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

Network motifs for desensitization and history of treatment exposure

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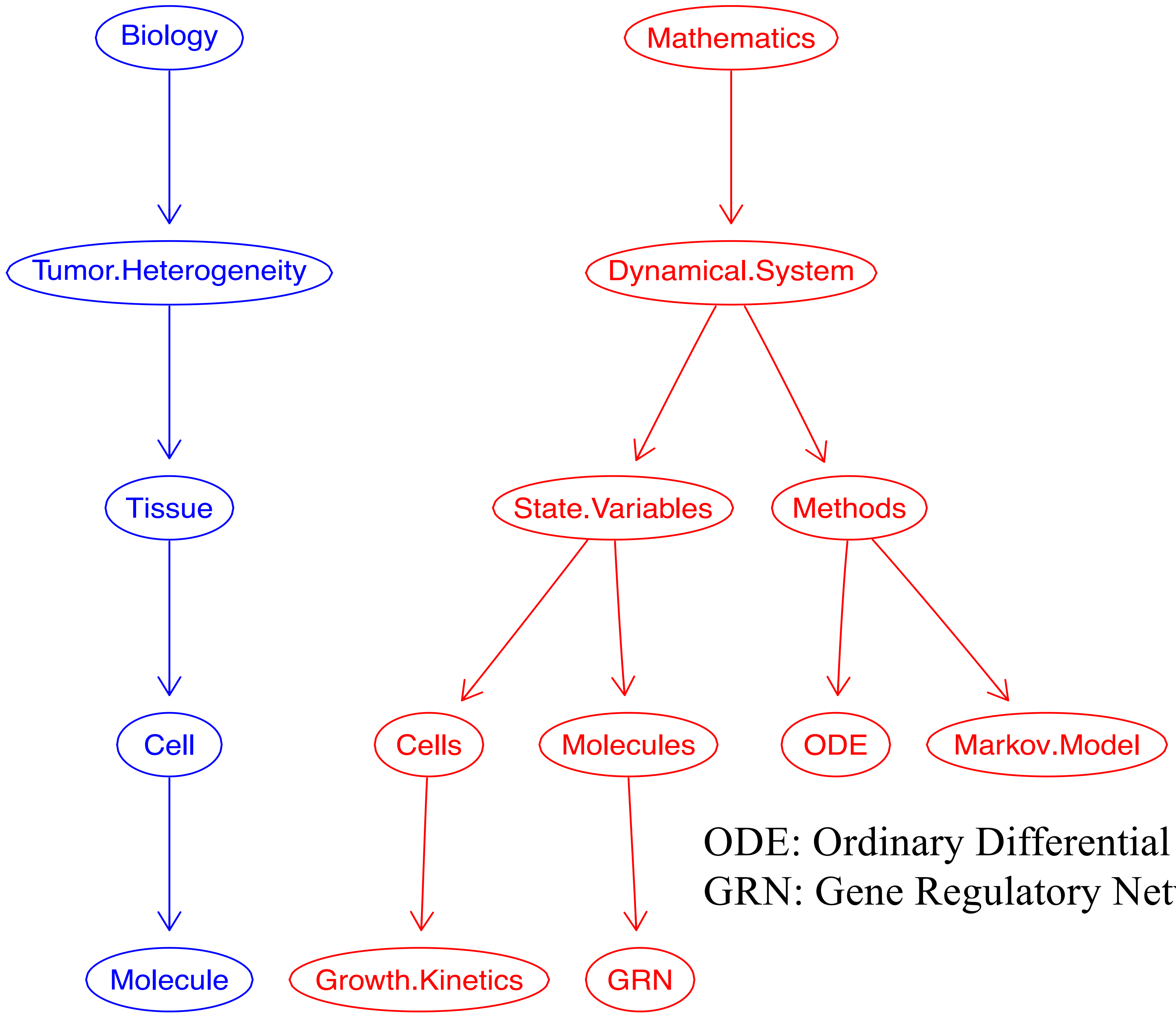
Understanding Biology with Mathematical Modeling



