

# *Optimized Experimental and Analytical Tools for Reproducible Drug-Response Studies*

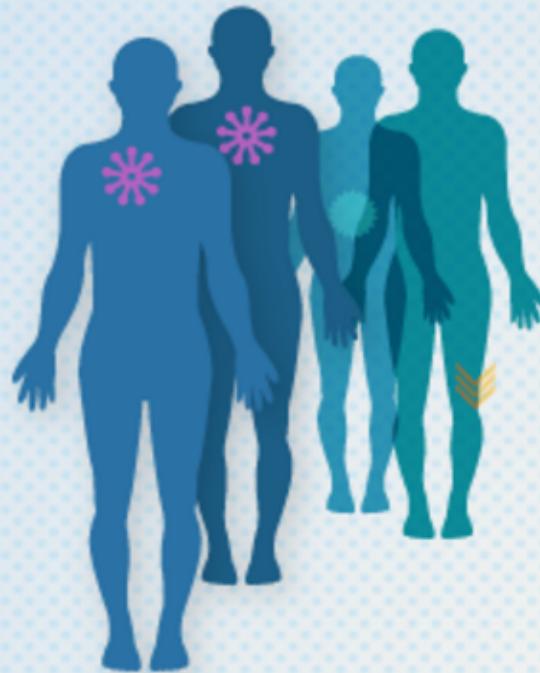
**CB399 – March, 2017**



**HiTS**  
Harvard Program  
in Therapeutic Science

## Motivation: Making better drugs and identifying patients who will benefit

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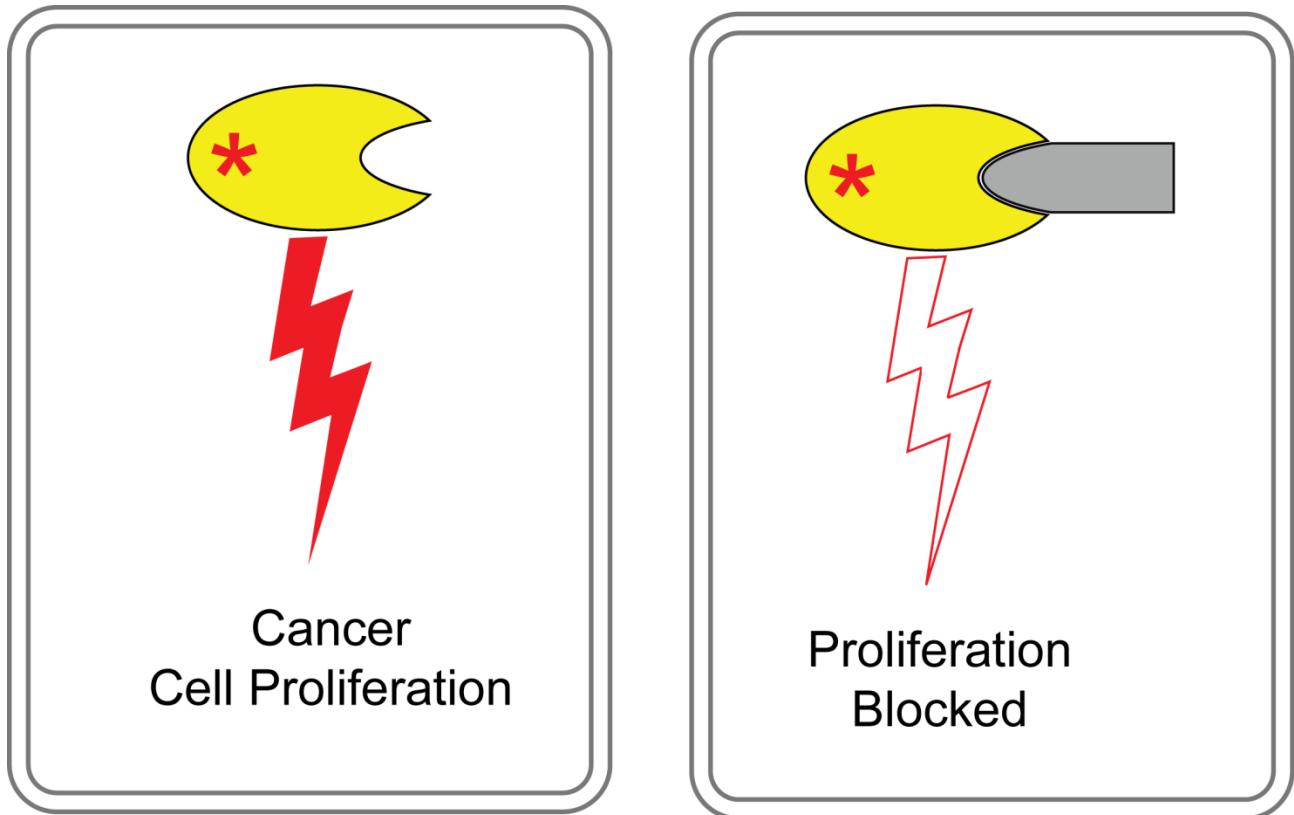


