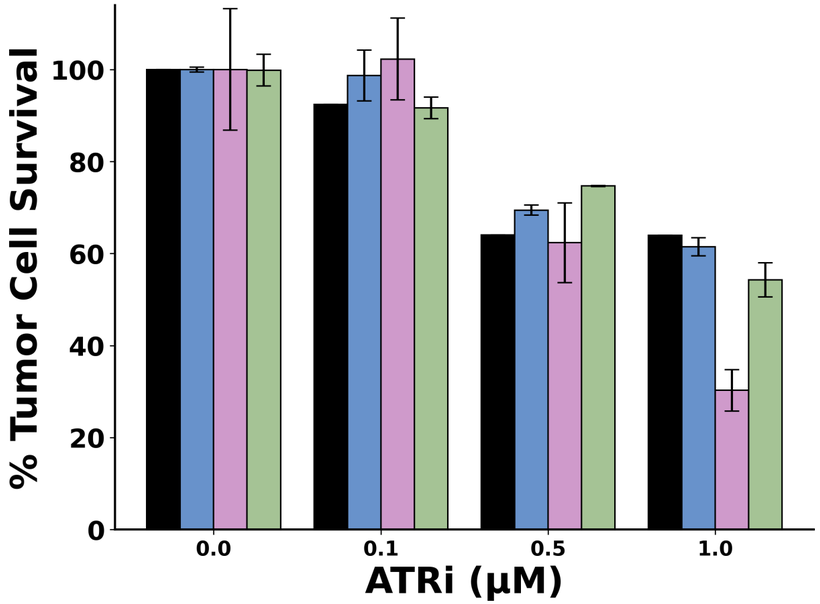


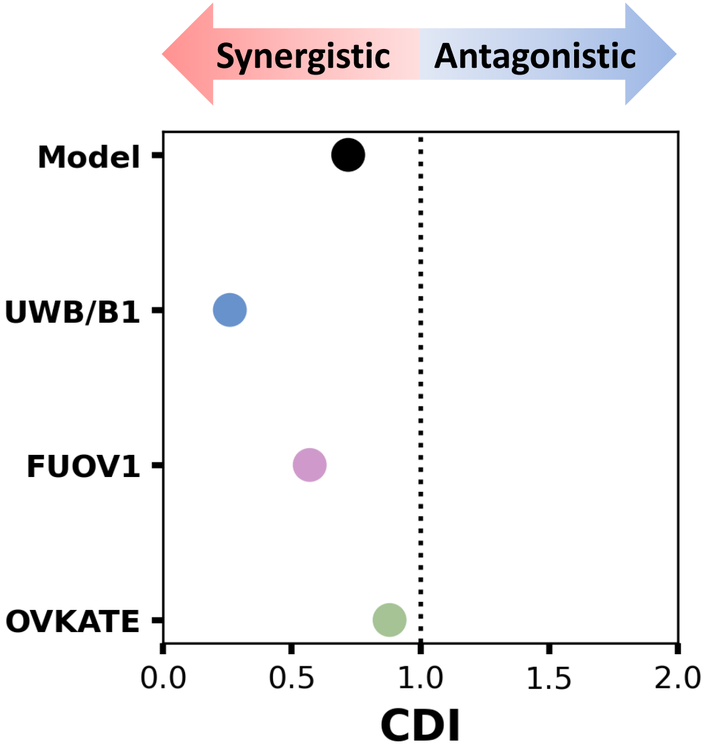


Reference: Smith, J., et al. JPET (2023).

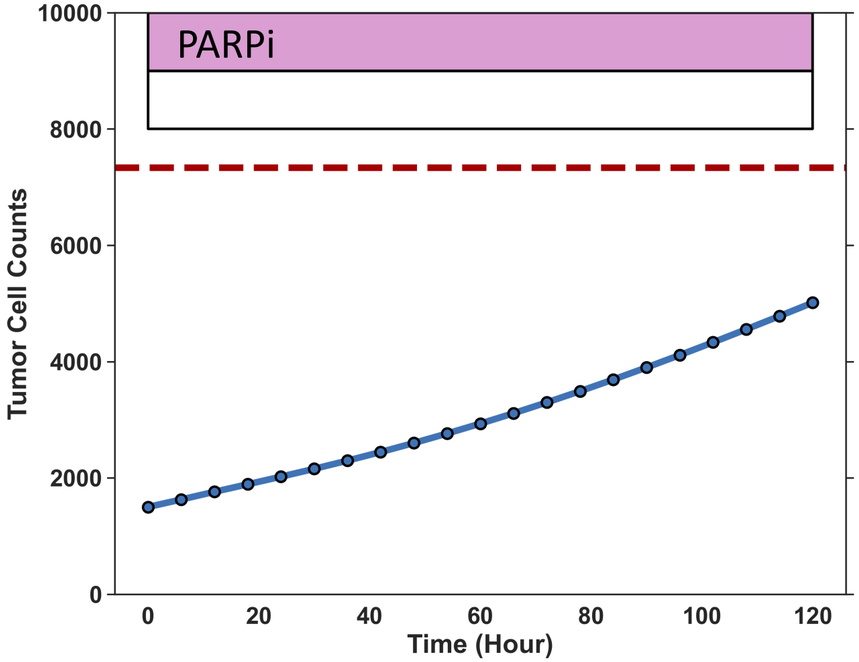
II. Mathematical Model Recapitulates Cell Data