ODE: Ordinary Differential Equation
GRN: Gene Regulatory Network

Negative Feedback Motif of NF-κB Signaling Pathway

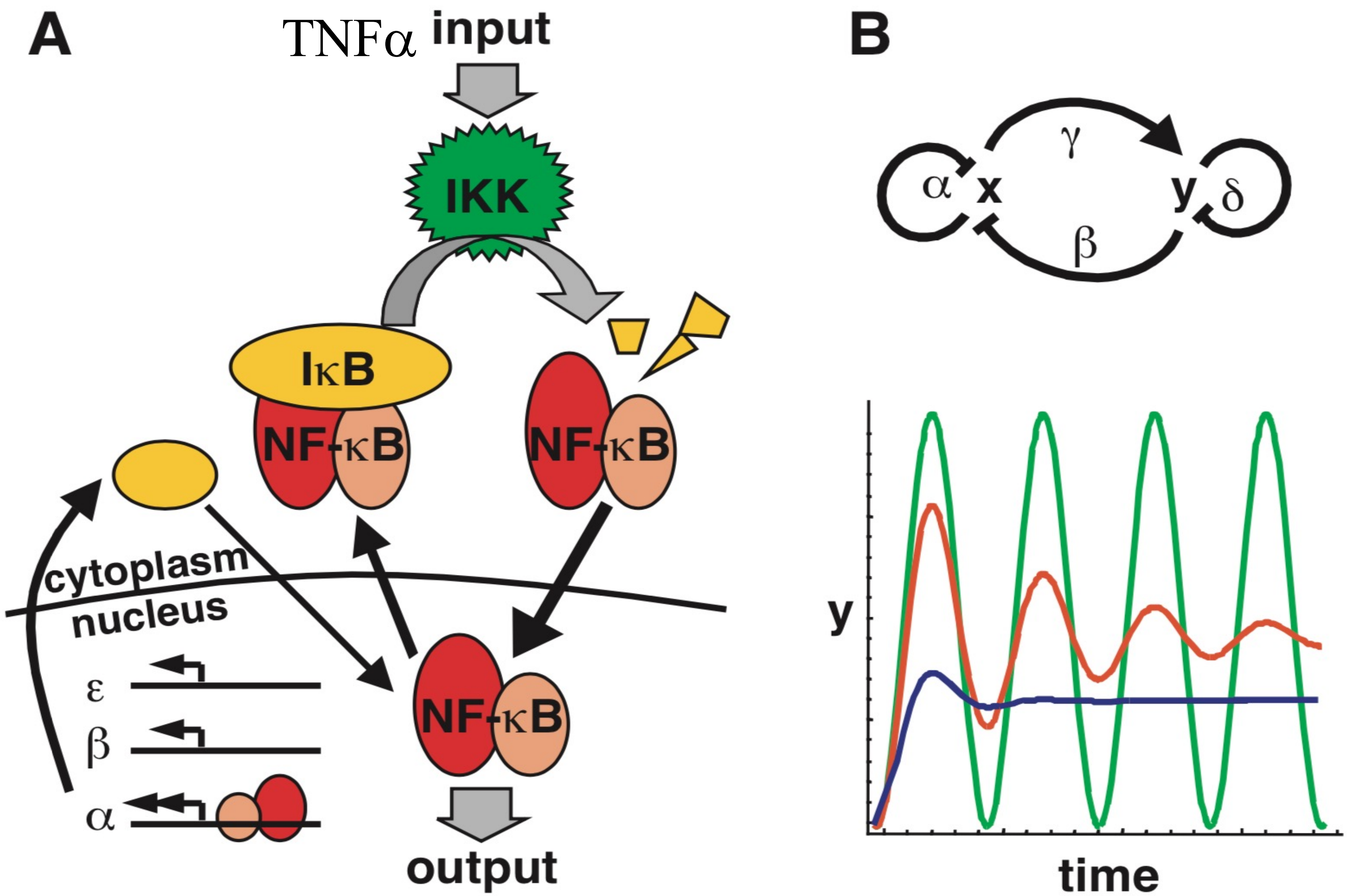


Figure 1

Hoffmann et al. Science 2002, 298:1241

Negative Feedback Motif of NF-κB Signaling Pathway

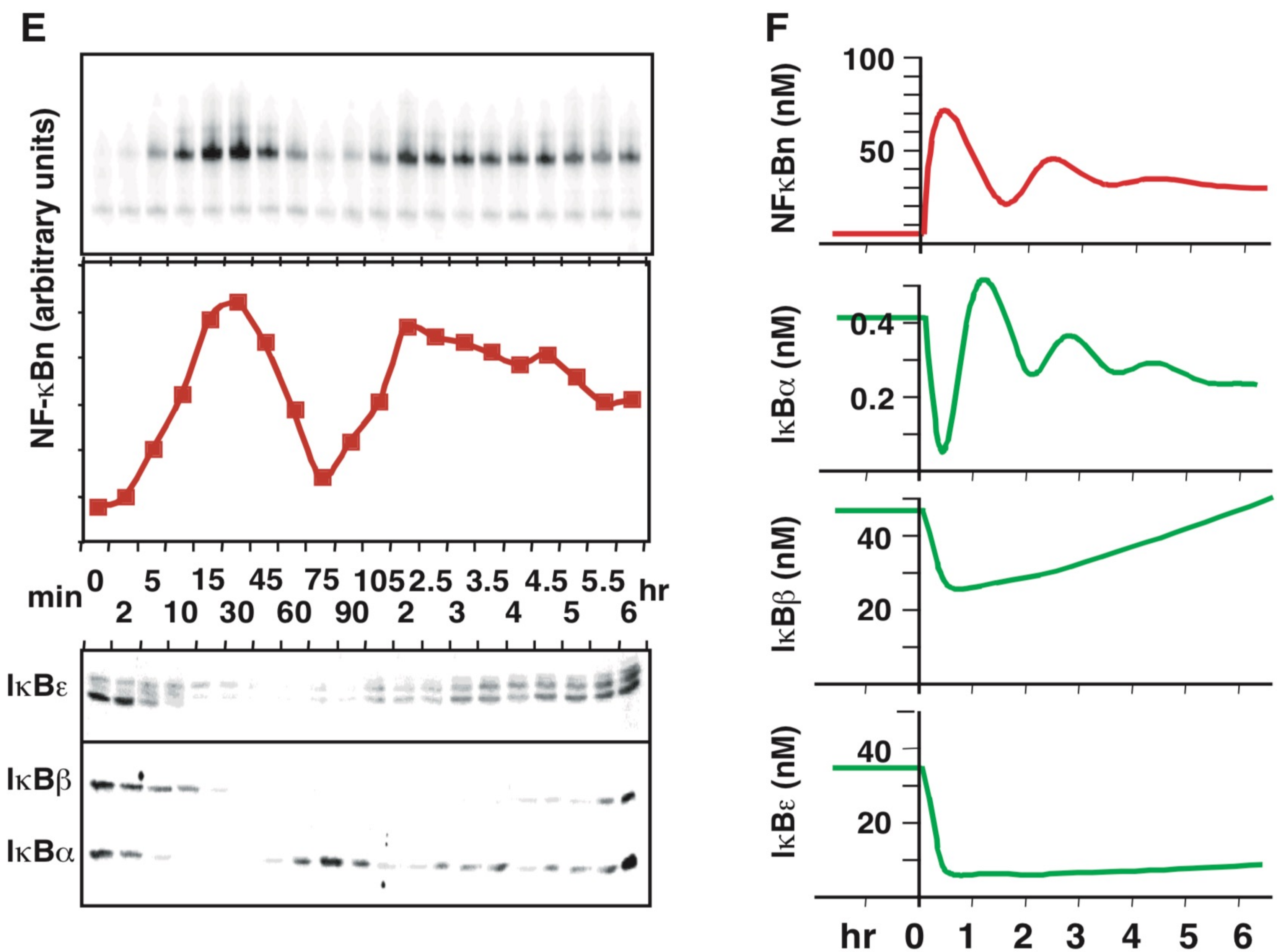


Figure 2 wild-type fibroblasts

IκBα Is Required For Oscillation of NF-κB Signal

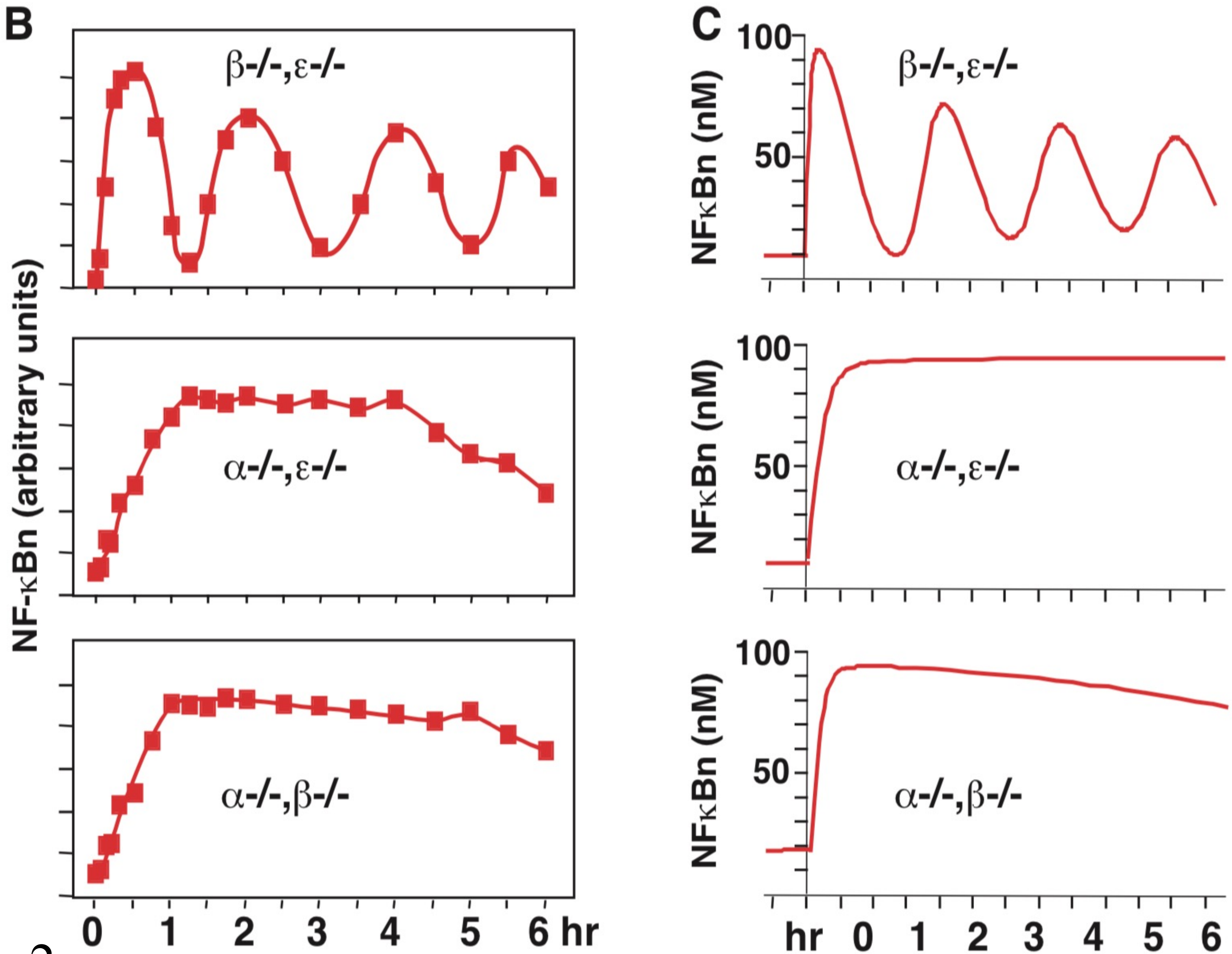


Figure 2

NF-κB response to TNFα of various durations

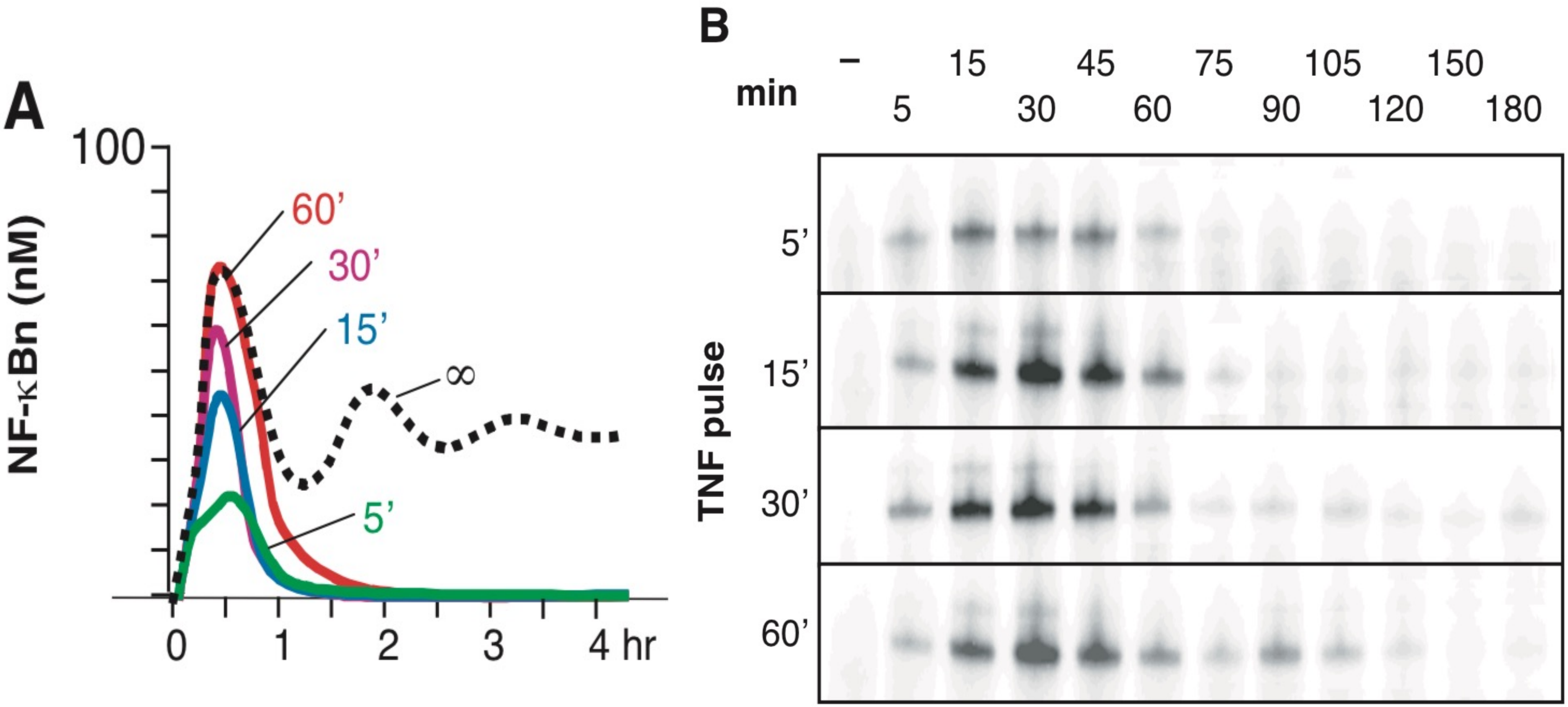
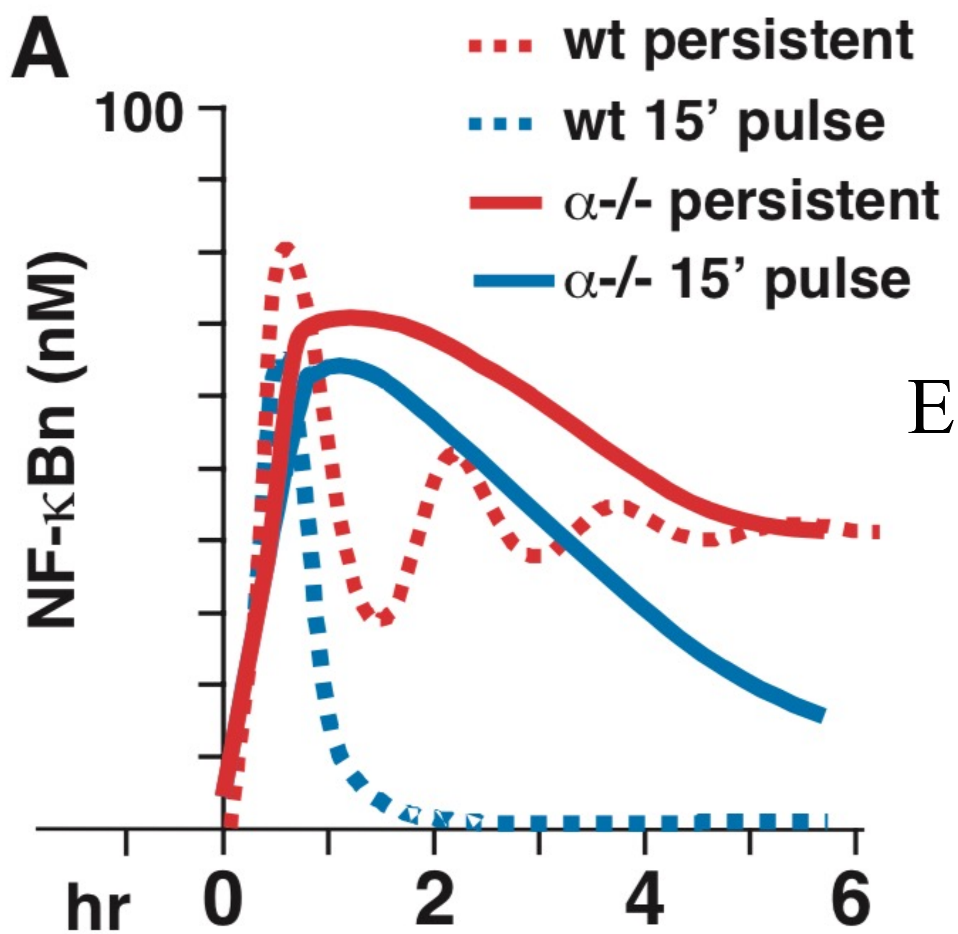


Figure 3

NF-κB Signal in WT Shows Bimodal Response

The Bimodal Response Requires IκBα



Effect of IκBα$^{-/-}$

Figure 4

RANTES Activation Requires Persistent TNFα Stimulation

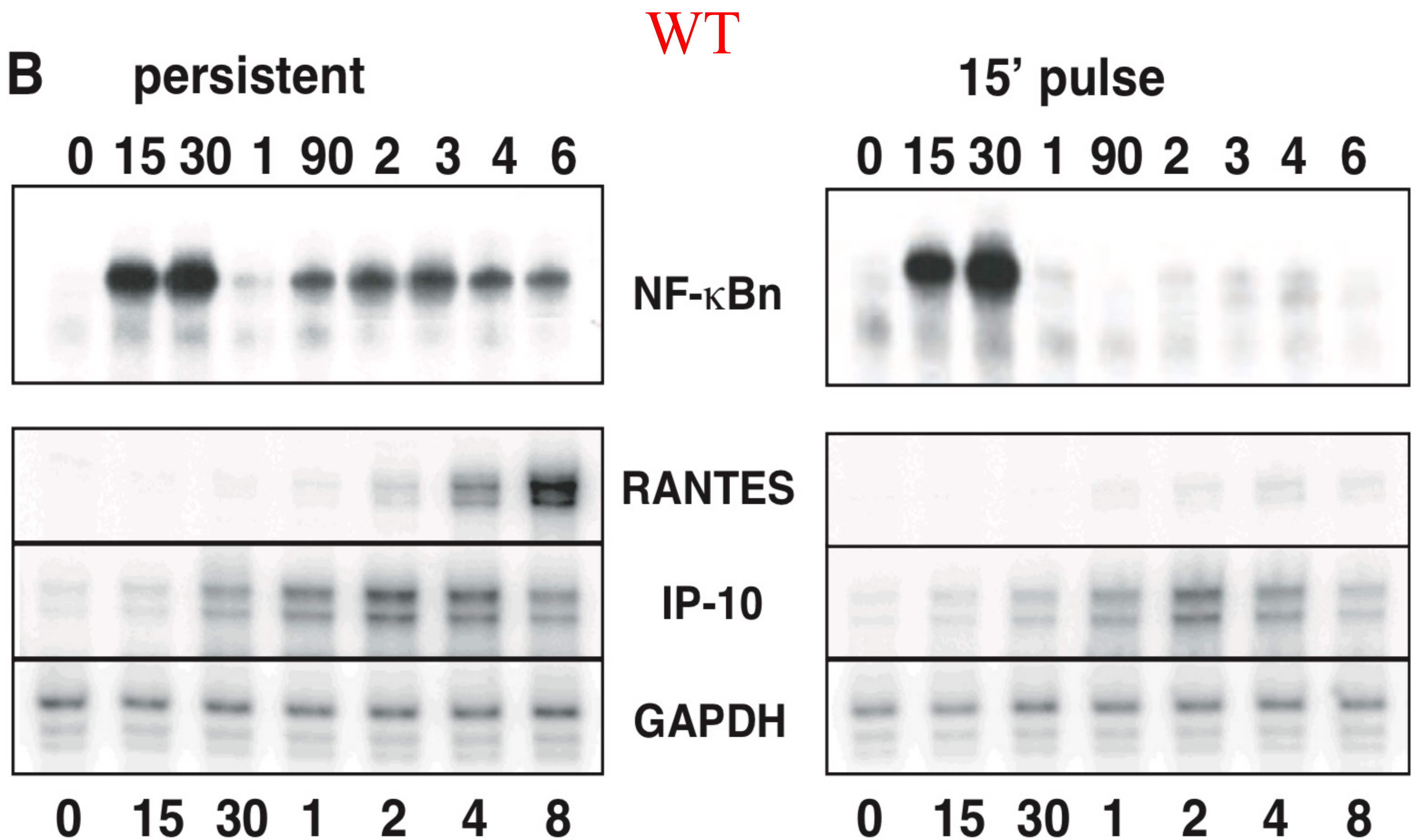


Figure 4

RANTES: CCL5
IP-10: CXCL10

RANTES Activation Requires Persistent TNFα Stimulation

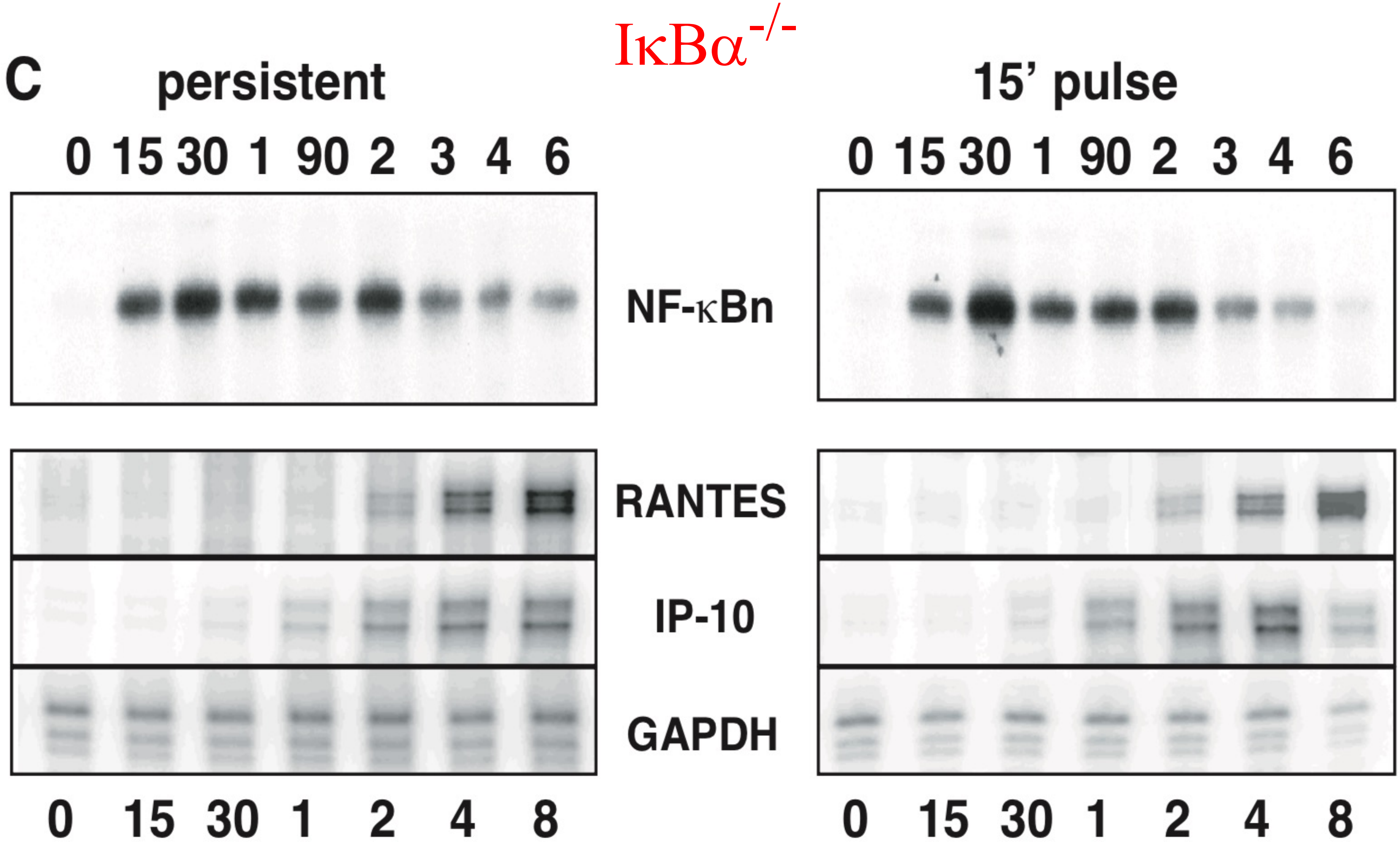
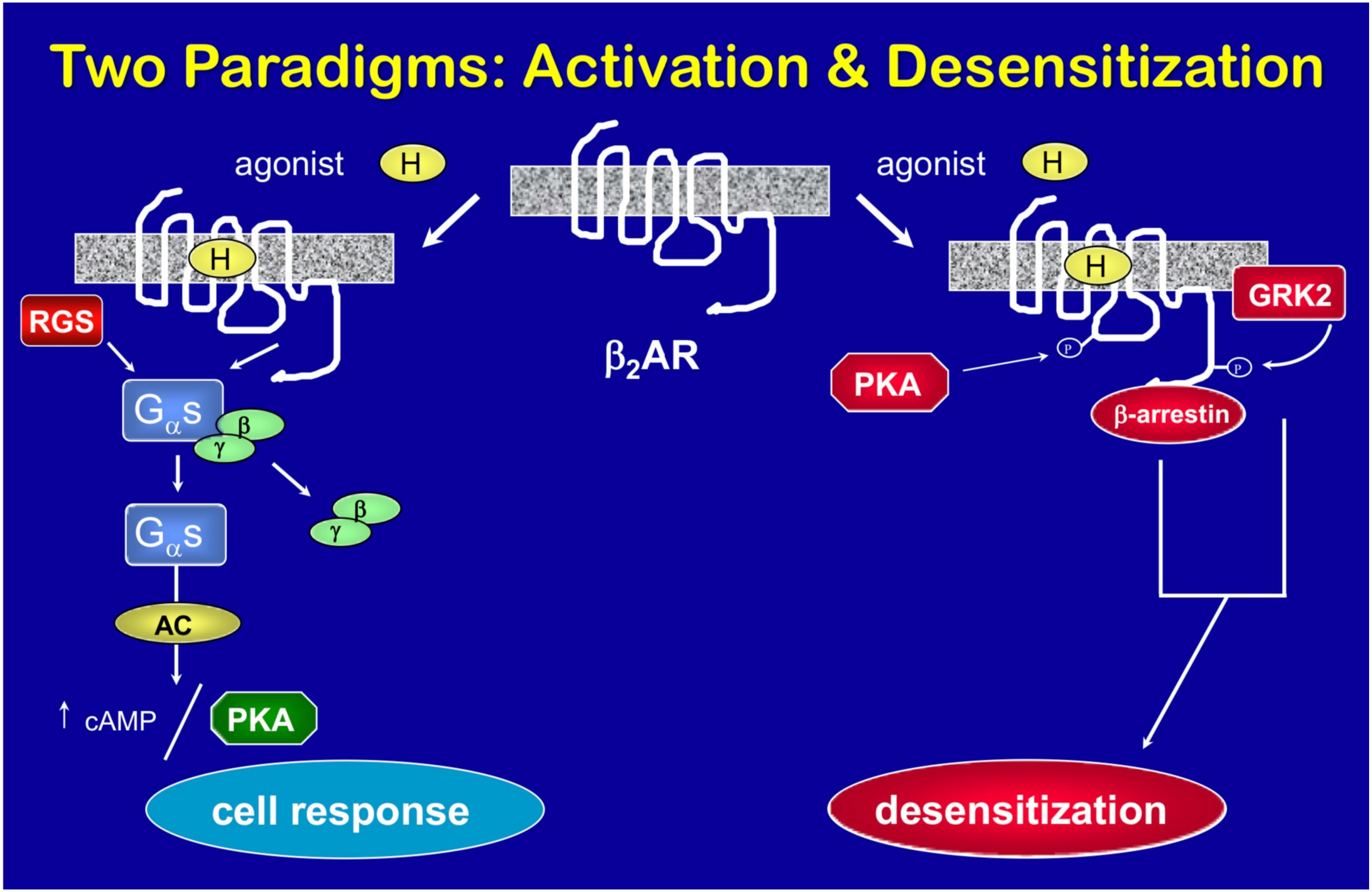