<http://www.cancer.gov/>

# Magic bullet therapies (Die Zauberkugeln)

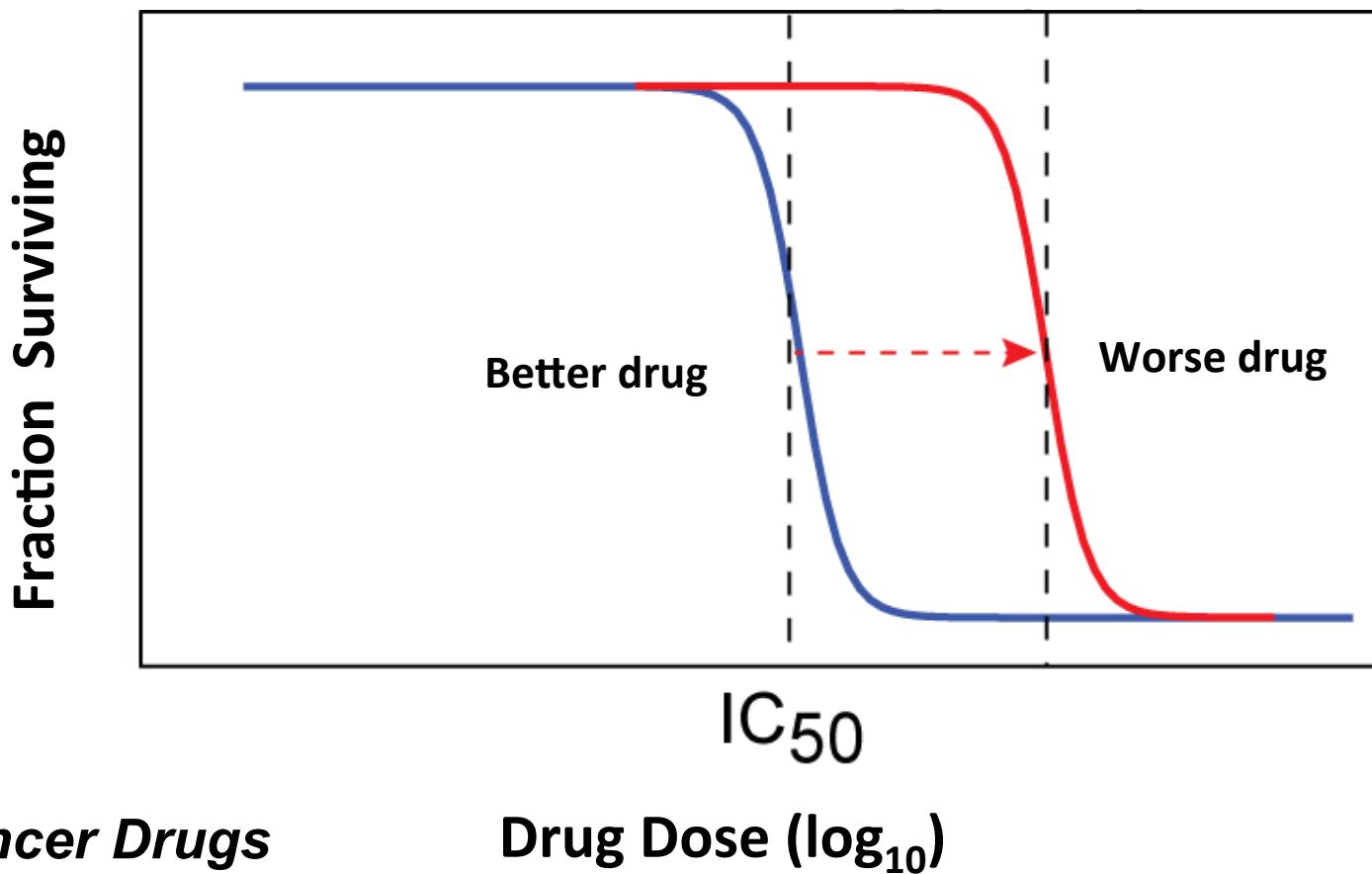


Paul Ehrlich  
(1854 -1915)