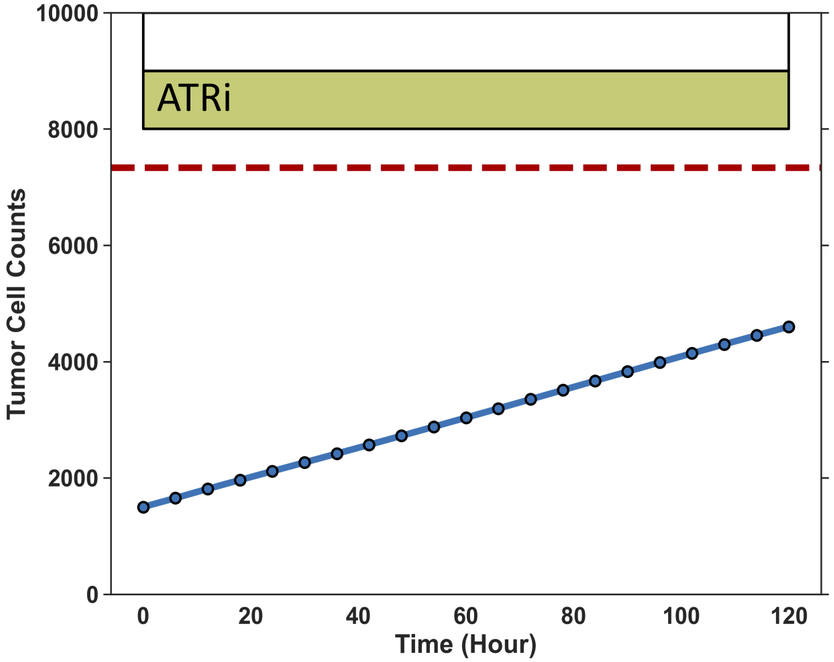


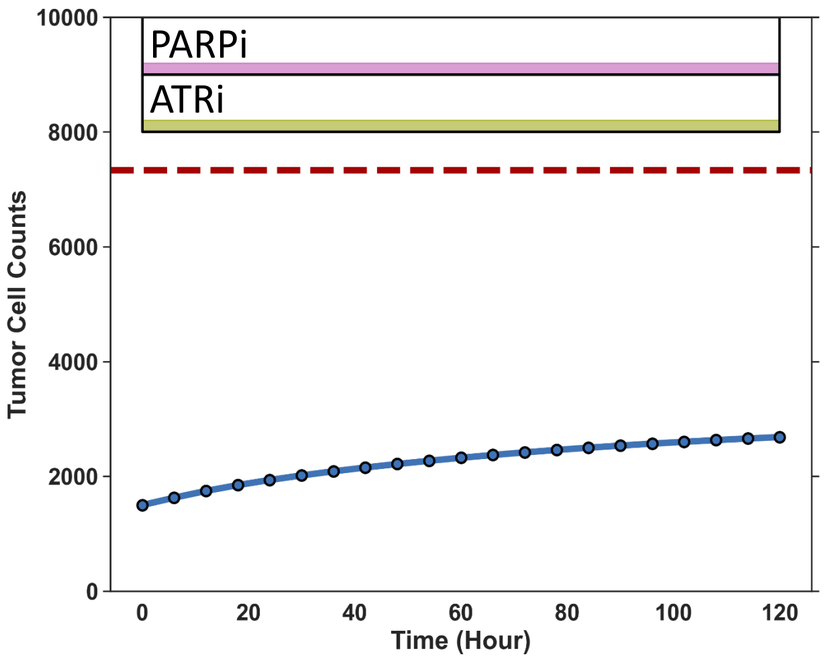




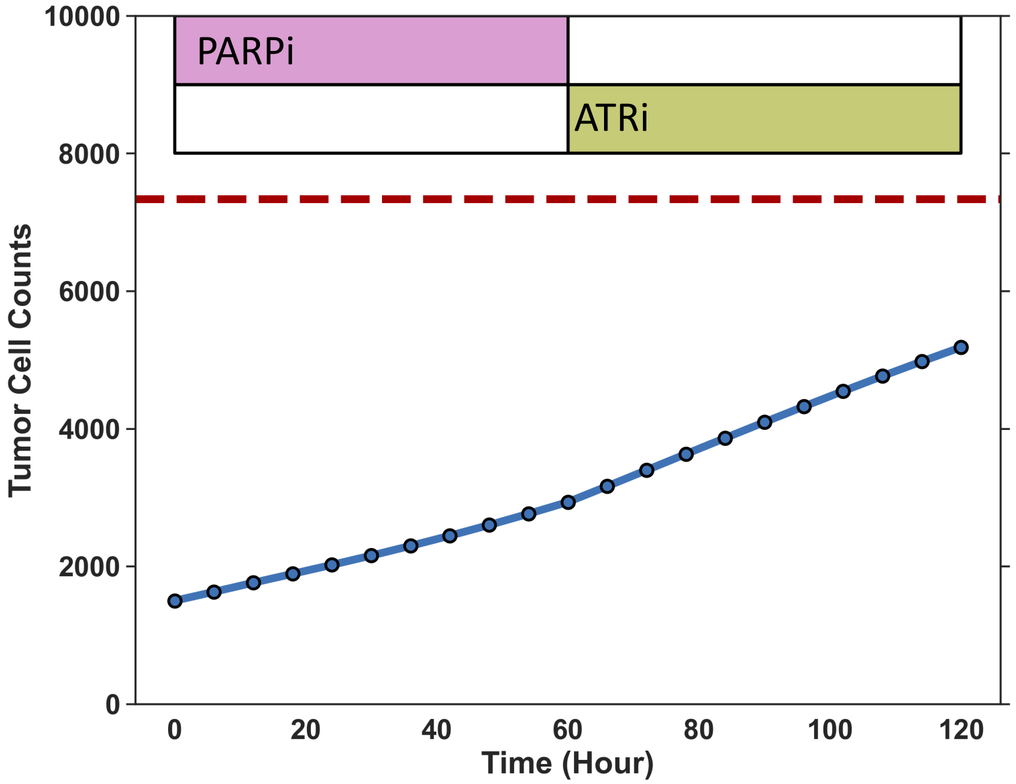
II. High Dose Monotherapy vs Low Dose Combo Therapy

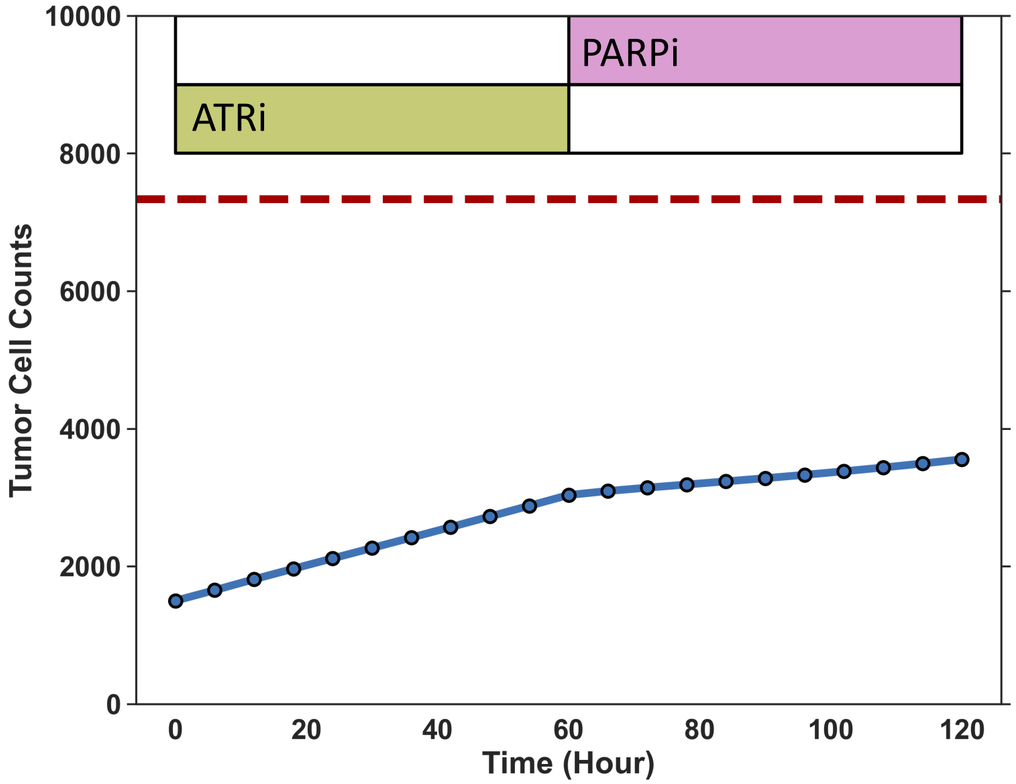






II. Sequence Shapes Therapy Outcome





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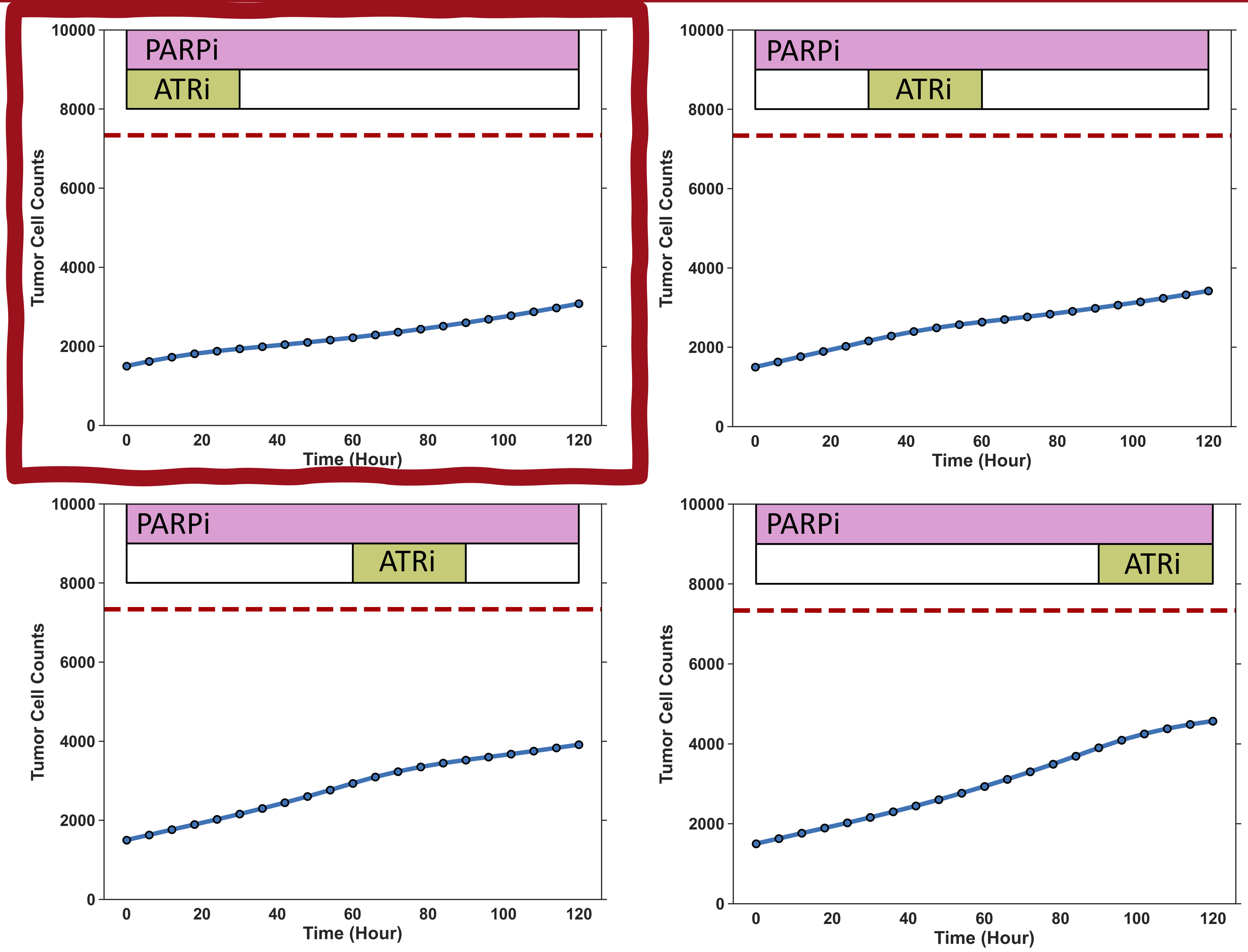
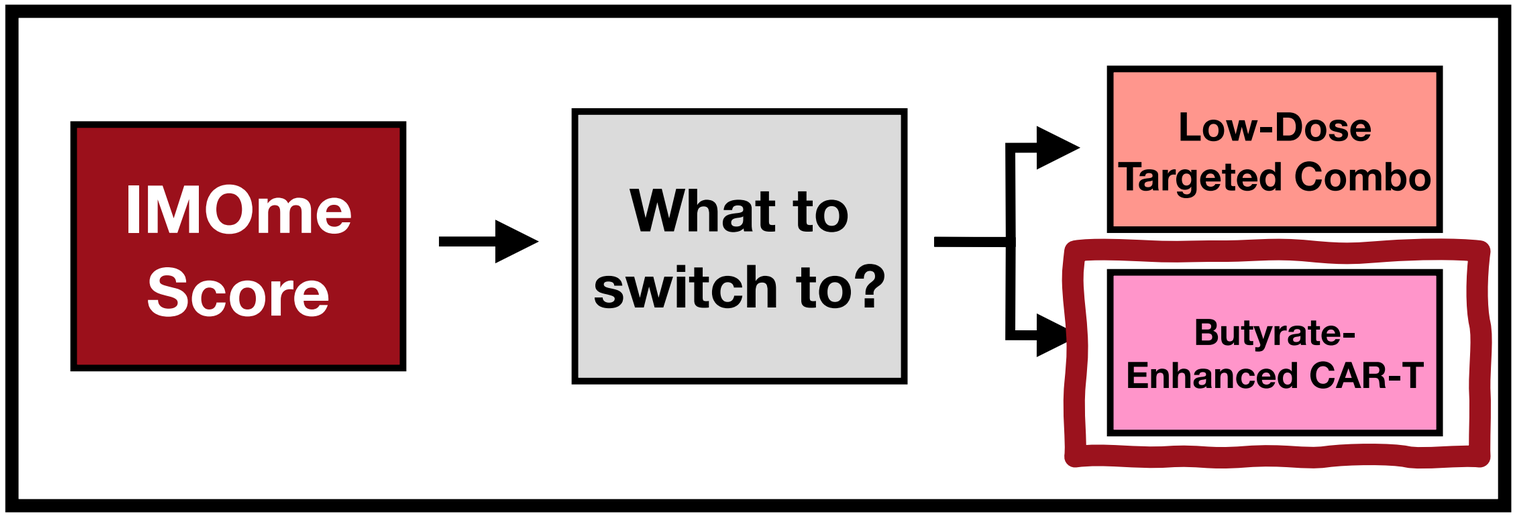