Figure 4

RANTES: CCL5
IP-10: CXCL10

Robert J. Lefkowitz's Nobel Lecture in 2012



Response of STAT1 and IRF9 to IFN-α Treatment

STAT1/2
IRF9

IFNAR
JAK1
TYK2

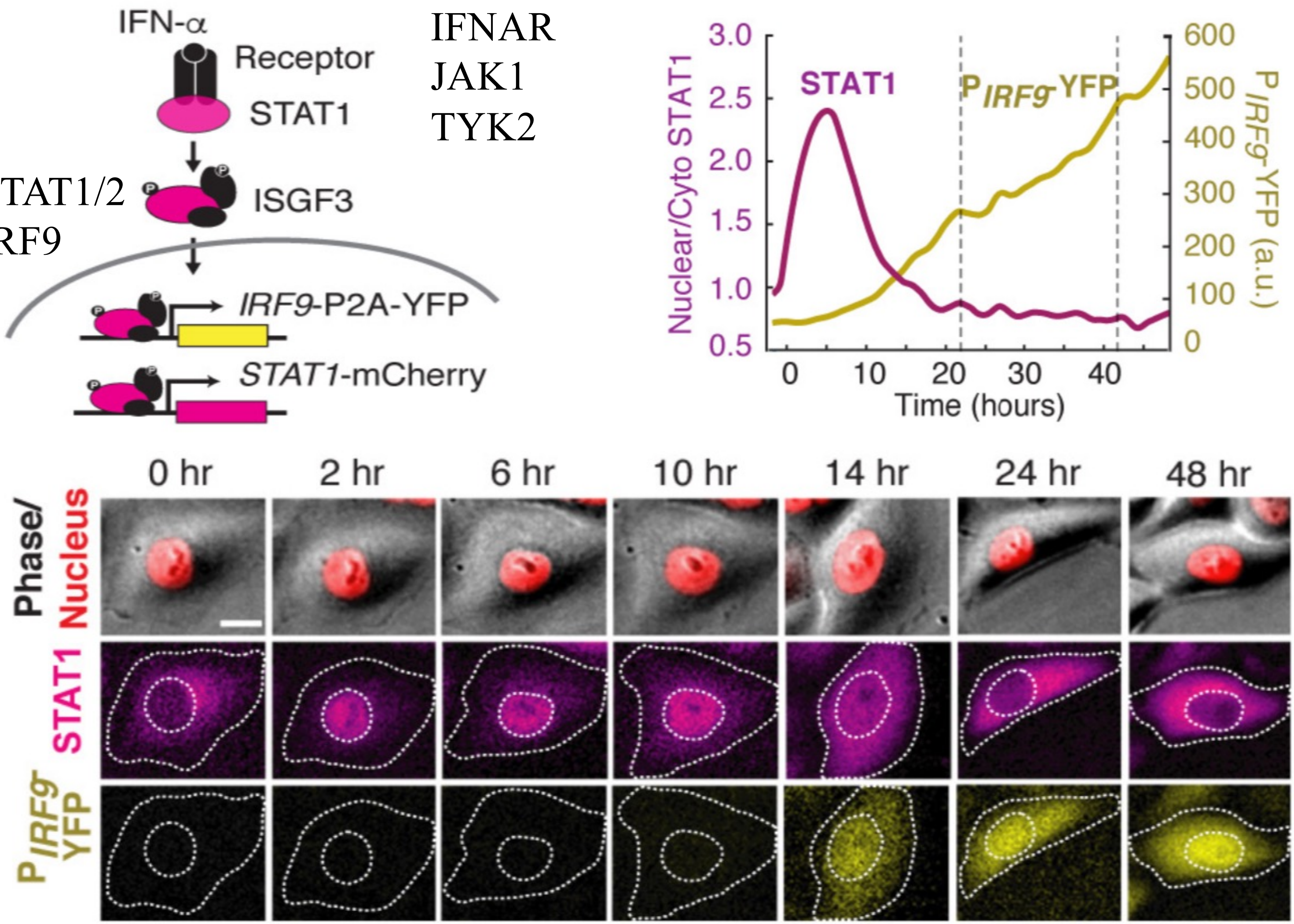
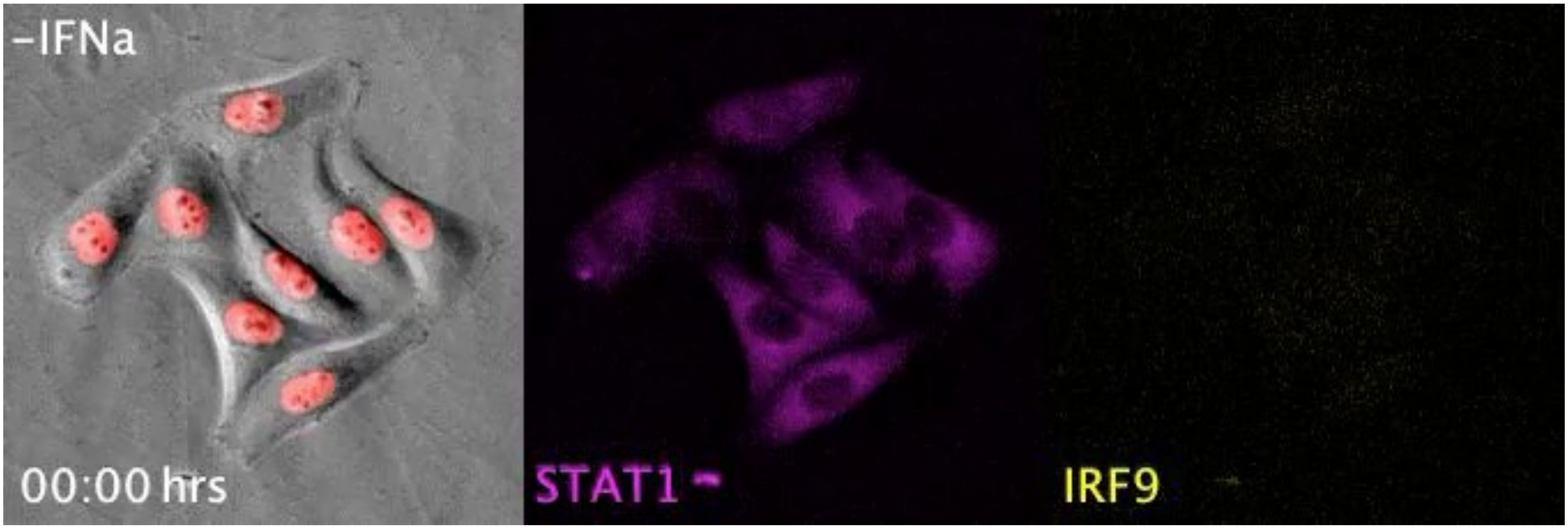


