Understanding Tumor Heterogeneity and Plasticity Through the Lens of Cancer Stem Cell Model and Mathematical Modeling

Drug-tolerant persister (DTP) and cancer dynamics

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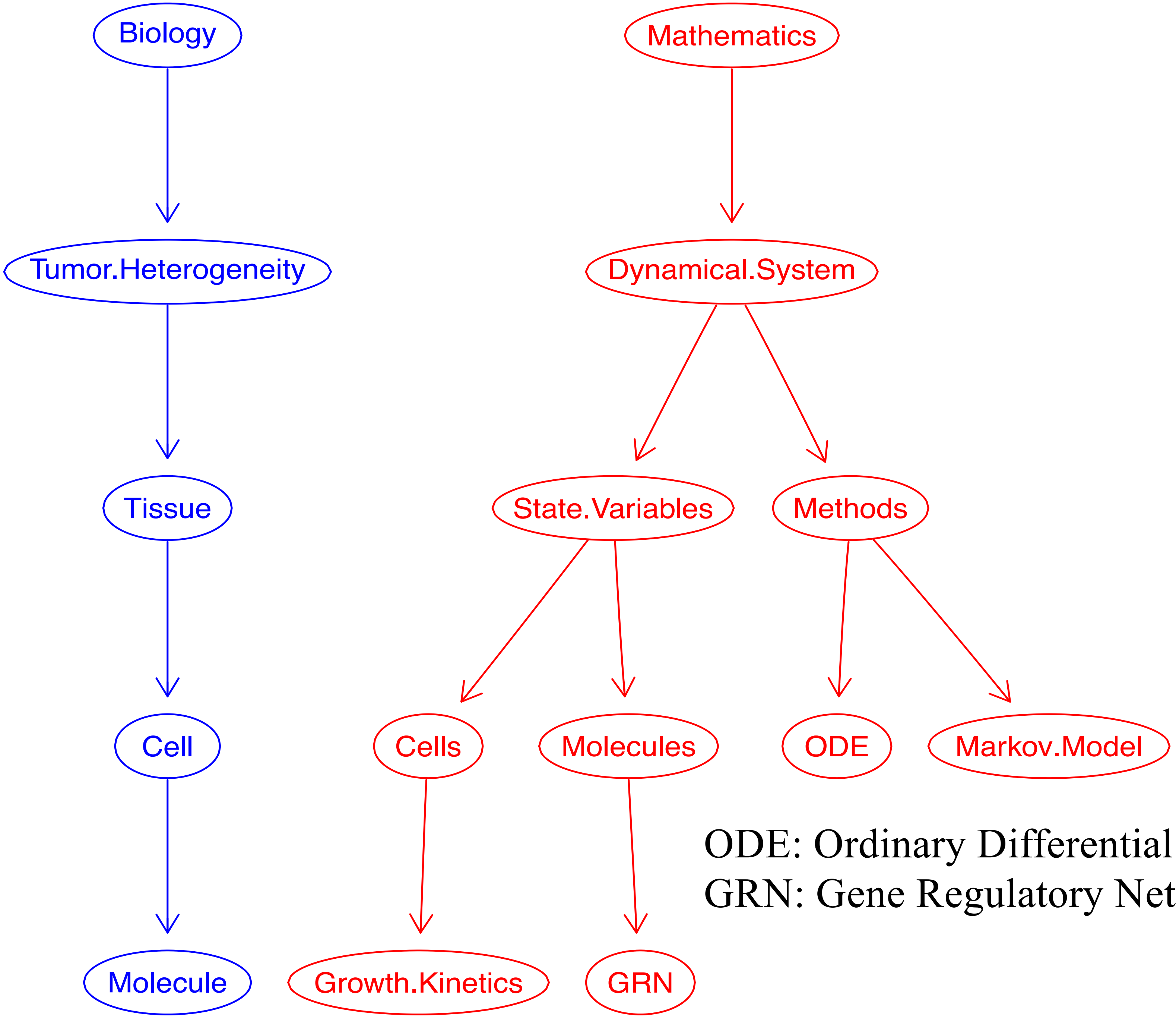
Understanding Biology with Mathematical Modeling



ODE: Ordinary Differential Equation
GRN: Gene Regulatory Network

Priming vs. Desensitization

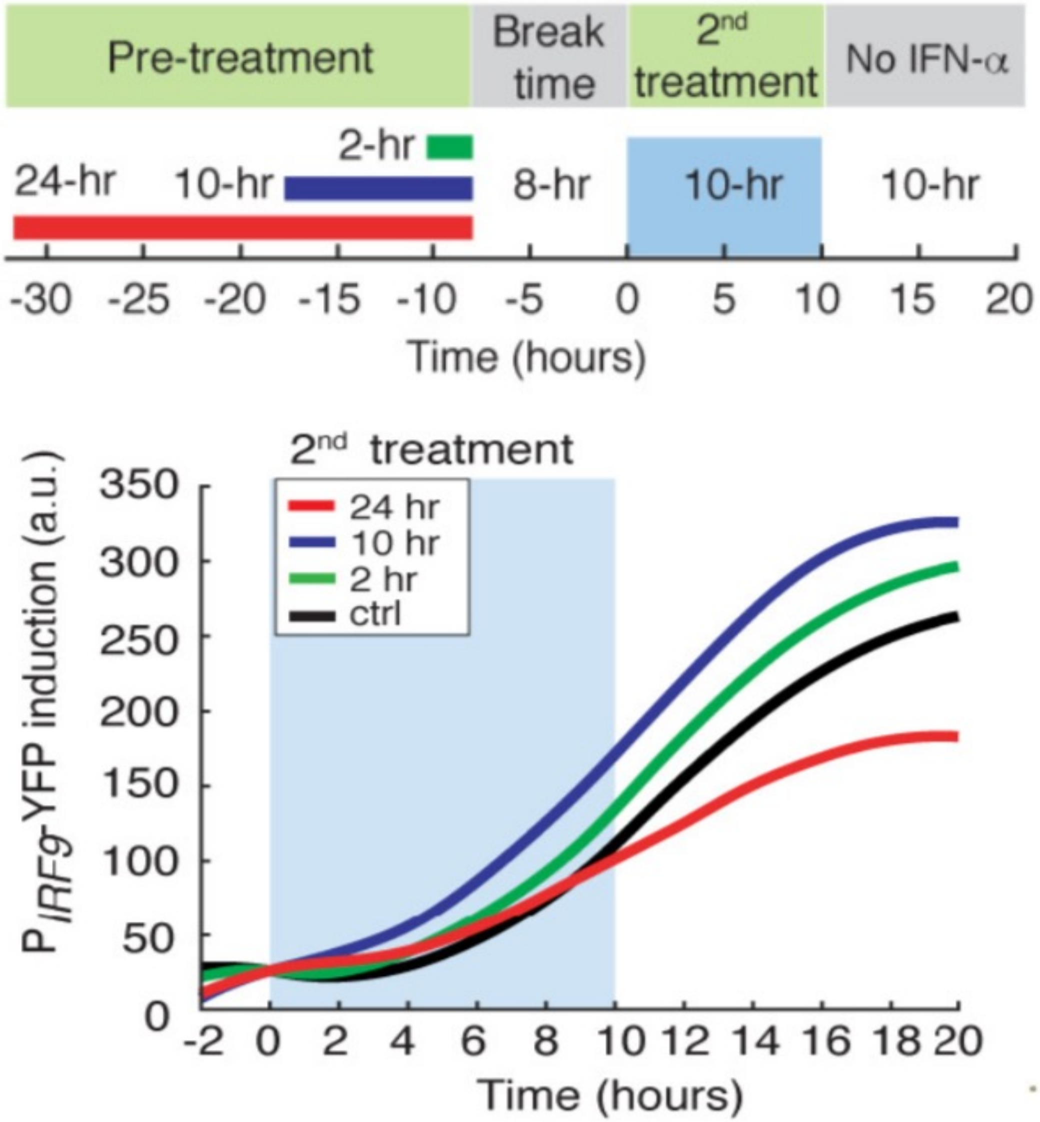
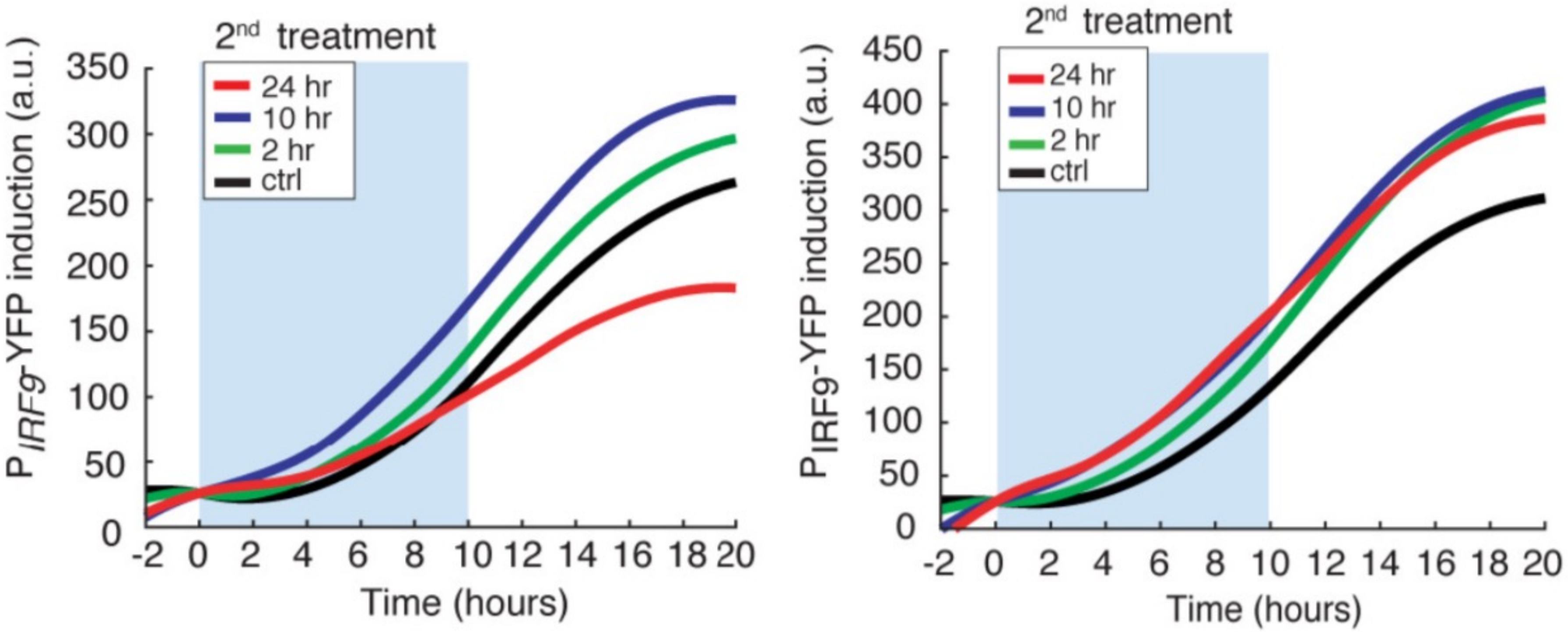


Figure 1 Averaged time traces

Mudla et al. Elife 2020, 9:e58825

USP18 is Required for Desensitization

USP18: ubiquitin-specific peptidase 18



WT

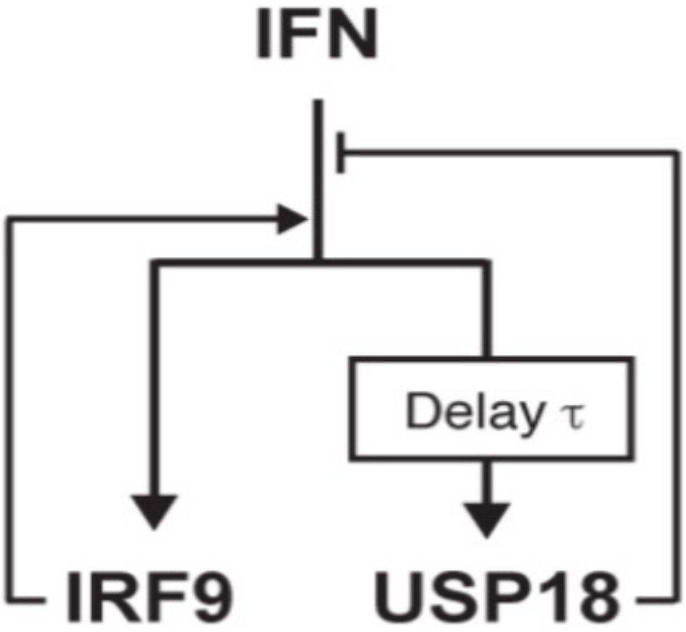
USP18-KD

Averaged time traces

Figure 2

Mudla et al. Elife 2020, 9:e58825

Kinetic Model



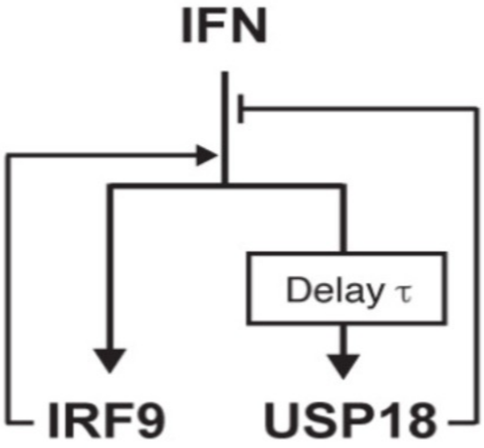
Positive feedback

Negative feedback

Figure 3

Mudla et al. Elife 2020, 9:e58825

ODE for the Kinetic Model



$$\frac{d}{dt}IRF9 = I(t) \bullet (k_4 + pf) \bullet nf$$

$$\frac{d}{dt}USP18 = I(t) \bullet S_u \bullet (k_5 + pf) \bullet nf$$

$$pf = k_1 \bullet \frac{IRF9}{k_2 + IRF9} \qquad nf = \frac{k_3}{k_3 + USP18}$$

$I(t)$ = 0 (without IFN)
$I(t)$ = 1 (with IFN)

$$S_u = \begin{cases} 0, & \text{when the IFN input time} < \tau \\ \boxed{1, \text{when the IFN input time} \geq \tau} \end{cases}$$

