A Predictive, Biology-Driven Framework to Guide Cancer Therapy

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Disclosures: Unravel Genomics, ARPA-H


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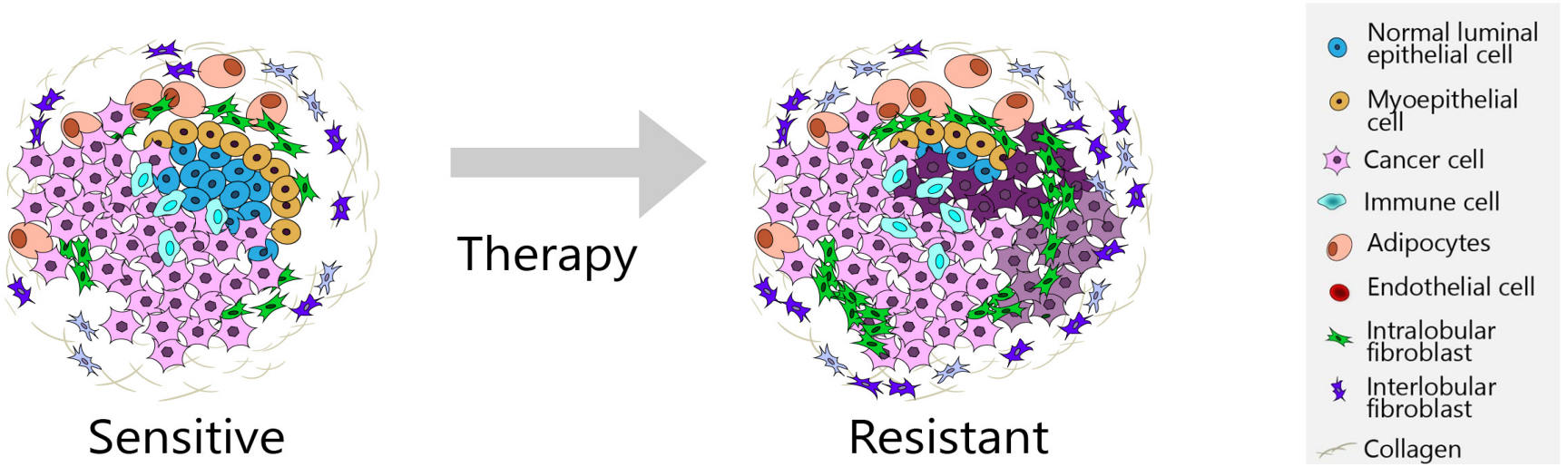
Background on ER+ breast cancer



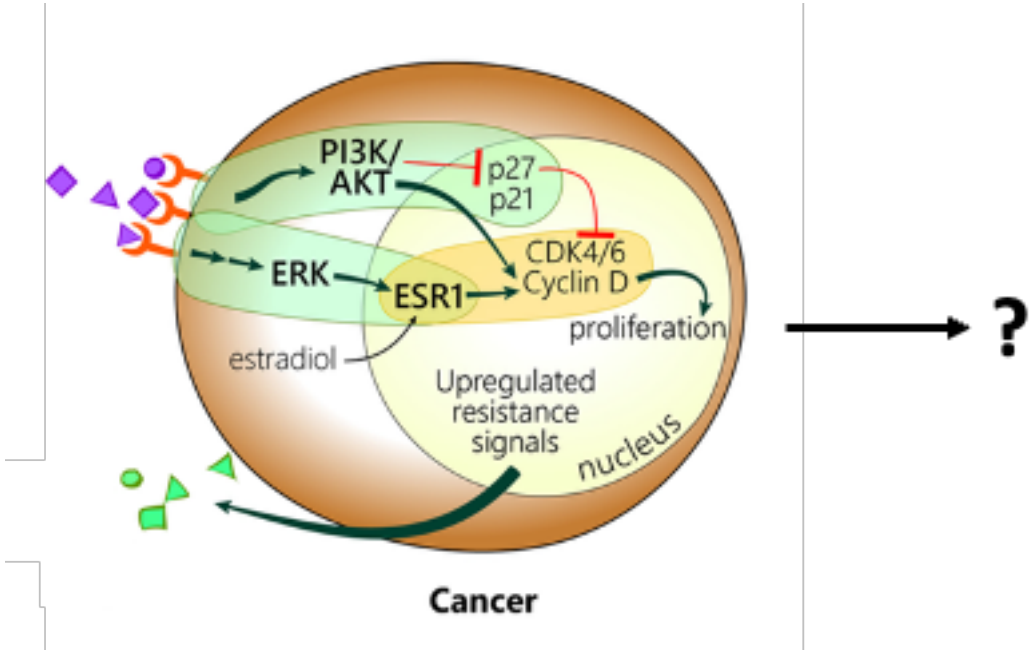
- Tumors are heterogeneous evolve during treatment
- ~70% of breast cancer patients are ER+, and endocrine and cell cycle therapies are the SOC for these patients
- ~40-50% of Stage II/III patients will acquire resistance and recur with metastatic disease, and almost all metastatic patients progress to a refractory state
- We don’t know which patients progress and we don’t have a method to predict evolution or optimize therapy combinations and sequences for durable response

Objectives

Framework: Discovery (patient) → Testing (cells/in vitro) → Prediction (new patient)

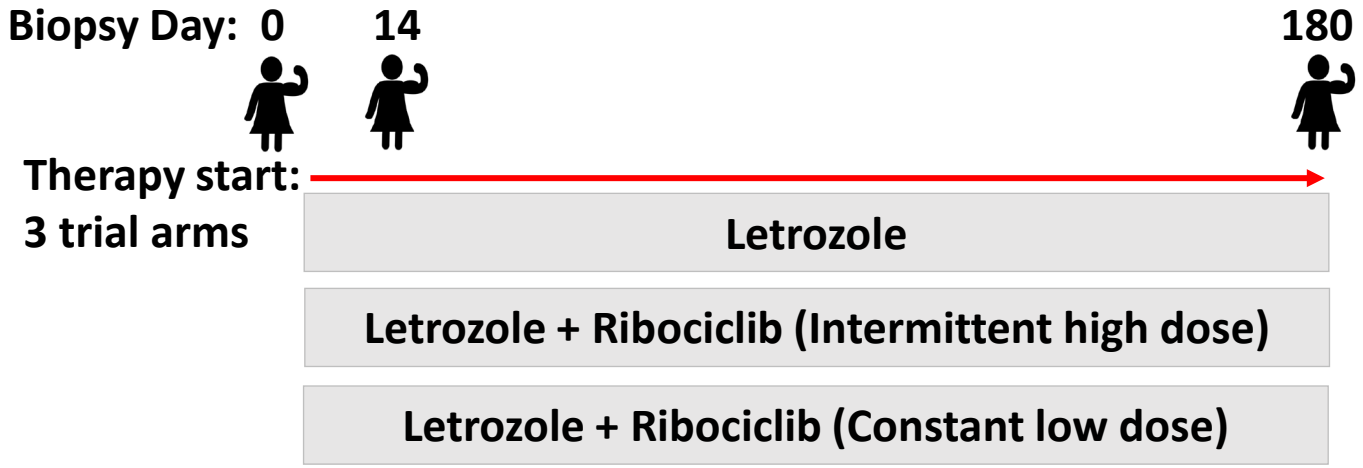
Research Questions:

1. What are the common and reproducible resistance phenotypes in ER+ tumors?
2. Do resistant cancer cells respond to treatments targeting these phenotypes?
3. Can we predict tumor trajectories to forecast drug response and outcomes from early data?



FELINE: neoadjuvant ER+ HER2- breast cancer clinical trial

Assessing effectiveness of cell cycle (CDK4/6) inhibitor therapy (Ribociclib/Kisqali)
in combination with hormone therapy (Letrozole, an AI/lowers estrogen production) for potentially curable patients



1) Tumor size assessed at differing times : various imaging and physical examinations:

Measurement method: Clinical assessment Ultrasound Mammogram MRI Surgical pathology

2) Data from biopsy:

Single cell (nuclear) RNA expression, DNA sequencing

3 Biopsies => same times all patients (day: 0, 14, 180)

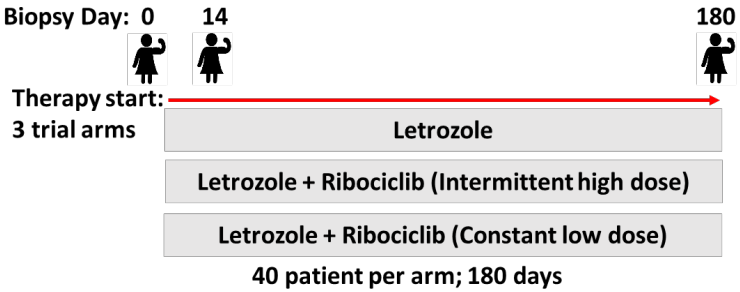
Following treatment, we do not know who will recur.