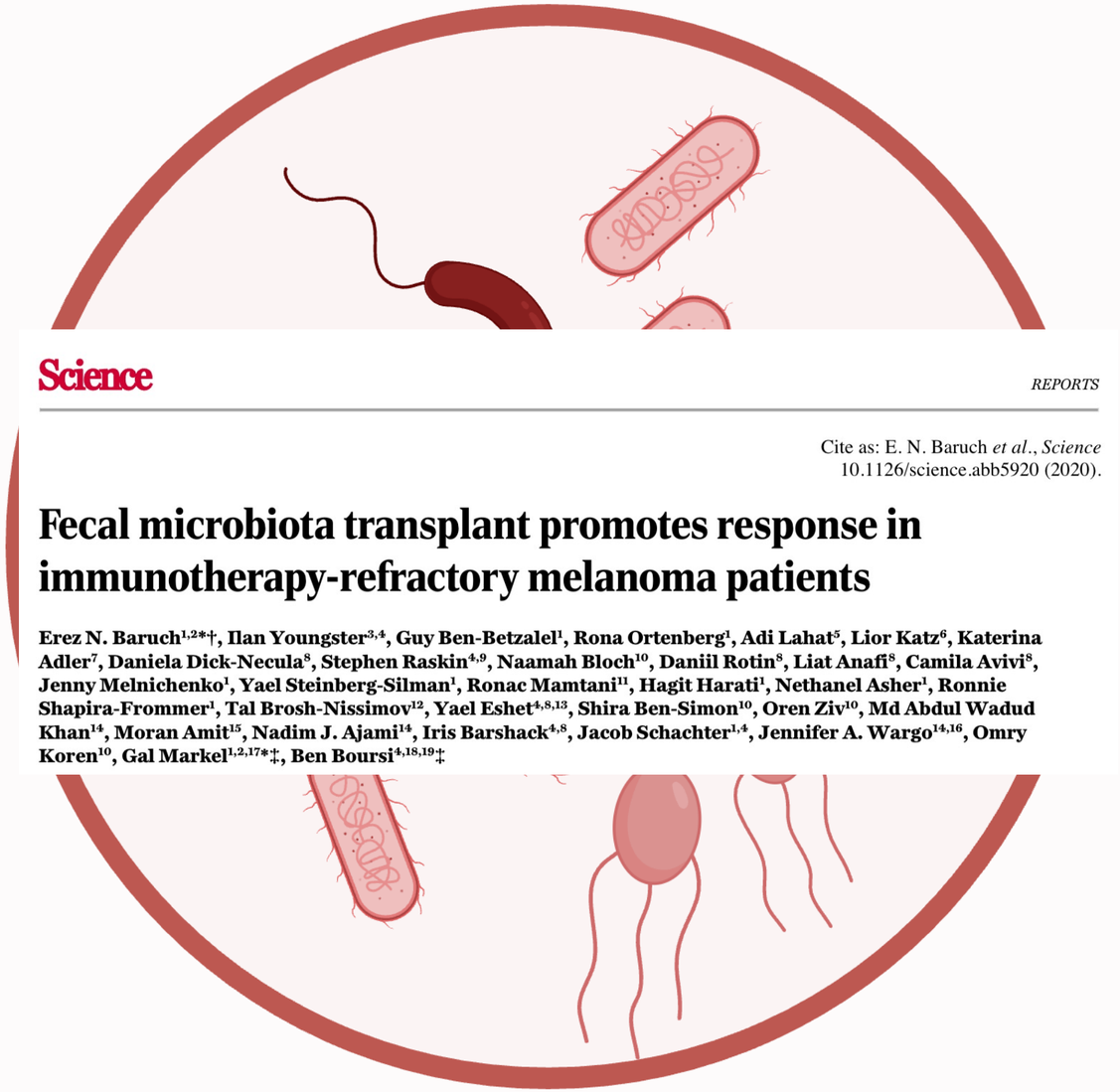
Aim 3: Mitigate indirect toxicity induced by chemotherapy on the gut microbiome to prime the patient for curative intent immunotherapy



III. Microbiome and Short Chain Fatty Acid

Short Chain Fatty Acid

- 2-4 Carbons: (e.g. Butyrate, Pentanoate)
- Differentiate Immune cells: Myeloid cells to M1 cells
- Suppress Tumor Growth



Science REPORTS

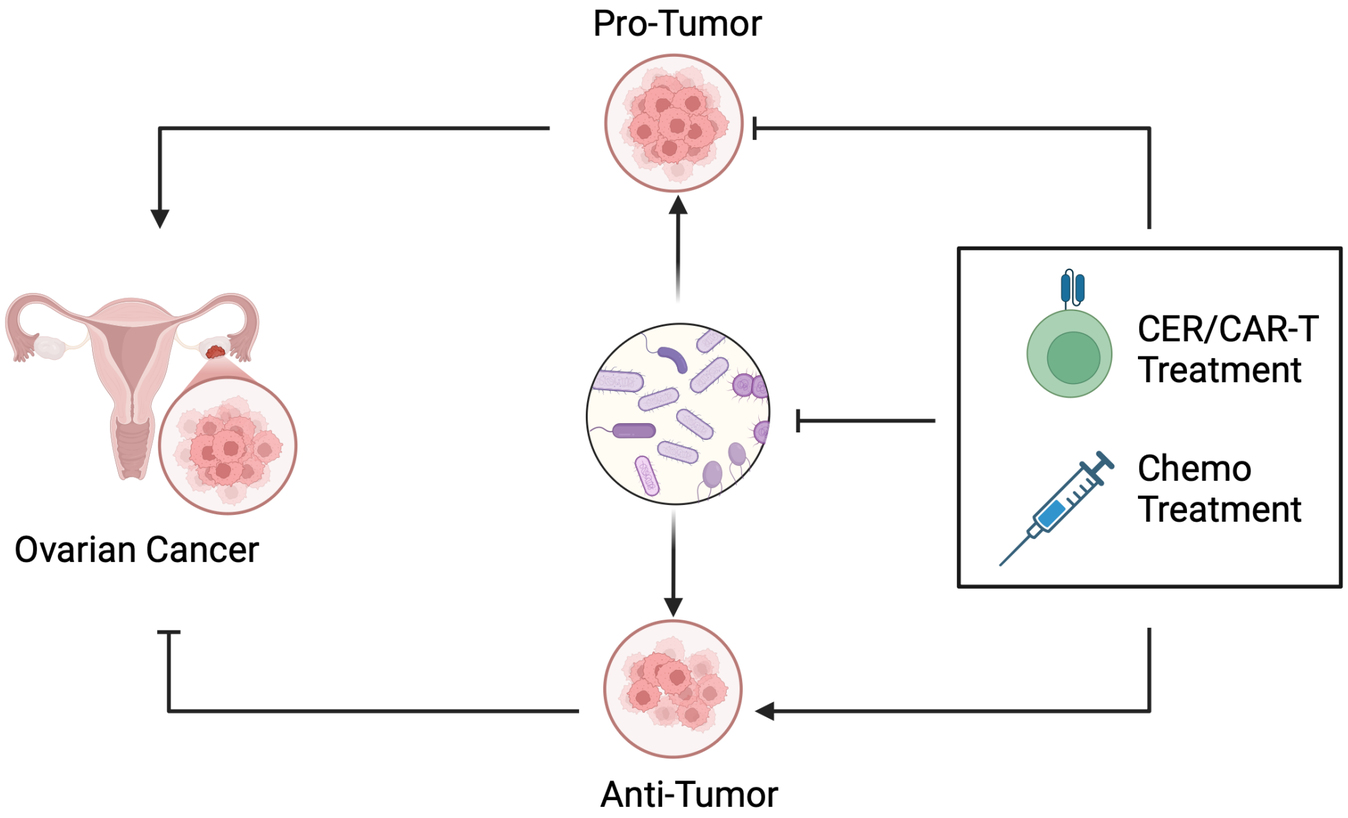
Cite as: E. N. Baruch *et al.*, *Science* 10.1126/science.abb5920 (2020).

Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients

Erez N. Baruch[1,2*†], Ilan Youngster[3,4], Guy Ben-Betzalel[1], Rona Ortenberg[1], Adi Lahat[5], Lior Katz[6], Katerina Adler[7], Daniela Dick-Necula[8], Stephen Raskin[4,9], Naamah Bloch[10], Daniil Rotin[8], Liat Anafi[8], Camila Avivi[8], Jenny Melnichenko[1], Yael Steinberg-Silman[1], Ronac Mamtani[11], Hagit Harati[1], Nethanel Asher[1], Ronnie Shapira-Frommer[1], Tal Brosh-Nissimov[12], Yael Eshet[4,8,13], Shira Ben-Simon[10], Oren Ziv[10], Md Abdul Wadud Khan[14], Moran Amit[15], Nadim J. Ajami[14], Iris Barshack[4,8], Jacob Schachter[1,4], Jennifer A. Wargo[14,16], Omry Koren[10], Gal Markel[1,2,17*‡], Ben Boursi[4,18,19‡]

Hypothesis: injury to microbiota thwarts efficacy of ovarian cancer therapy, especially immune-based therapy

III. Microbiome Modeling



$$\frac{dS}{dt} = \alpha_S S\left(1 - \frac{S}{S_0} - K\right) - \gamma_{DS} DS - \gamma_{IS} IS - \gamma_{TS} TS$$

$$\frac{dT}{dt} = \left(\alpha_T + \alpha_{SF} S - \alpha_P IP(S)\right) TC(1-T) - \gamma_{DT} DT(1-T) - \delta_T T$$

$$\frac{dI}{dt} = \alpha_I I(1-I) - \gamma_{DI} DI$$

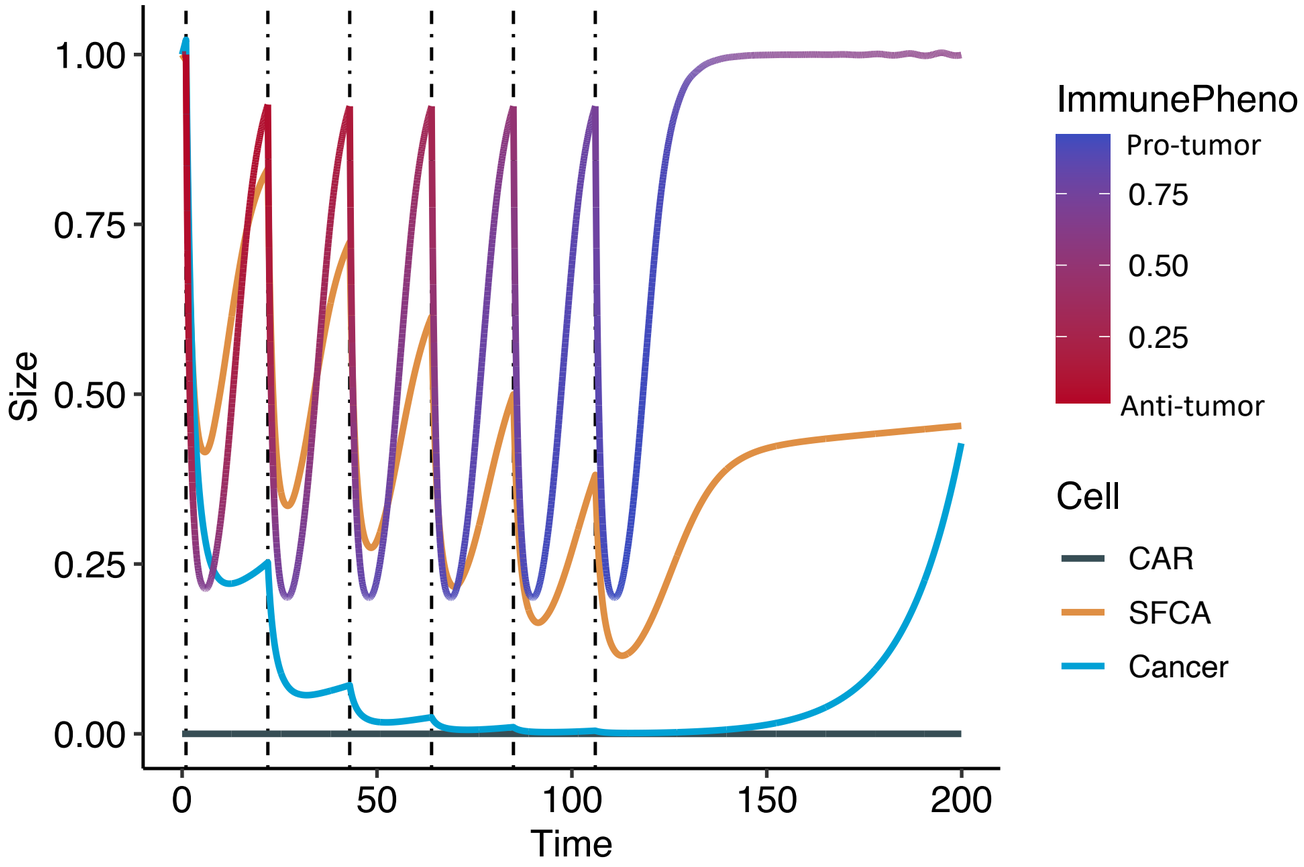
$$\frac{dC}{dt} = \left(\alpha_C + \alpha_{SF} P(S) + \alpha_P IP(S)\right) C - \gamma_{IC} IC(1-P(S)) - \gamma_{DC} DC - \gamma_{TC} CT$$