Figure 1

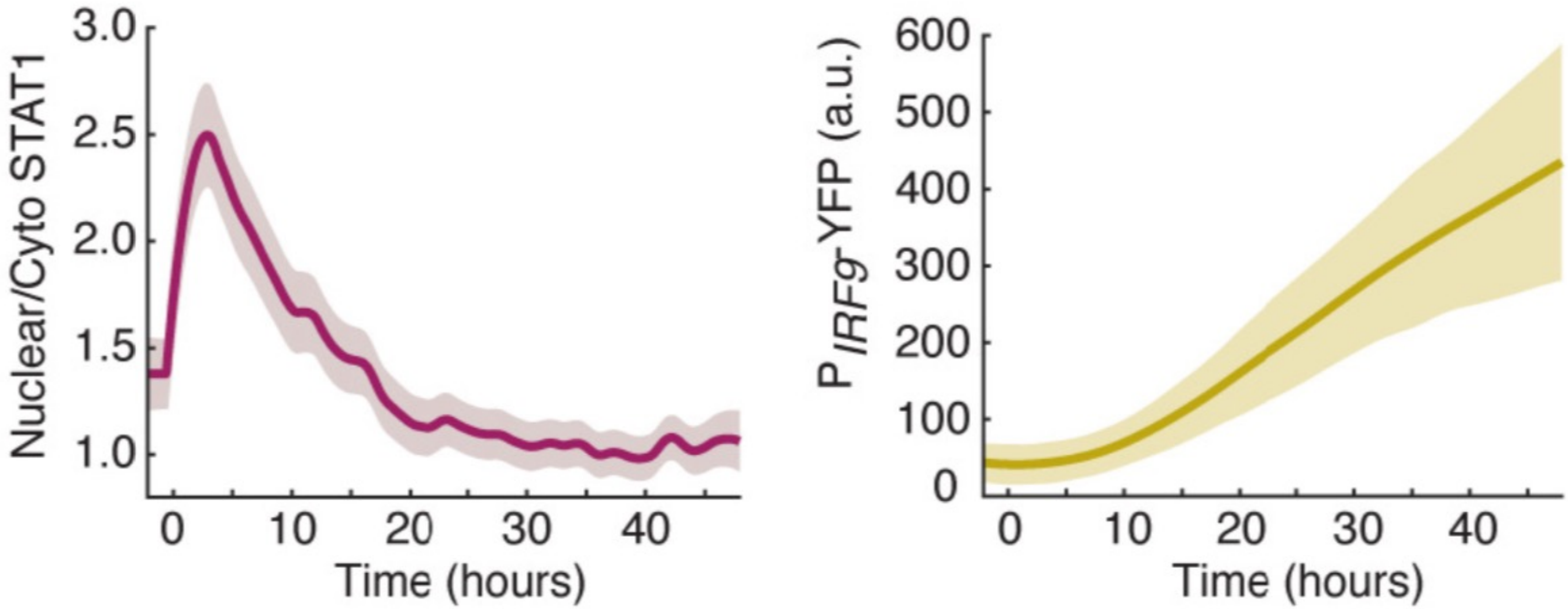
Mudla et al. Elife 2020, 9:e58825

Response of STAT1 and IRF9 to IFN-α Treatment



Mudla et al. Elife 2020, 9:e58825

Response of STAT1 and IRF9 to IFN-α Treatment



Averaged time traces of 257 cells

Figure 1

Mudla et al. Elife 2020, 9:e58825

Priming vs. Desensitization

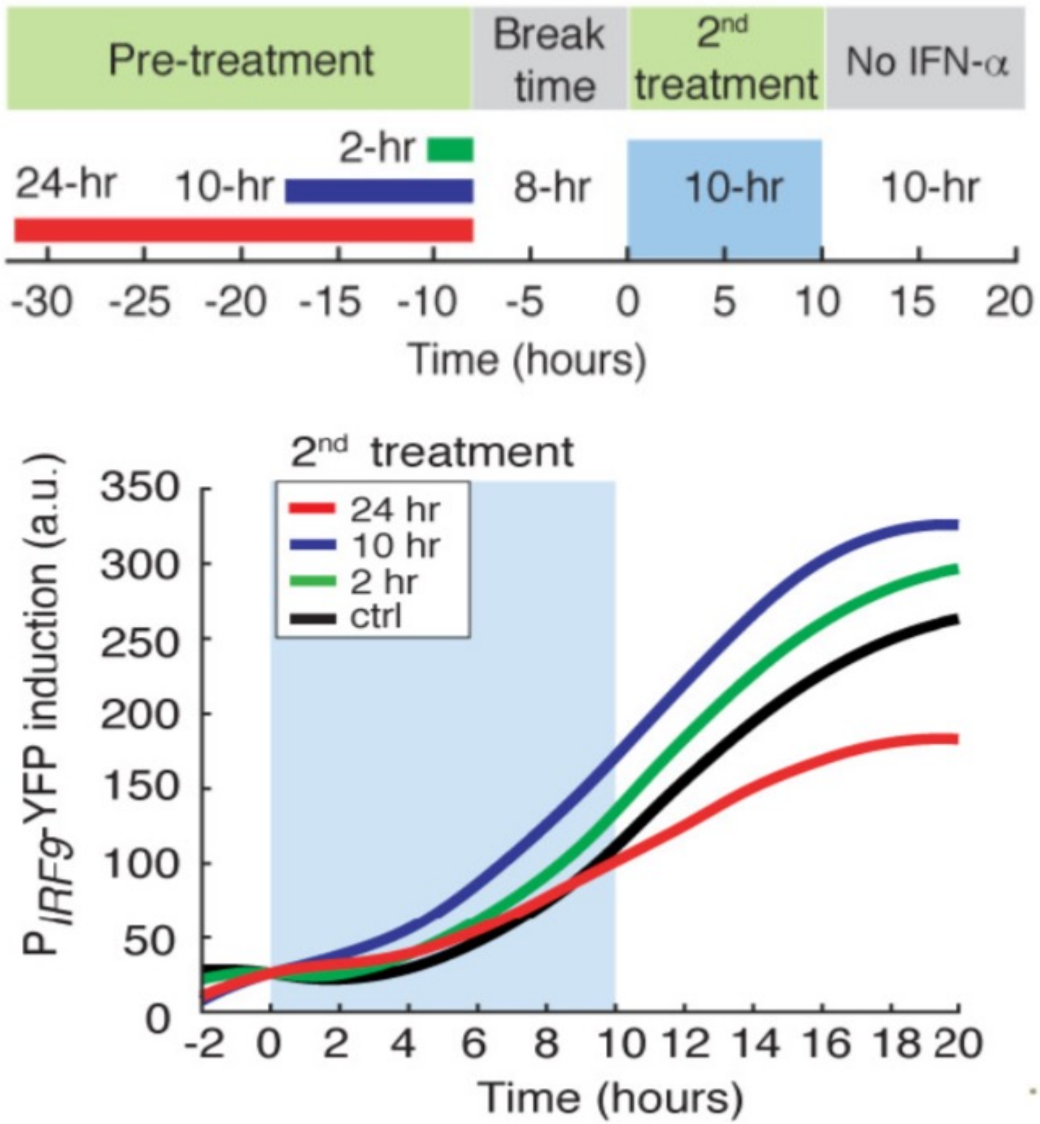


Figure 1 Averaged time traces

Mudla et al. Elife 2020, 9:e58825

Priming vs. Desensitization

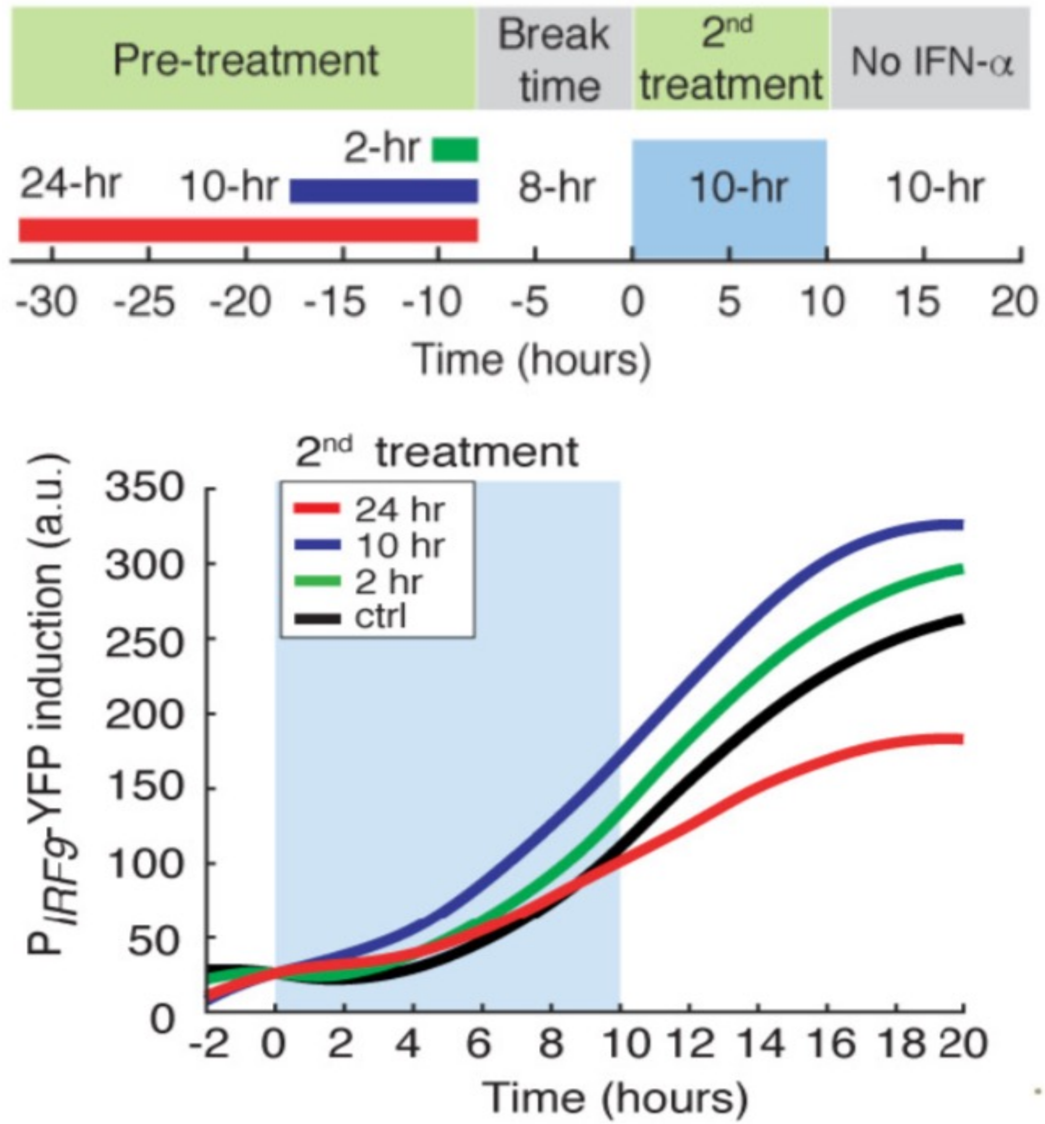


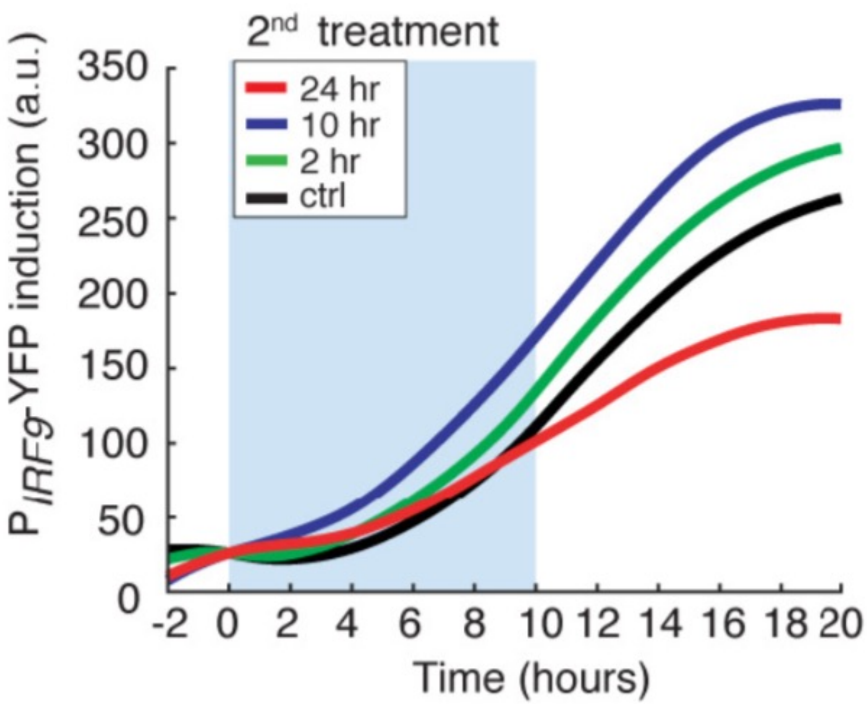
Figure 1 Averaged time traces

Mudla et al. Elife 2020, 9:e58825

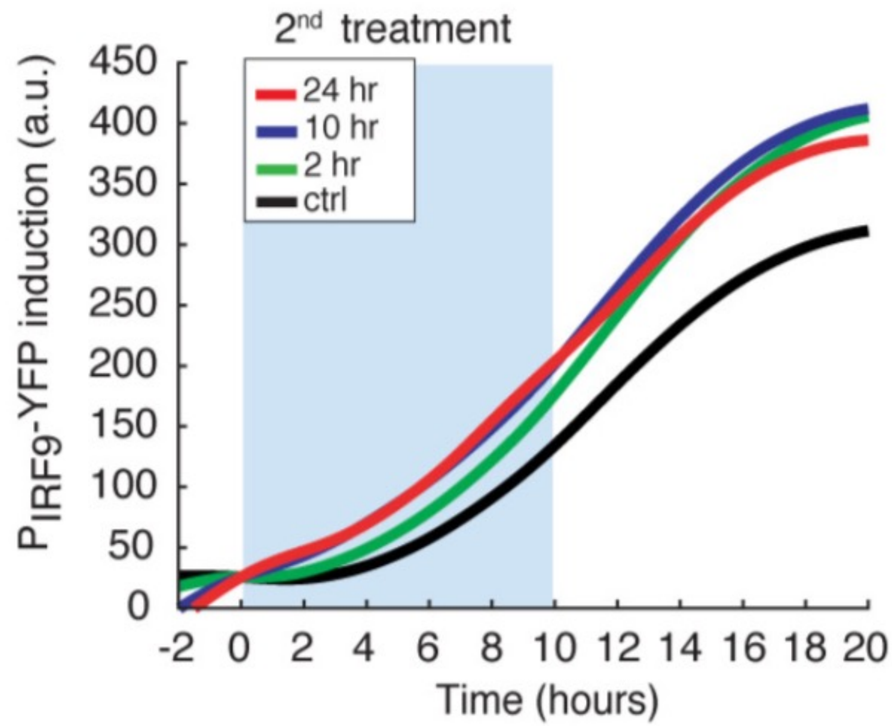
USP18 is Required for Desensitization

USP18: ubiquitin-specific peptidase 18

WT



USP18-KD



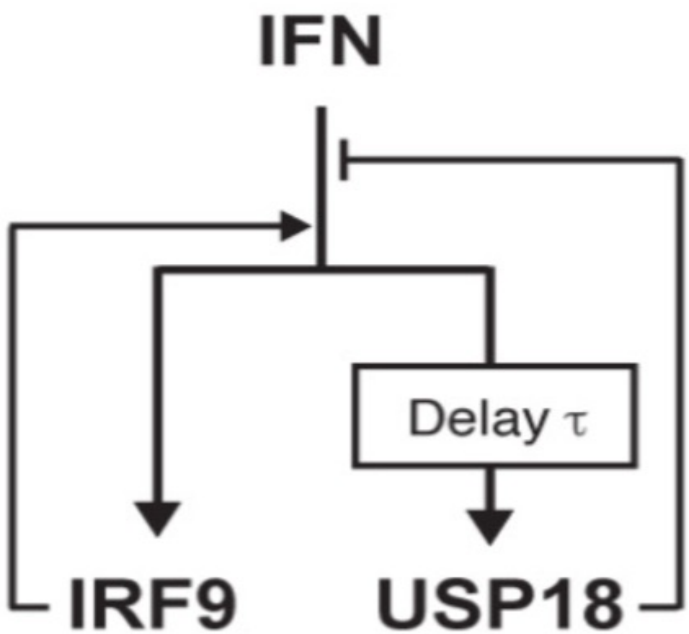
Averaged time traces

Figure 2

Mudla et al. Elife 2020, 9:e58825

Kinetic Model

Positive feedback

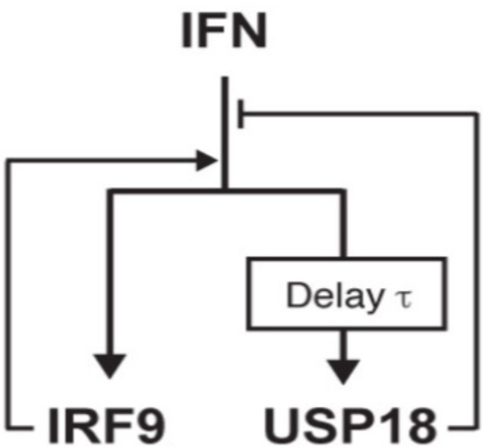


Negative feedback

Figure 3

Mudla et al. Elife 2020, 9:e58825

ODE for the Kinetic Model



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

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

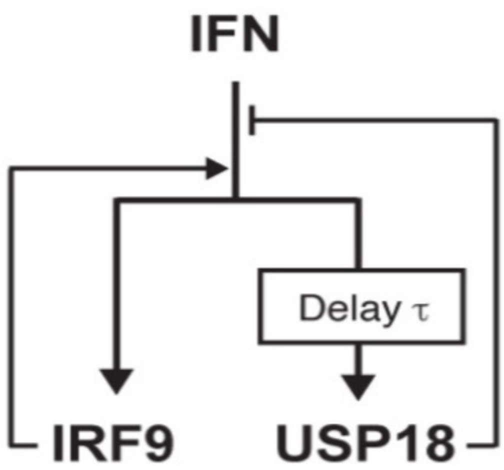
$$pf = k_1 \bullet \frac{IRF9}{k_2 + IRF9} \qquad nf = \frac{k_3}{k_3 + USP18}$$