Molecular and clinical data classification

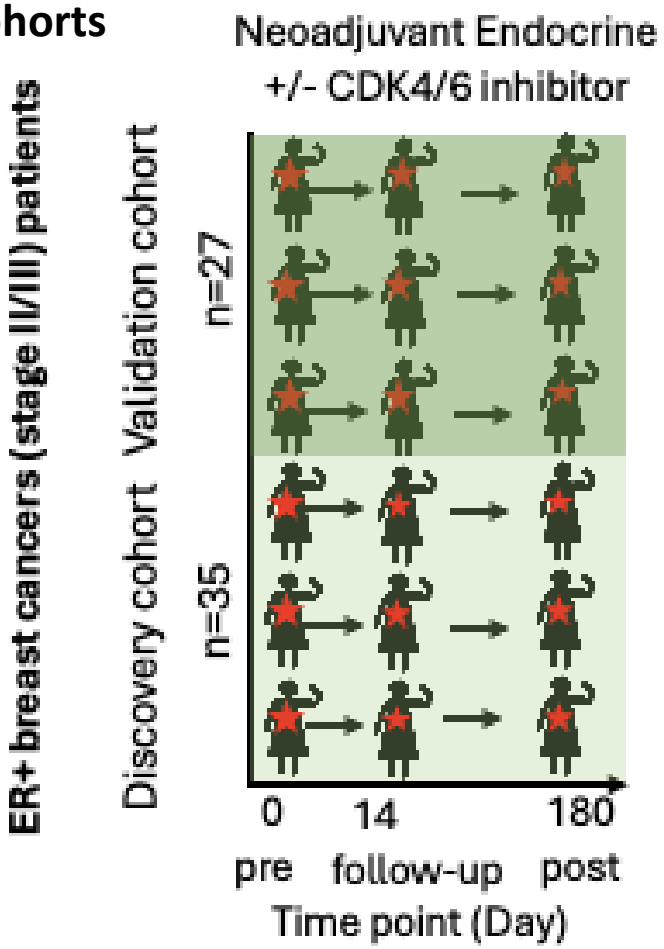
Cohort 1: *35 patients with ~3 timepoints, approximately half responsive to therapy*

Cohort 2: *(validation cohort) 27 patients with ~3 timepoints, approximately half responsive to therapy*

Total: *173 biopsy samples, 424k cells total*



Treatment cohorts



Methods summary:

DNA analysis

- Alignment: BWA
- Mutation calling (SNV/indel): FreeBayes
- CNA (copy number): VarScan
- Structural variants: Lumpy
- Subclone evolution: PyClone

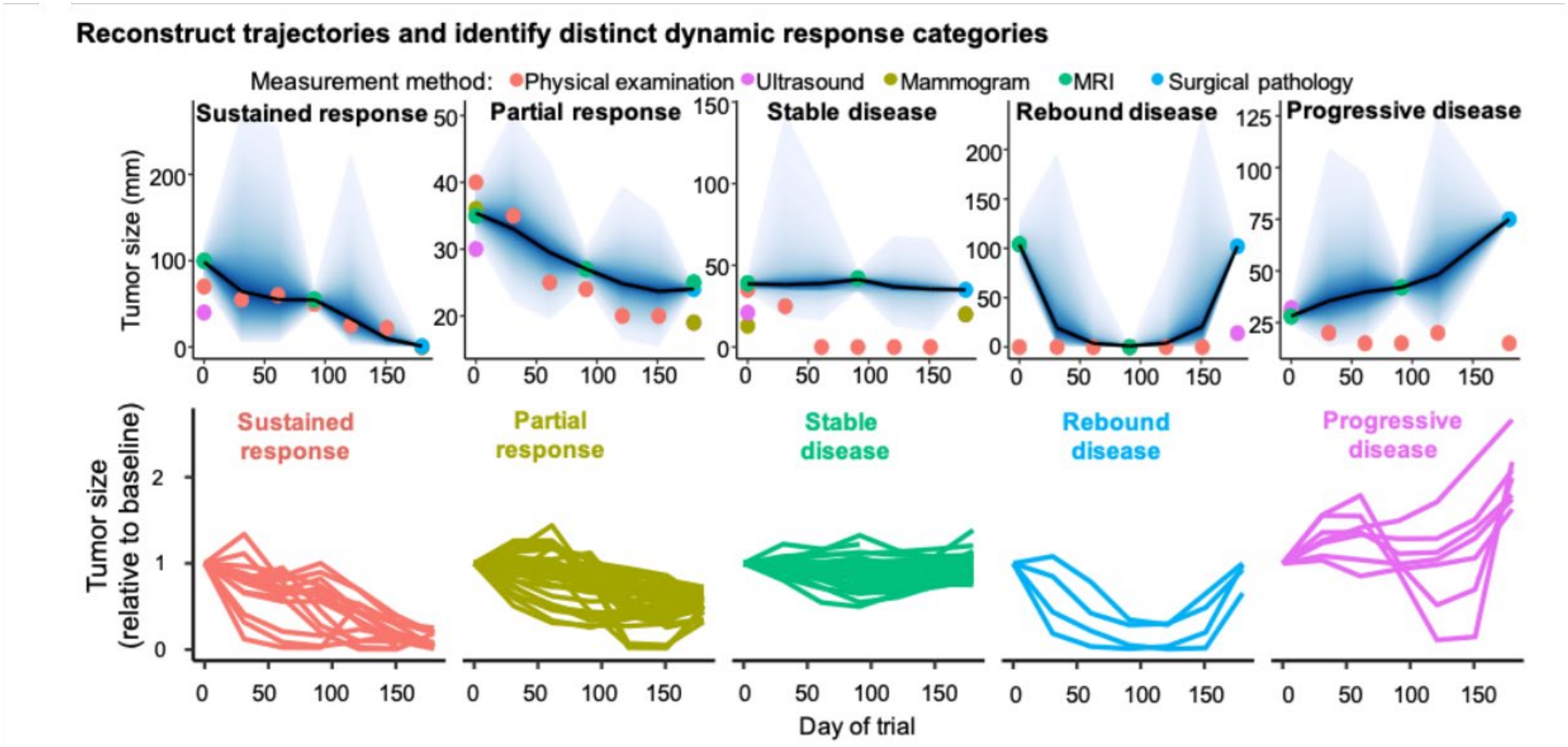
RNA analysis (bulk and scRNA-Seq)

- Transcript quantification: RSubread
- Pathway analysis: ssGSEA and ASSIGN
- Fusion transcripts: TopHat-Fusion
- EdgeR, ImmClassifier
- InferCNV
- reCAT (cell cycle reconstruction)

Mathematical models

- PhylinSiC (used to confirm cancer cells)
- ML-Classifier (used to confirm all cell subtypes)
- TWISTER (used to assess population level communication)
- GP-LVM
- GAM
- GP-VAE

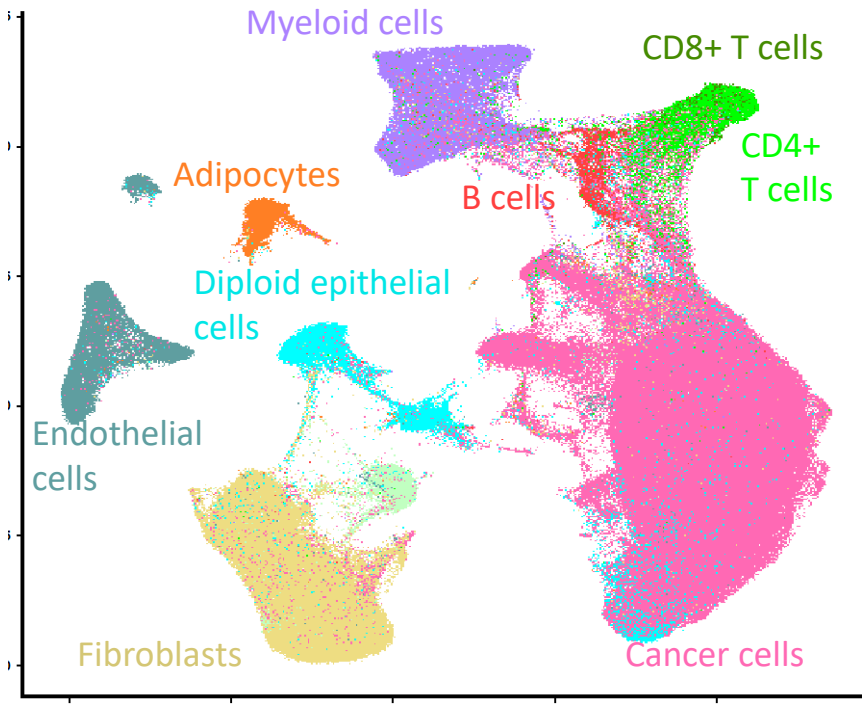
Reconstructing tumor trajectories: uncertainty aware multi-modal data integration



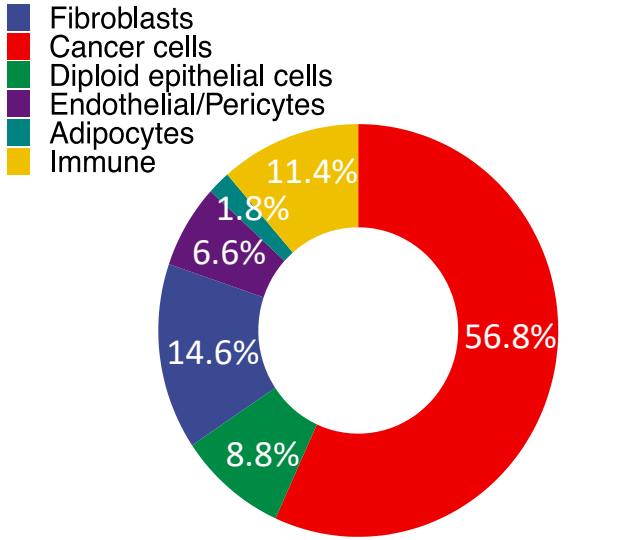
Dynamic Gaussian process latent variable model (GPLVM) that are **expressive** (capture non-linear relationships) and that i**ntegrate** different measurement modalities for trajectory predictions while accounting for differential modality bias and **uncertainty**.