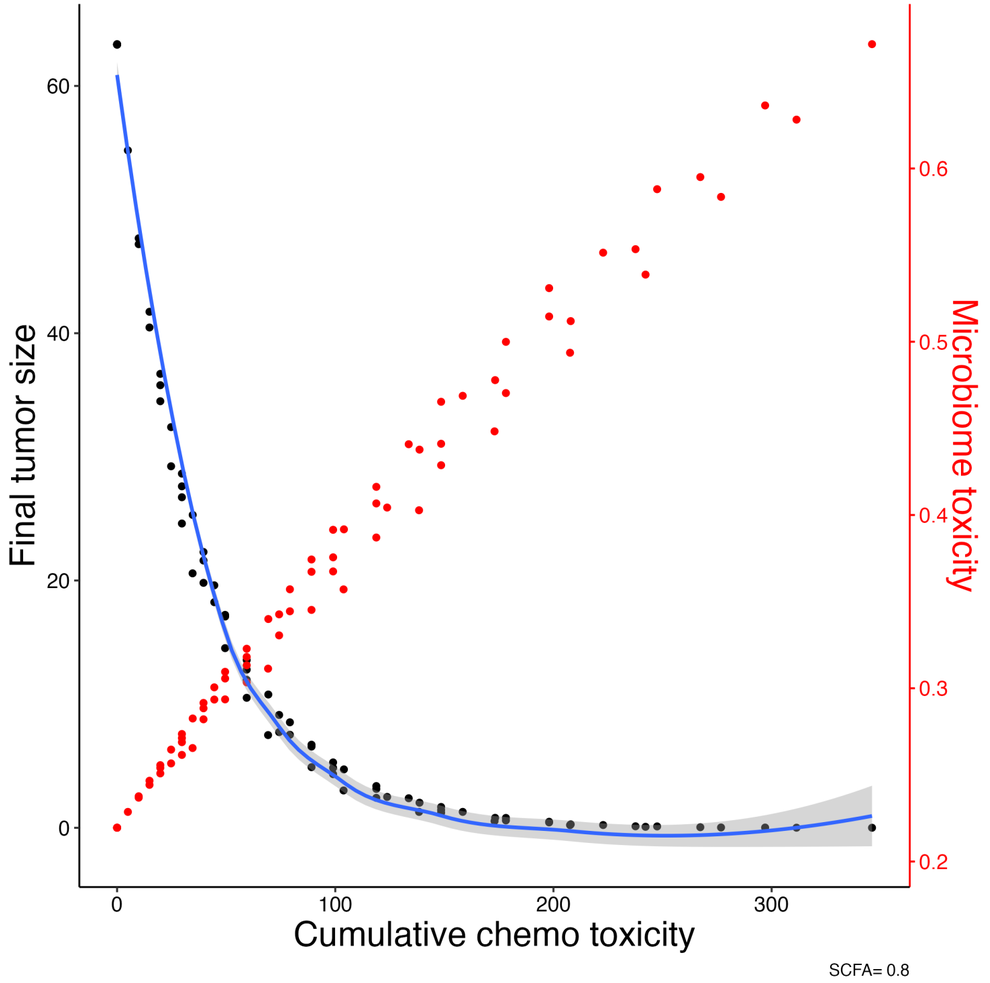
$$\frac{dD}{dt} = -\delta_D D$$

$$\frac{dK}{dt} = -\delta_K K$$

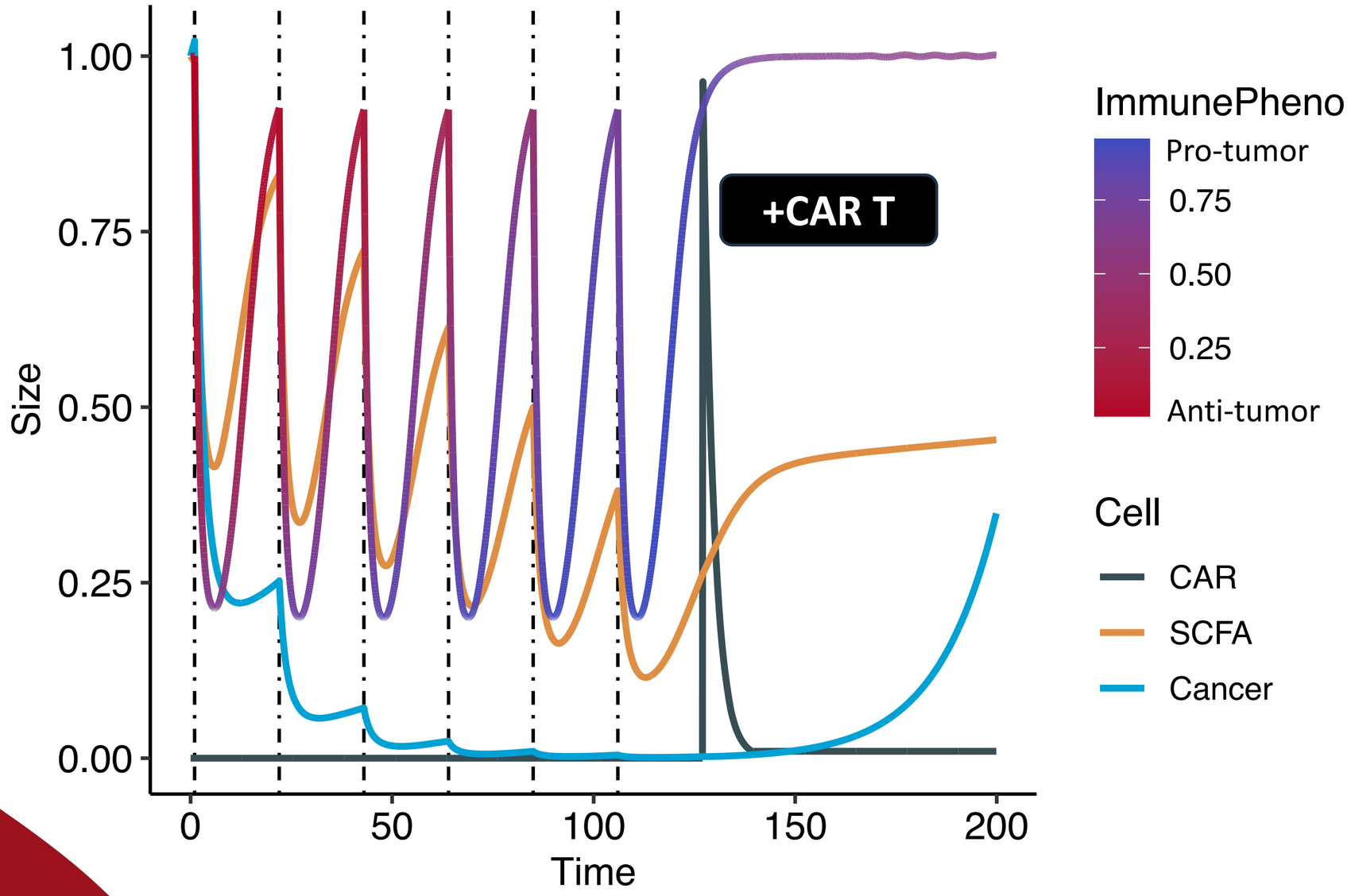
$$P(S) = 1 - \frac{1}{1 + e^{-(8S-4)}}$$