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

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

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

Estimation of Delay Time in ODE



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

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

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

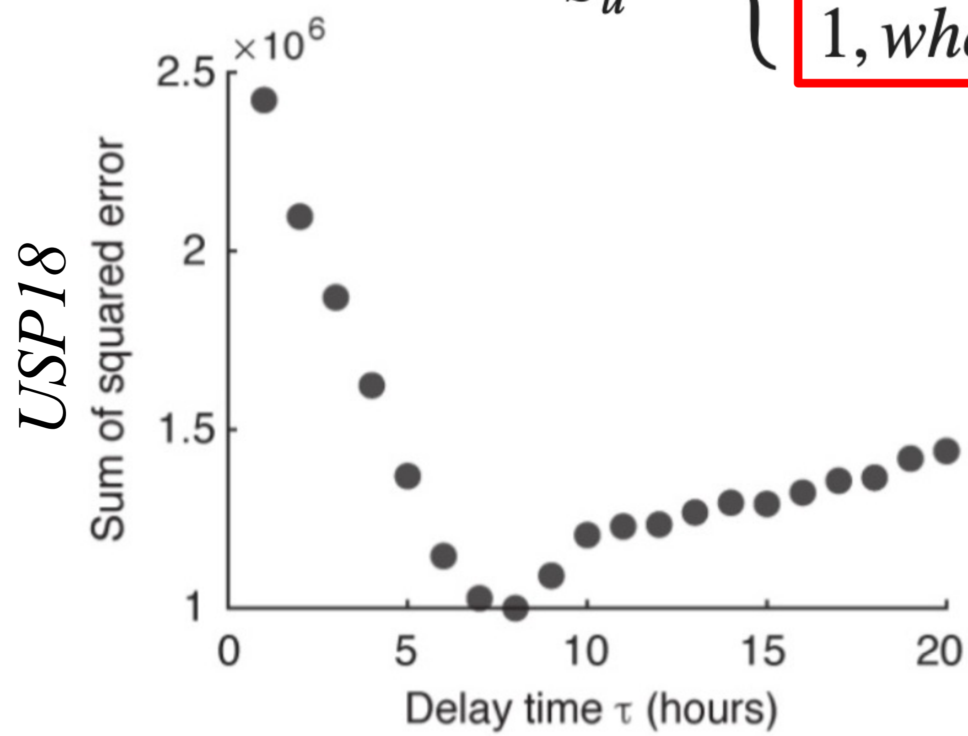


Figure 3B

Experimental Data vs. Model Prediction

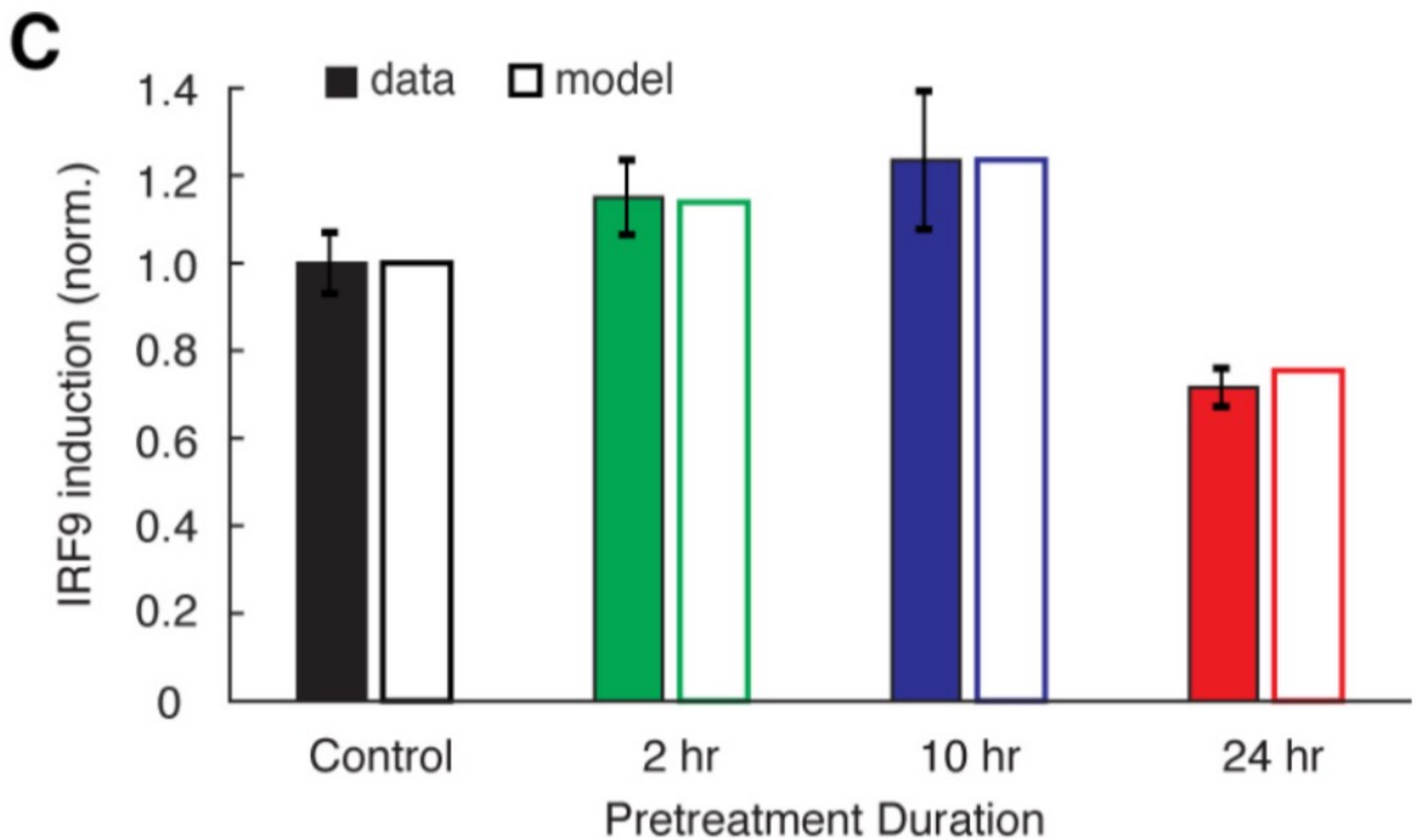


Figure 3

CFP-USP18 Reporter

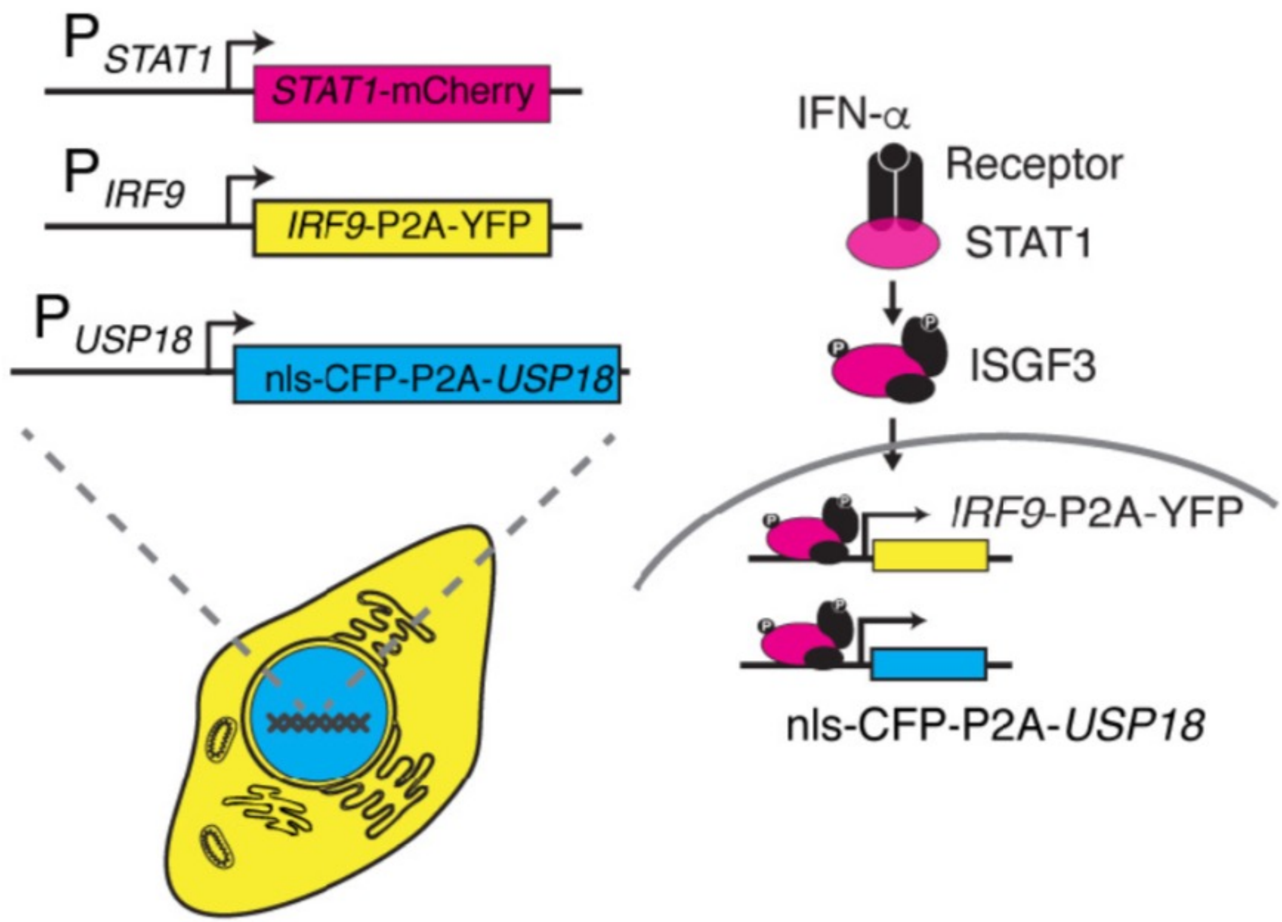


Figure 4

Images of Reporters in Response to IFN-α

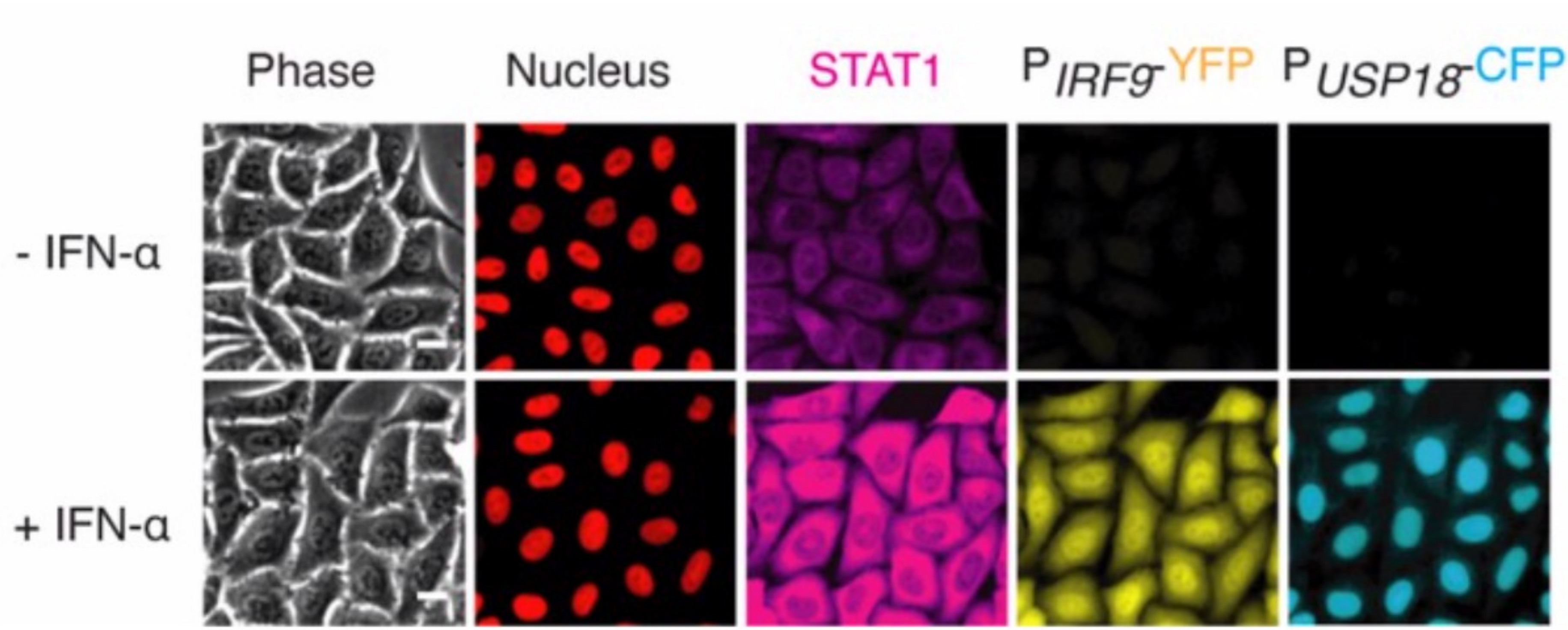


Figure 4-S1