Decay of IRF9 and USP18 is low,
therefore not included in the model

CFP-USP18 Reporter

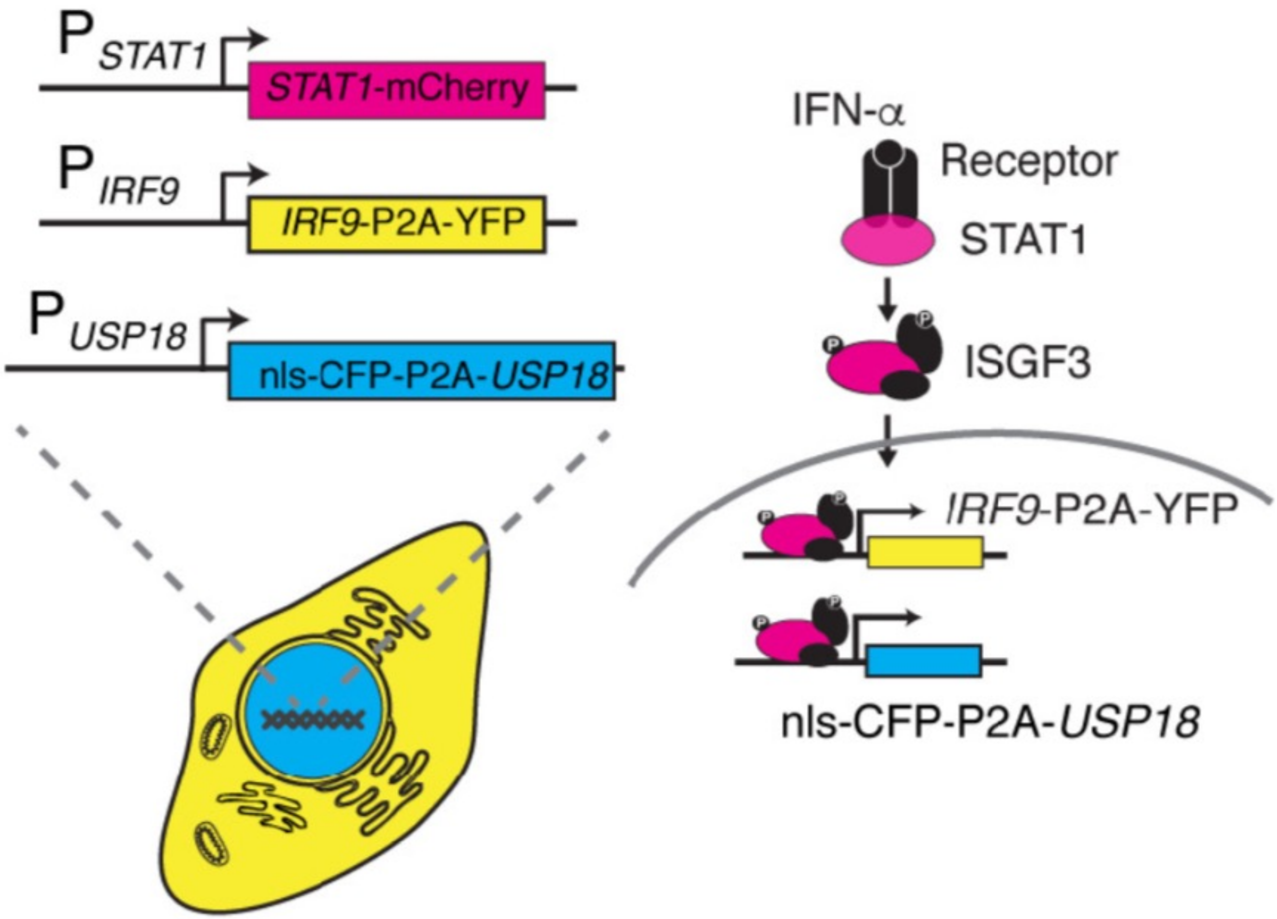


Figure 4

P_{IRF9}-YFP and P_{USP18}-CFP in Response to IFN-α

Time trace of a single cell

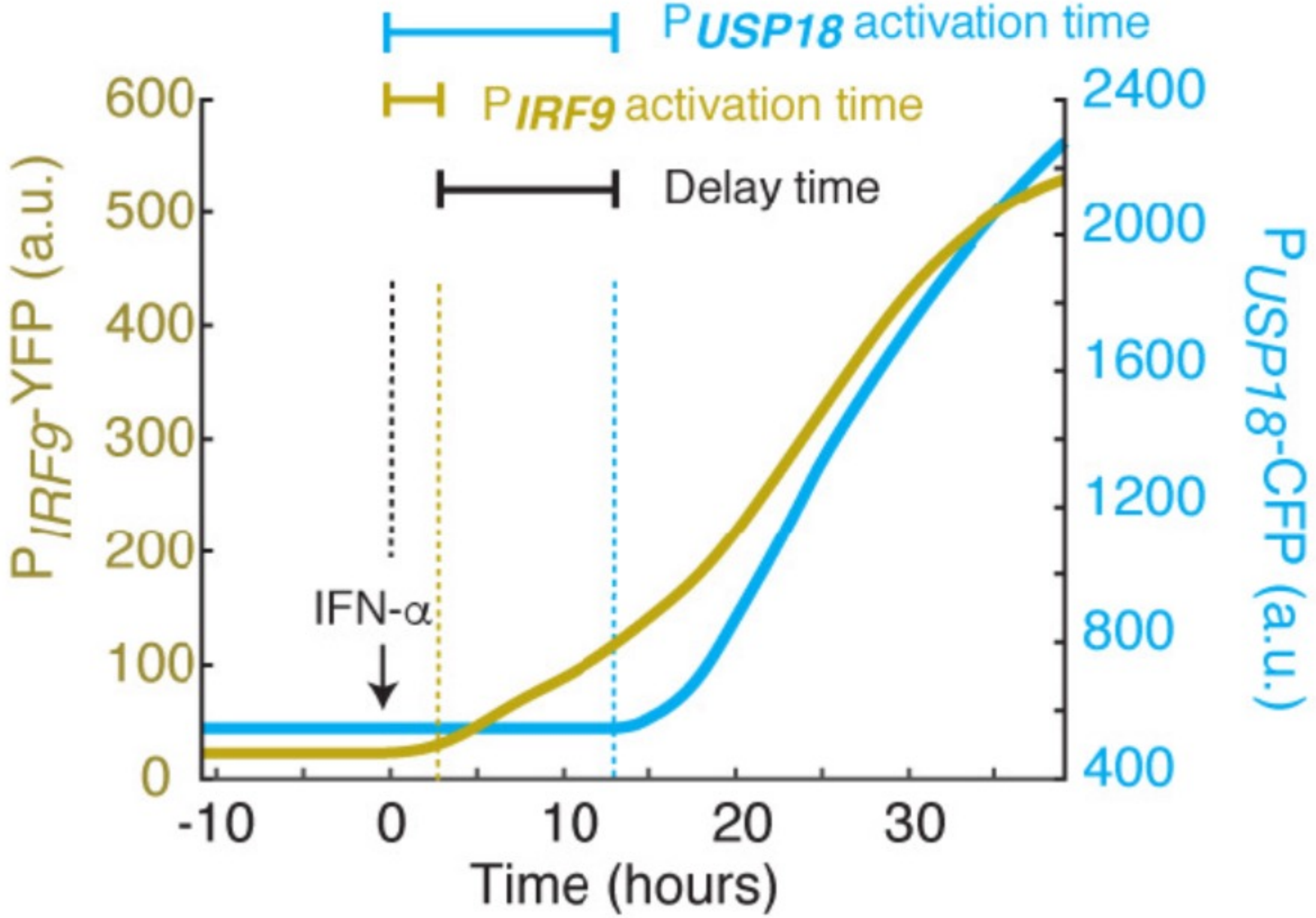
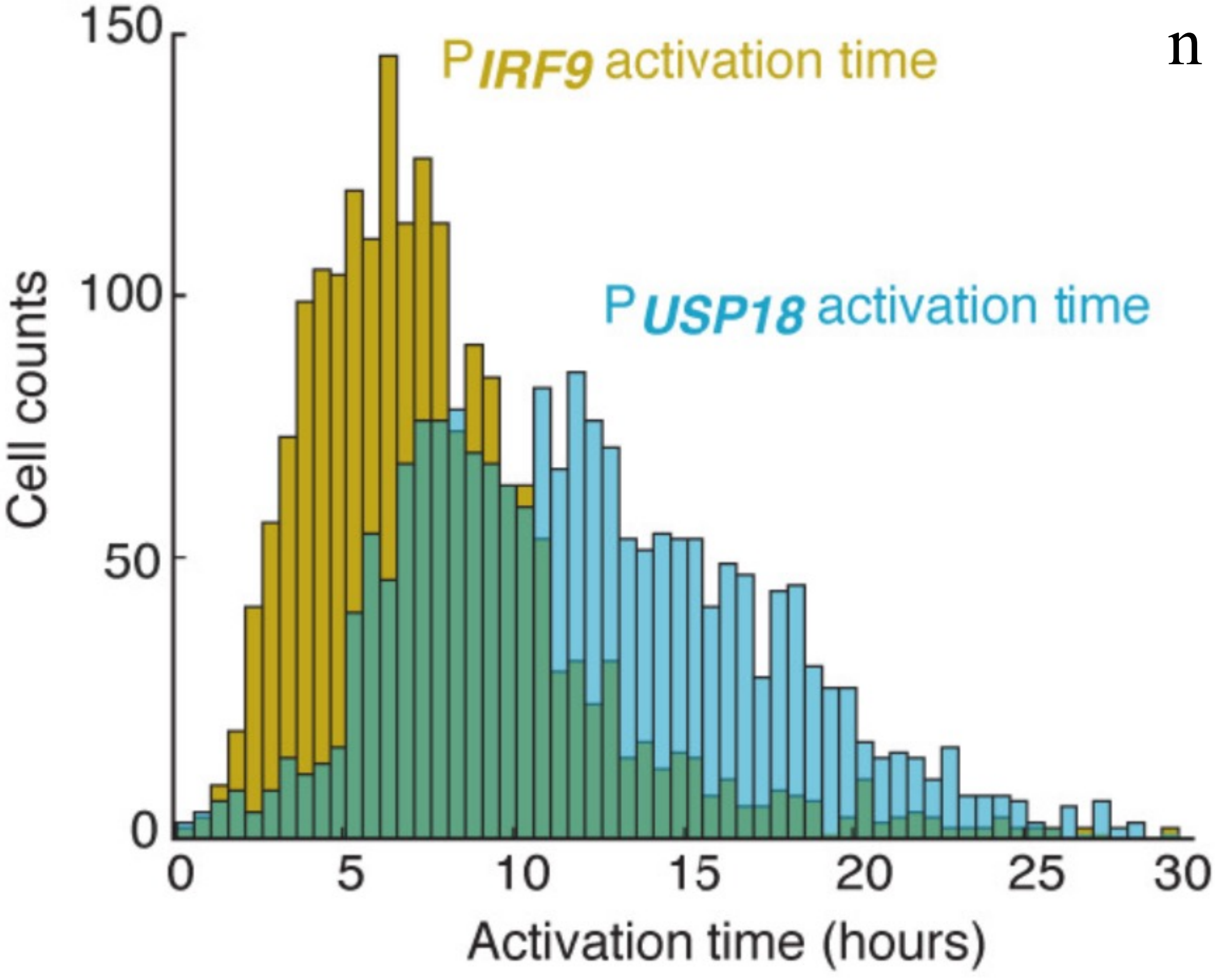


Figure 4B

Distributions of P_{IRF9} and P_{USP18} Activation Times in Single Cells



n = 2021 cells

Figure 4C

Distributions of Delay Times in Single Cells

n = 2021 cells

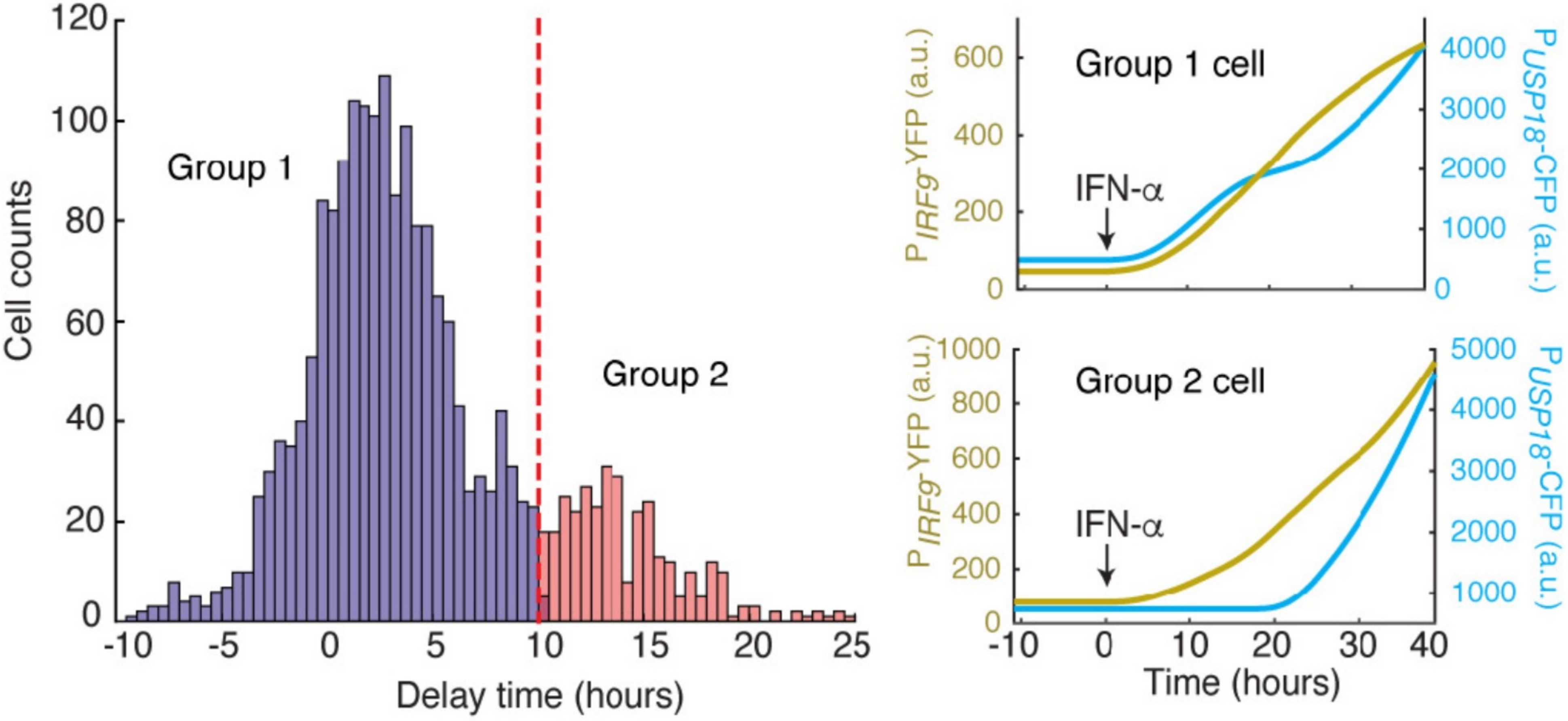


Figure 4D

Time-lapse Images of Cells over Multiple Cell Divisions

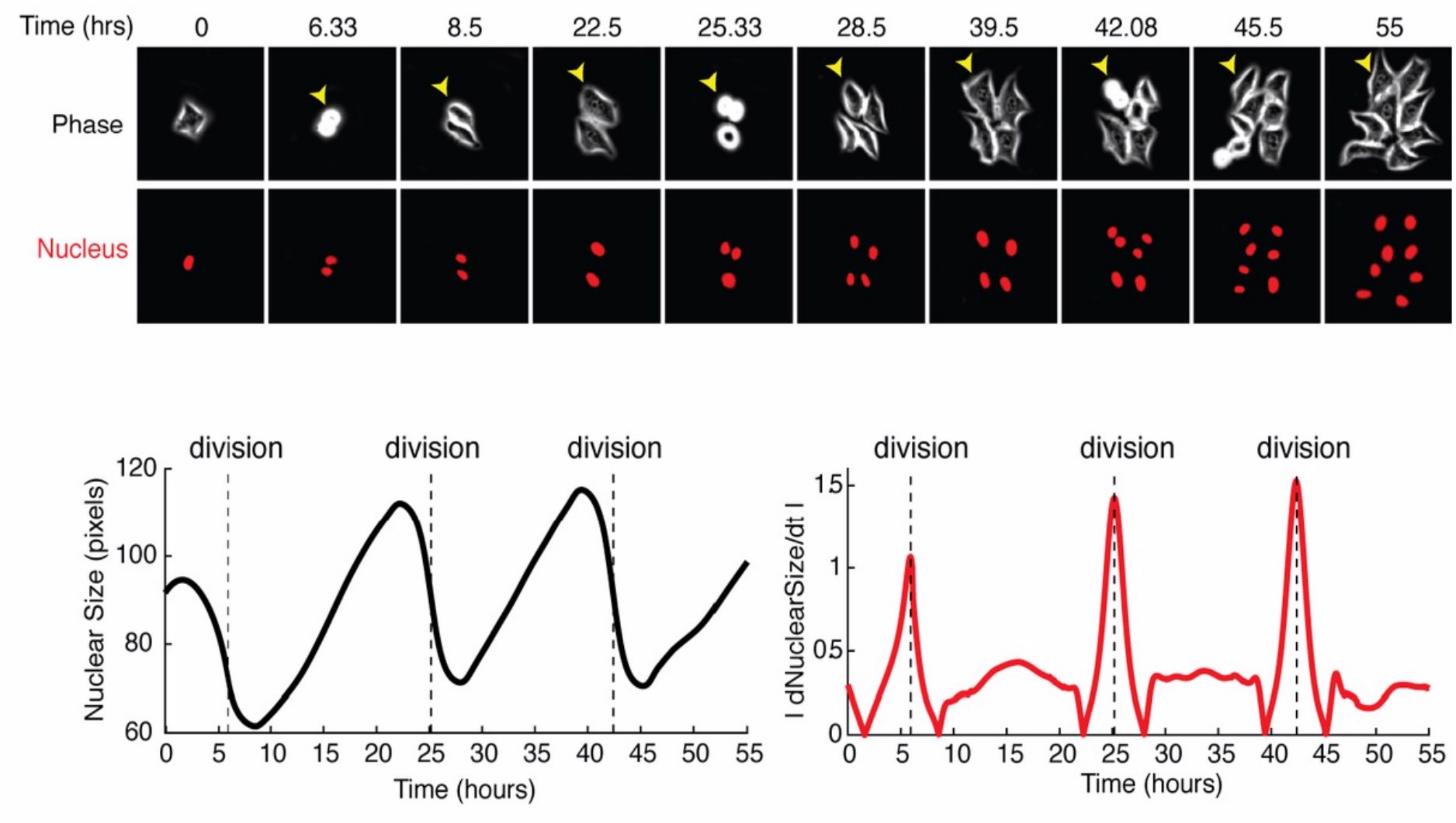


Figure 4-S3A

Distributions of Delay Times vs. Cell Cycle Progression

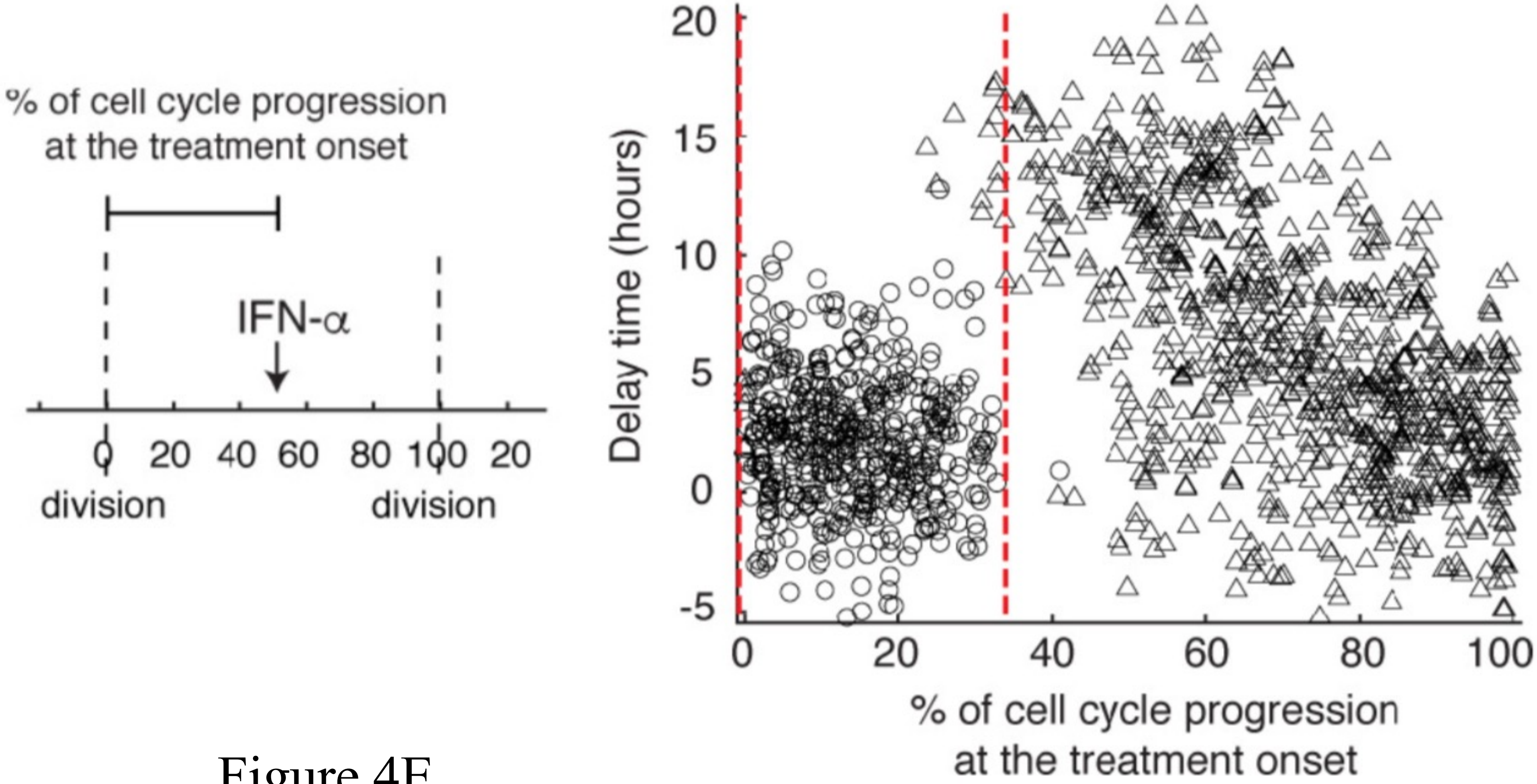
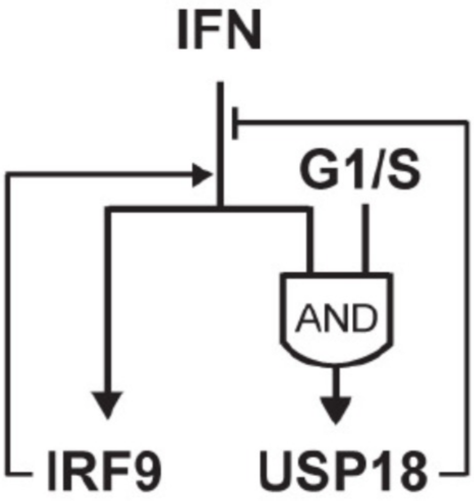