III. Microbiome Modeling





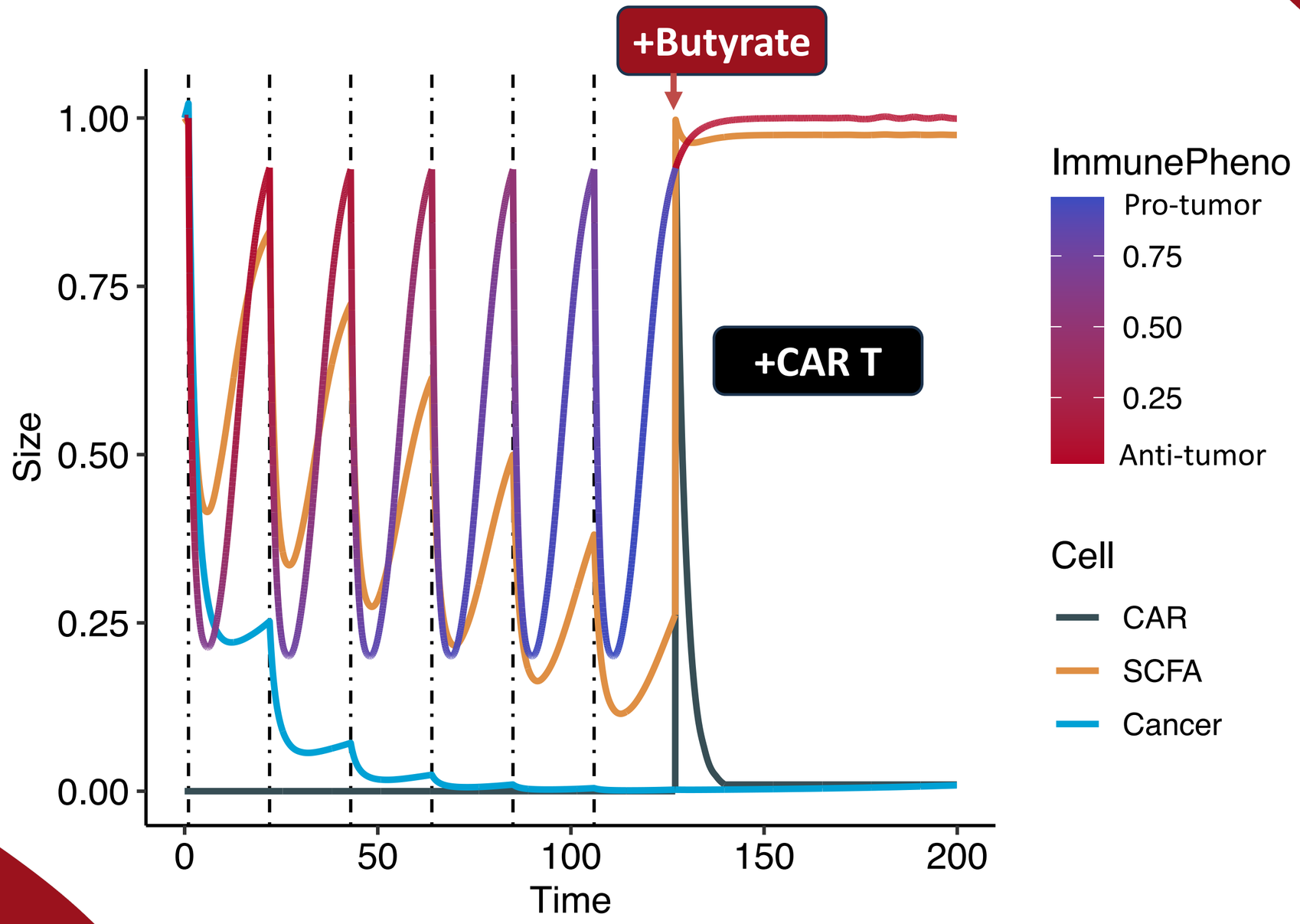
III. Primed for Failure



III. Modeling predicts butyrate supplement can enhance CAR efficacy

+

Butyrate Supplement



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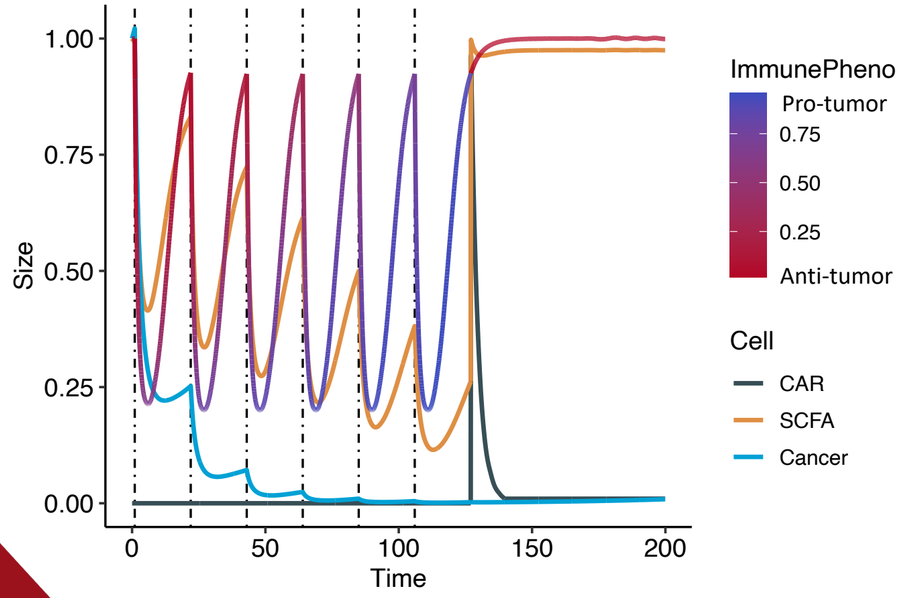


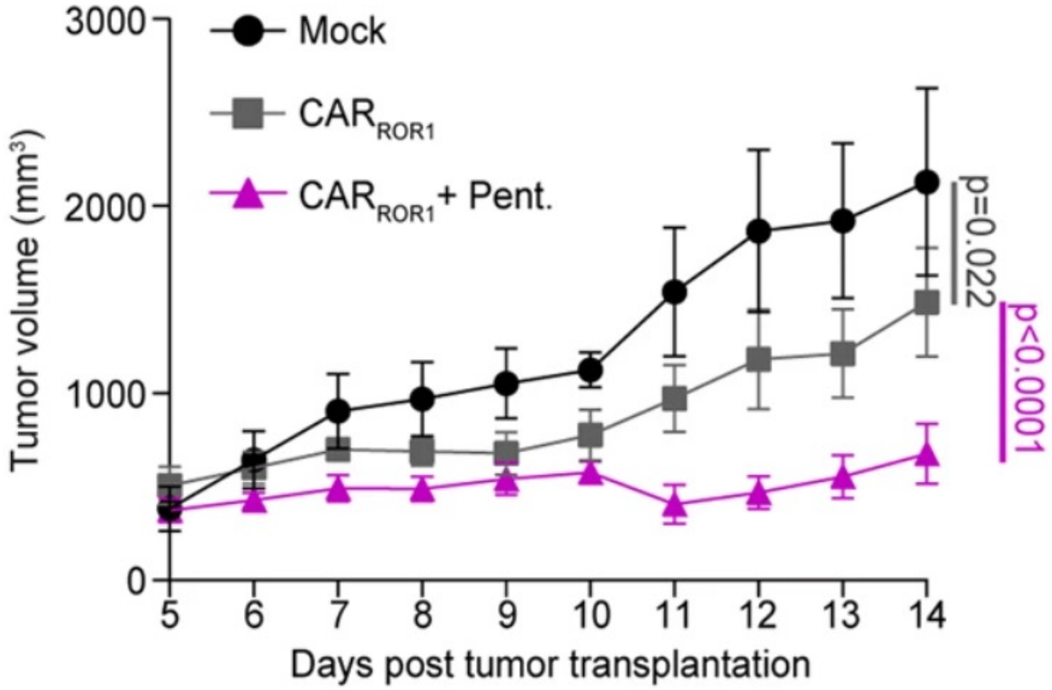
nature COMMUNICATIONS

ARTICLE

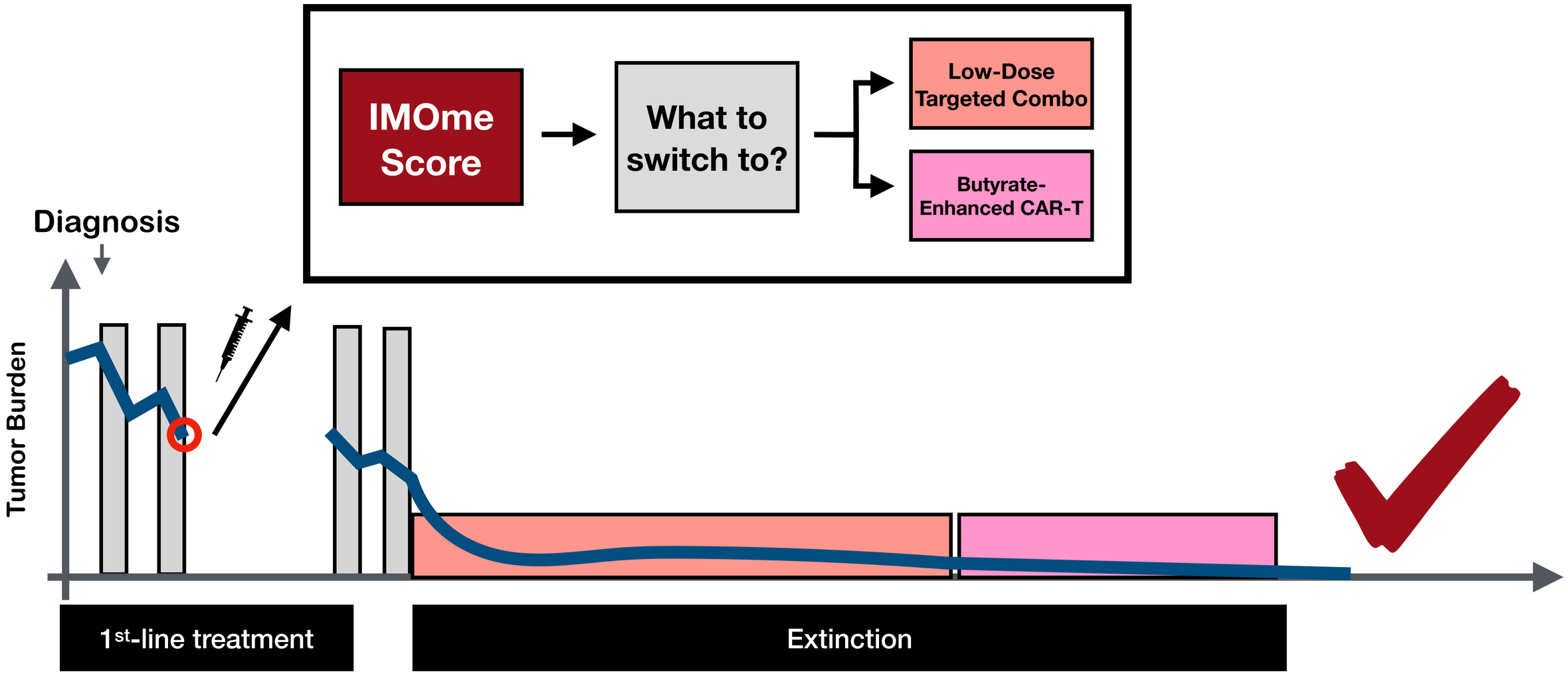
https://doi.org/10.1038/s41467-021-24331-1 OPEN

Microbial short-chain fatty acids modulate CD8+ T cell responses and improve adoptive immunotherapy for cancer

Maik Luu[1,2], Zeno Riester[2], Adrian Baldrich[2], Nicole Reichardt[3], Samantha Yuille[3], Alessandro Busetti[3], Matthias Klein[4], Anne Wempe[1], Hanna Leister[1], Hartmann Raifer[5], Felix Picard[1], Khalid Muhammad[6], Kim Ohl[7], Rossana Romero[1], Florence Fischer[1], Christian A. Bauer[8], Magdalena Huber[1], Thomas M. Gress[8], Matthias Lauth[9], Sophia Danhof[2], Tobias Bopp[4], Thomas Nerreter[2], Imke E. Mulder[3], Ulrich Steinhoff[1], Michael Hudecek[2,10]✉ & Alexander Visekruna[1,10]✉