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

Time trace of a single cell

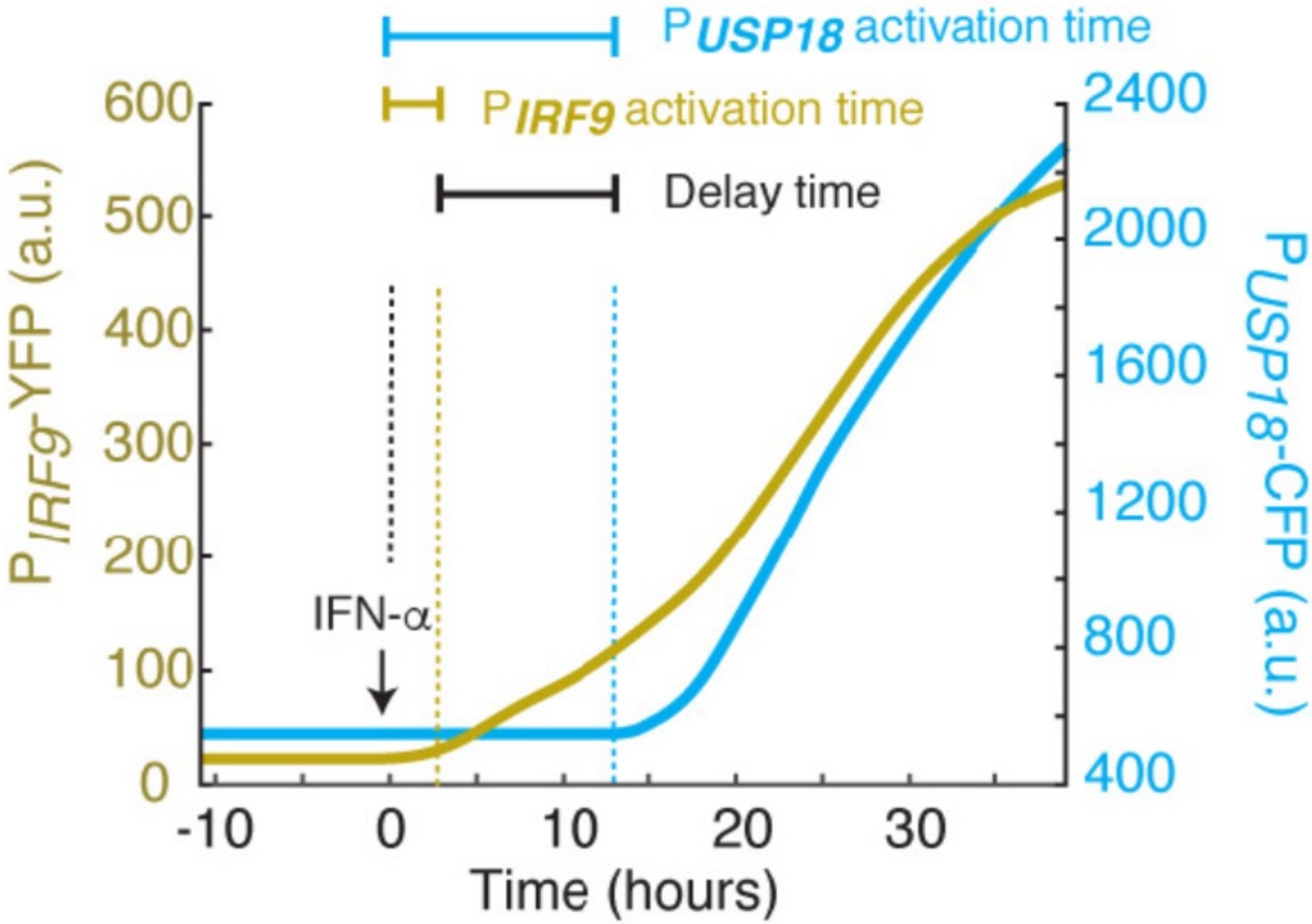


Figure 4B

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

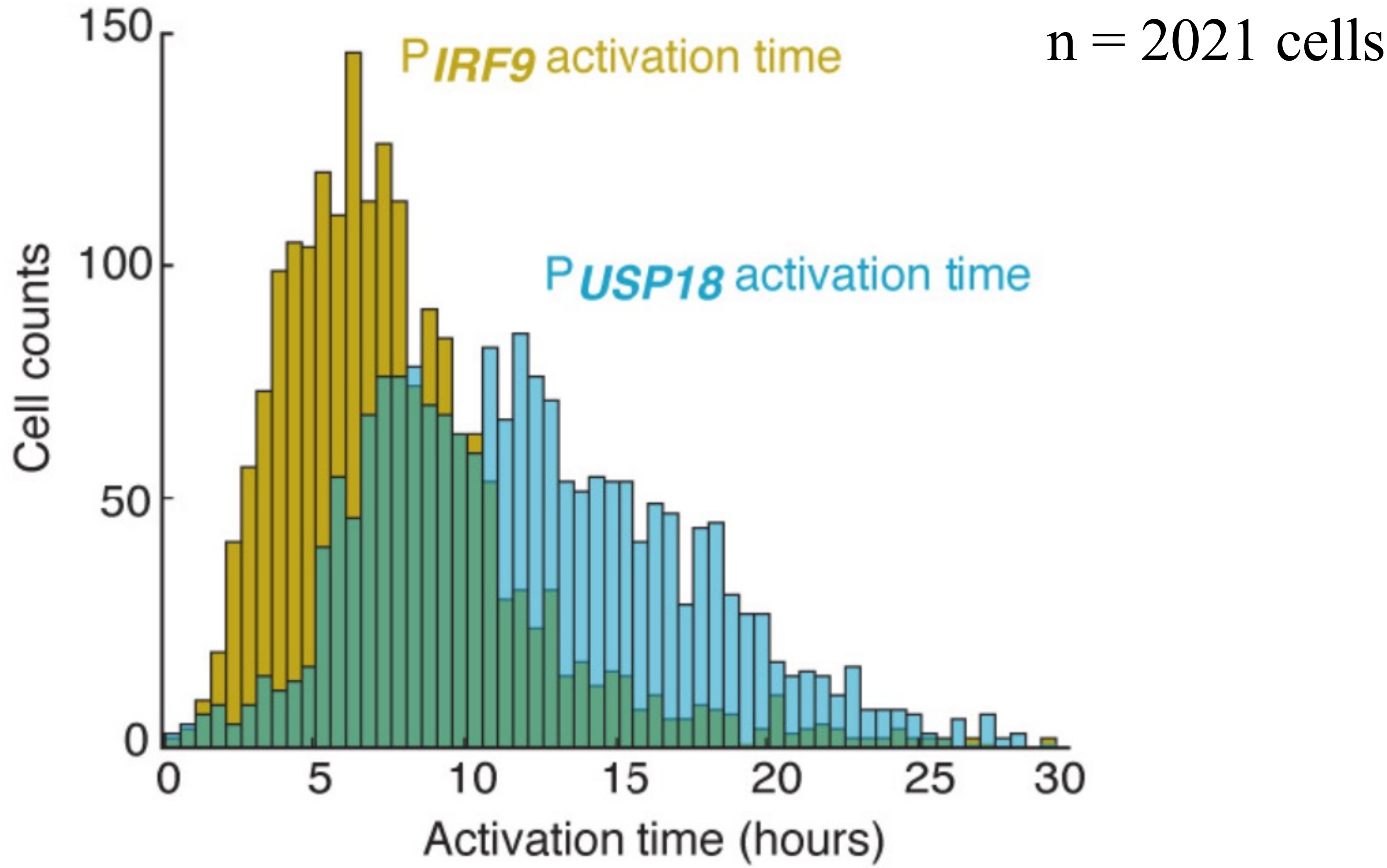


Figure 4C

Distributions of Delay Times in Single Cells

n = 2021 cells

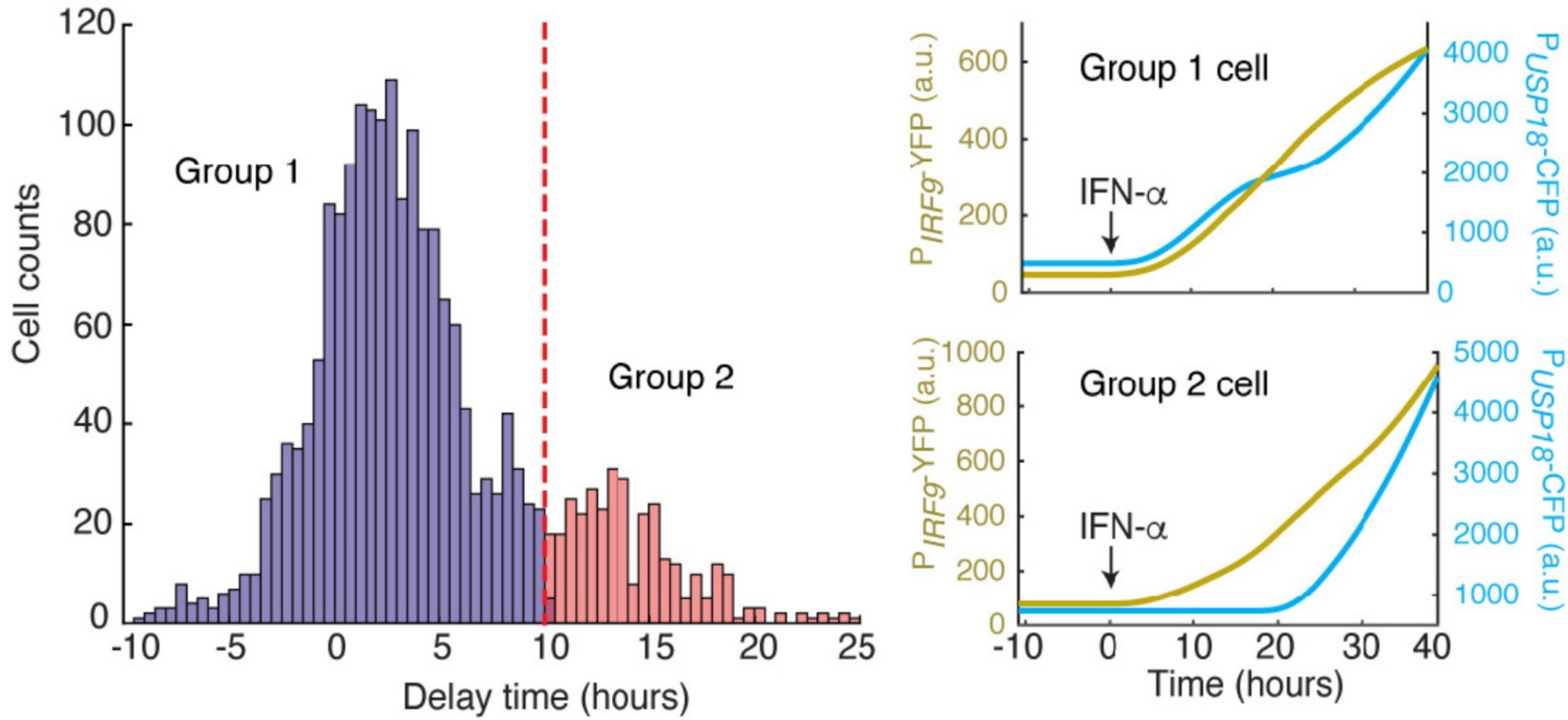


Figure 4D

Time-lapse Images of Cells over Multiple Cell Divisions

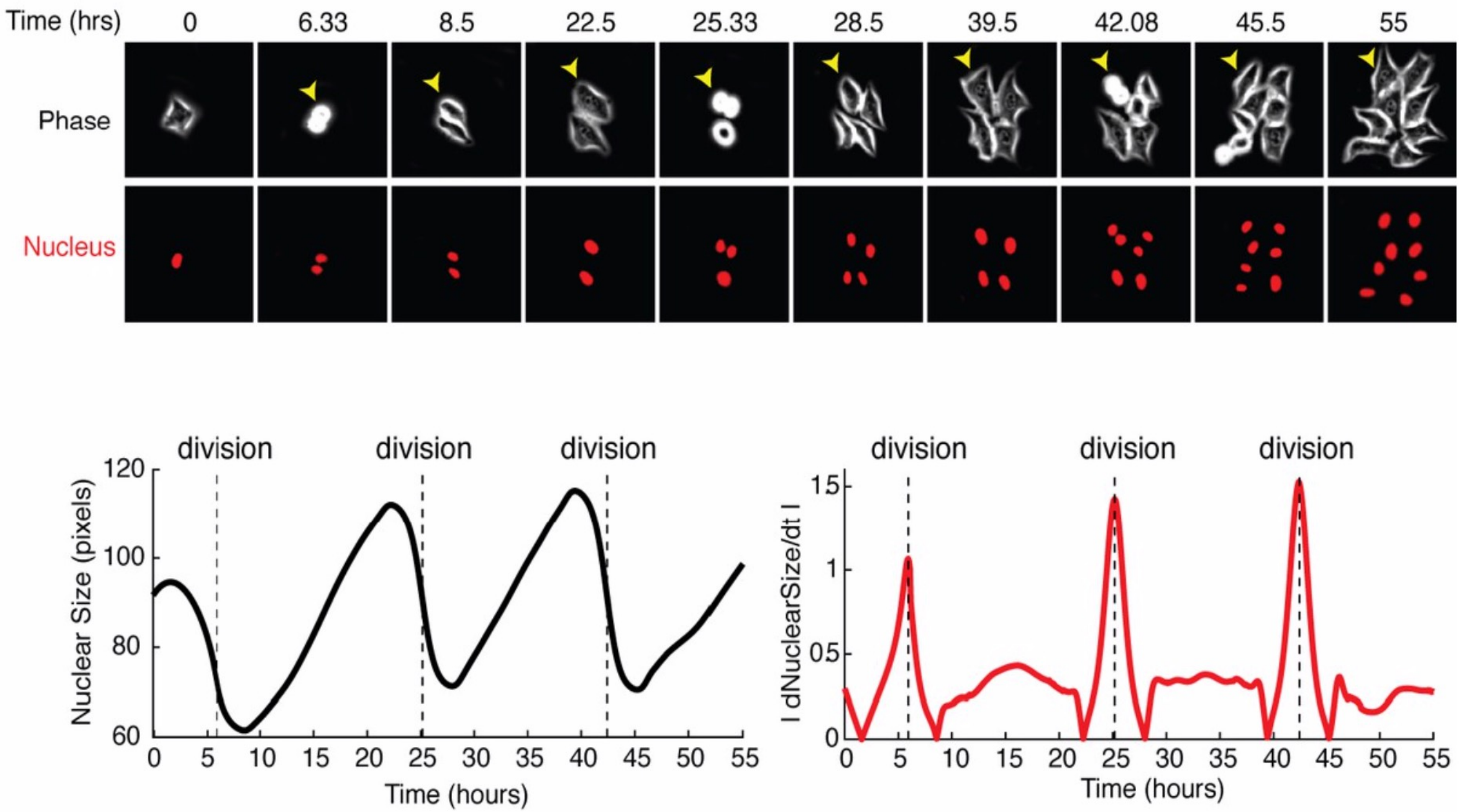
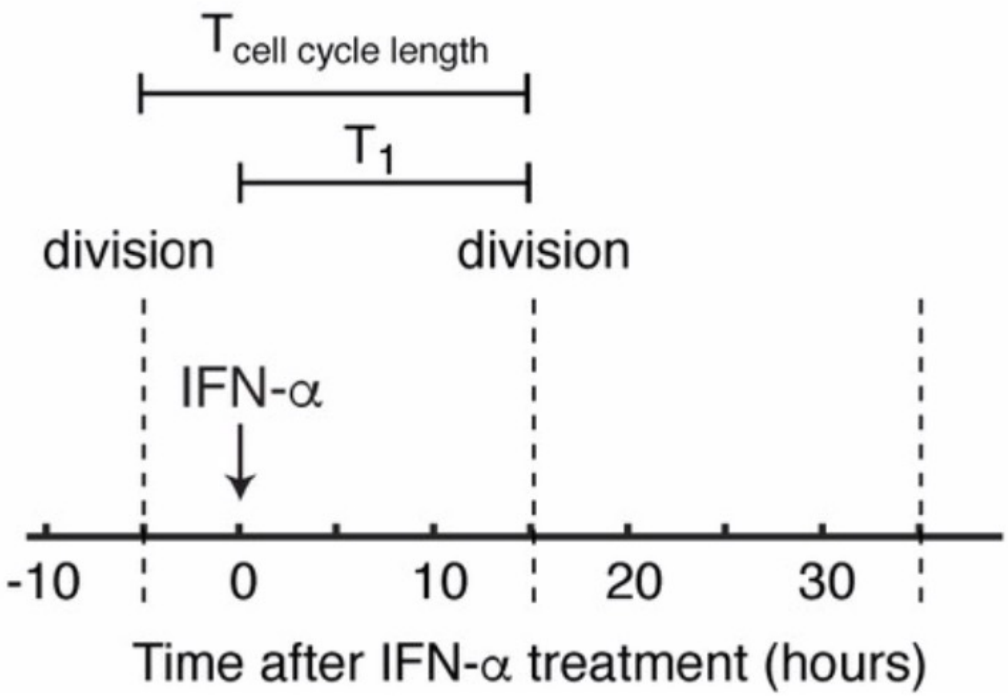


Figure 4-S3A

Percentage of Cell Cycle Progression at the Treatment Onset

$$\% \text{ cell cycle progression} = (T_{\text{cell cycle length}} - T_1) / T_{\text{cell cycle length}} \times 100$$