Figure 4E

Stochastic DE with Cell Cycle Gating of USP18 Upregulation



$$\frac{d}{dt} IRF9 = I(t) \bullet (k_4 + pf) \bullet nf + \xi_{IRF9}$$

$$\frac{d}{dt} USP18 = I(t) \bullet S_u\,(k_5 + pf) \bullet nf + \xi_{USP18}$$

ξ_{IRF9} and ξ_{USP18} are white noise terms

S_u is a stochastic step function,
sampled from uniform distribution within a cell cycle

Figure 6A

Drug-Tolerant Persister (DTP)

Bacterial Persistence as a Phenotypic Switch: non-genetic and reversible

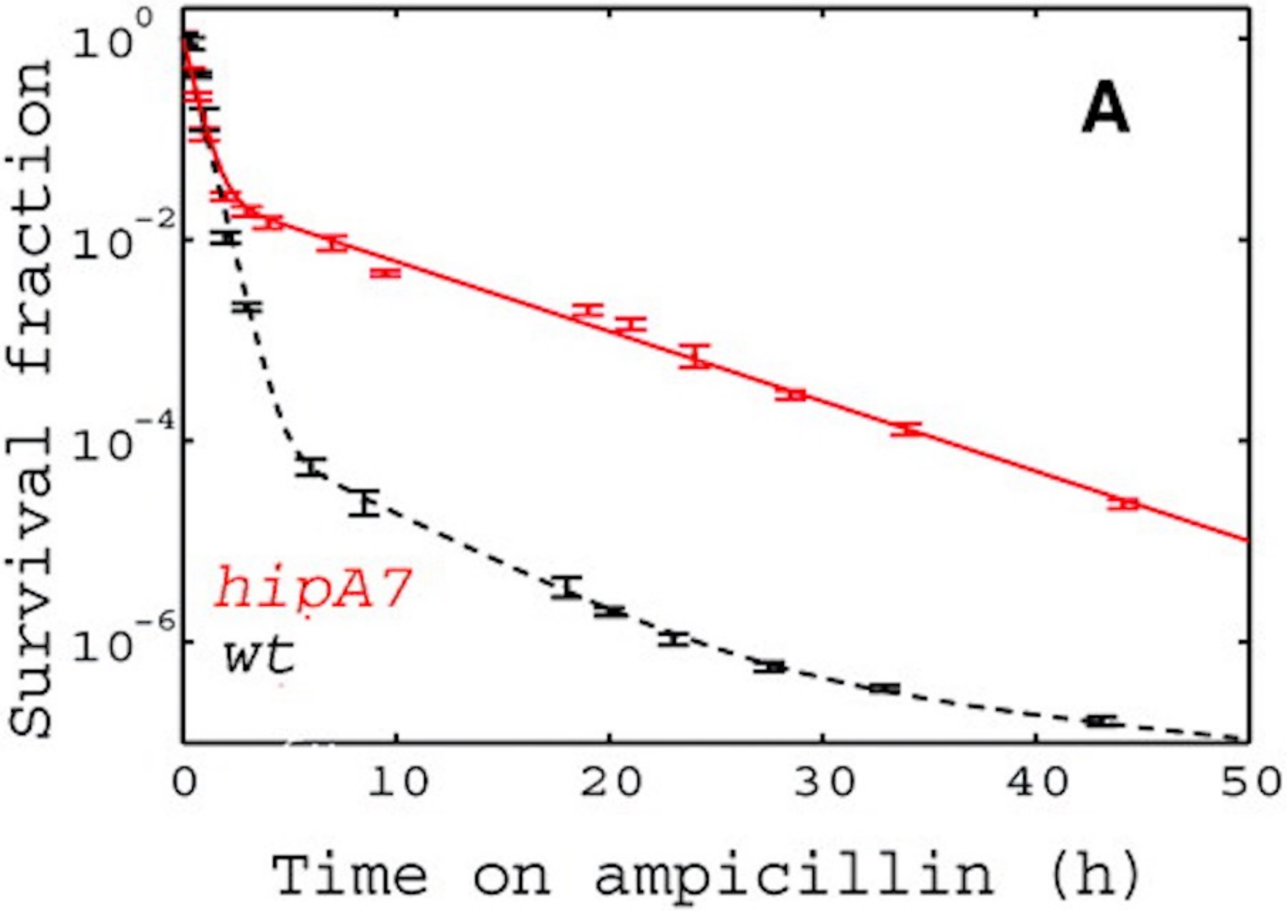


Figure 1

Balaban et al. Science 2004, 305:1622 WB Bigger, *Lancet* **ii**, 497 (1944)

Drug-Tolerant Persister (DTP)

Bacterial Persistence as a Phenotypic Switch: non-genetic and reversible

hipA7

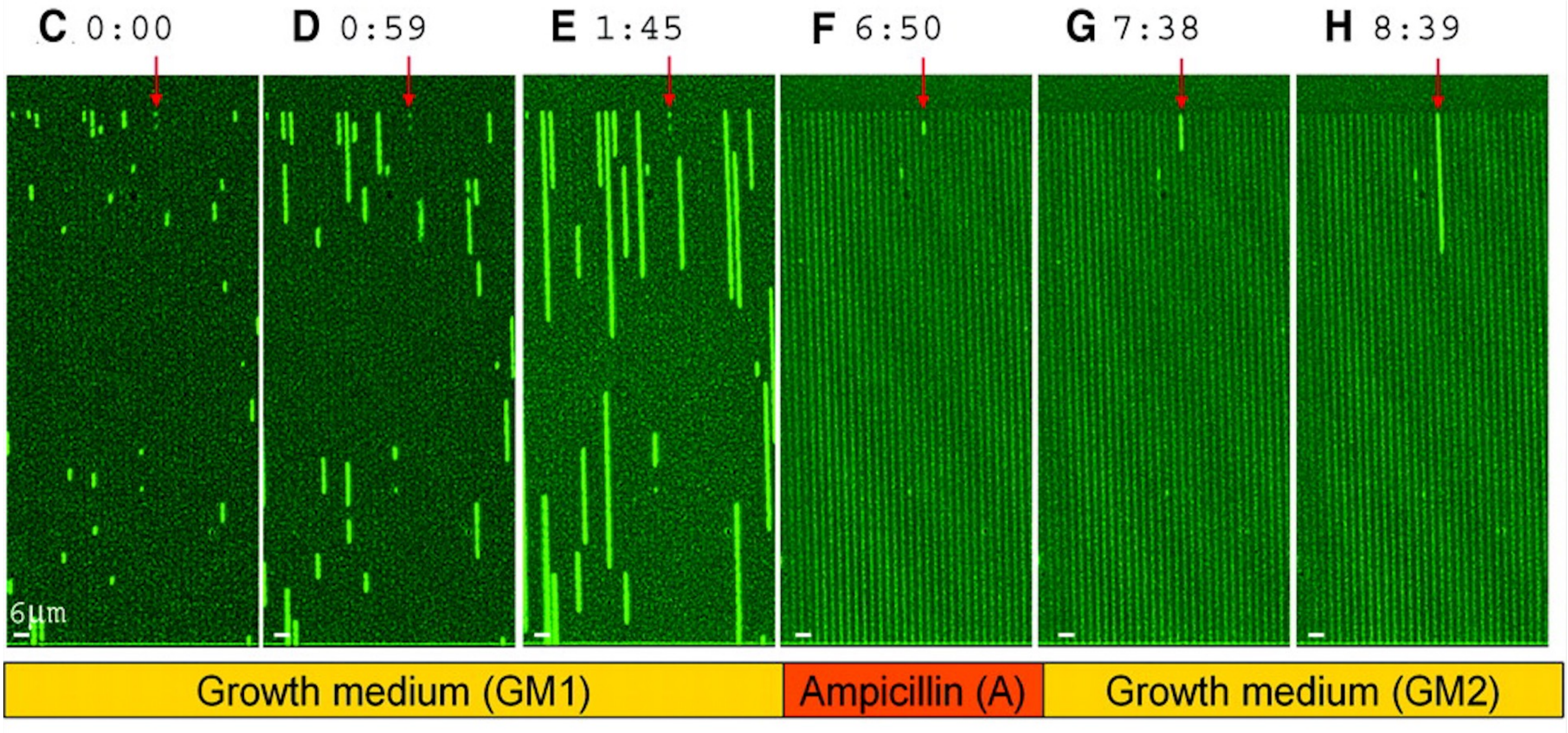
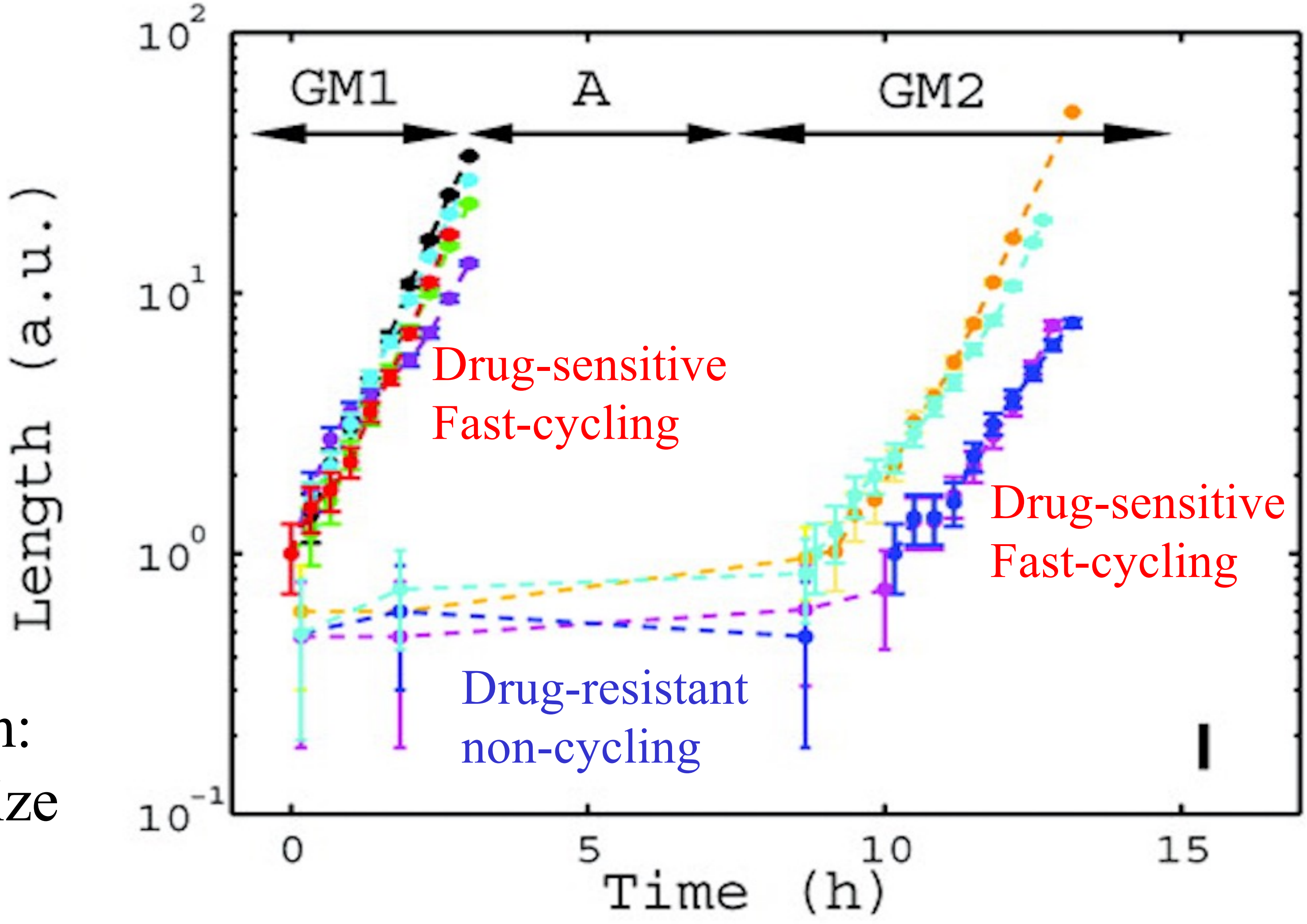


Figure 1 Balaban et al. Science 2004, 305:1622

Bacterial Persistence as a Phenotypic Switch: non-genetic and reversible

hipA7



Drug-sensitive
Fast-cycling

Drug-sensitive
Fast-cycling

Drug-resistant
non-cycling

Length:
clone size

Persisters constitute 1~5% of cells

Figure 1 Balaban et al. Science 2004, 305:1622

Bacterial Persistence as a Phenotypic Switch: non-genetic and reversible

hipA7

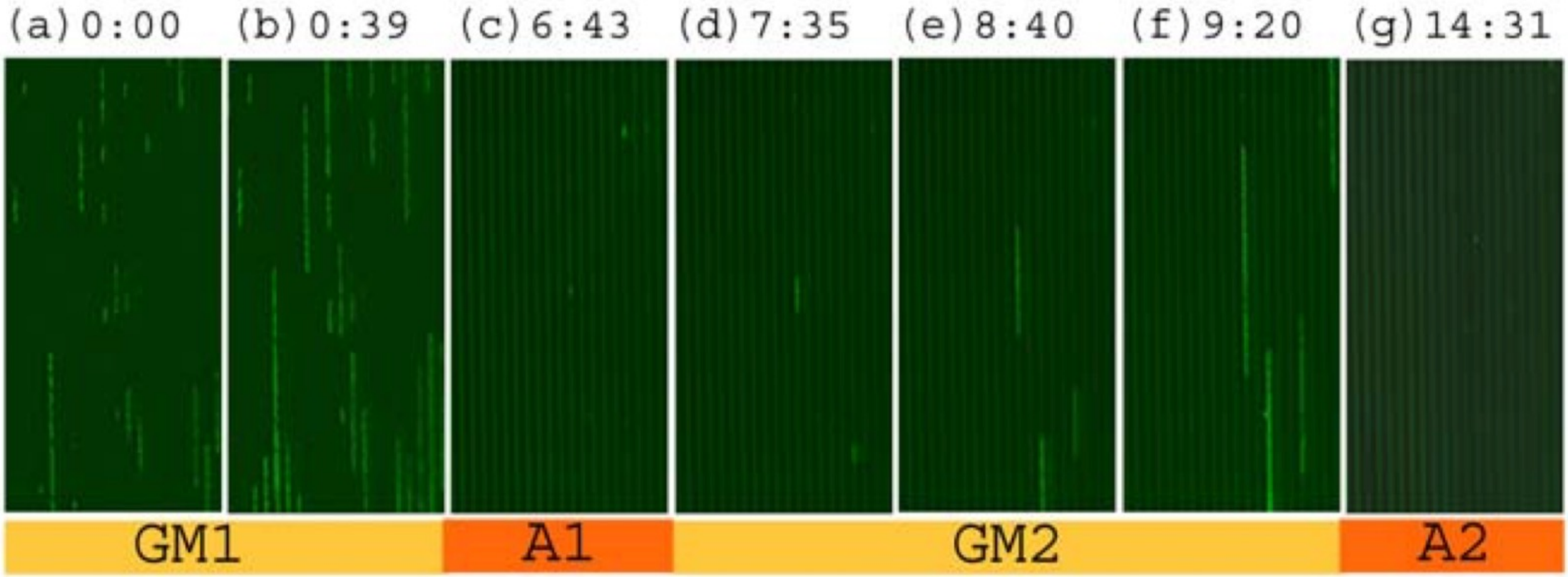
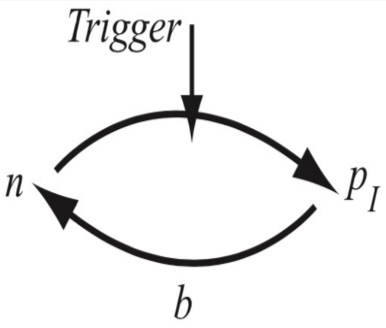
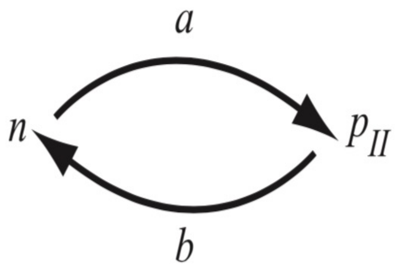


Figure S1 Balaban et al. Science 2004, 305:1622

Bacterial Persistence as a Phenotypic Switch: non-genetic and reversible

Type I persisters	Type II persisters
hipA7 	 *hipQ*
$\begin{cases} \frac{dp_I}{dt} = -bp_I + \mu_p p_I \\ \frac{dn}{dt} = bp_I + \mu_n n \end{cases}$ Eq.(1)	$\begin{cases} \frac{dn}{dt} = -an + bp_{II} + \mu_n n \\ \frac{dp_{II}}{dt} = an - bp_{II} + \mu_p p_{II} \end{cases}$ Eq. (2)