Single cell RNA profiles over time & across clinical cohorts

Cell types classification UMAP



Cell type composition

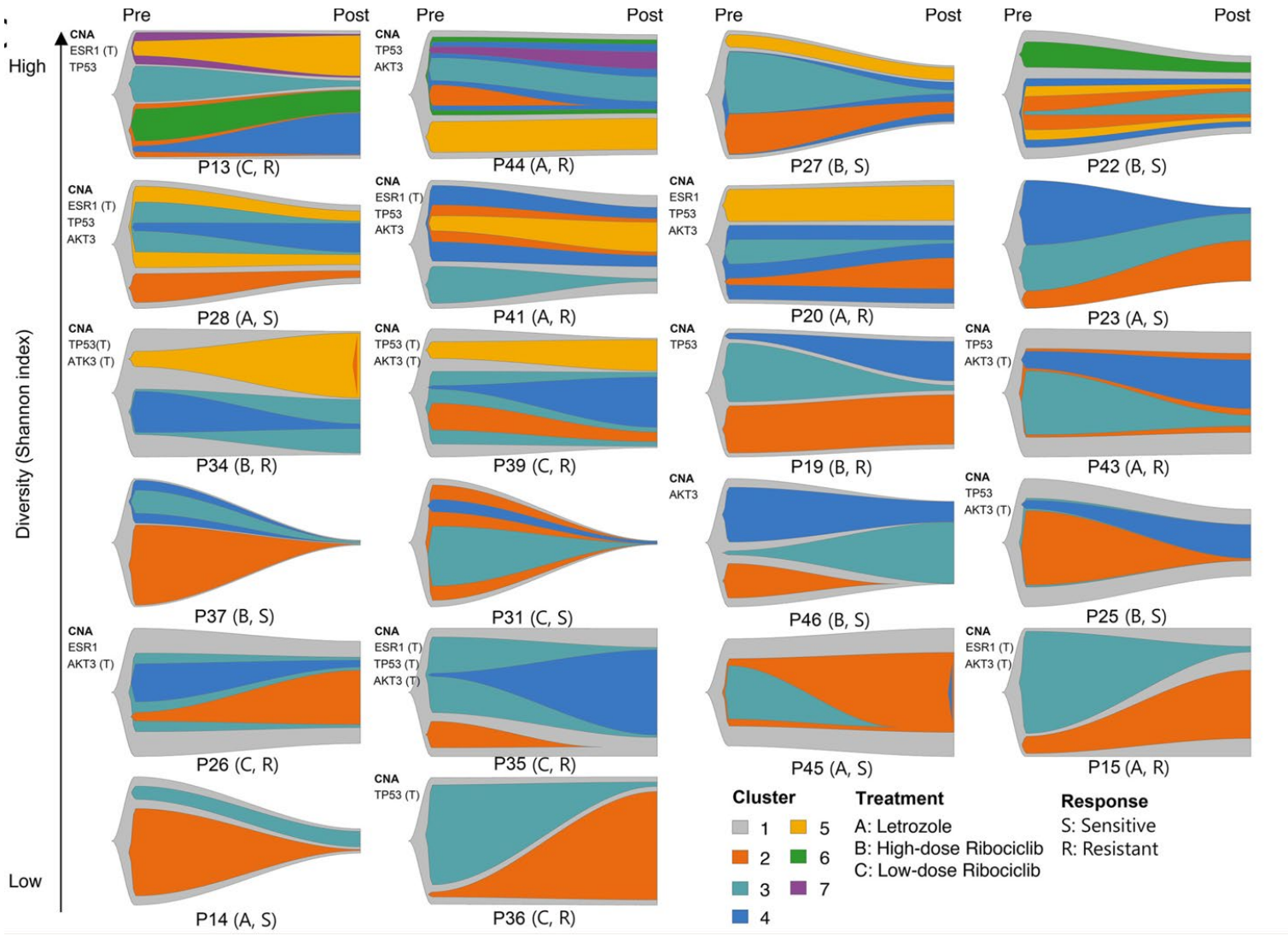


Serial scRNAseq dataset
424,581 cancer/non-cancer cells
173 tumor biopsy samples
62 patients

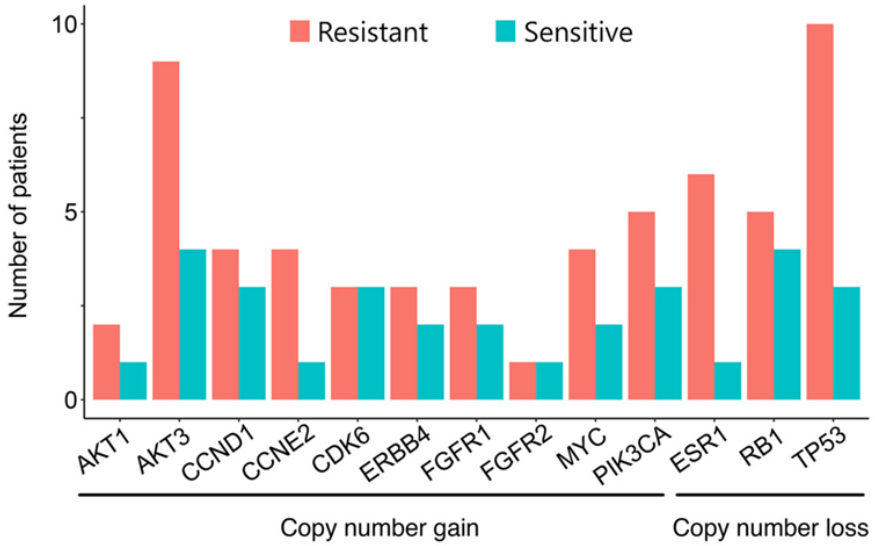
How tumor composition differs during between CDK4/6i-resistant and sensitive tumors?

Griffiths et al, Nature Cancer, 2021
Griffiths et al, MSB, 2025
Griffiths et al, Nature Communications, 2025

Real world tumor genetic evolution



Driver mutations didn't clearly distinguish CDK4/6i resistant and sensitive tumors



Do tumors exhibit convergent emergent phenotypes?

Convergent phenotypic evolution in patients

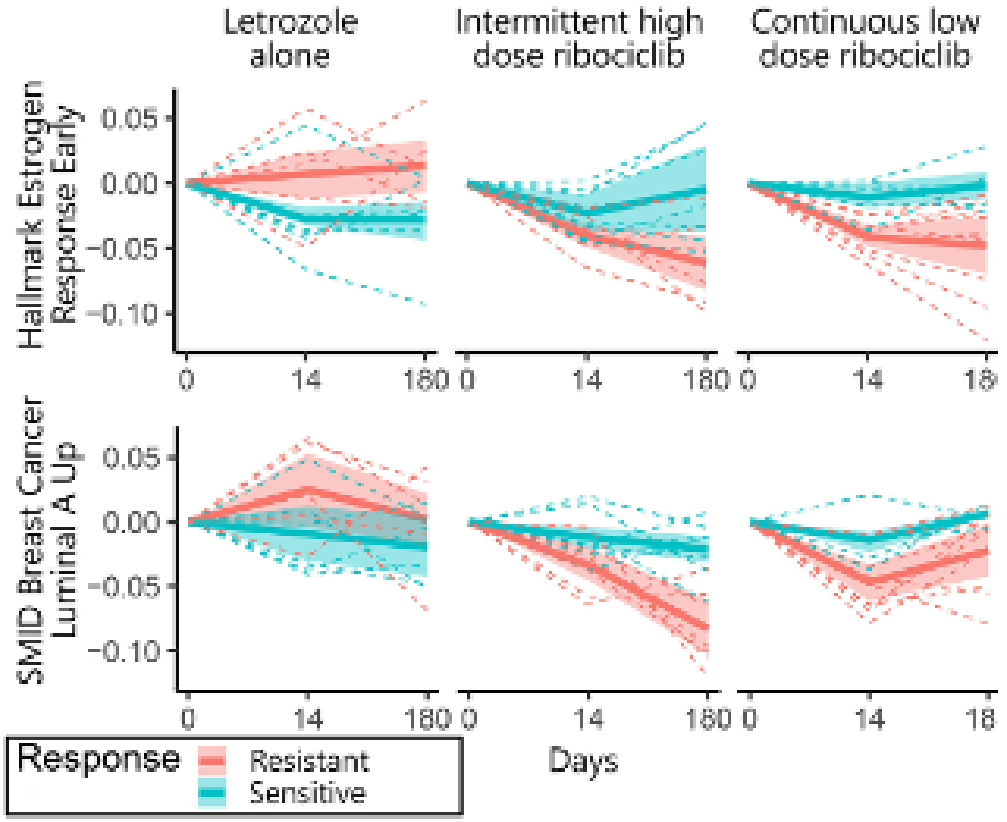
Discovery cohort
(Patients whose tumors were persistent and growing at EOT)

scRNAseq
ssGSEA

pathway activity score across all cancer cells

hierarchical regression

identify most significantly dysregulated pathways post-treatment



Reproducible phenotypes in patient samples: Upregulation of ERBB signaling in resistant tumors