Conclusion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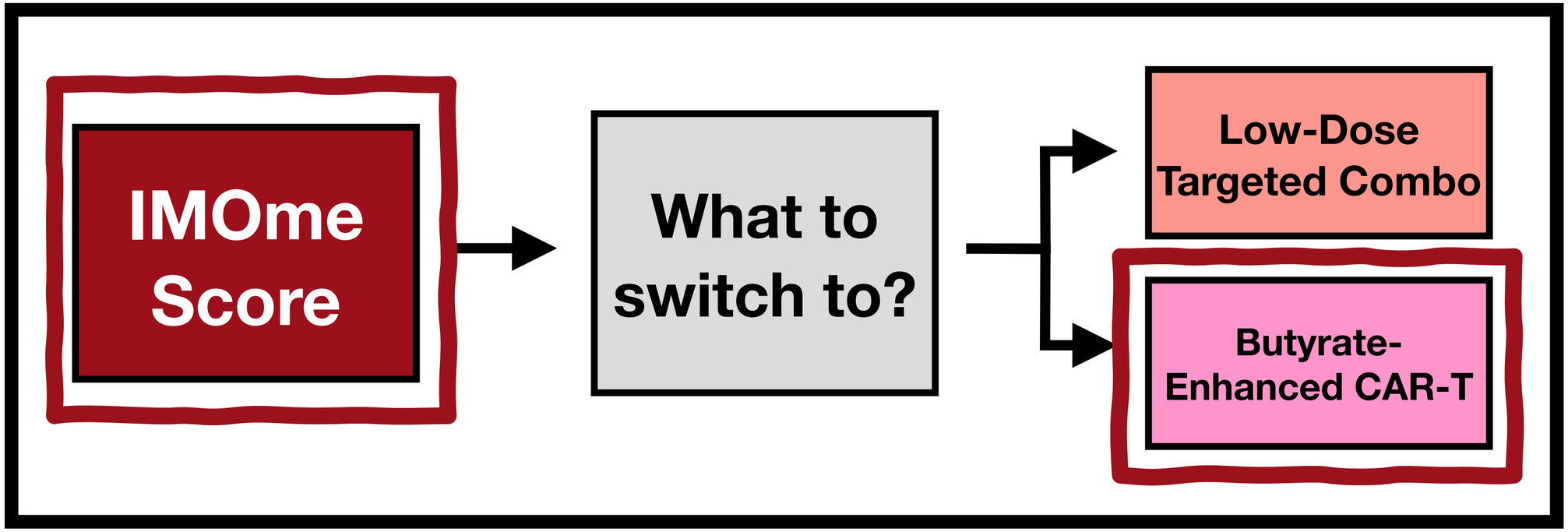
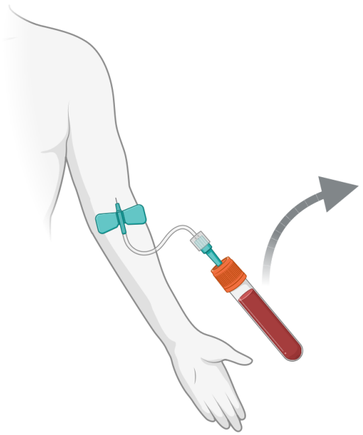


1. IMOme Score:

- Develop toxicity prediction biomarker
- Validate on 30 patients

IRB: MCC 21244 (approved)

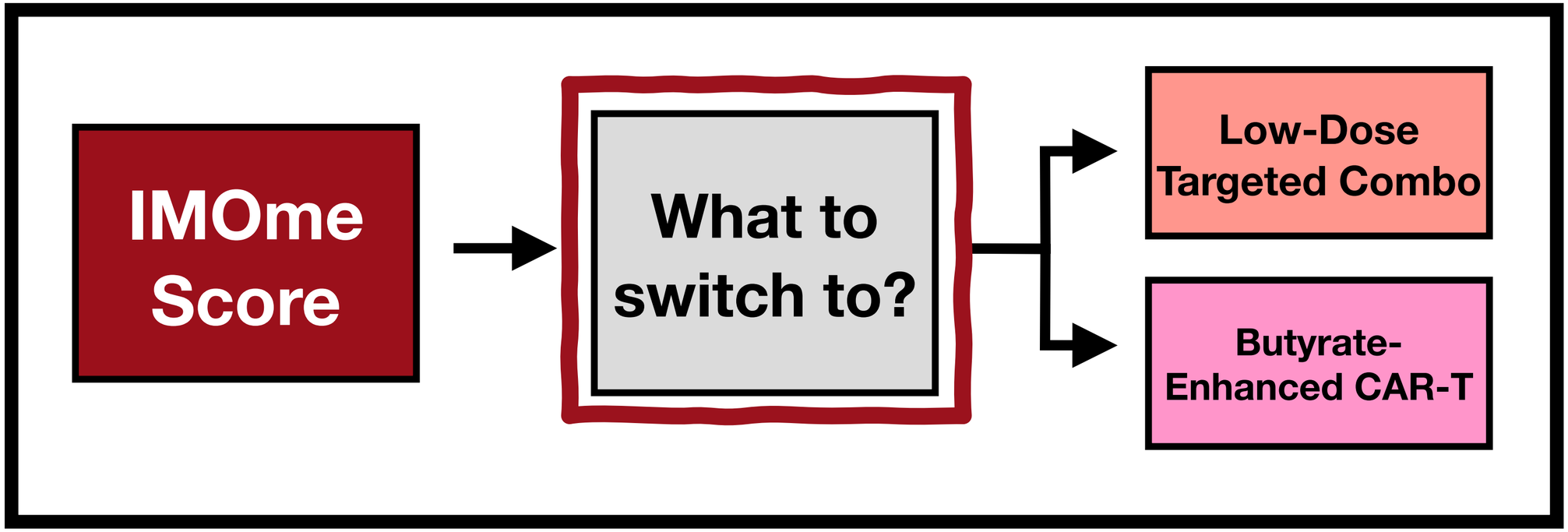


DNA Methylation

Short/Long Chain Fatty Acid

3. Butyrate-enhanced CER:

- L/S testing in 30 patients



1. IMOme Score:

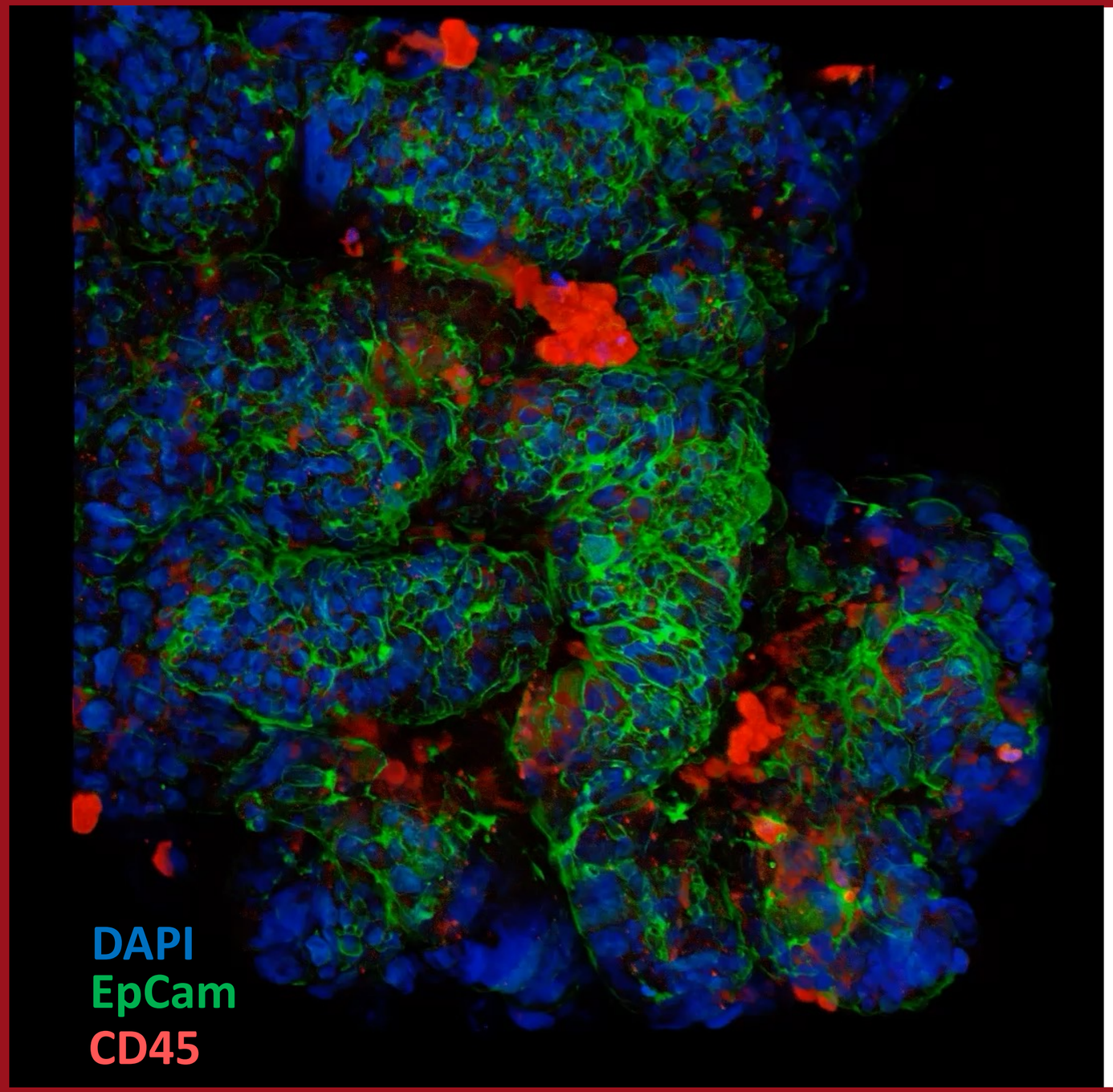
- Develop toxicity prediction biomarker
- Validate on 30 patients