$\mu_p \approx 0$

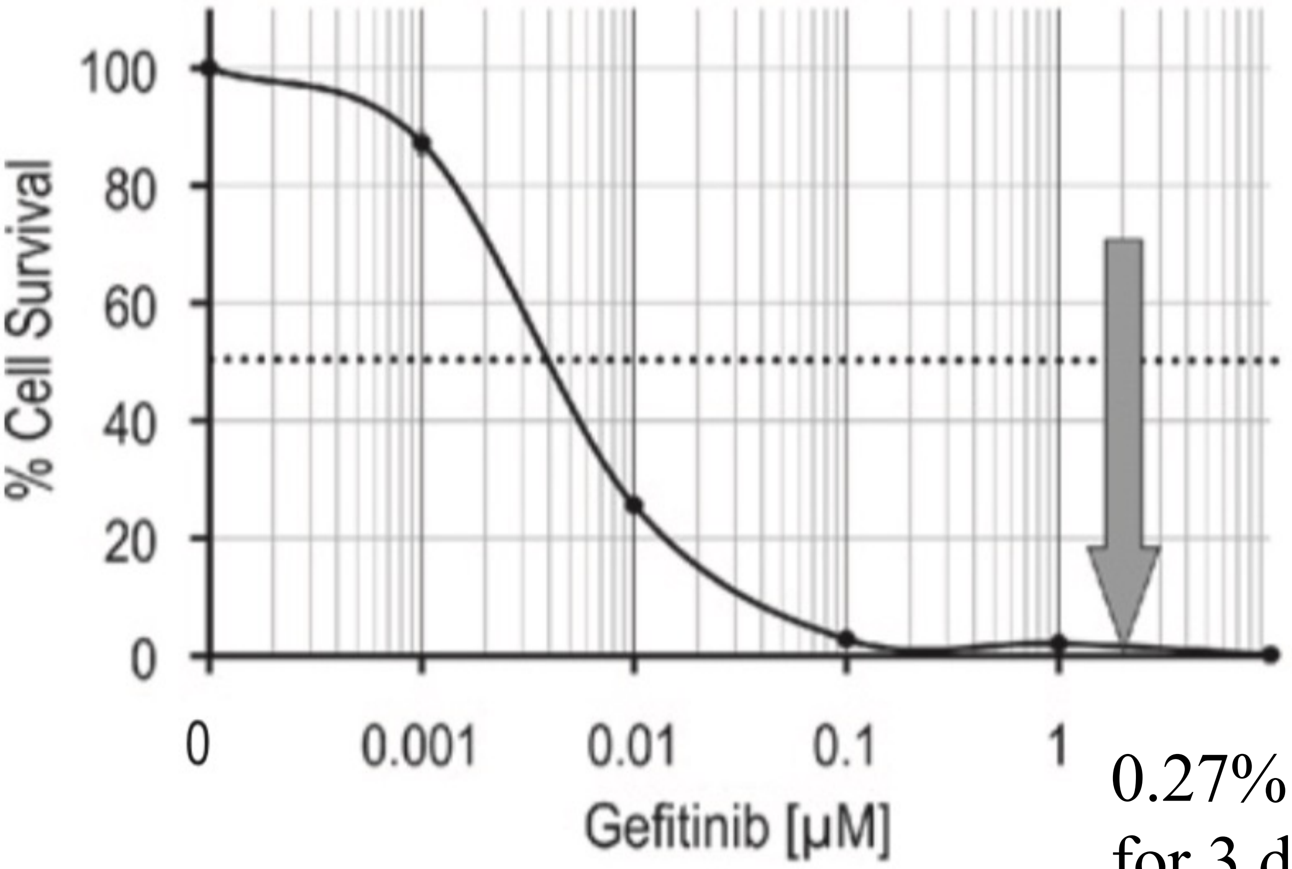
$a \approx 0$

$b \approx 0.07$

Figure 2 Balaban et al. Science 2004, 305:1622

Drug-Tolerant Persister (DTP)

PC9 NSCLC cells



0.27% at 2 μM
for 3 days

EGFR tyrosine kinase inhibitors (TKIs)

Figure 1A

Sherma et al. Cell 2010, 141:69

Drug-Tolerant Persister (DTP)

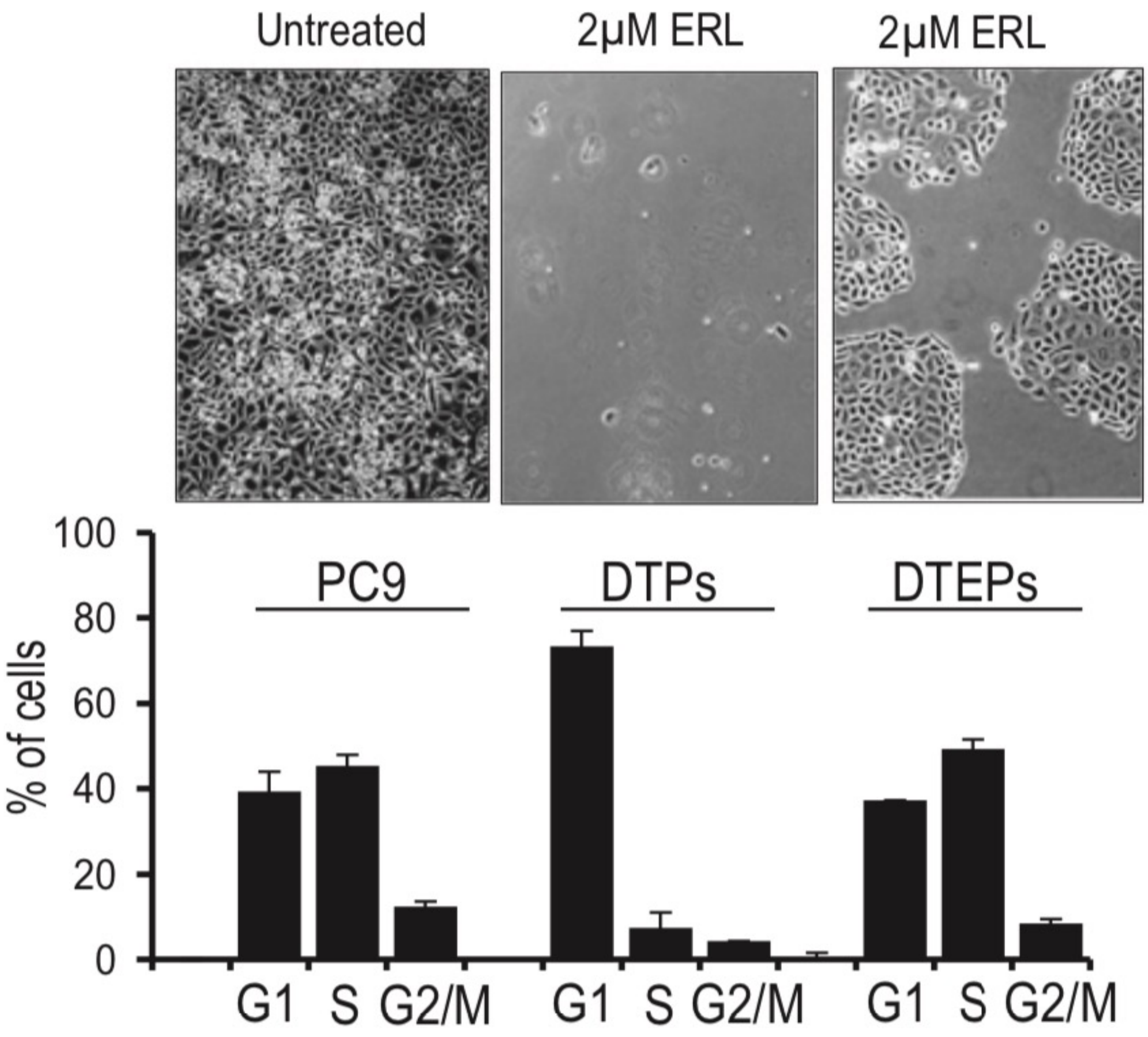


Figure 1B

Sherma et al. Cell 2010, 141:69

ERL: erlotinib

DTP:
treated with drug
For 9 days

DTEP:
drug-tolerant
expanded persister
treated with drug
For 33 days
20% DTPs develop
into DTEPs

CSC Marker CD133 is Expressed in DTPs

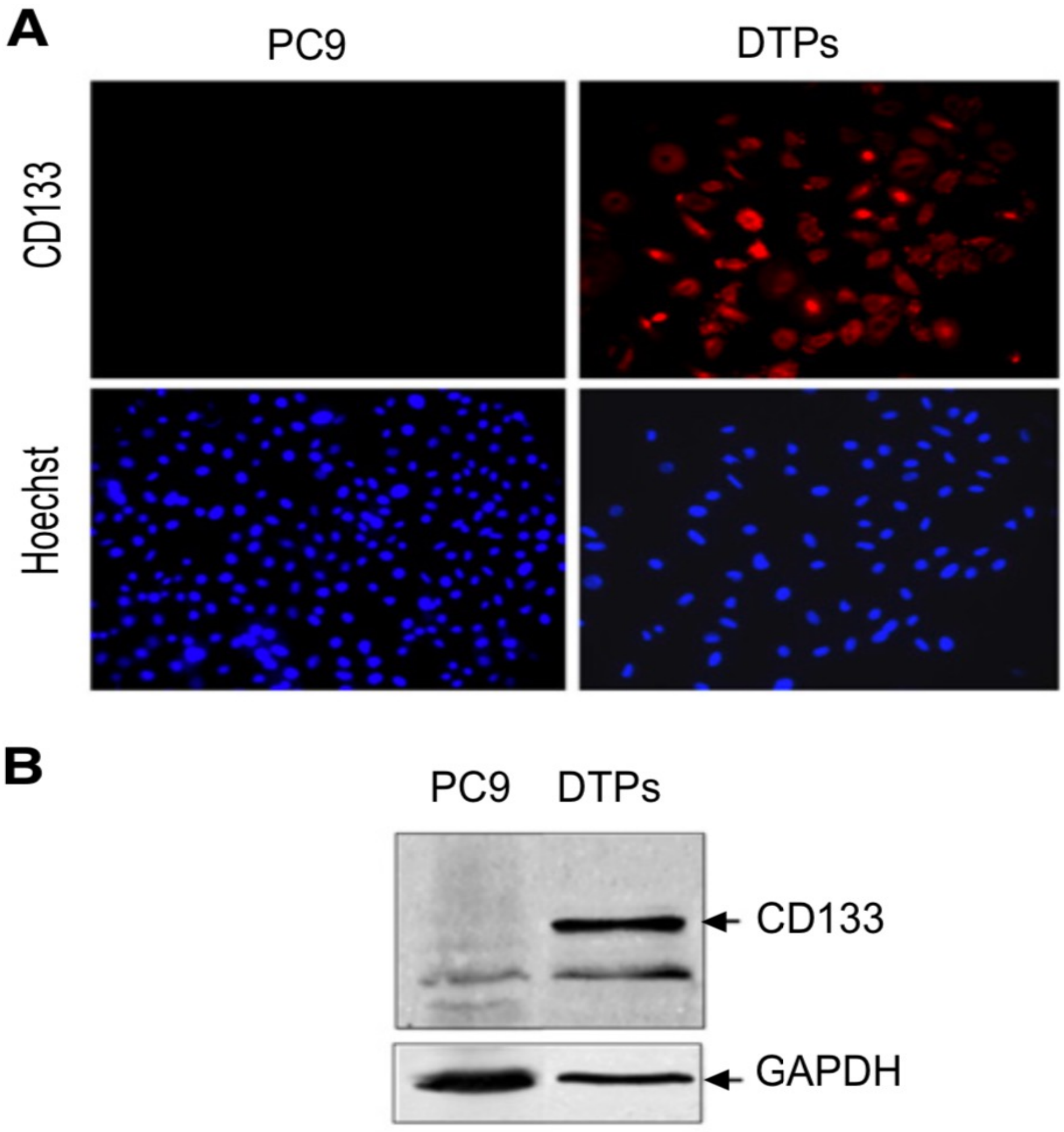


Figure 2

CD133 Expression in DTEP Is Similar to PC9

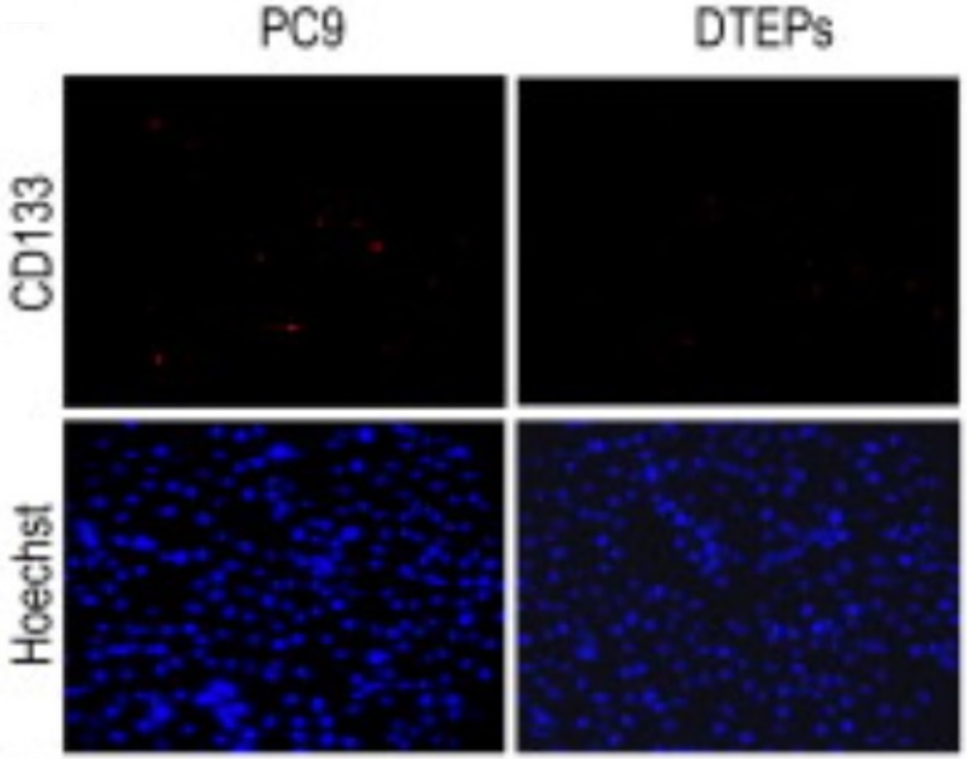


Figure S2B

DTPs Revert back to Drug-Sensitive Phenotype after Re-expansion in Drug-free Medium

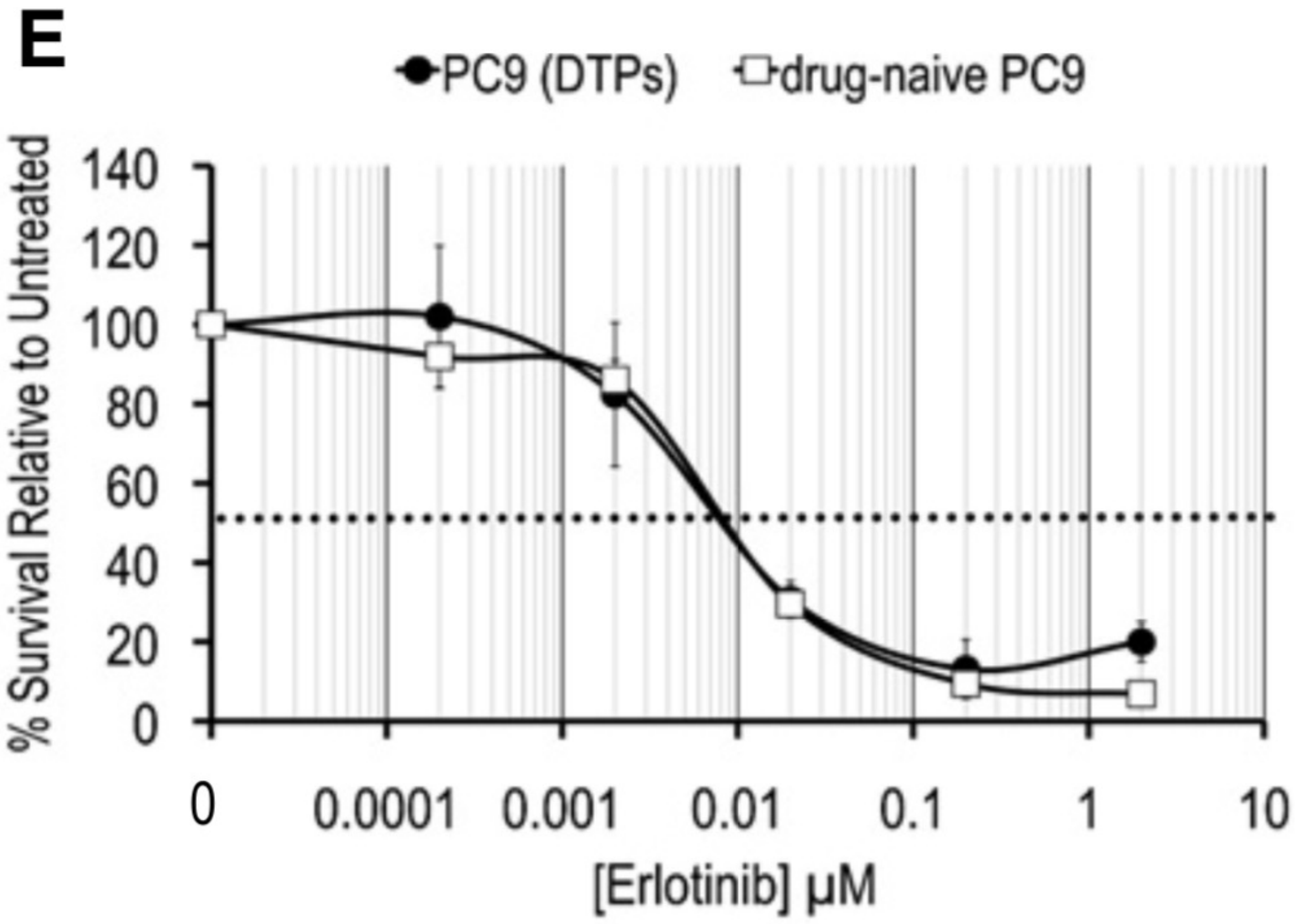


Figure 2E

DTEPs Revert back to Drug-Sensitive Phenotype after 29 Passages in Drug-free Medium