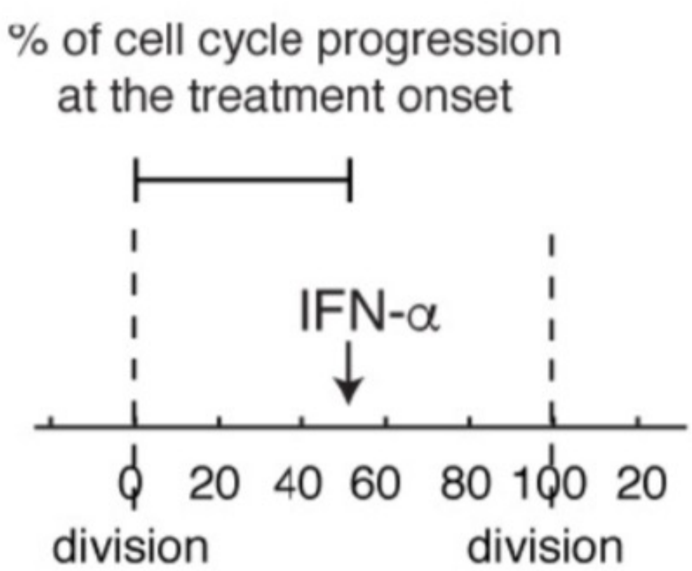


begin end

Inter-division interval

Figure 4-S3B

Distributions of Delay Times vs. Cell Cycle Progression



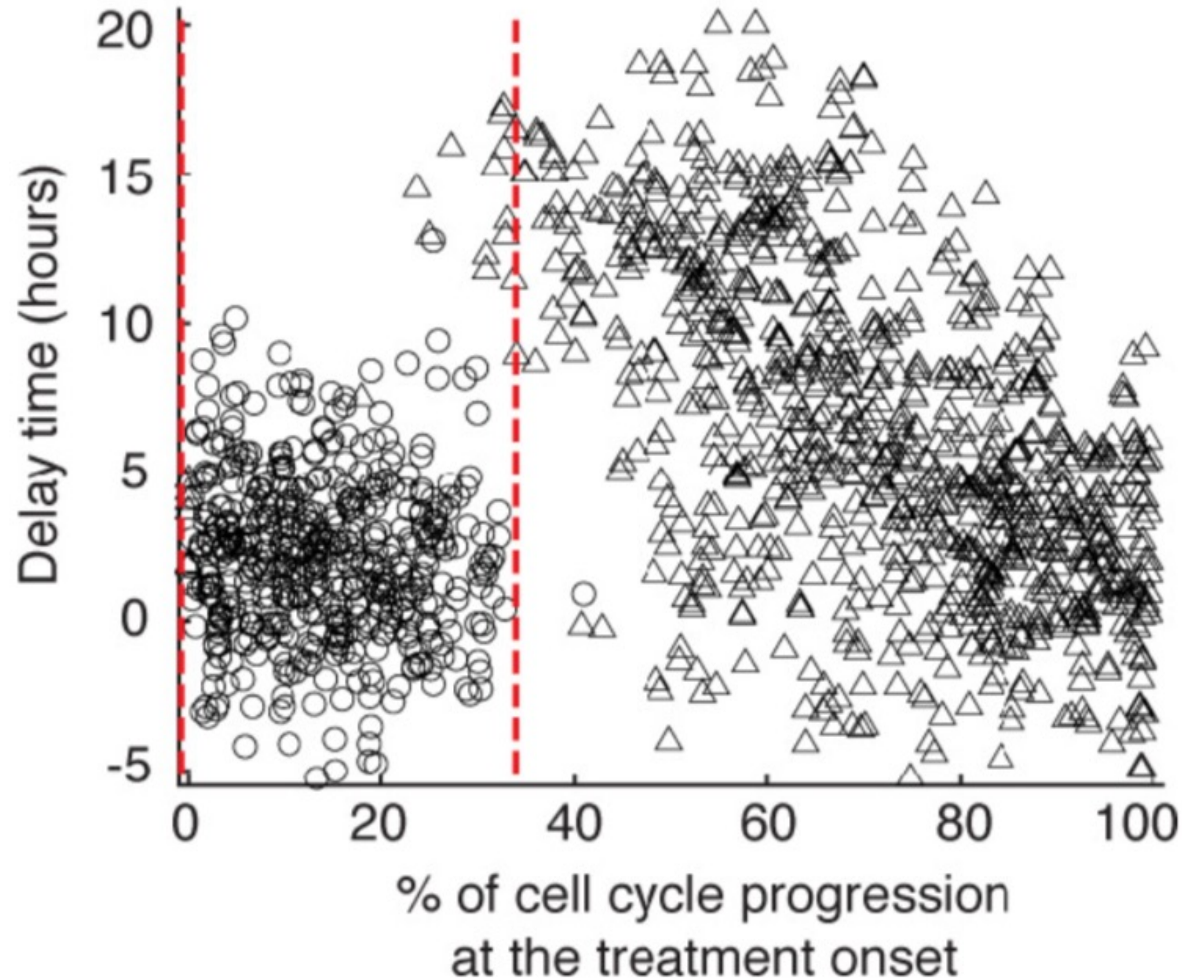


Figure 4E

Reduction of Delay Times with G1 Arrest

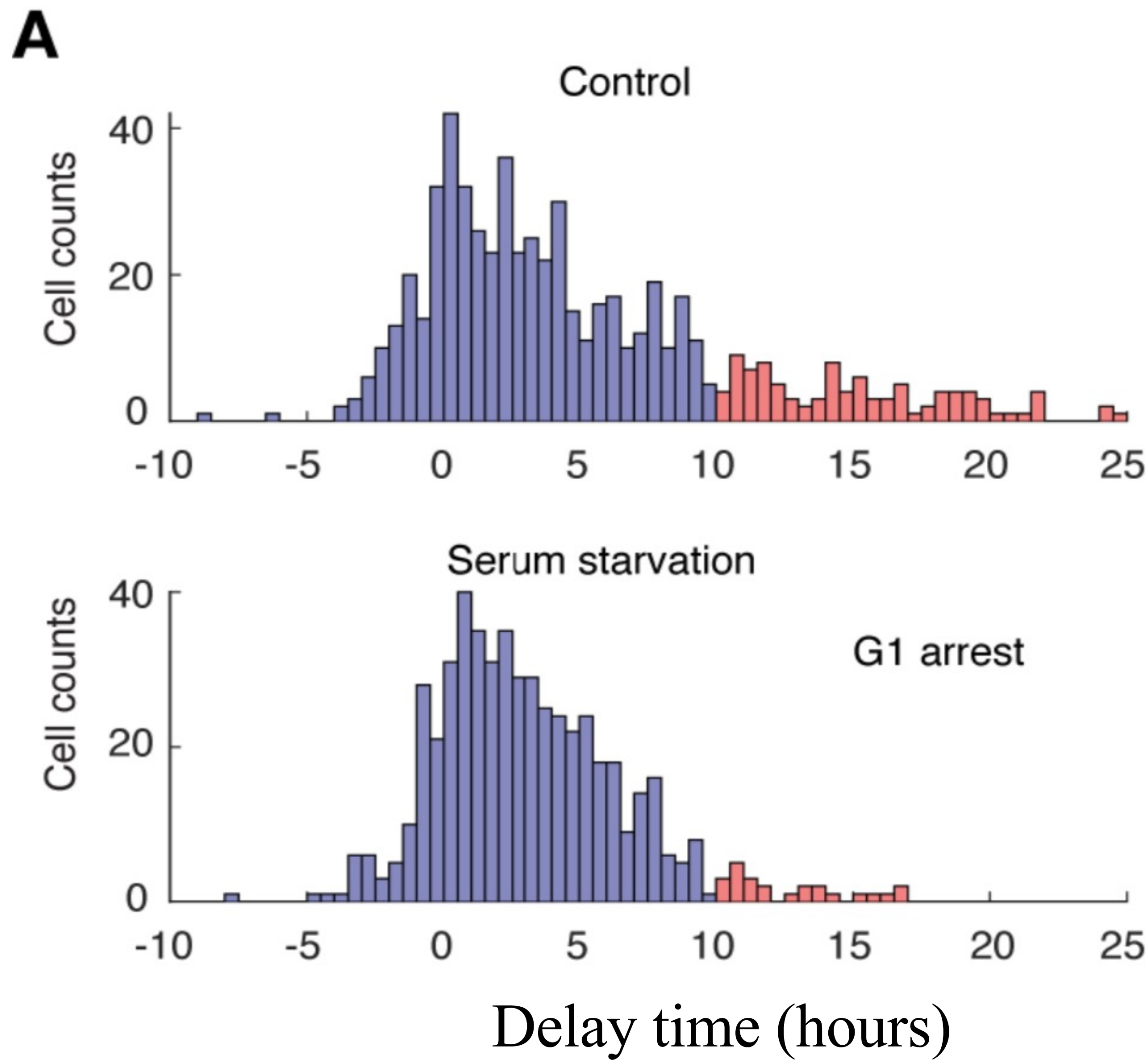


Figure 5A

DNA Helicase B (DHB) Reporter for CDK2 Activity

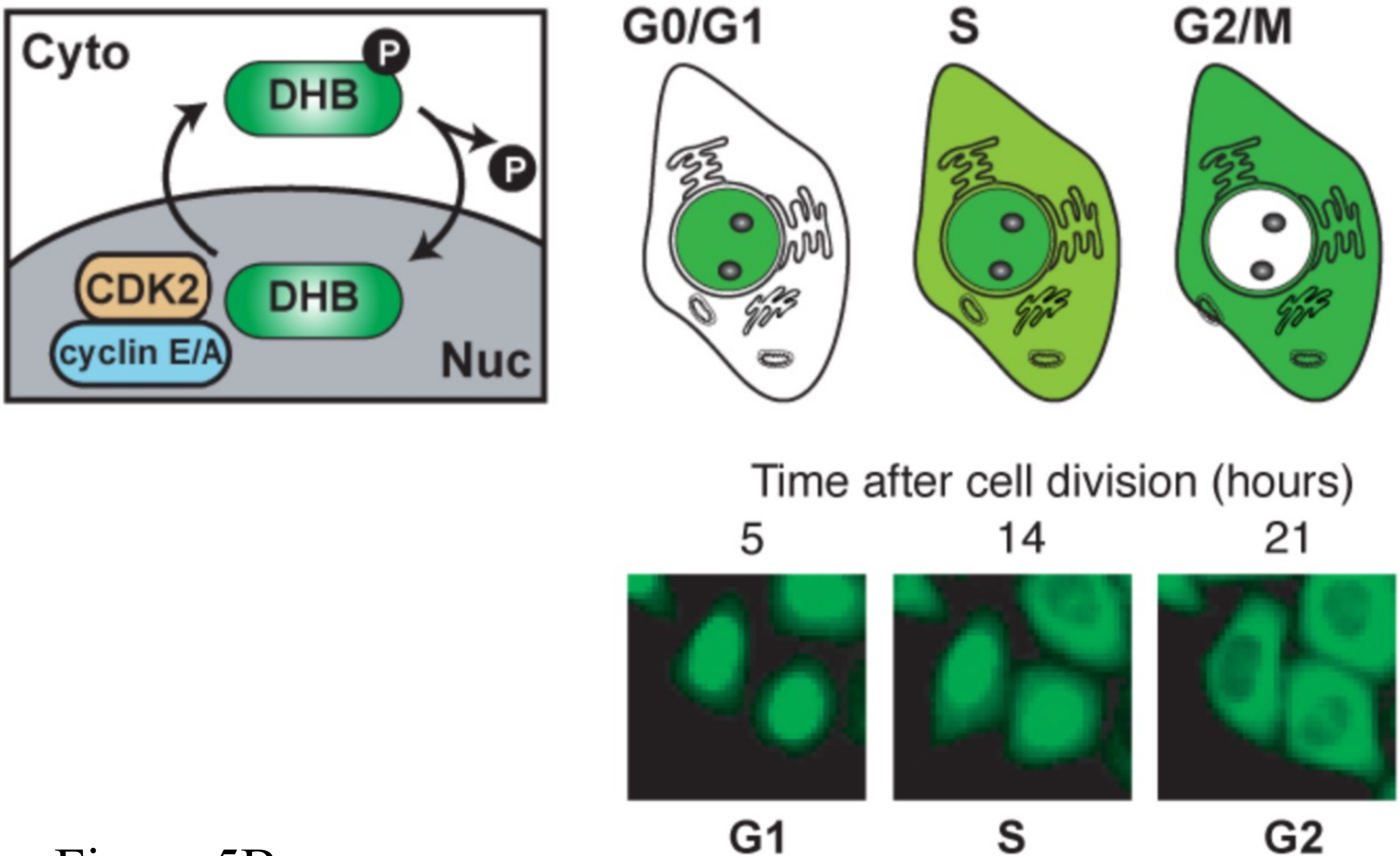


Figure 5B

DNA Helicase B (DHB) Reporter for CDK2 Activity

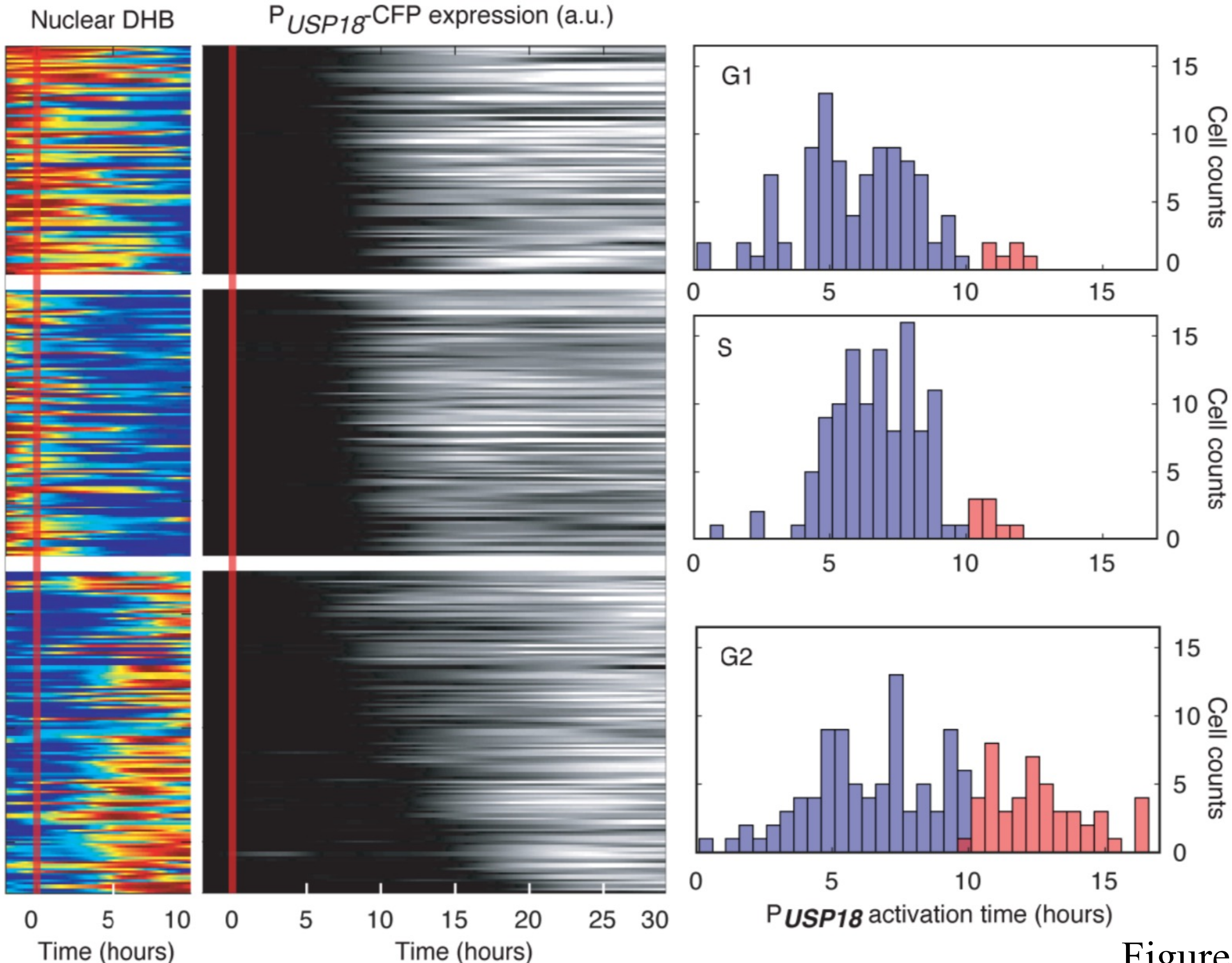


Figure 5C

Reduction of Delay Times by Decitabine

Decitabine: a DNA methyltransferase (DMNT) inhibitor

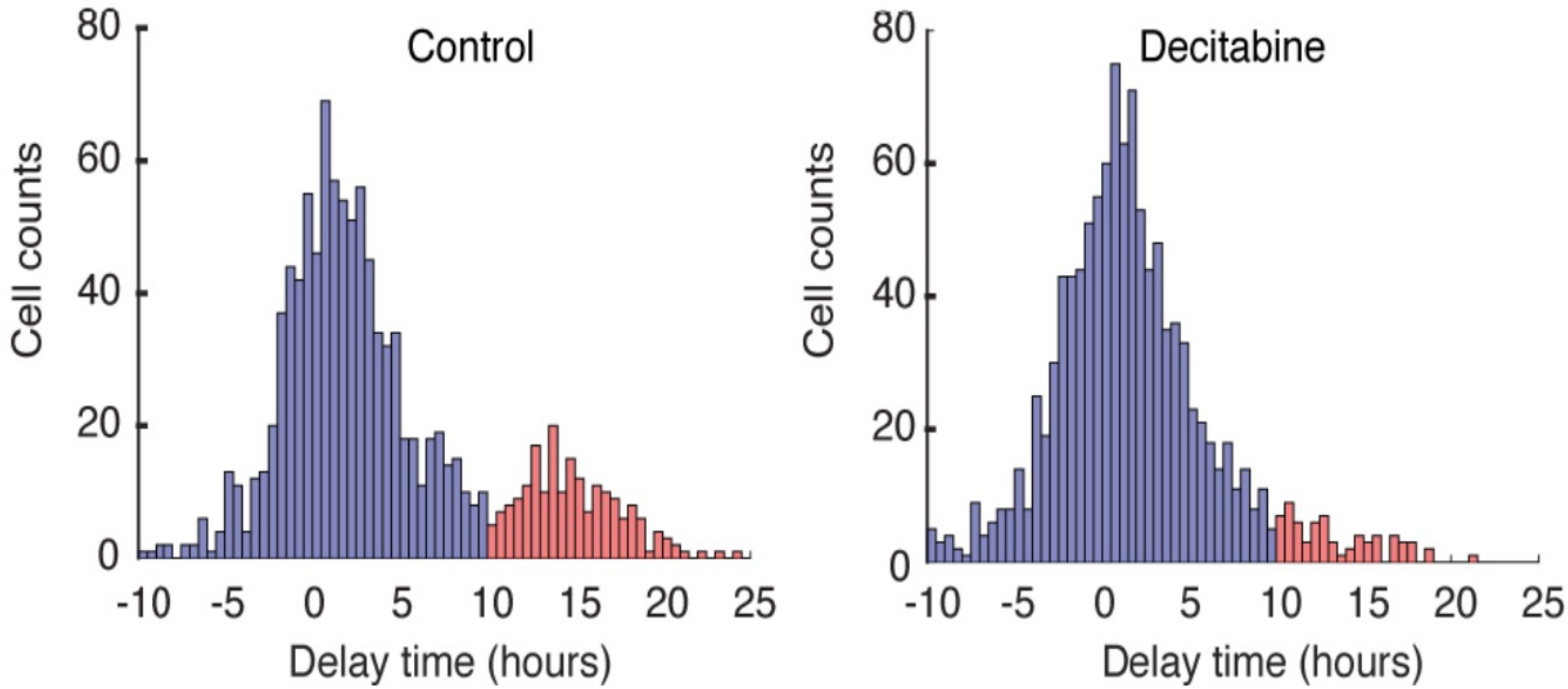
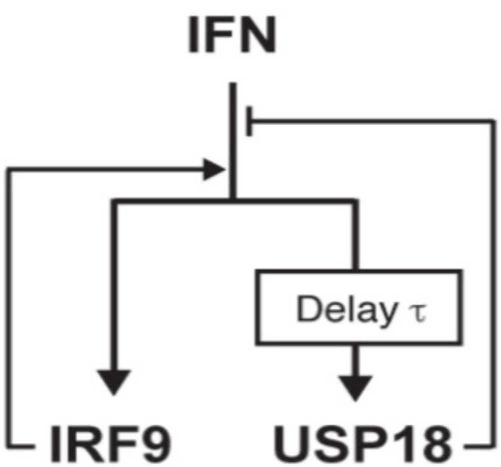


Figure 5D

Kinetic Model with Delay Time in ODE



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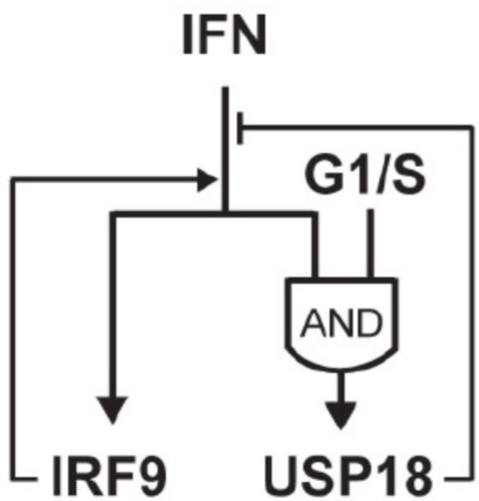
$$S_u = \begin{cases} 0, & \text{when the IFN input time } < \tau \\ 1, & \boxed{\text{when the IFN input time } \geq \tau} \end{cases}$$