2. Low-dose Combos:

- Validate PARPi/ATRi/PERKi combo in 3D organoids

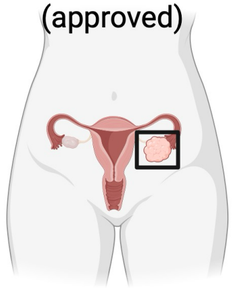
3. Butyrate-enhanced CER:

- L/S testing in 30 patients
- Validate in 3D organoids



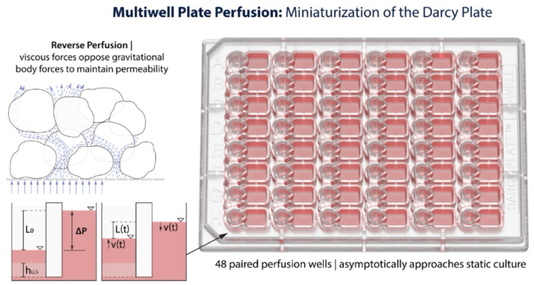
Experimental Design

IRB: MCC22609 (approved)



Patient Sample

Tumor Dissociation

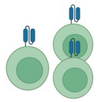


Ex vivo Culture

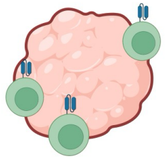
Condition

Tumor

CAR-T



CAR-T & Tumor



Treatment

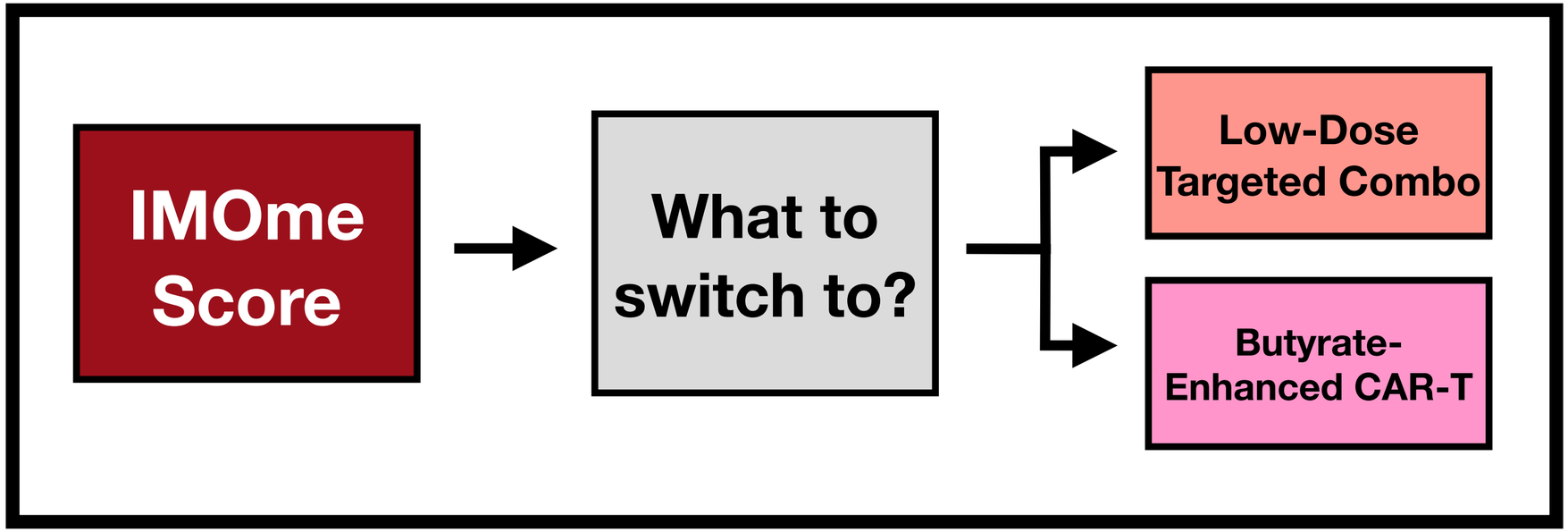
- Carbo & Taxol
- Combo: ATRi/ PARPi/PERKi
- Fluorescent-labeled butyrate

Readouts

Tumor:
Live/Dead Imaging
Morphological Analysis
(volume/size..)

CAR-T:
Proliferation Ki67/
Granzyme B/ IFNγ
Imaging & FACS

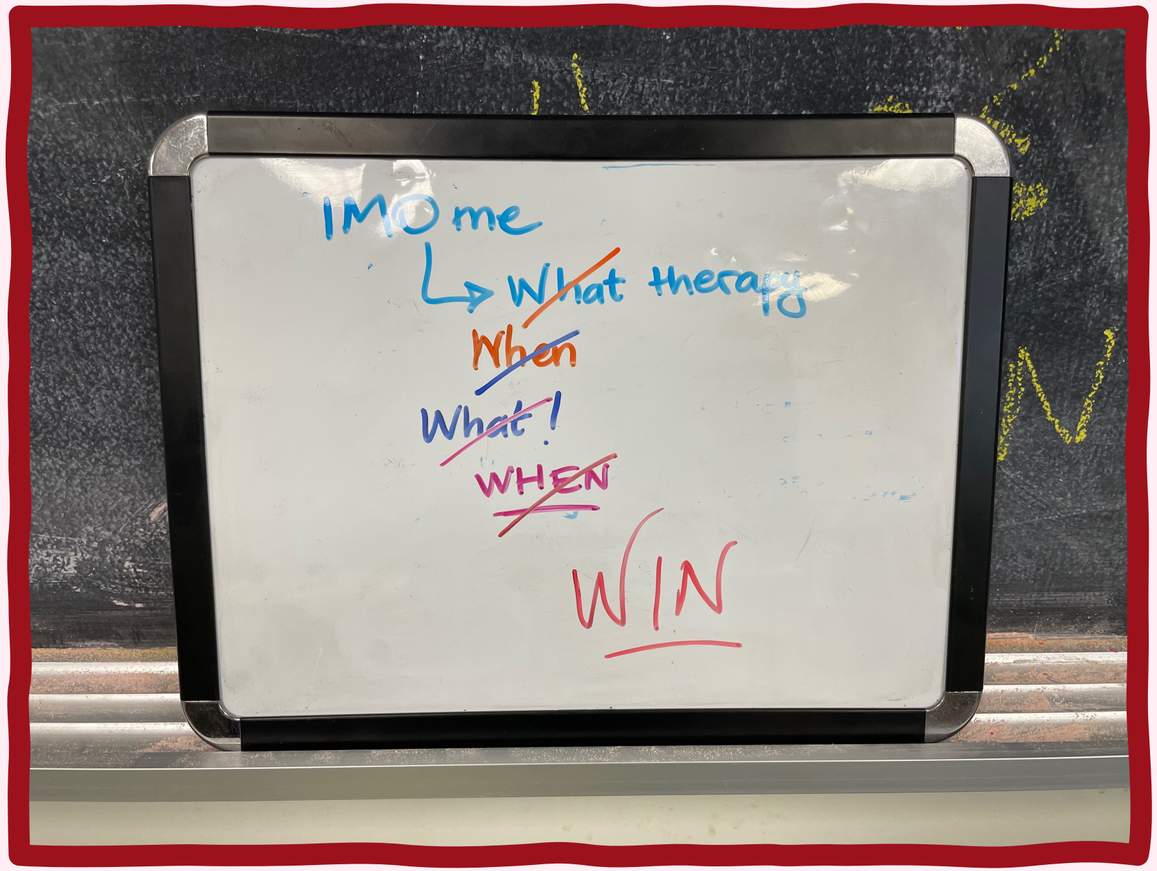
Butyrate:
Fluorescent butyrate
flow cytometry



Budget

- DNA Methylation sequencing (30 patients): $10k
- Short-chain fatty acid panel (30 patients): $5k
- uTumor culture and treatment: $10k
- Postdoc: $25k

Thank you



Team Members:

Rachel Sousa
Agata Xella
Peng Chen
Lucia Mazzacurati
Ryan Schenck
Sydney Leither
Kit Gallagher
Chandler Gatenbee
Timon Citak
Zoe Zhou
Dawn Lemanne
Maxi Strobl
Pauzo Rodriguez
Erin George