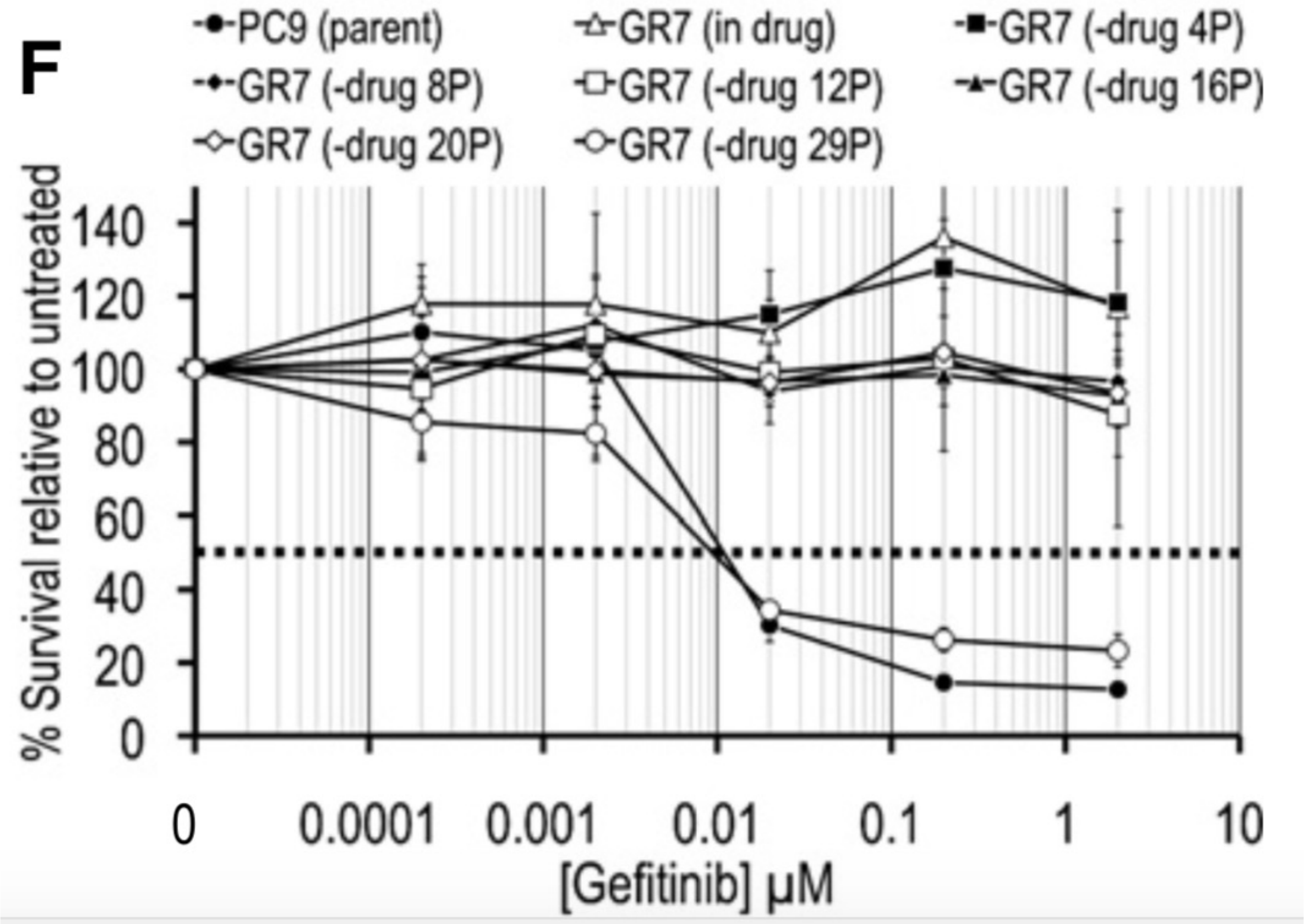


Figure 2F

DTEPs Revert back to Drug-Sensitive Phenotype after 31 Passages in Drug-free Medium

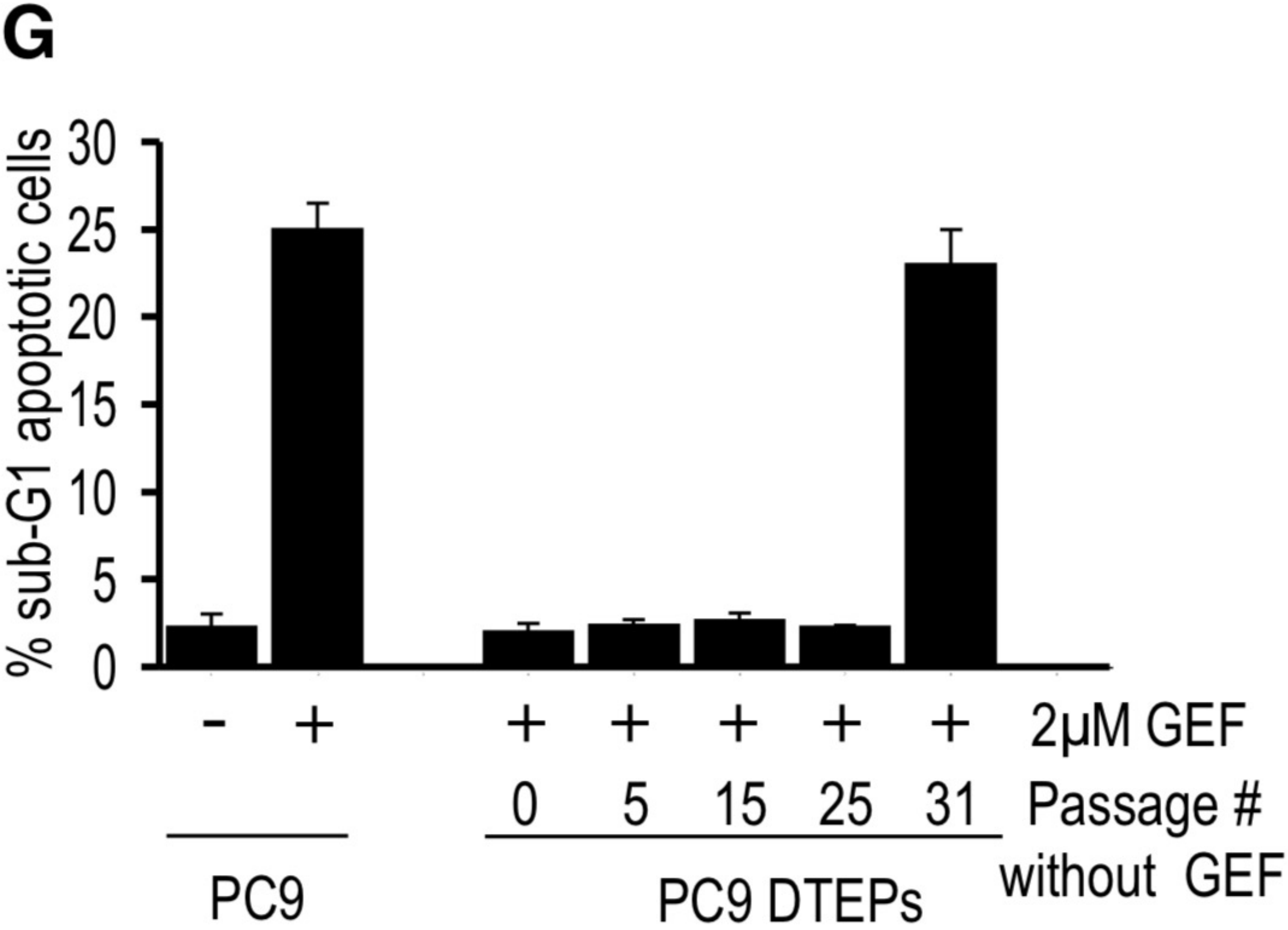


Figure 2G

Drug Tolerance Requires Histone Demethylase KDM5A

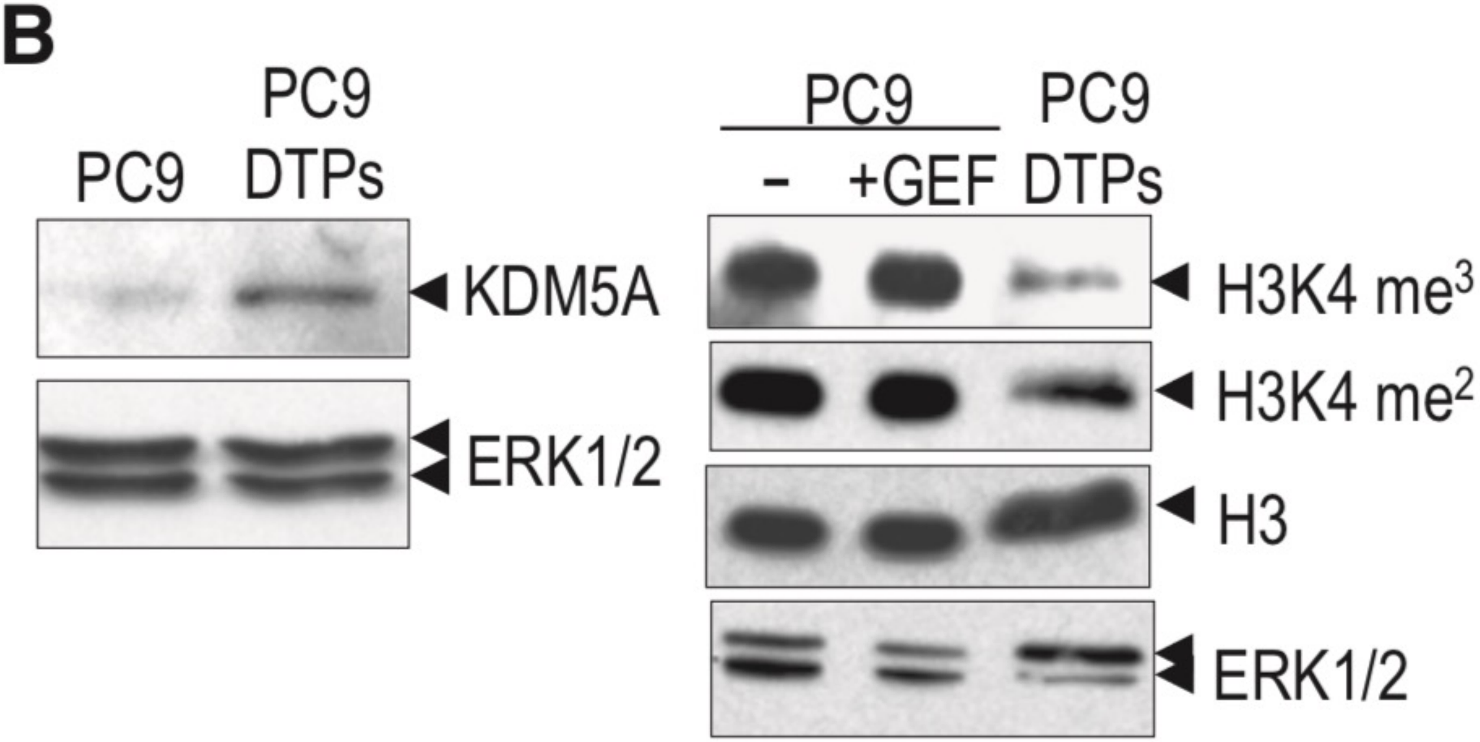


Figure 3B

Drug Tolerance Requires Histone Demethylase KDM5A

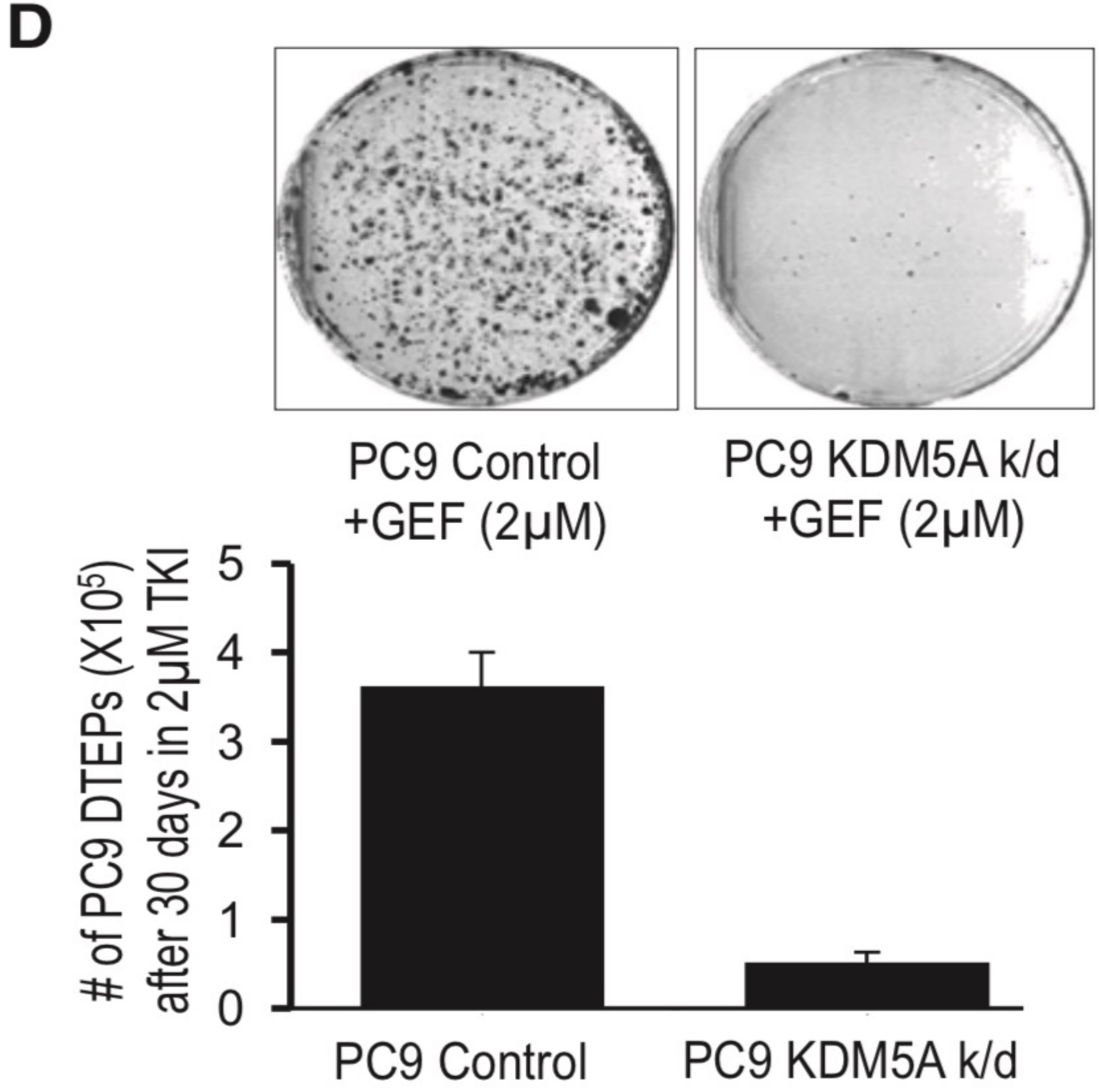


Figure 3D

Colorectal Cancer Cells Enter a Diapause-like DTP State to Survive Chemotherapy

5-FU/LV: 5-fluorouracil and leucovorin
CPT-11: irinotecan
FOLFIRI: 5-FU/LV and CPT-11
CPT: Camptothecin