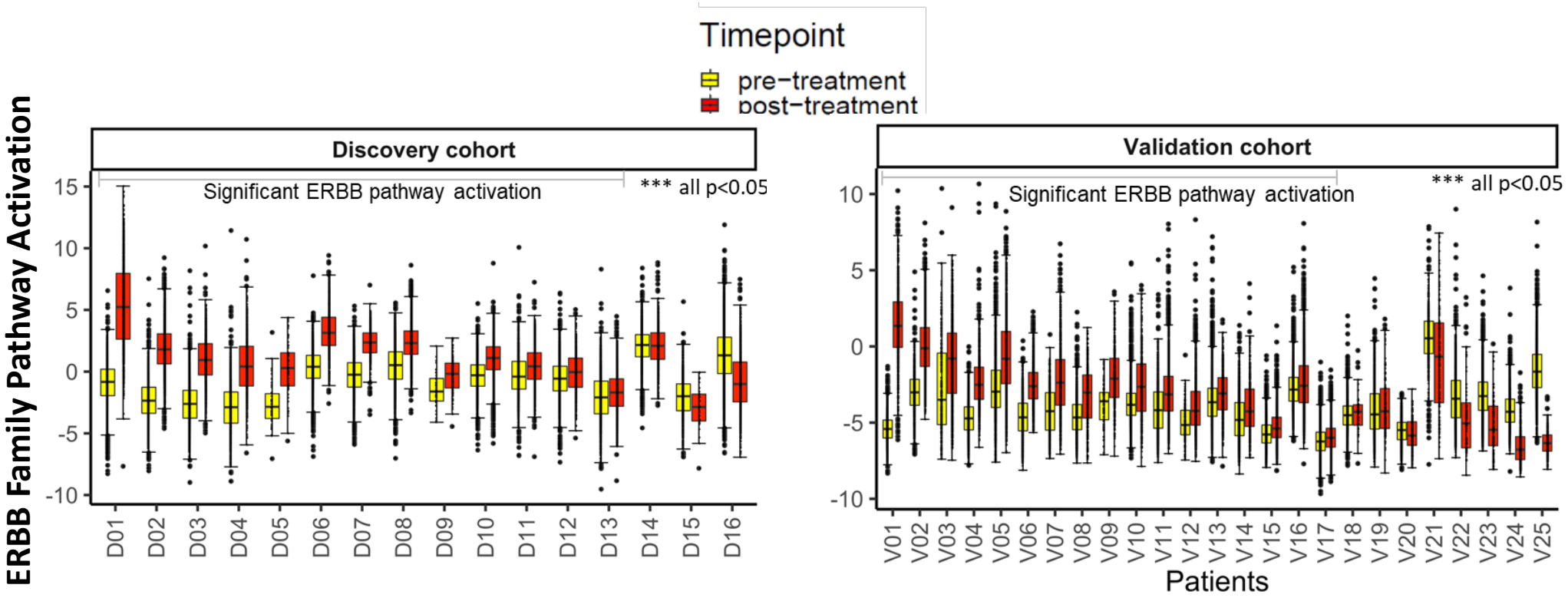
Discovery cohort (Patients whose tumors were persistent and growing at EOT)

scRNAseq ssGSEA →

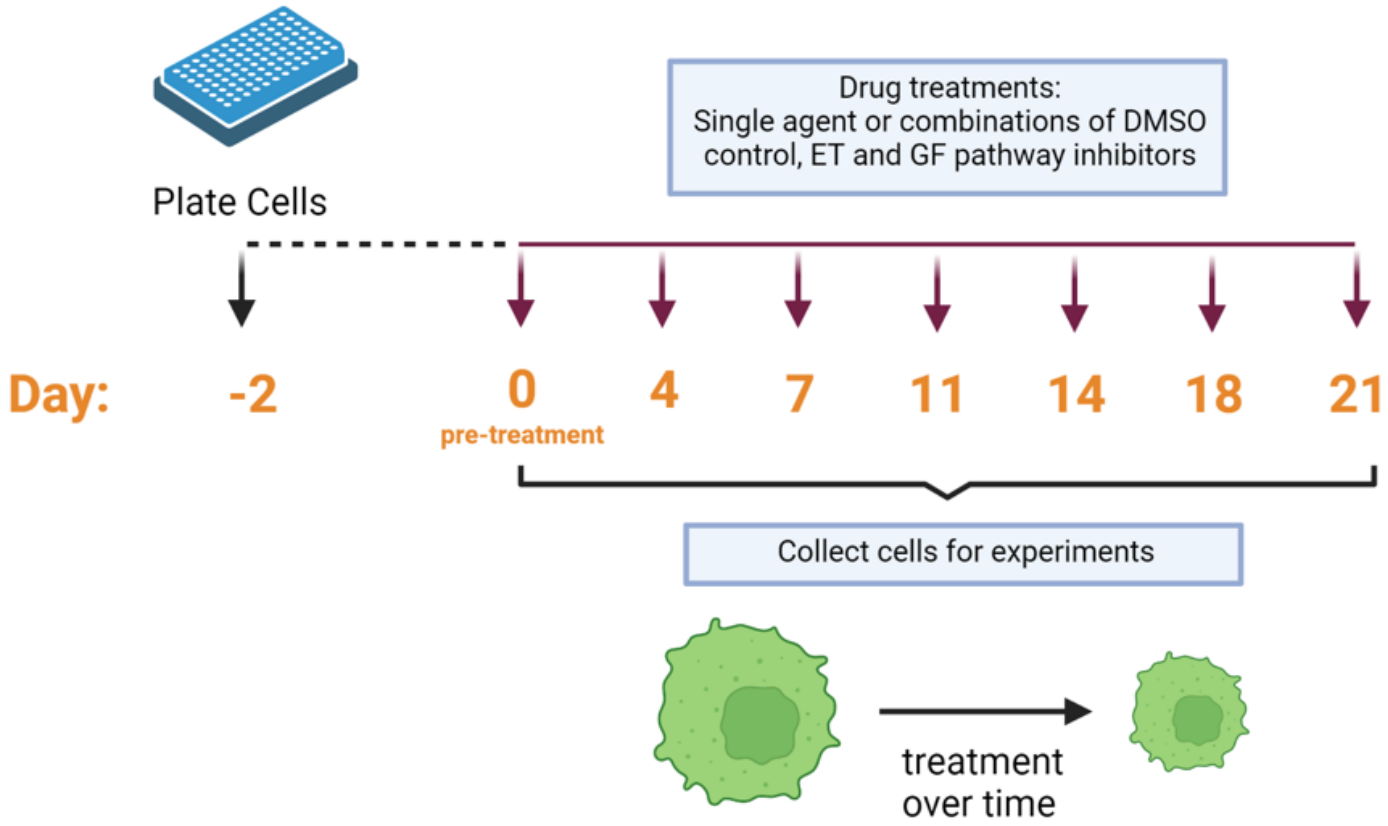
pathway activity score across all cancer cells

hierarchical regression →

identify most significantly dysregulated pathways post-treatment



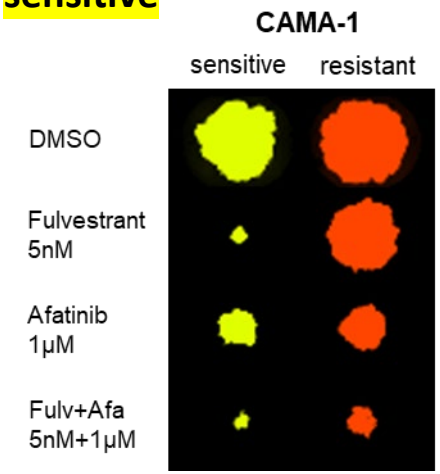
Testing resistant phenotypes in cancer cells

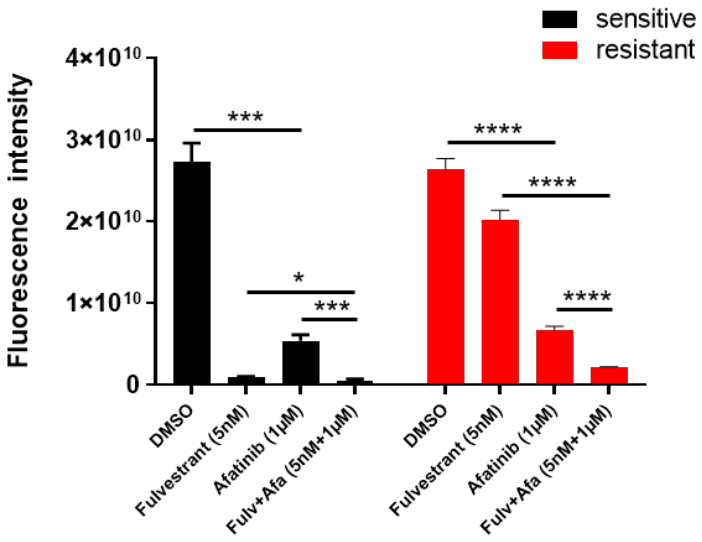


Reproducible Phenotype: Upregulation of ERBB signaling with in vitro model systems

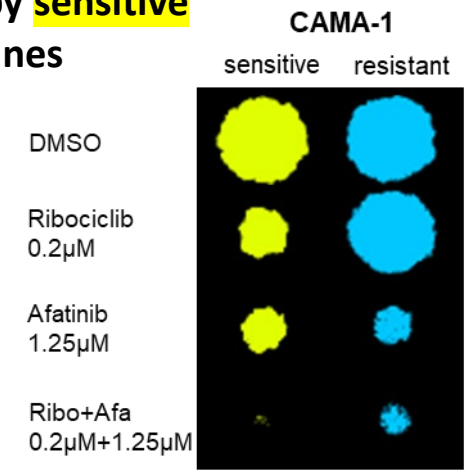
Acquired sensitivity to pan-ERBB inhibitors in ET/CDK4/6 resistant cancer cell lineages