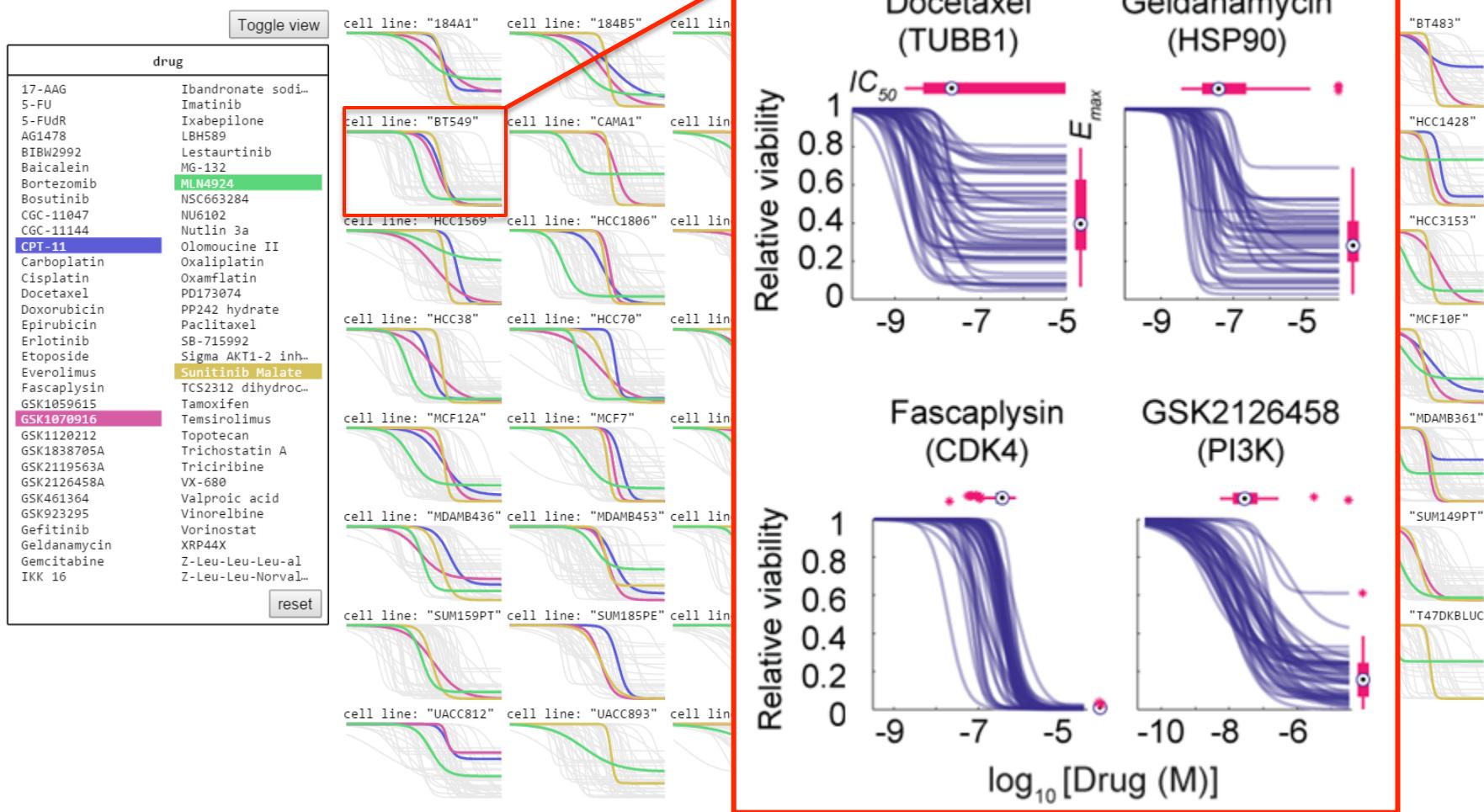


Mutation Activity	Disease	Drug	
Her2/ErbB2	Kinase (RTK)	Breast Cancer	Trastuzumab
BCR-ABL	Kinase (Y)	CML	Imatinib
EGFR <sup>L858R</sup>	Kinase (RTK)	Lung Cancer (NSLC)	Gefitinib/erlotinib
BRAF <sup>V600E</sup>	Kinase (S/T)	Melanoma	Vemurafenib
EML4/ALK	Kinase (RTK)	Lung Cancer (NSLC)	Crizotinib