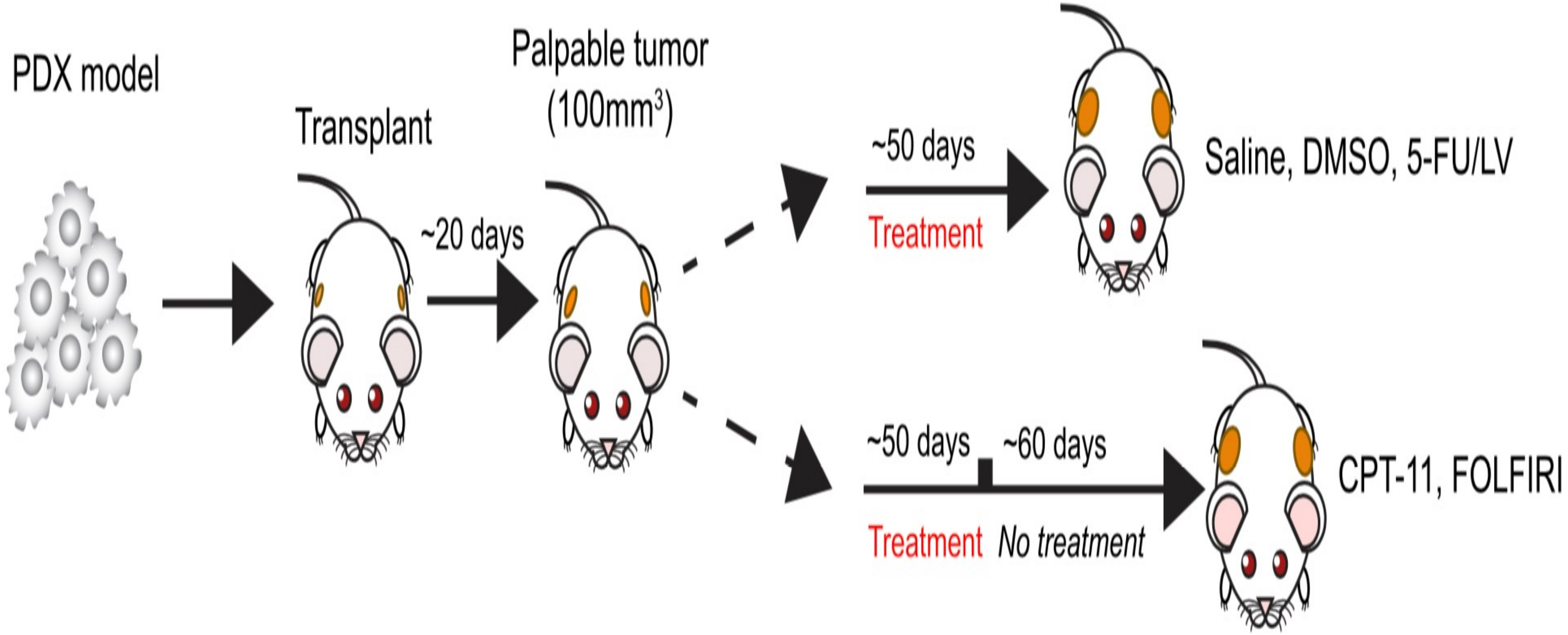


Figure 1A

Rehman et al. Cell 2021, 184:226

Colorectal Cancer Cells Enter a Diapause-like DTP State to Survive Chemotherapy

POP66: a PDX model

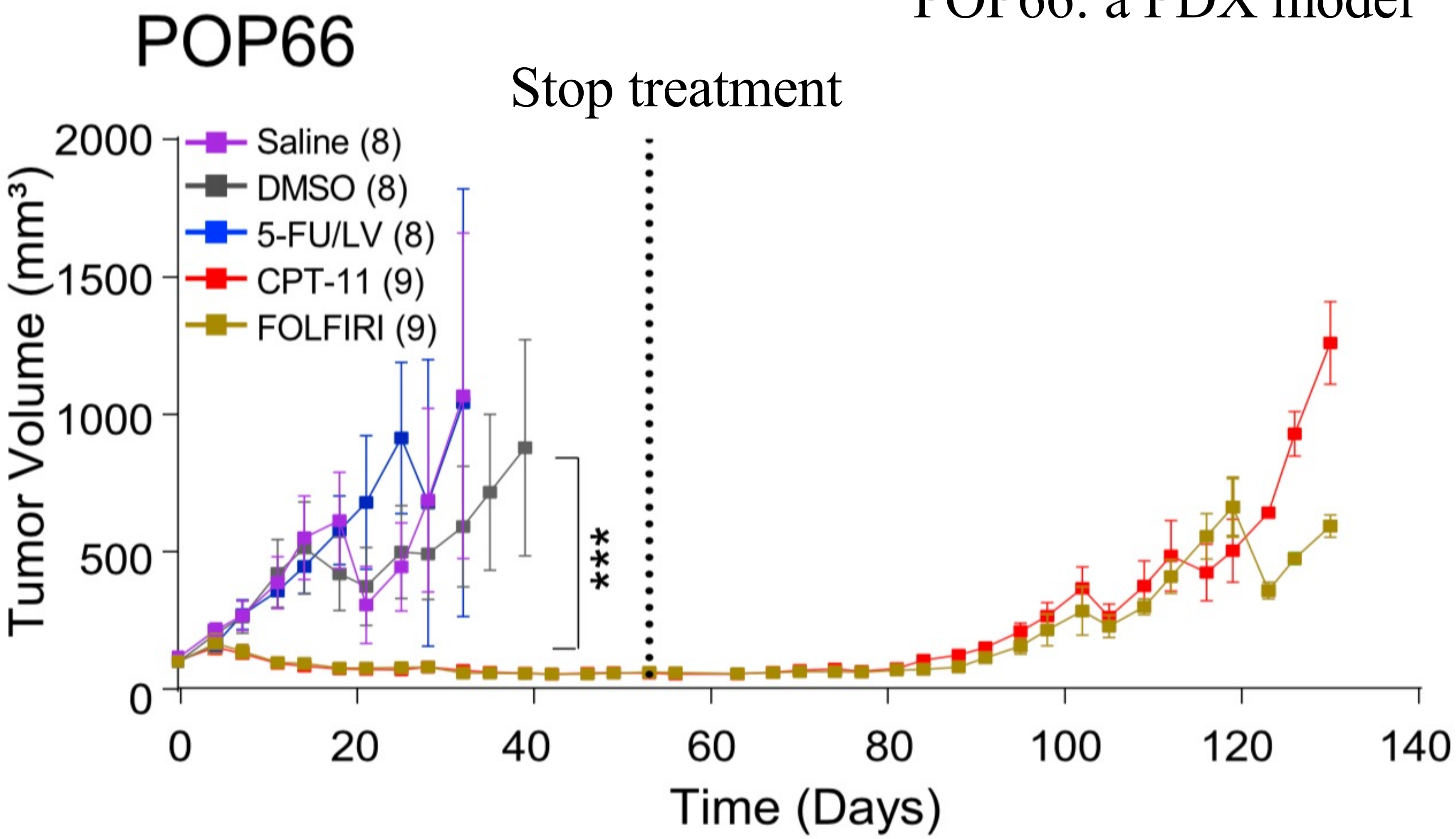


Figure 1B

Rehman et al. Cell 2021, 184:226

Colorectal Cancer Cells Enter a Diapause-like DTP State to Survive Chemotherapy

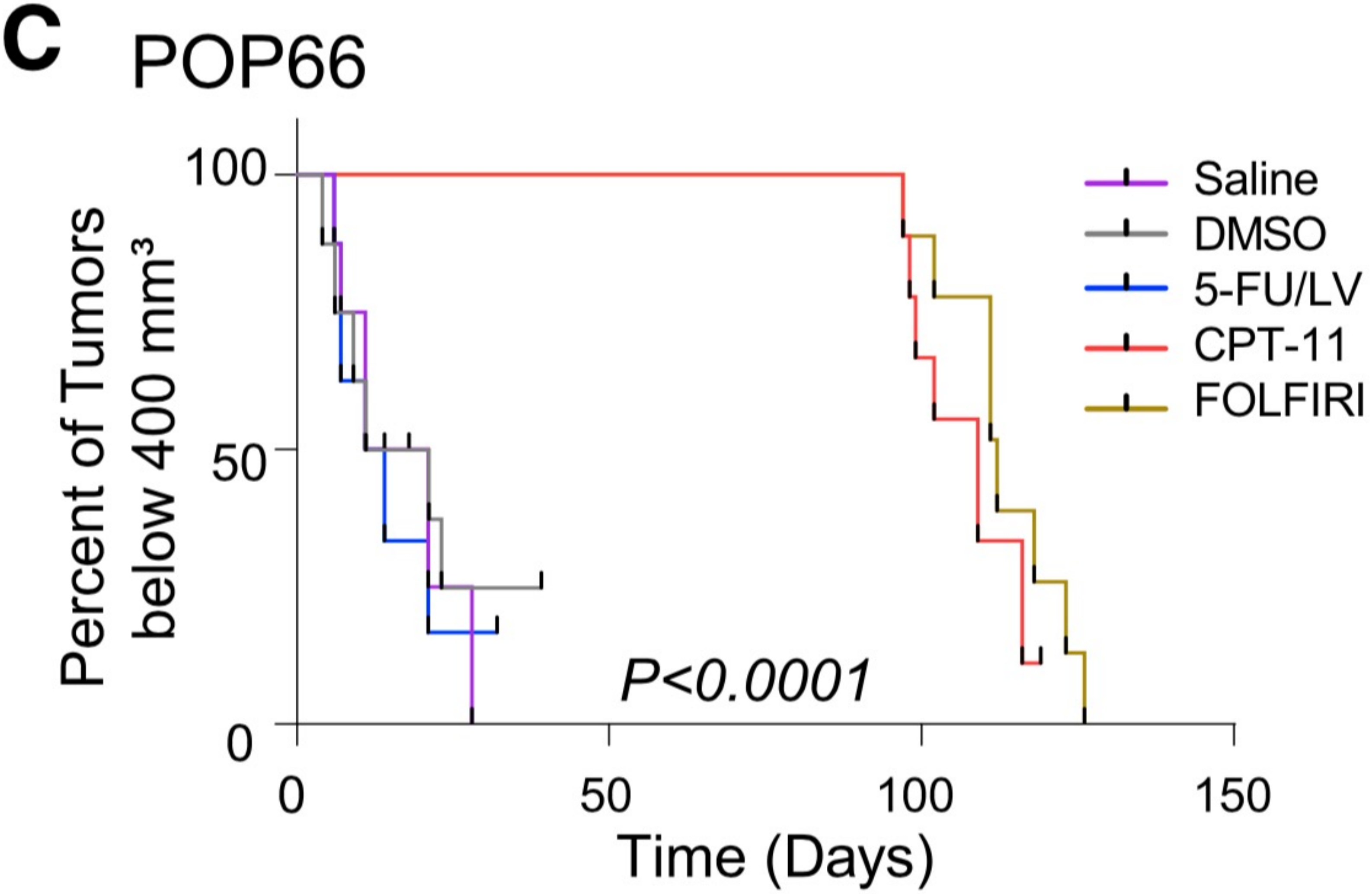


Figure 1C

Rehman et al. Cell 2021, 184:226

Colorectal Cancer Cells Enter a Diapause-like DTP State to Survive Chemotherapy

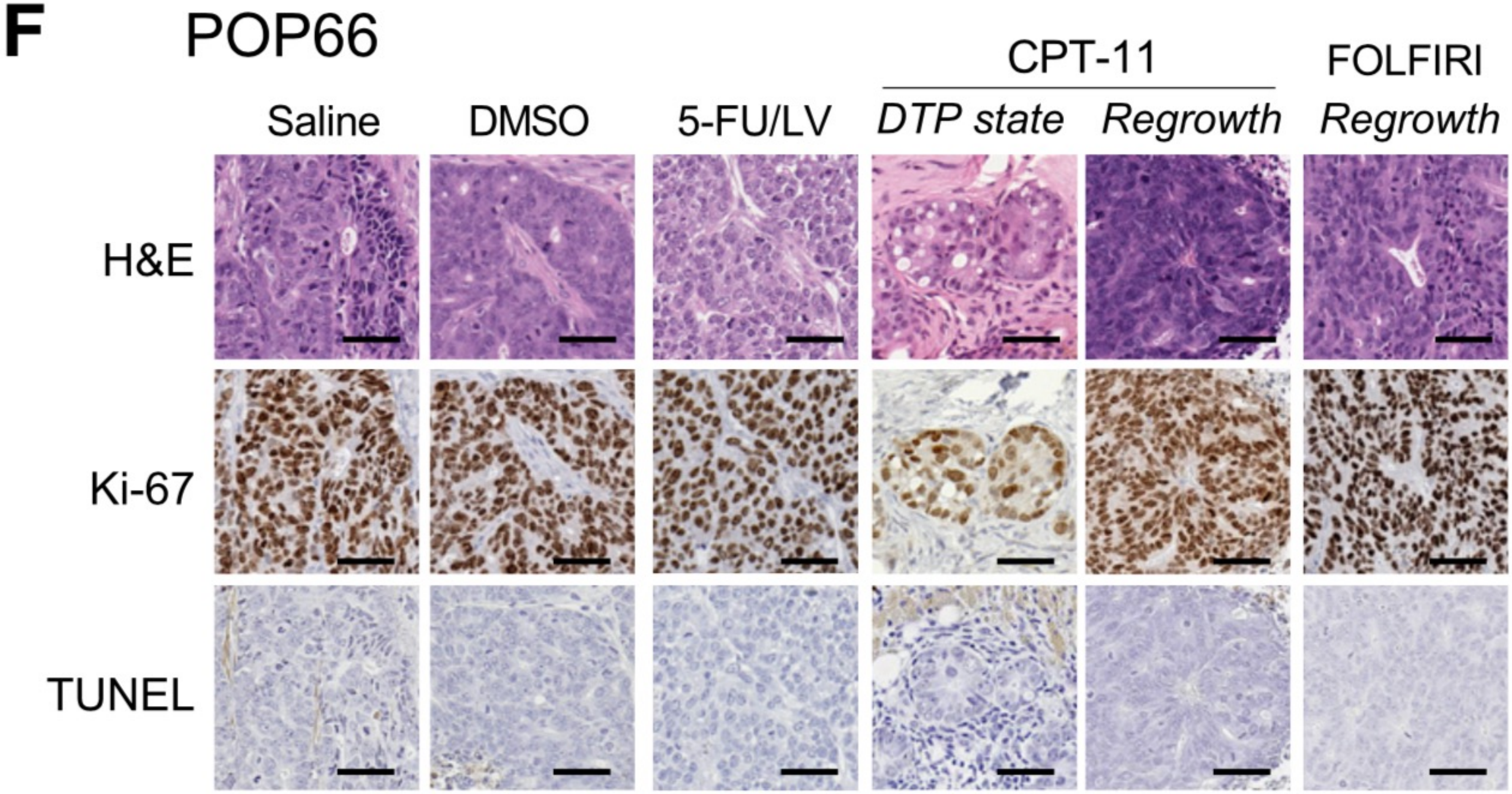


Figure 1F

Rehman et al. Cell 2021, 184:226

Reinjection of CPT-11-treated Tumors into New Mice Remained Sensitive to CPT-11 Treatment