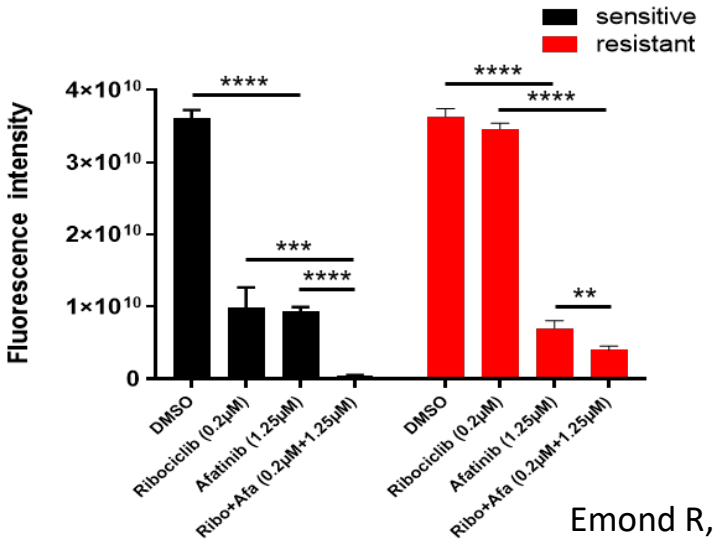
Endocrine therapy sensitive and resistant lines





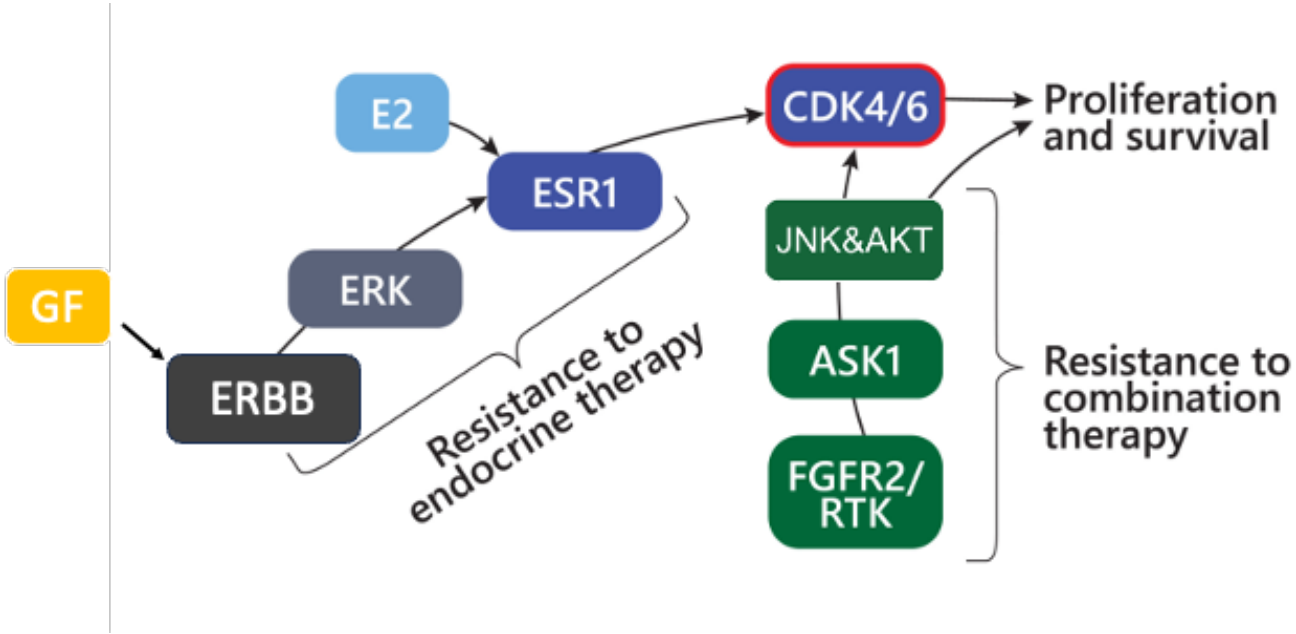
CDK4/6 therapy sensitive and resistant lines





Emond R, et al, Nat Commun, 2023
Griffiths J, et al, Mol Syst Biol, 2025

Mechanisms of resistance

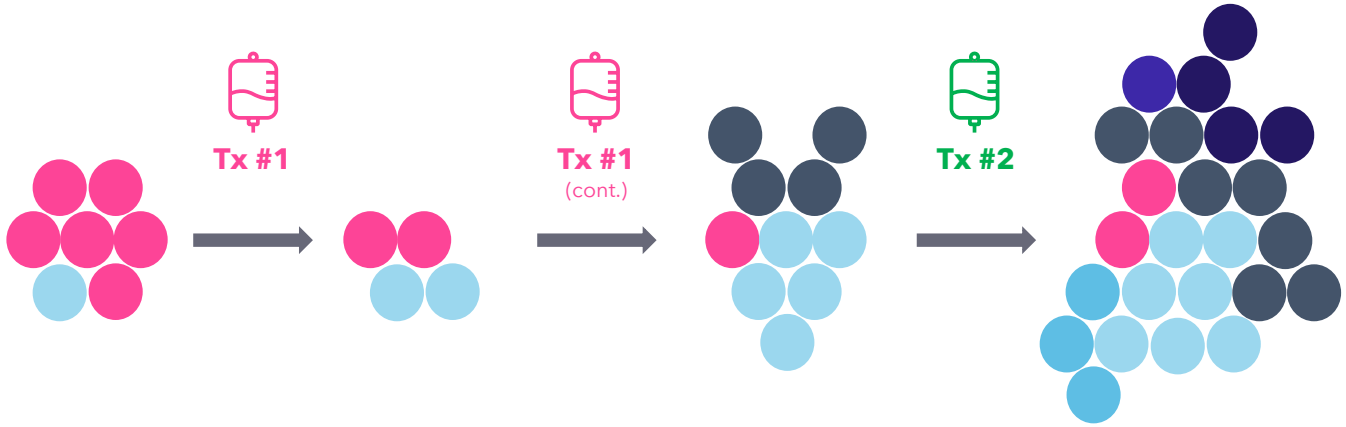


1. Patient tumors that continue to grow on treatment quickly become estrogen signaling independent.
2. In both discovery and validation cohorts, there are rapid and sustained upregulation of ERBB1-4 receptors in cells non-responsive to ET.
3. In separate experiments with ER+ BC cell lines, there is rapid upregulation of ERBB1-4 following treatment with ET (and to a lesser extend CDK4/6i).
4. Resistant cells are sensitive to ERBB inhibitors.

From Mechanisms to Prediction

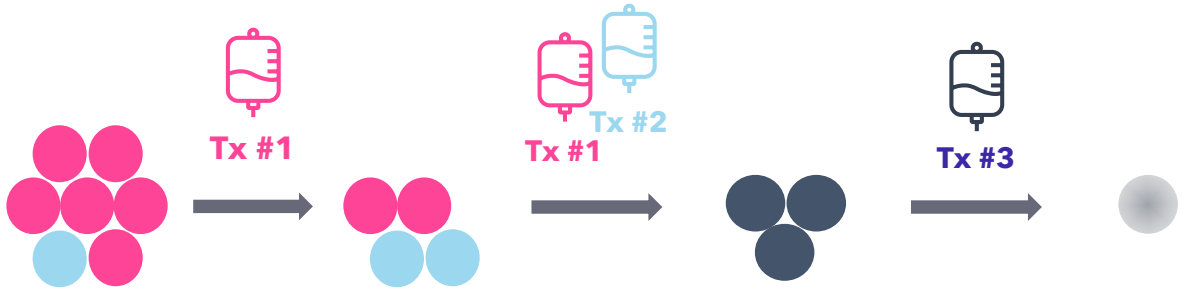
Current State

- Cancer changes during treatment. Therapies are not often informed by tumor changes or tailored to cancer resistance traits.



Future State

- Therapies informed by and tailored to observed cancer resistance traits using biomarkers.



Predicting tumor trajectories: a start with synthetic data

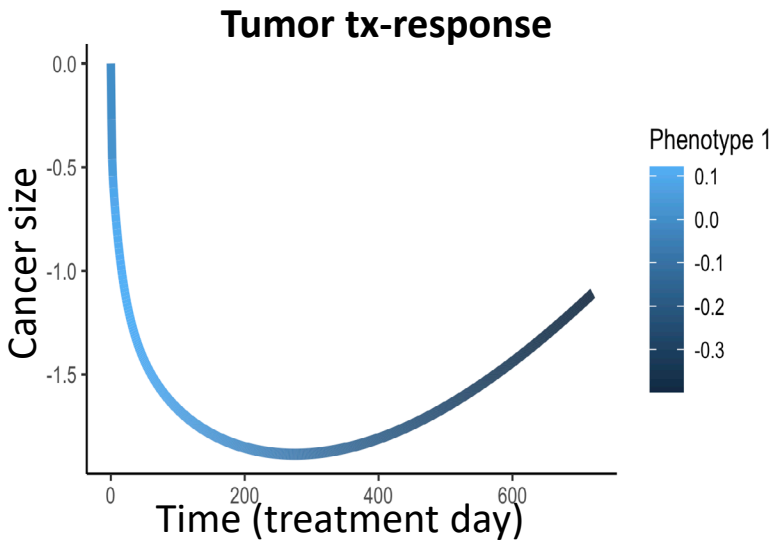
Model synthetic data in a controlled setting to test if reconstruction methods can accurately recover the true underlying dynamics before we apply them to real patient data.