Figure 3B

Stochastic DE with Cell Cycle Gating of USP18 Upregulation



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

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

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

Cell-cycle-dependent Delay Time

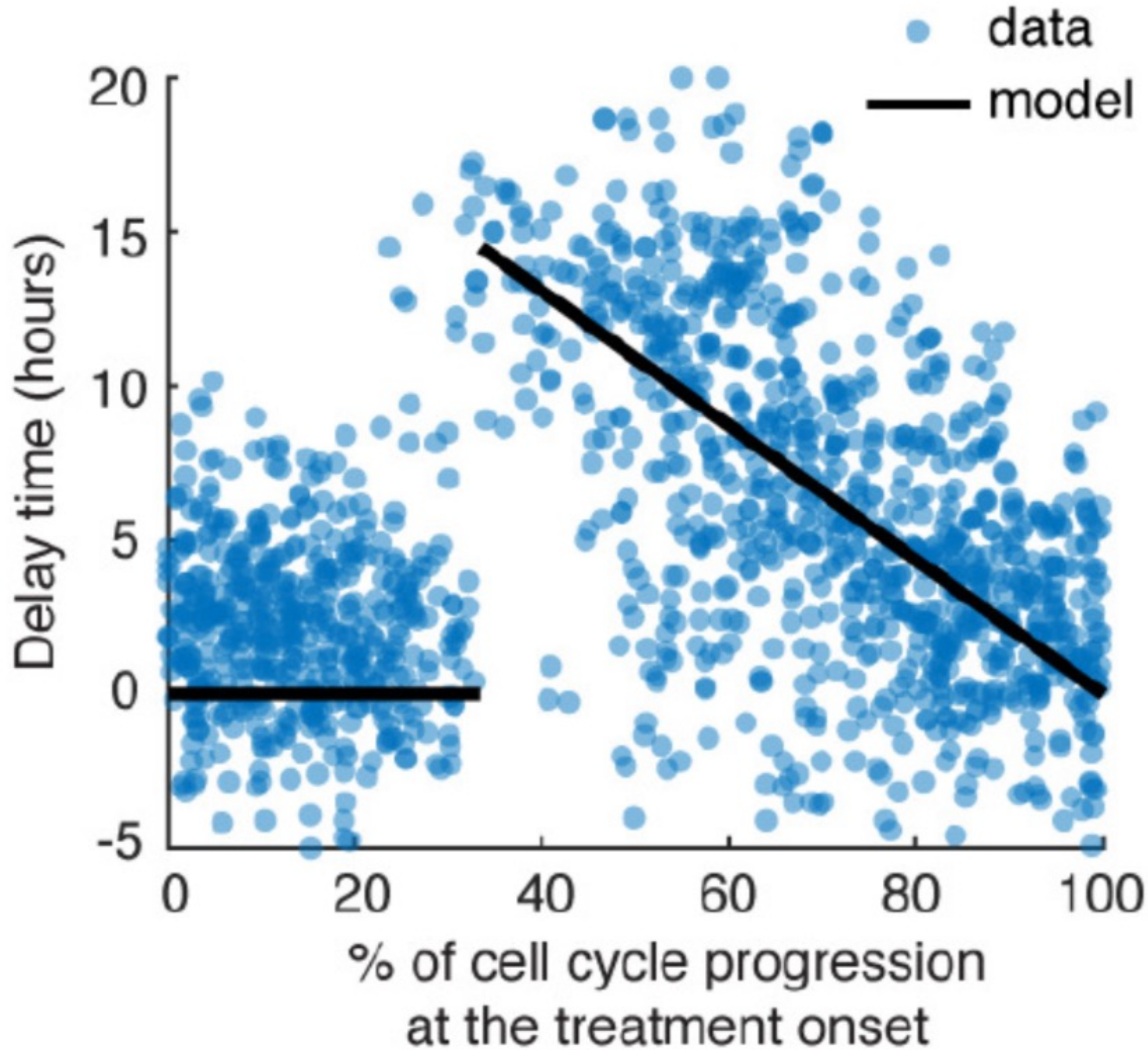


Figure 6B

Simulation vs. Experiment

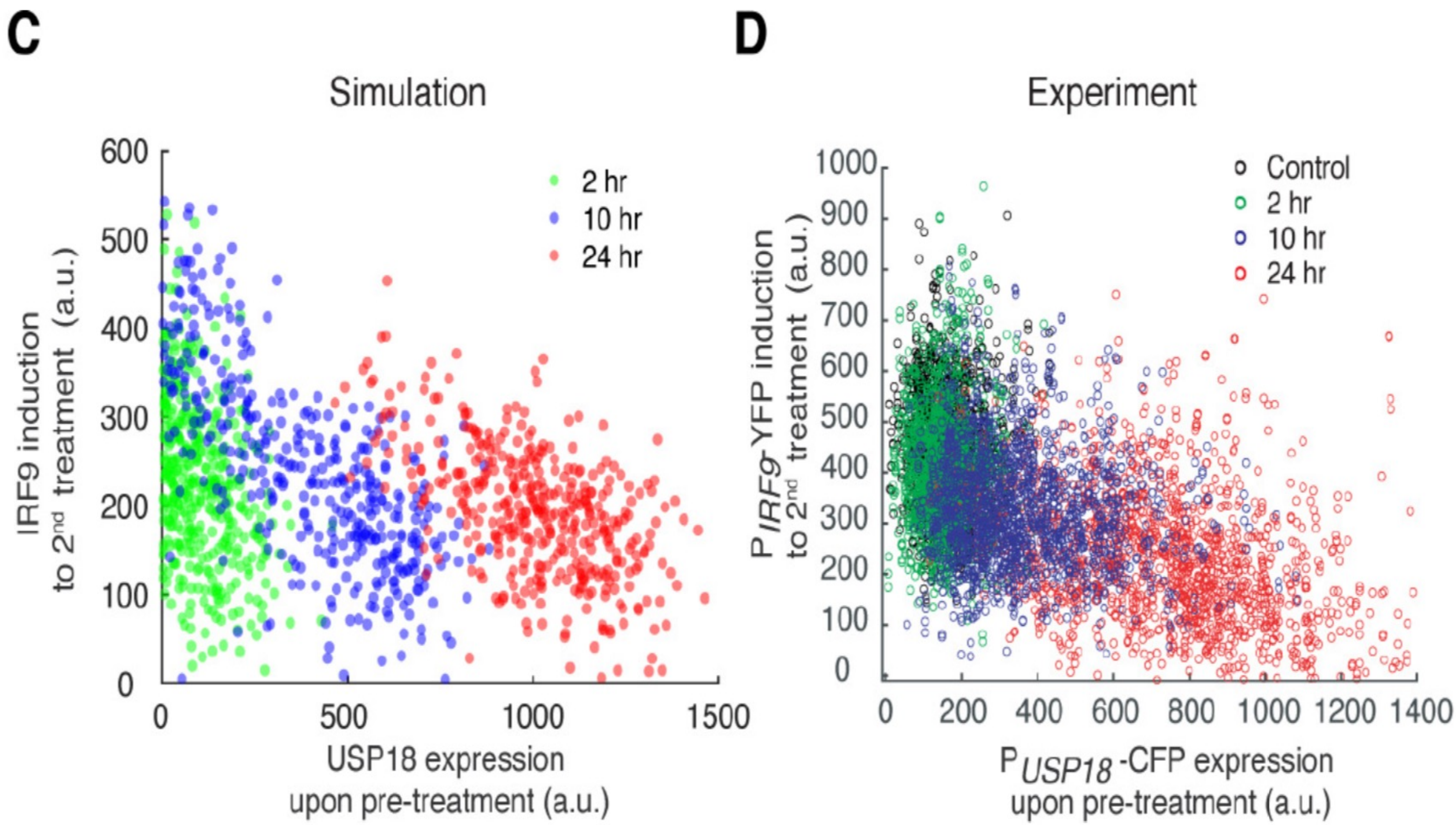
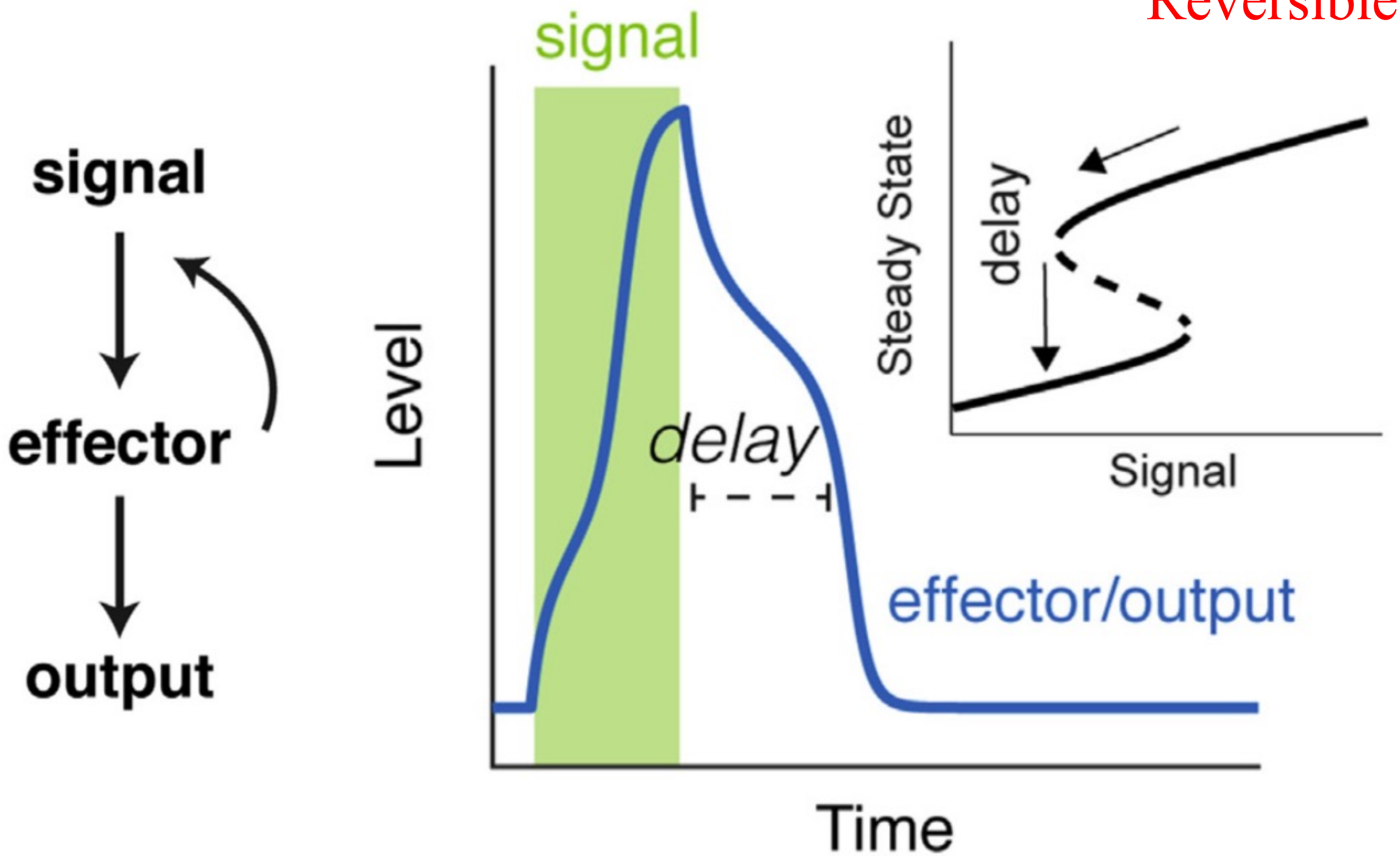


Figure 6C and 6D

Positive Feedback Loop (PFL)

Hysteresis: history-dependent behavior

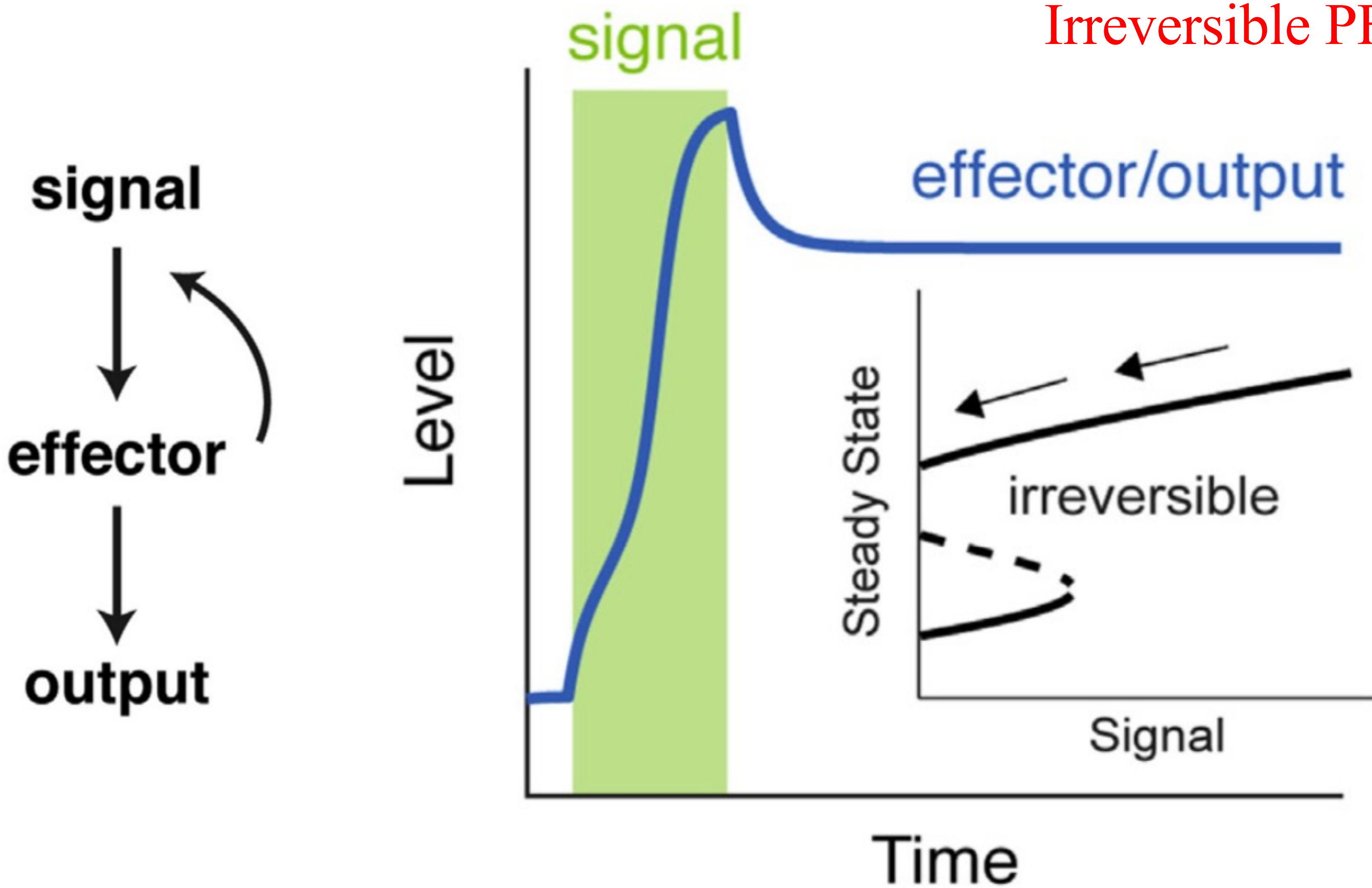
Reversible PFL



Jiang and Hao, Current Opinion in Cell Biology 2021, 69:96–102

Positive Feedback Loop (PFL)

Irreversible PFL



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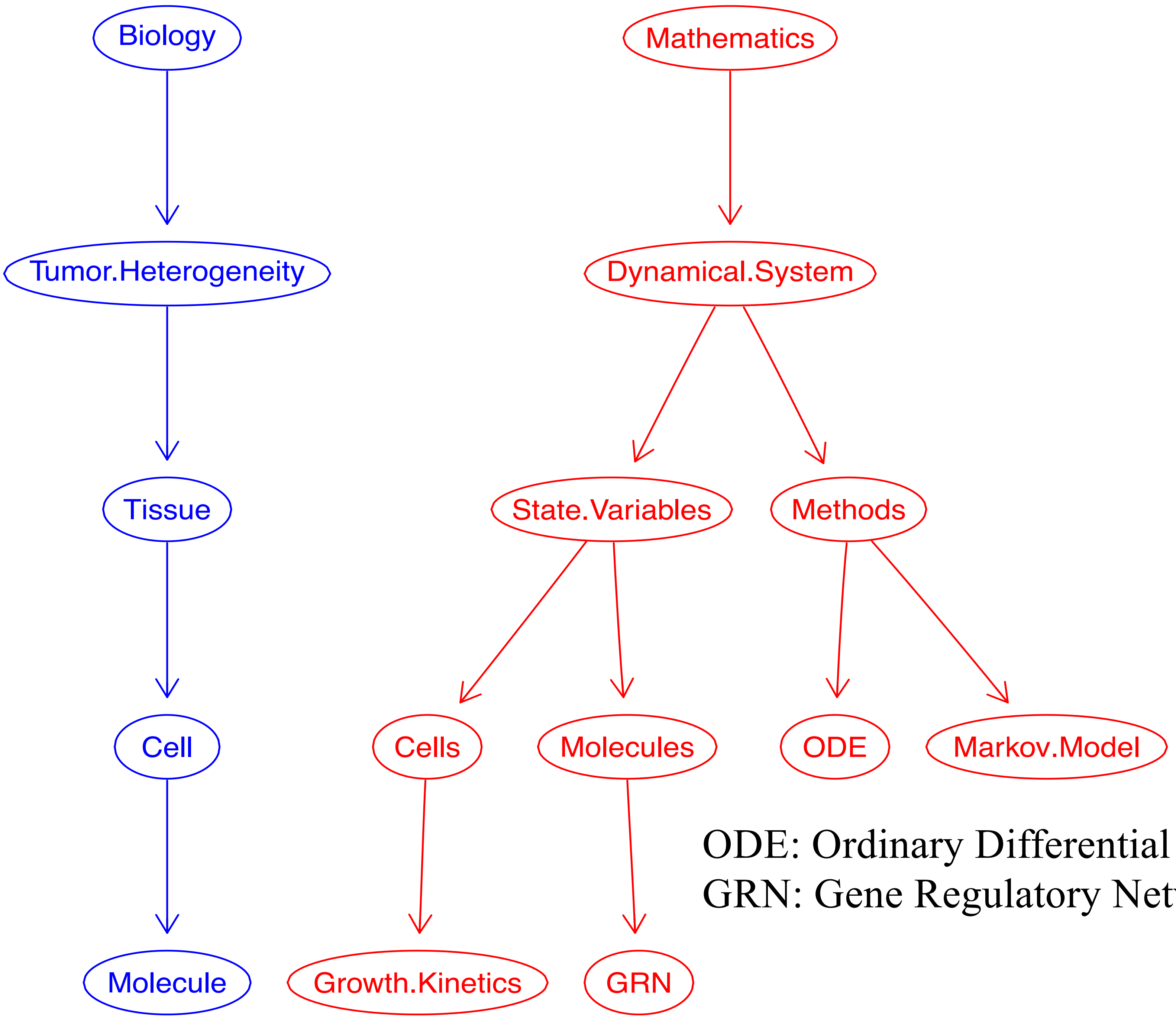

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