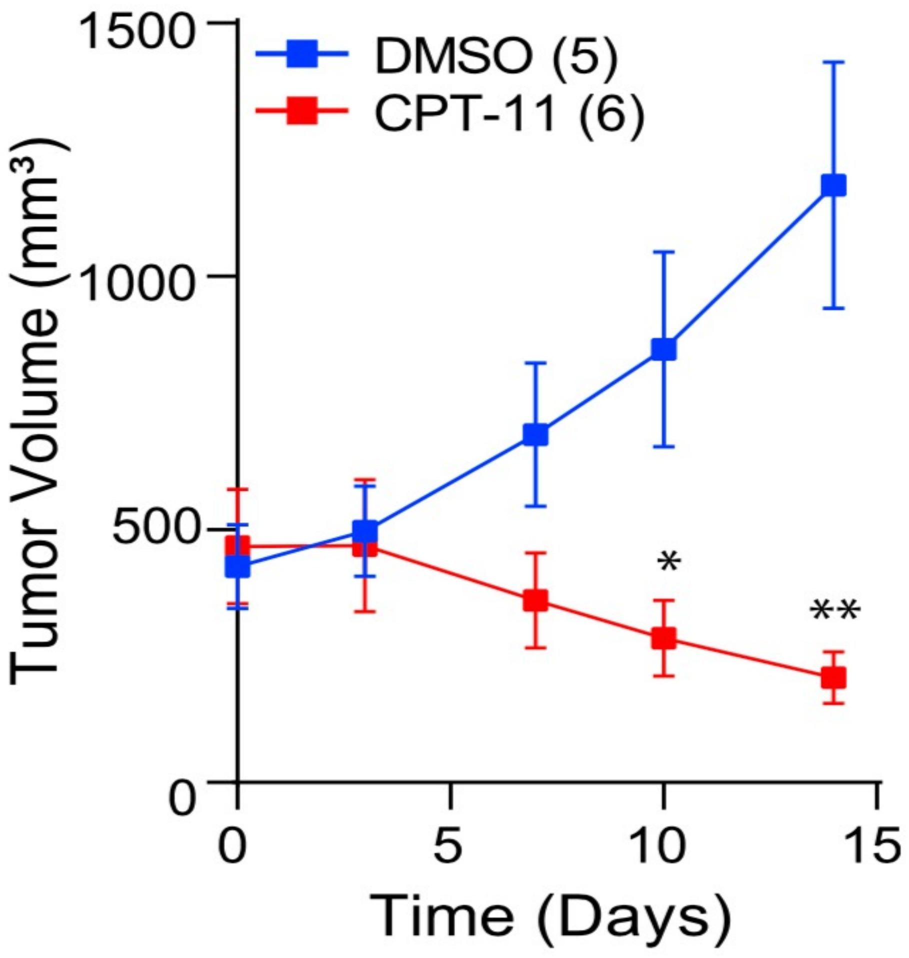


Figure 1H

Rehman et al. Cell 2021, 184:226

Long-Term CPT-11 Treatment Gives Rise to Irreversibly Resistant Tumors

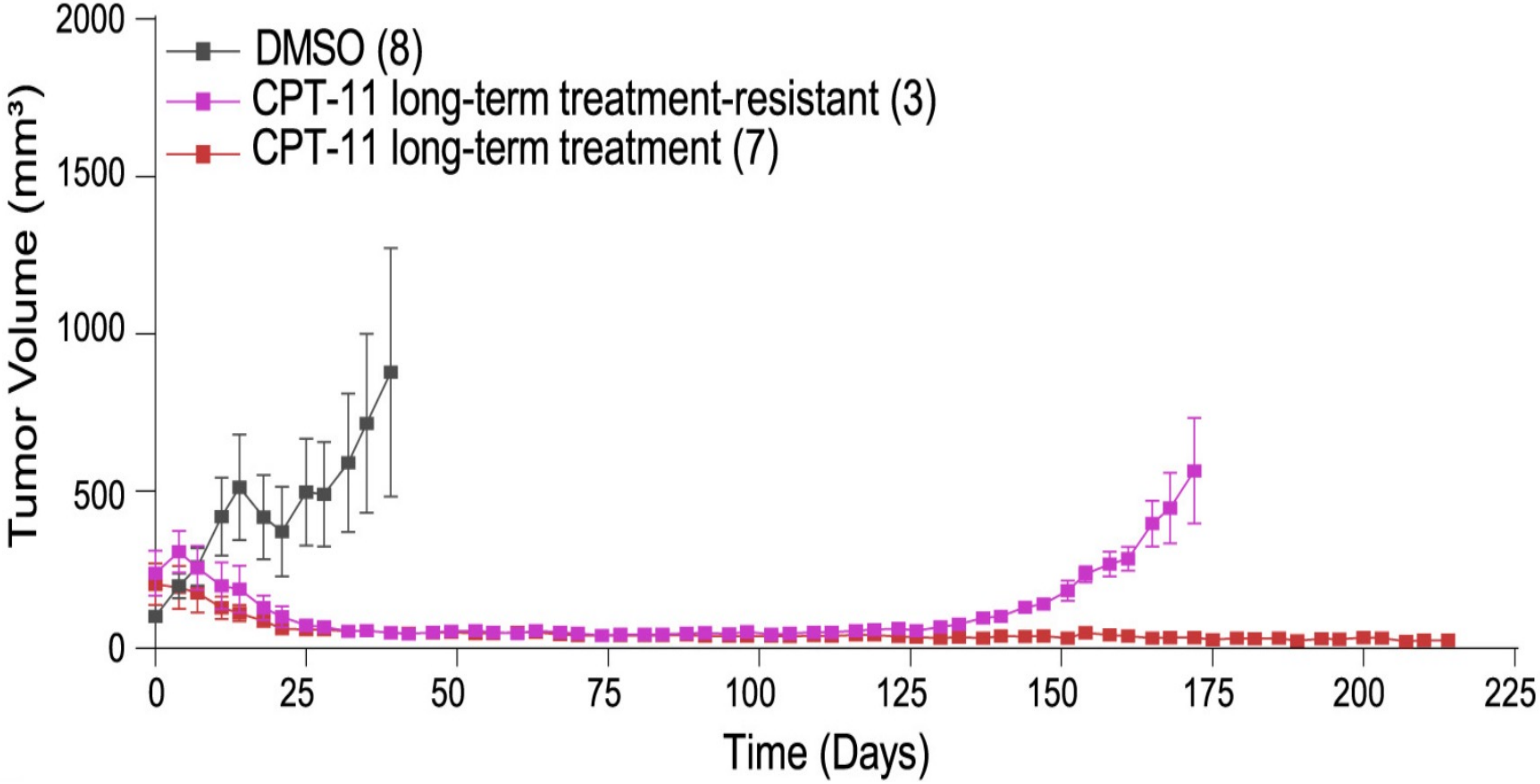


Figure S2D

Rehman et al. Cell 2021, 184:226

Long-Term CPT-11 Treatment Gives Rise to Irreversibly Resistant Tumors

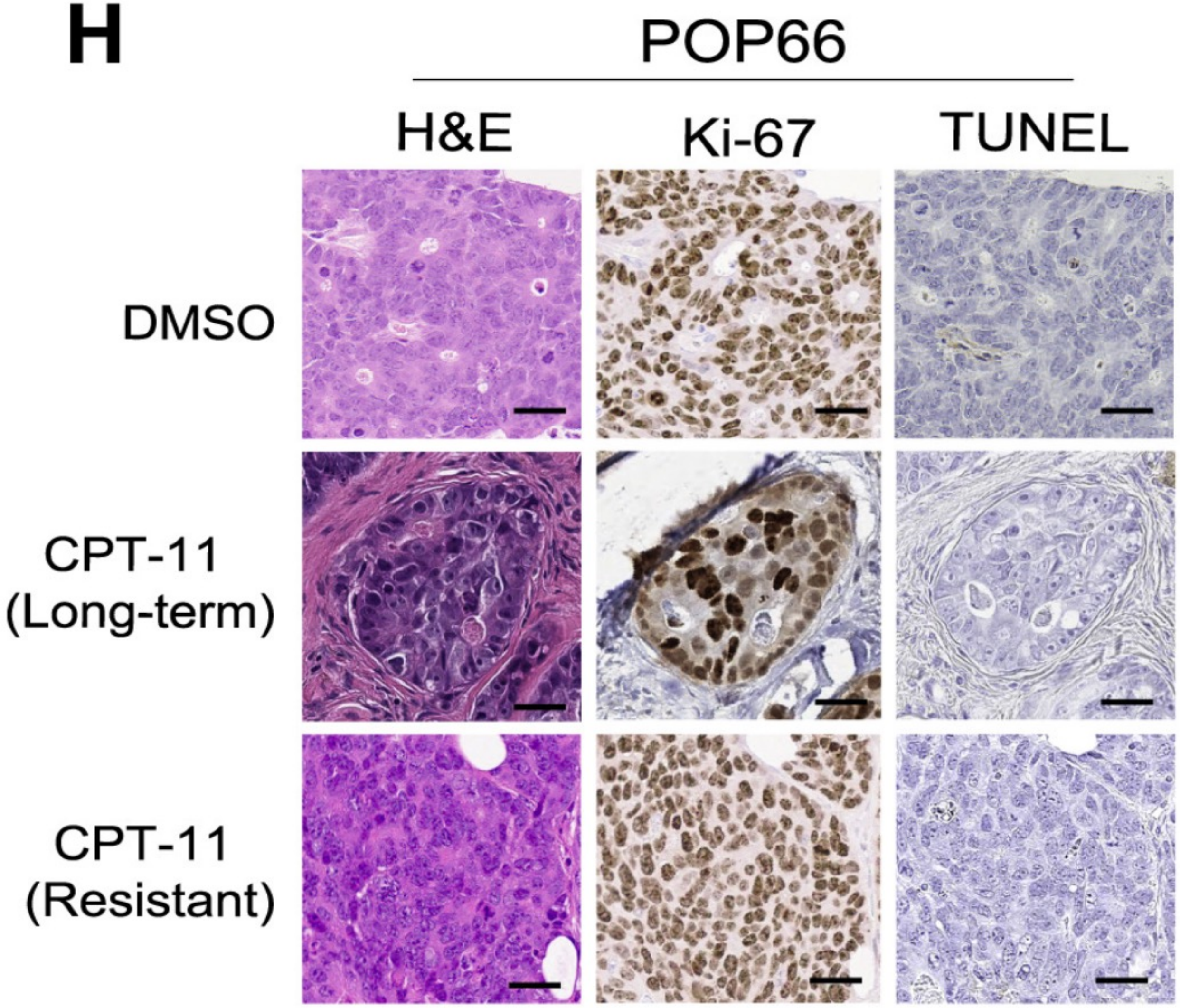


Figure S2H

Rehman et al. Cell 2021, 184:226

Reinjection of CPT Resistant Tumors into New Mice Maintained Resistance to CPT

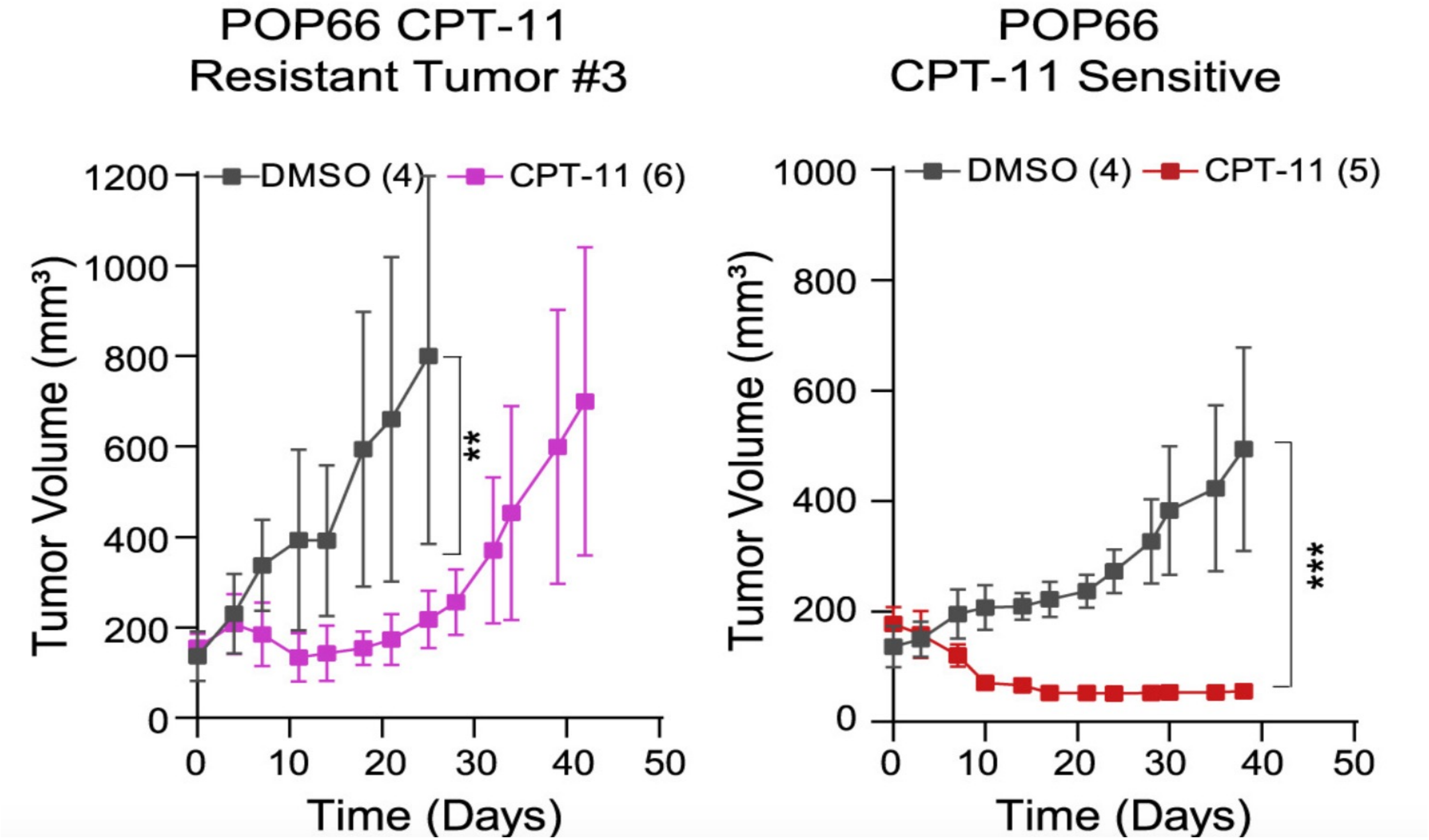


Figure S2I

Rehman et al. Cell 2021, 184:226

Barcode Experiment to Study Genetic Heterogeneity

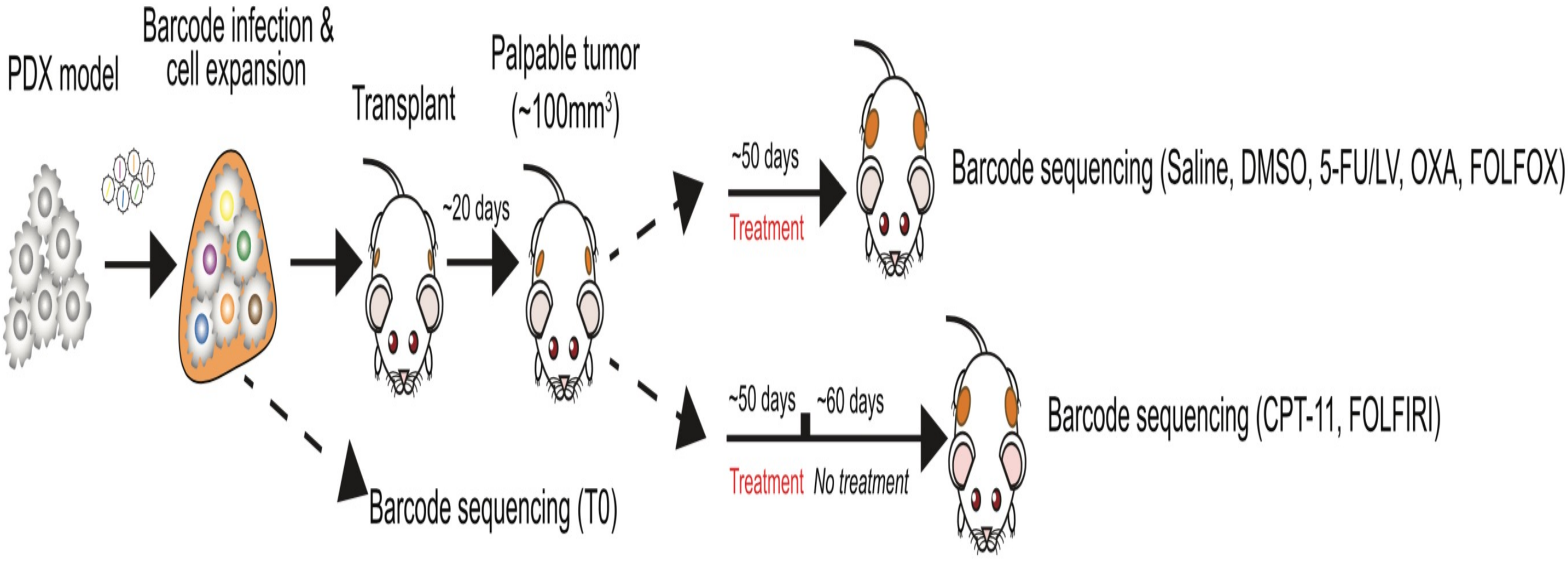


Figure 2A

Rehman et al. Cell 2021, 184:226

The Enriched Barcodes Were Unique Across All Tumors

No selection of a pre-existing cell subpopulation that gave rise to DTPs

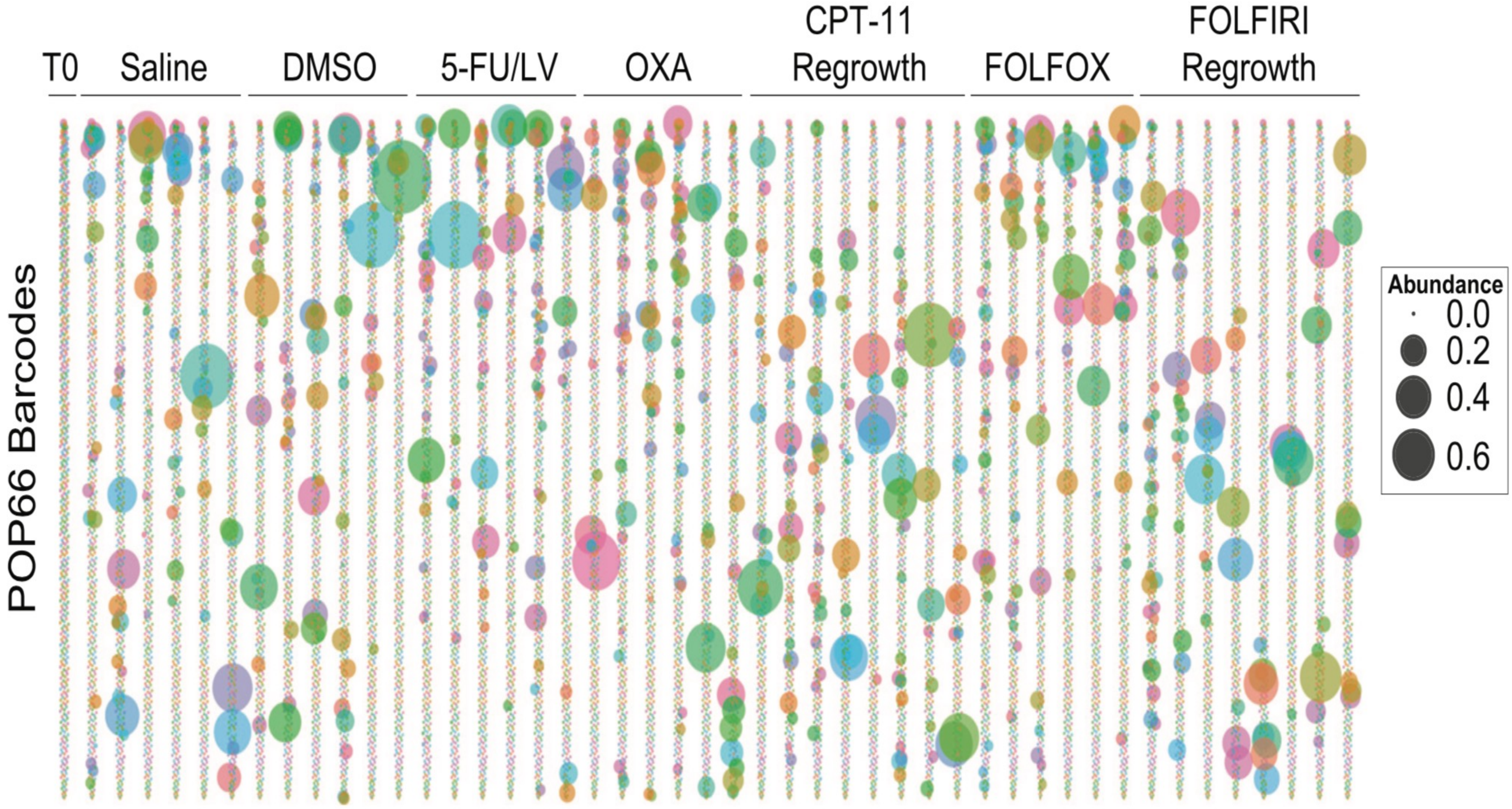


Figure 2B

Rehman et al. Cell 2021, 184:226

Mean Cumulative Clone Size Distribution

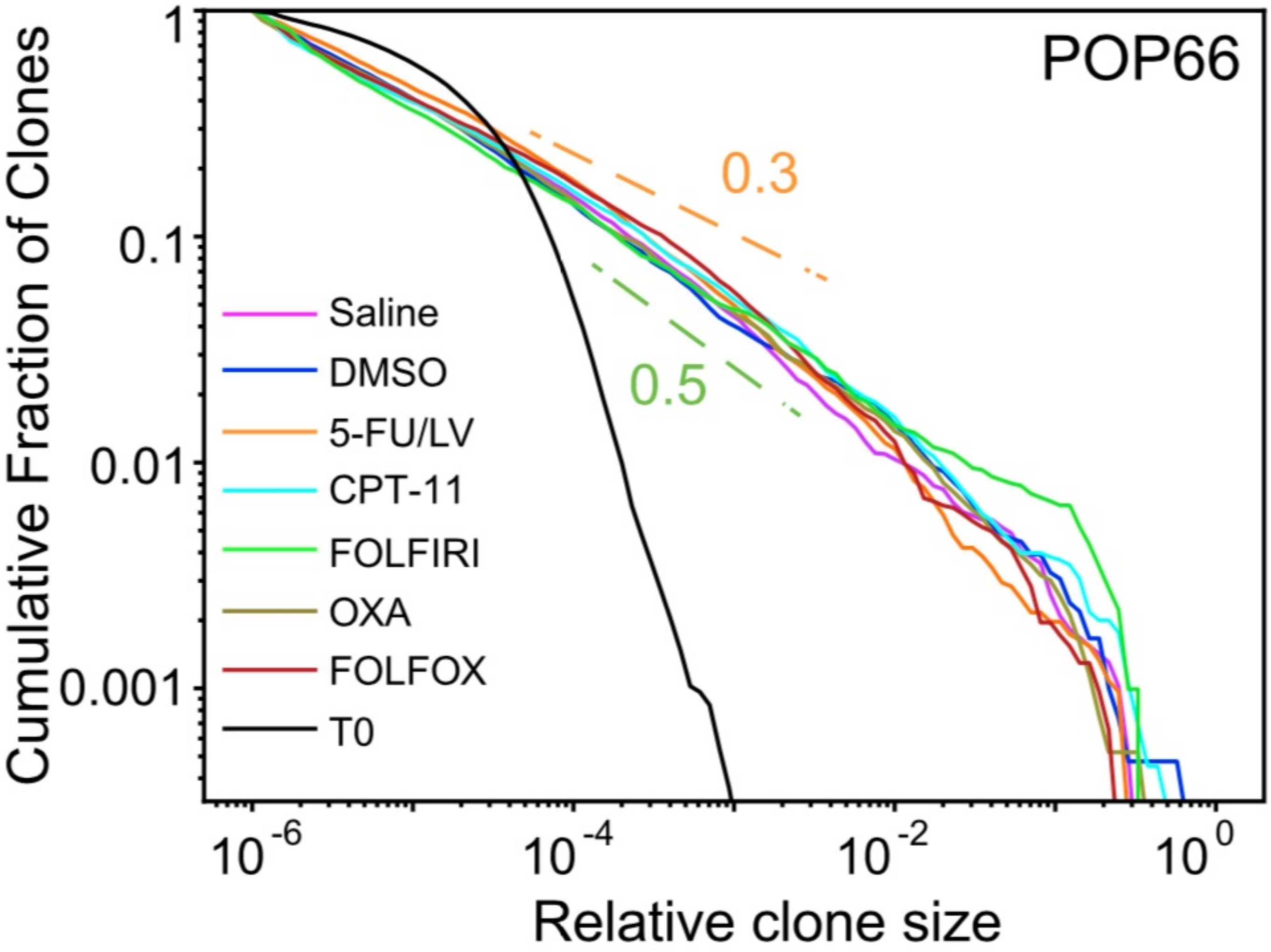


Figure 3A

Rehman et al. Cell 2021, 184:226

Mean Cumulative Clone Size Distribution

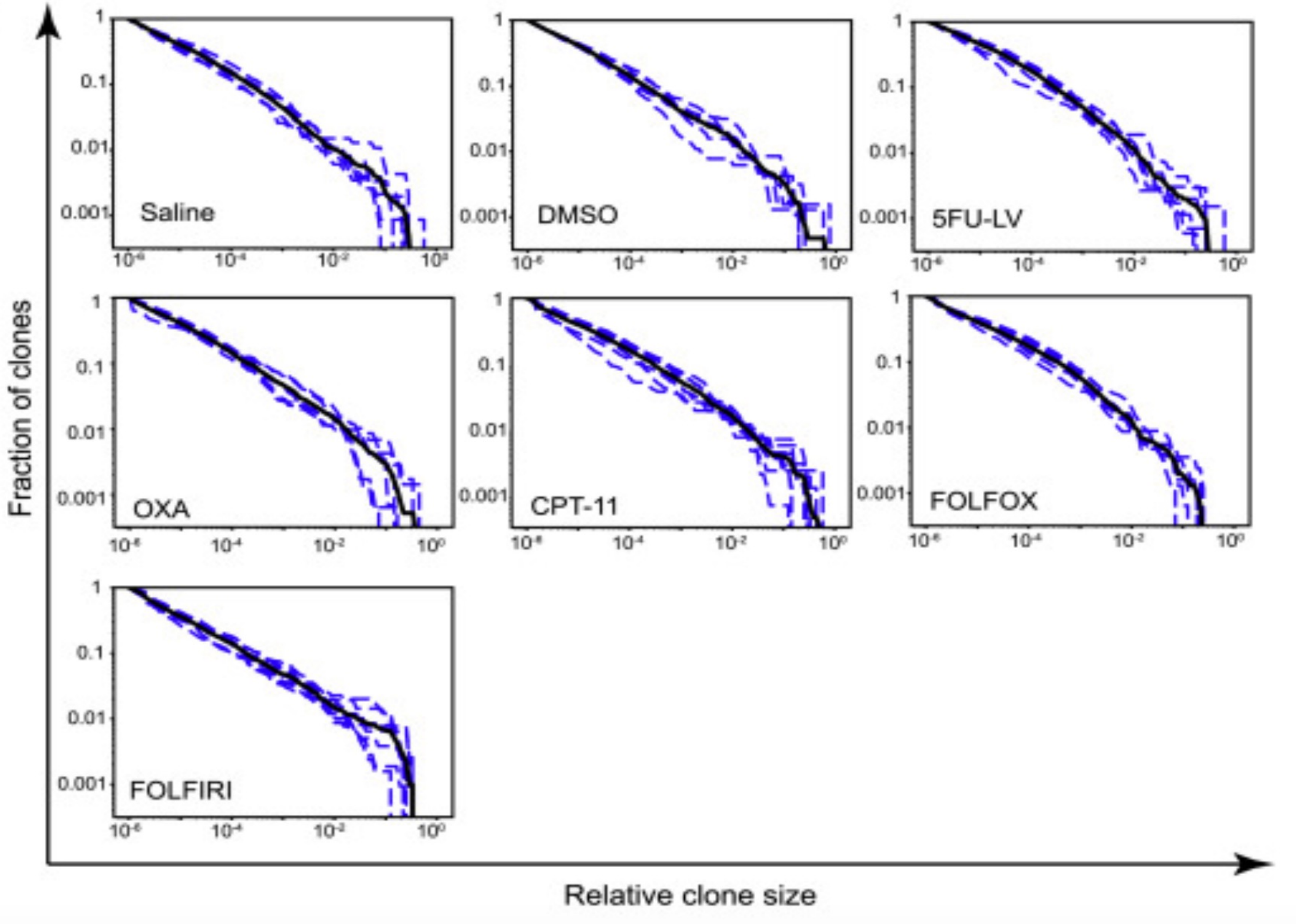


Figure S5A

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Estimated Power law Slope for Individual Tumors