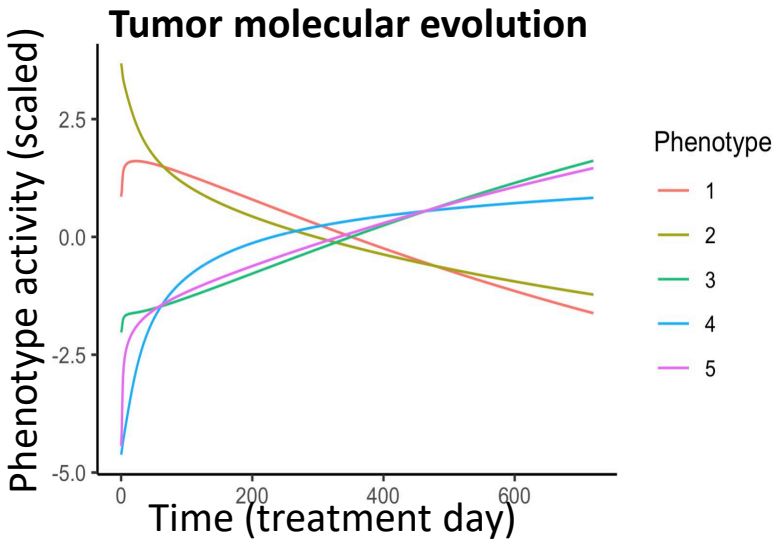
CHALLENGES

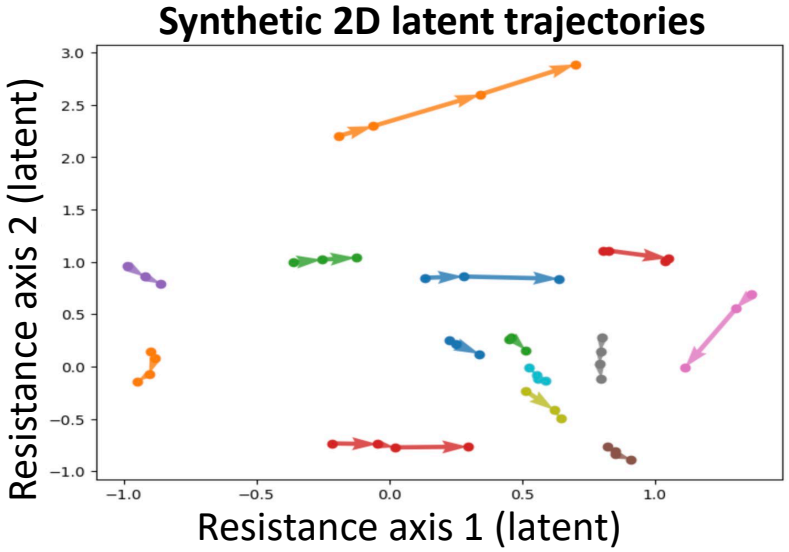
- Multi-dimensional systems
- Phenotypes evolve over time
- Sparse, noisy data

SOLUTION

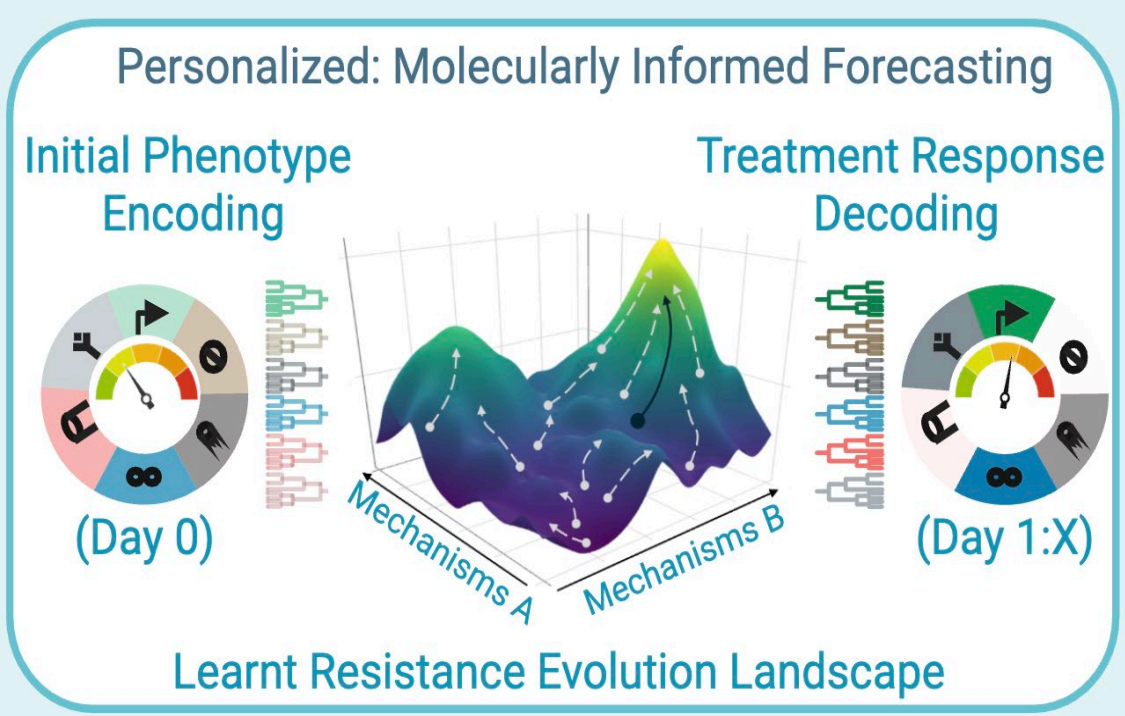
- Adaptive dynamics (ODE) simulates phenotype co-evolution
- Provides ground truth latent trajectories: $z(t) = [z_1, z_2, \ldots z_D]$
- Input data = high-dimensional, noisy, non-linear, heteroskedastic transformations of latent trajectories sampled irregularly.
- Validate model recovers dynamics







GP-VAE: learning latent tumor dynamics



ENCODER

Features → Latent: $q(z|x) = N(\mu, \sigma_E^2)$

Maps high dimensional molecular features into low dimensional latent space

GP prior over latent trajectories

Temporal smoothness: $z(t) \sim GP(t, z(0))$

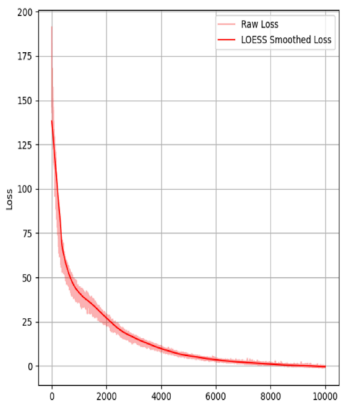
Characterizes continuous time coevolution;
Handles irregular sampling

DECODER

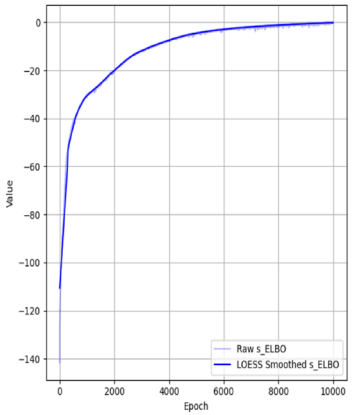
Latent → Features: $p(x|z) = N(f(z), \sigma_D^2)$

Reconstruction enables molecular prediction at later times and evaluates information compression