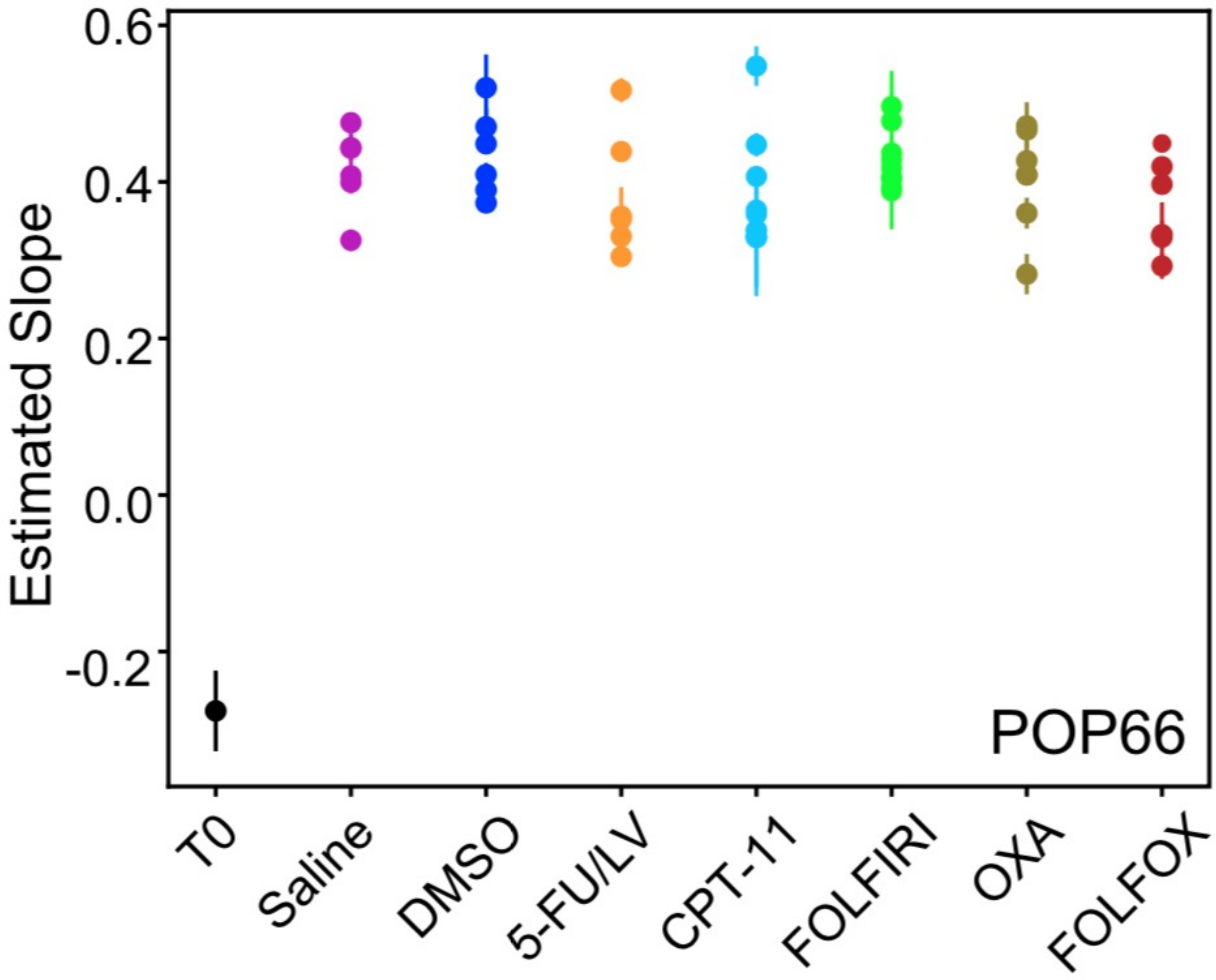

Figure 3C

Rehman et al. Cell 2021, 184:226

Power Law Distribution

$$p(n) \sim n^{-(1+\alpha)}$$

$$Q(n) = \sum_{n'>n} p(n') \sim n^{-\alpha}$$

Q(n): cumulative distribution

Rehman et al. Cell 2021, 184:226

Log-linear Distribution from Selective Dynamics

n is the size of clone *i* undergoing stochastic birth-death process

$$p_i\left(n\right) = \lambda_i e^{-n\lambda_i}$$

$$p\left(\lambda\right) = b^a e^{-b\lambda} \lambda^{a-1} / \Gamma\left(a\right)$$

$$p\left(n\right) = \int d\lambda \lambda e^{-n\lambda} p\left(\lambda\right) = \frac{a/b}{\left(n/b+1\right)^{1+a}}$$

$$p\left(n\right) \sim n^{-\left(1+a\right)}$$

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Sub-exponential Tumor Growth Kinetics

$$\dot{N} \sim N^{1-\alpha}$$

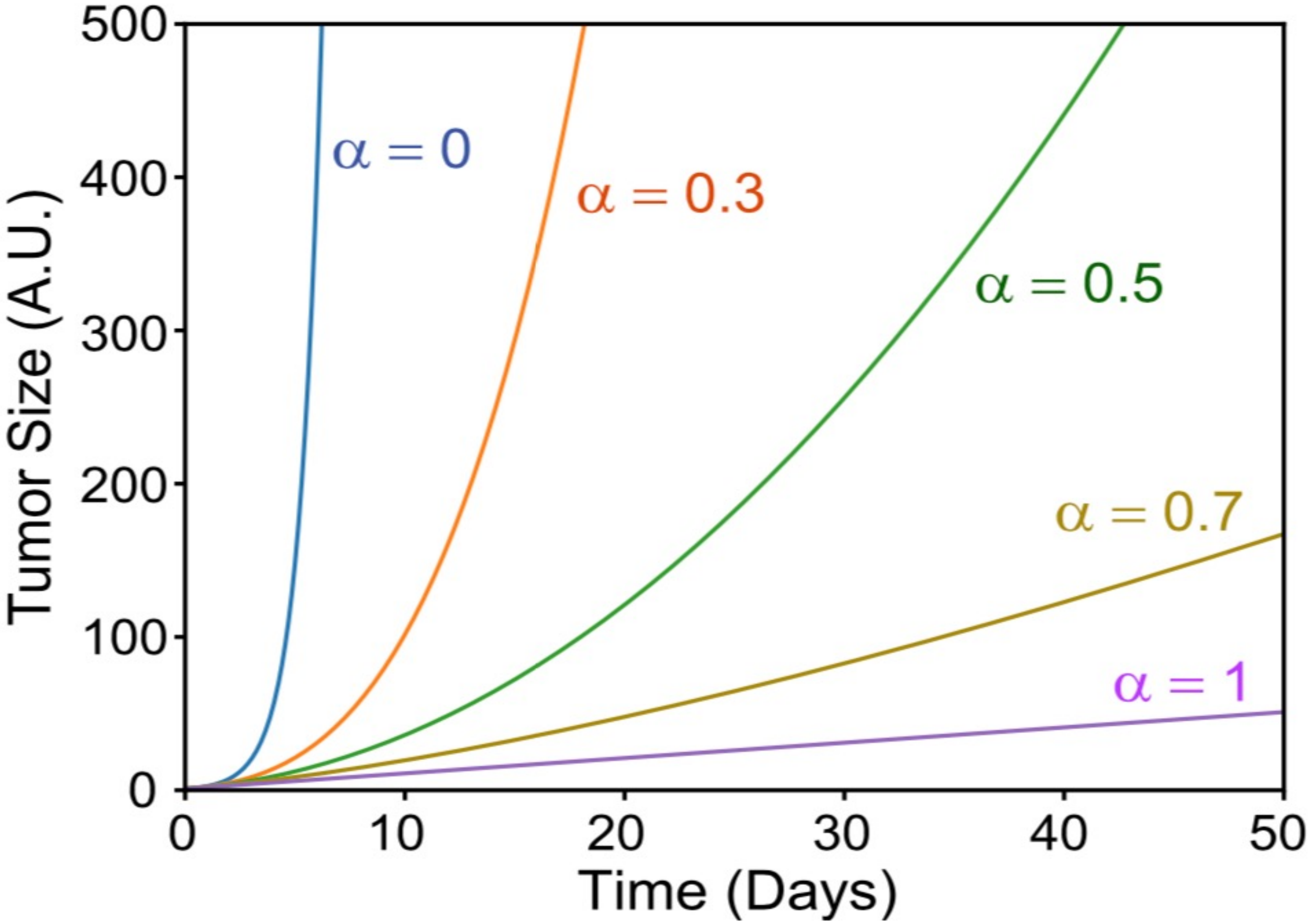

Figure 3E

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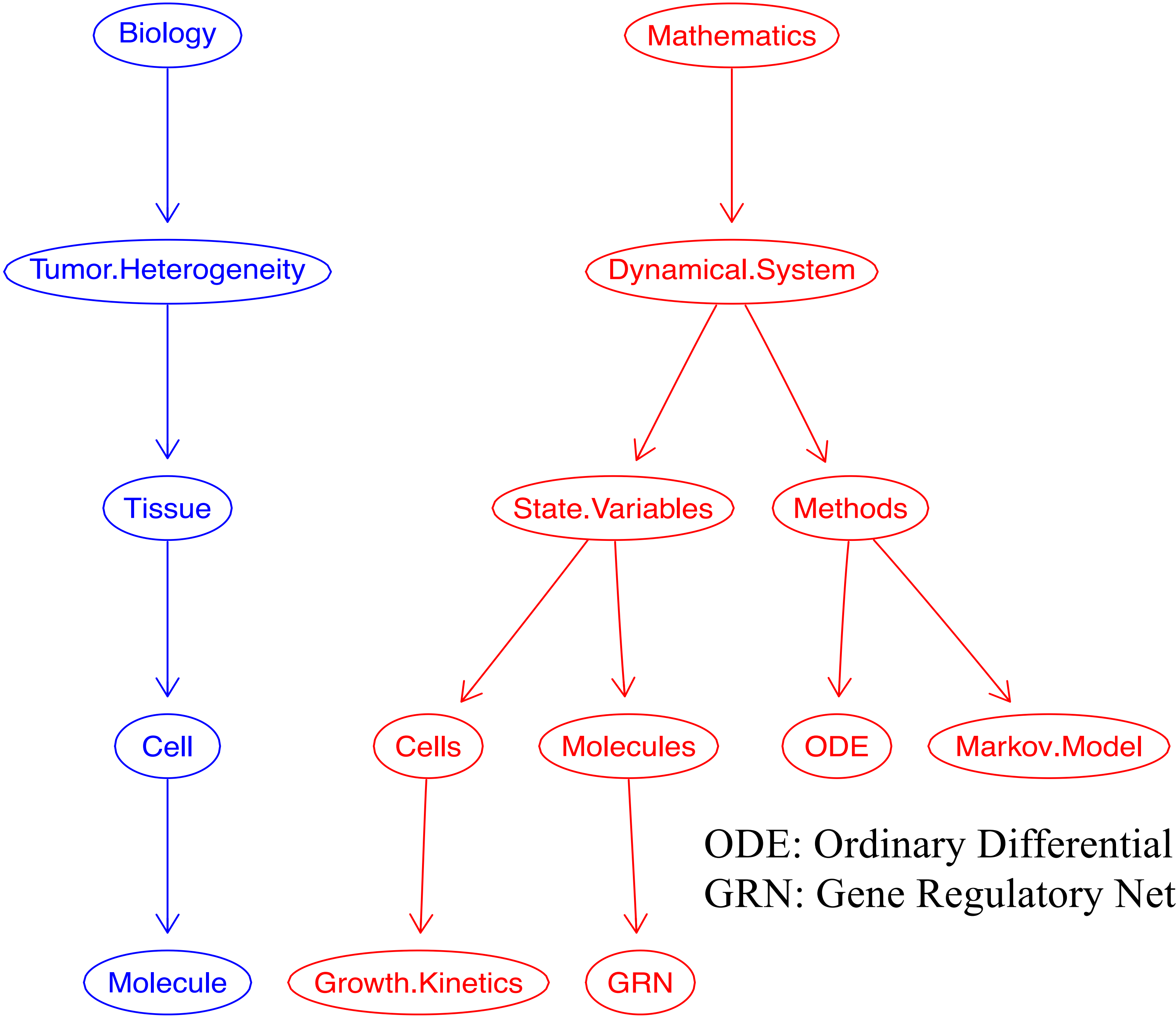
Understanding Biology with Mathematical Modeling



Biology

Tumor.Heterogeneity

Tissue

Cell

Molecule

Mathematics

Dynamical.System

State.Variables

Methods

Cells

Molecules

ODE

Markov.Model

Growth.Kinetics

GRN

ODE: Ordinary Differential Equation
GRN: Gene Regulatory Network