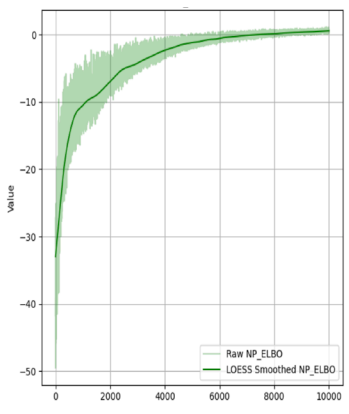
GP-VAE loss



Reconstruction ELBO



Forecasting ELBO

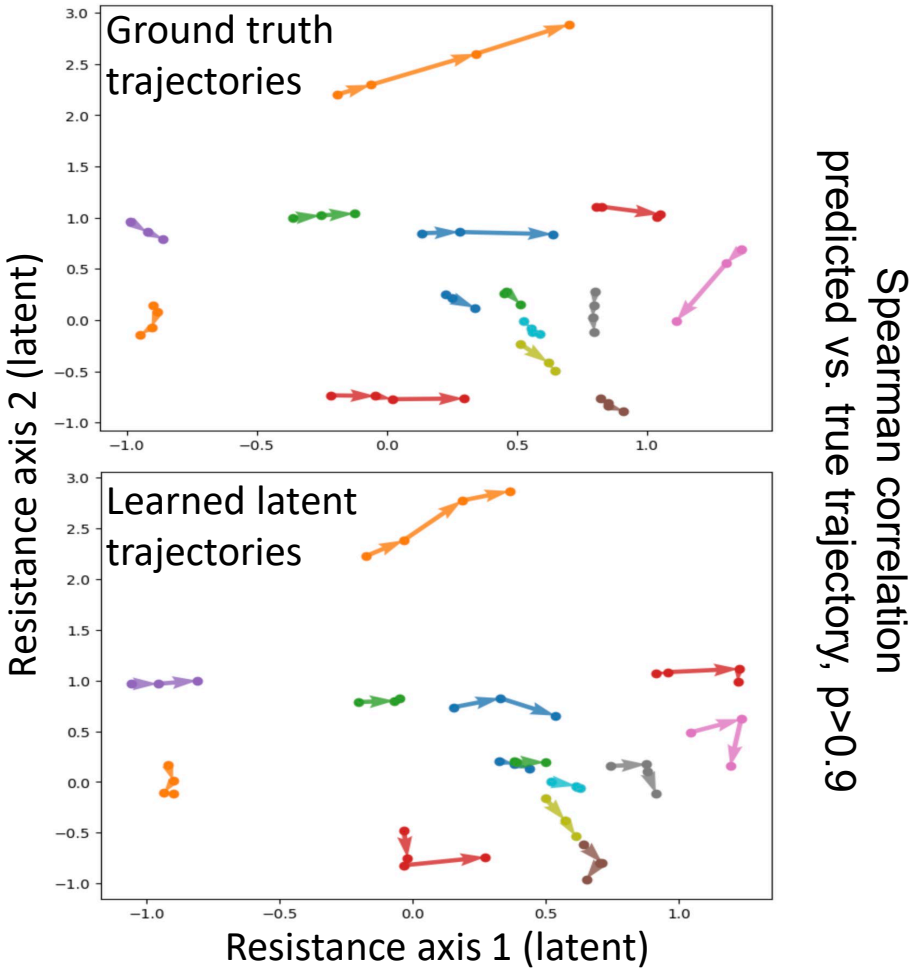


TRAINING

- **GP prior on latent space:** keeps latent trajectories smooth over time
- **Reconstruction ELBO :** model must accurately rebuild input features from latent state
- **Forecasting ELBO:** Neural process loss term penalizes poor future forecasts from early timepoints

Validation: model recovers true dynamics

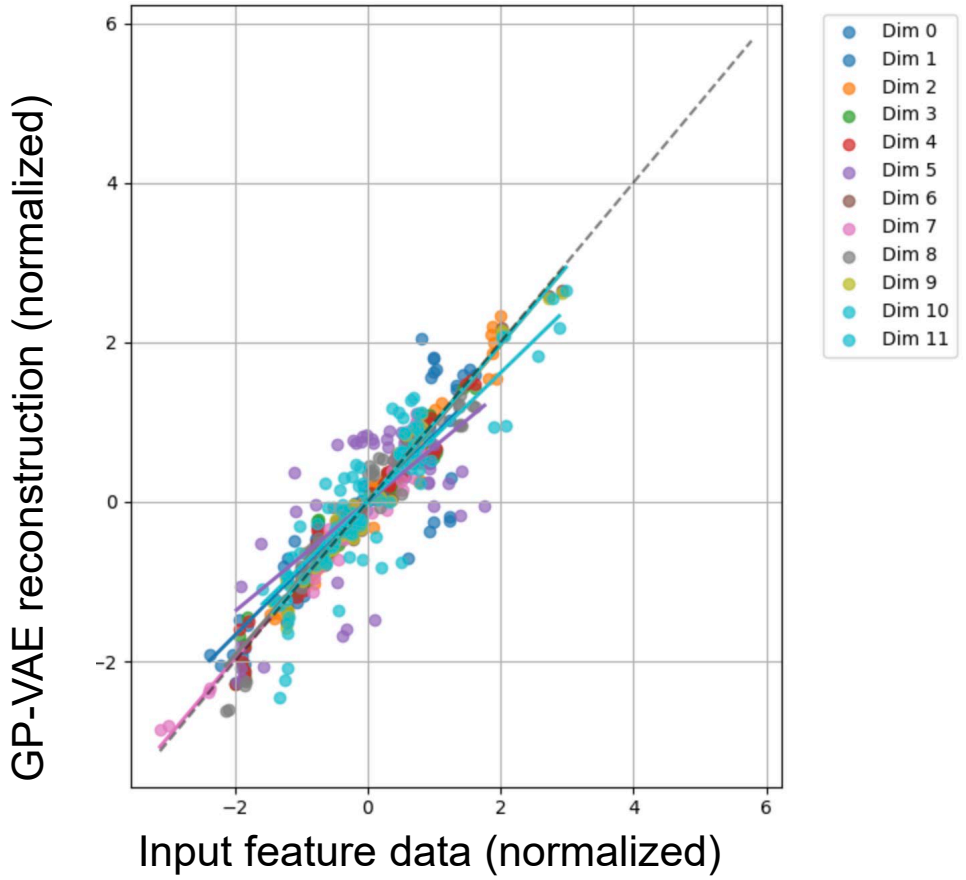
GP-VAE latent process learning quality



Direction recovery: Correct evolutionary direction
Speed recovery: Captures rate of change
Parameter accuracy: Recovers biological rates

Model recovers true dynamics from limited, irregular observations

GP-VAE reconstruction quality



Mean reconstruction correlation: 0.93+/- 0.10 across feature dimensions

Input data reconstruction: compresses high-dimensional data into compact latent space while preserving key phenotypic information needed to reconstruct the original input.

Application: patient data from FELINE trial

Data:

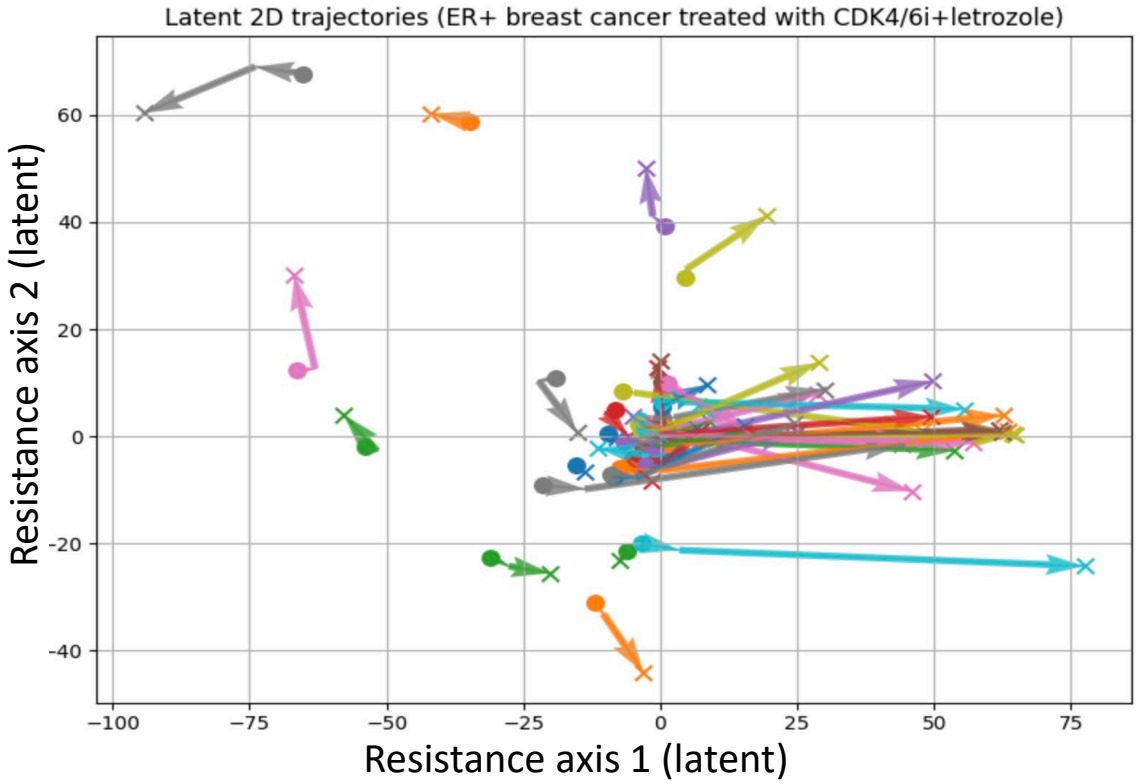
FELINE: ET ± CDK4/6i
ER+ Stage II/III, n=62
Day 0, 14, 180

Analysis:

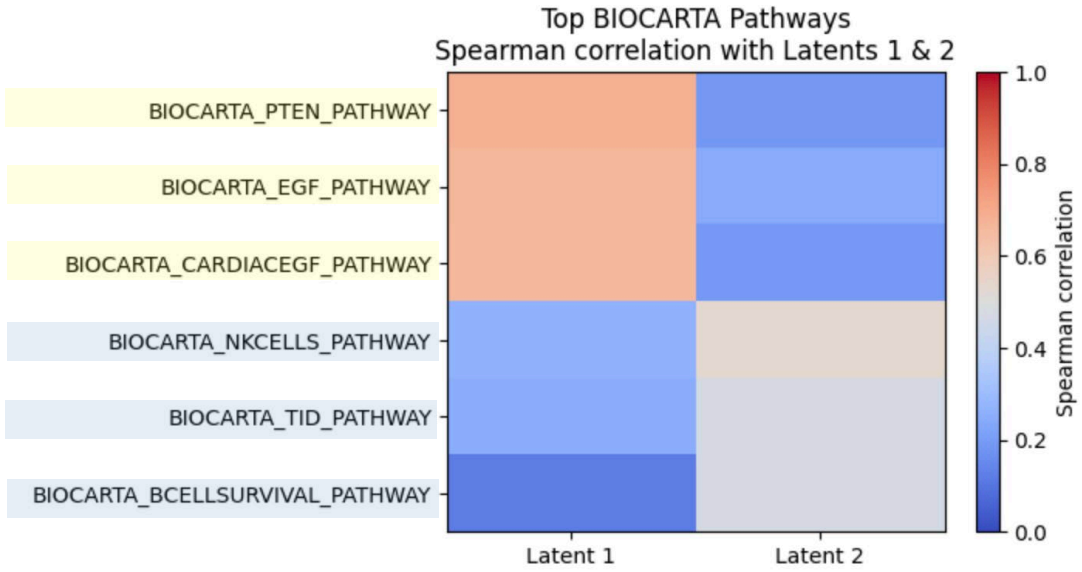
Model NOT informed of:
- Patient outcomes
- Prior scRNA-seq results
- ERBB as target

Result:

ERBB pathway emerges as top feature



Learned evolutionary trajectories of patient tumors



ERBB signaling/response

Immune activation/stress

Griffiths J, Nat Commun, 2025

Interpretable evolutionary insights:
Uncovered convergent evolution of compensatory ERBB signaling shown to be driving CDK4/6i-resistance in ER+ breast cancer.

Clinical application: trajectory-guided decisions

DECISION WORKFLOW

1. BIOPSY

Collect molecular profile during treatment

↓

2. MODEL PREDICTS TRAJECTORY

GP-VAE maps to latent space, forecasts evolution and resistant traits (proof-of-principle ERBB)

↓

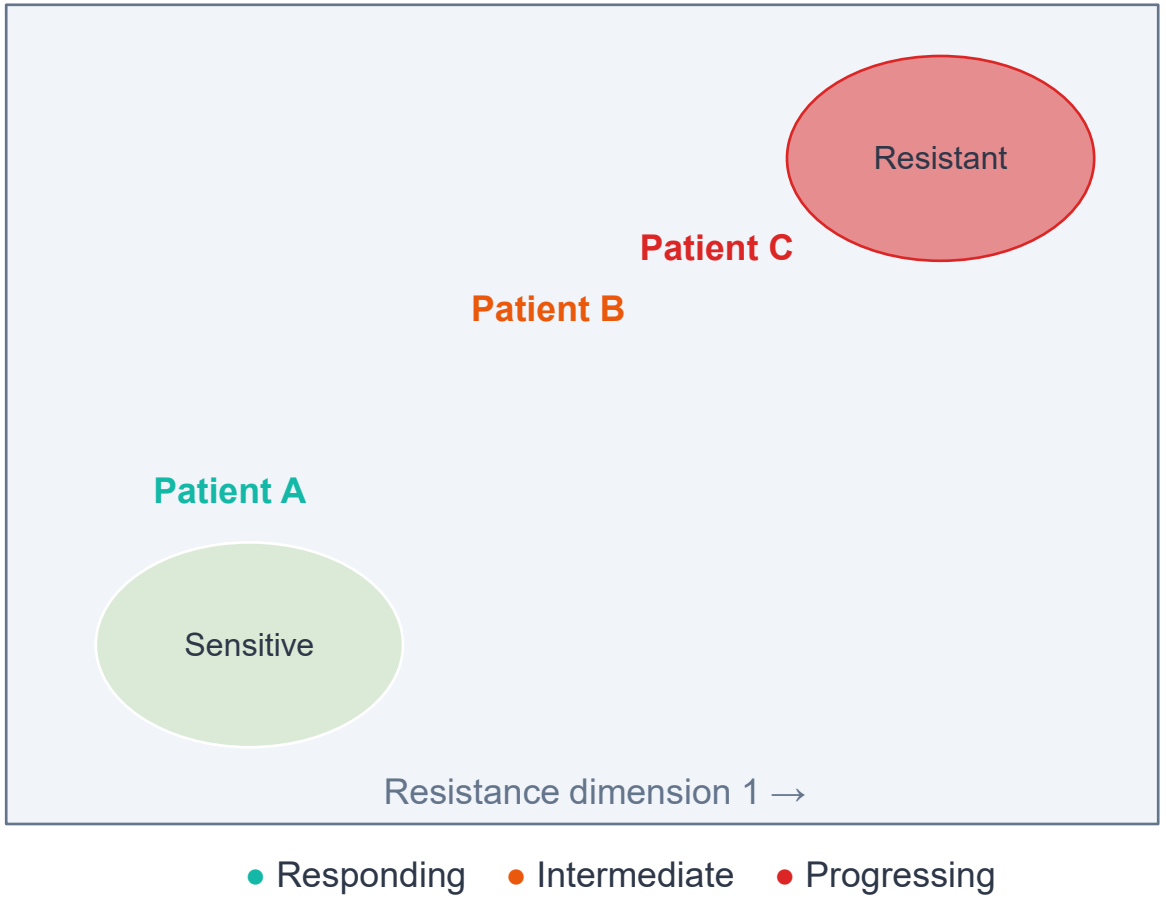
3. TRAJECTORY CLASSIFICATION

Is patient heading toward resistant state?

LOW RISK
Continue current therapy

HIGH RISK
Add ERBBi or switch therapy

LATENT TRAJECTORY SPACE



Clinical Implications

PREDICT

Identify resistance trajectories and resistant traits from patient (and experimental data)

INTERVENE

Identify optimal intervention windows before escape to resistant states

COMBINE

Guide rational combination therapy (e.g., ERBBi + CDK4/6i) based on predicted trajectory

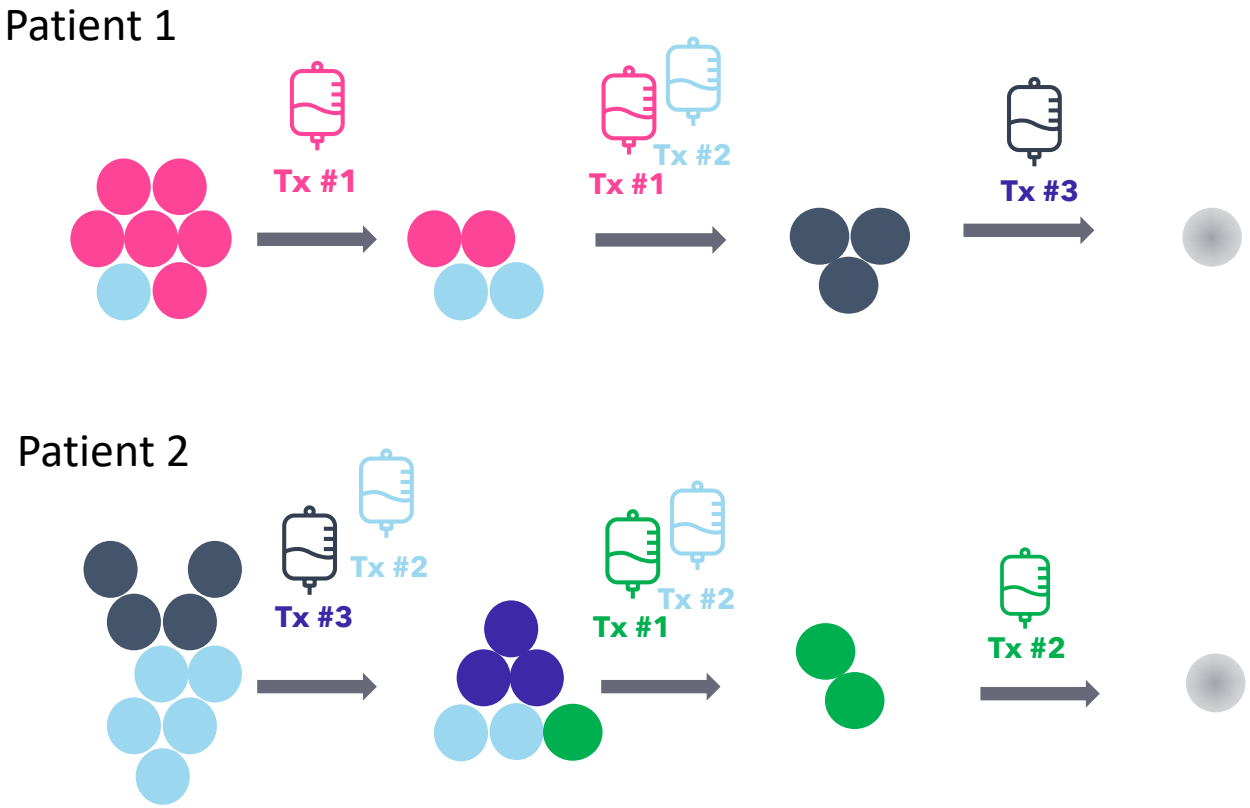
NEXT STEPS

Can we identify common tumor trajectories across patients and optimal treatment sequences?
Can we identify complex heterogeneity of resistant traits over time?
How can we best integrate diverse data types for biologically interpretable predictors?
Can we scale general approach (Framework: Discovery →Testing → Prediction) to a national trial?

From Mechanisms to Prediction

Future State

- Therapies informed by and tailored to observed cancer resistance traits using biomarkers.
- Optimal sequences of therapies that avoid refractory disease and/or durable response



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