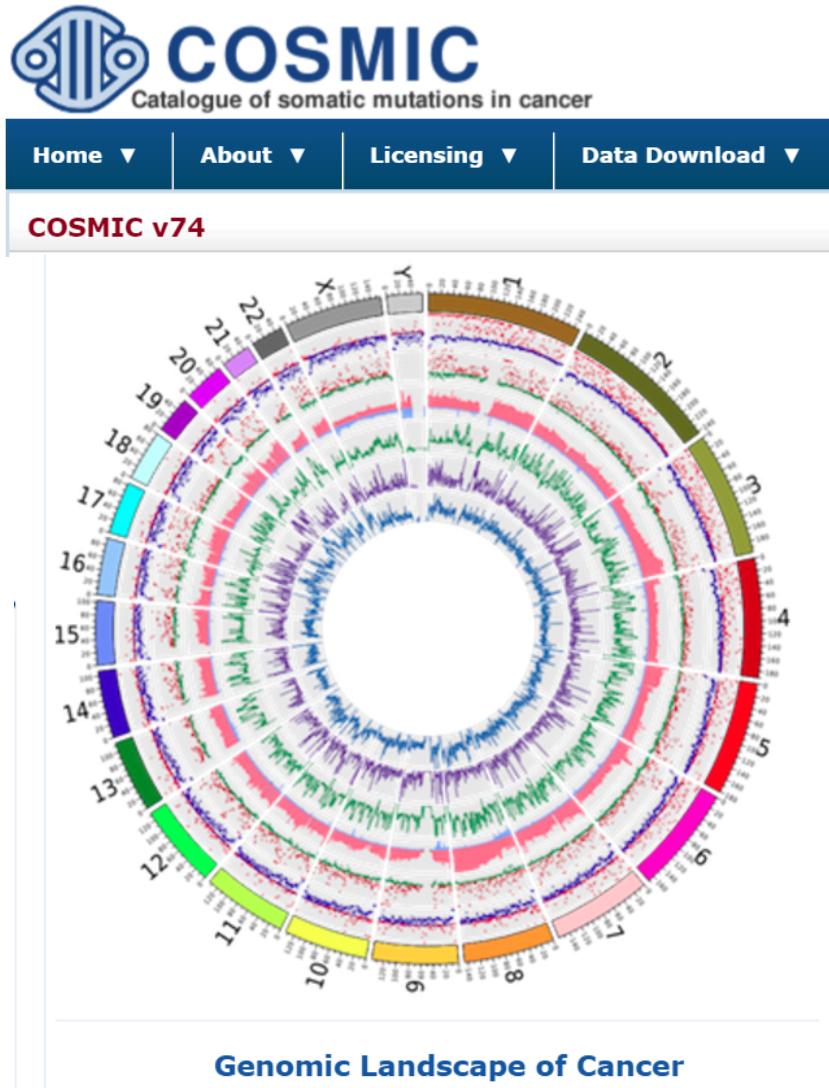
# Dose-response relationships: the basic figure of merit for a drug



# Dose-response on a large scale

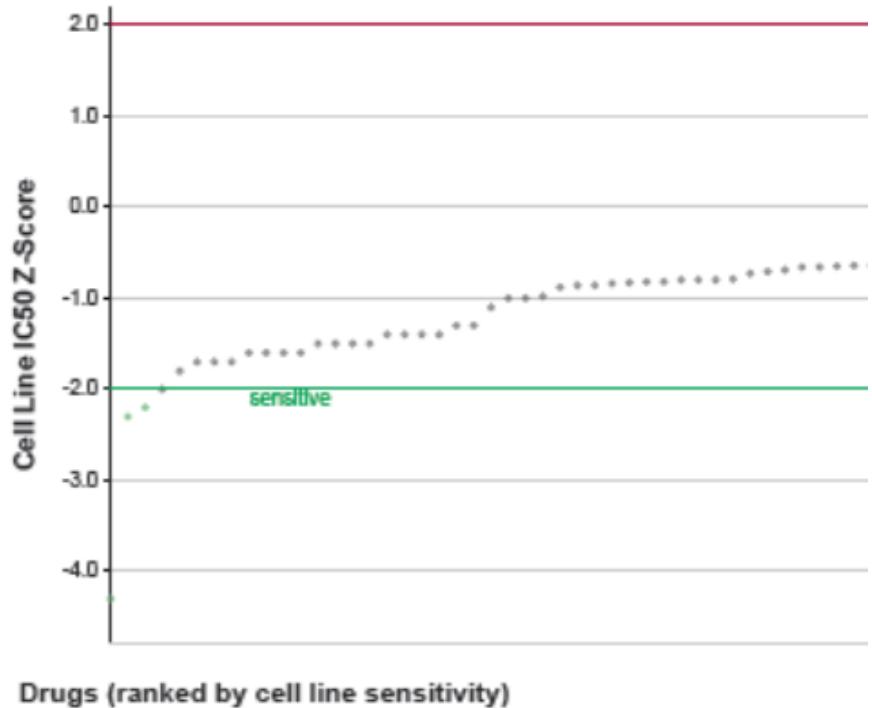


# Why is this data valuable: drug pharmacogenomics



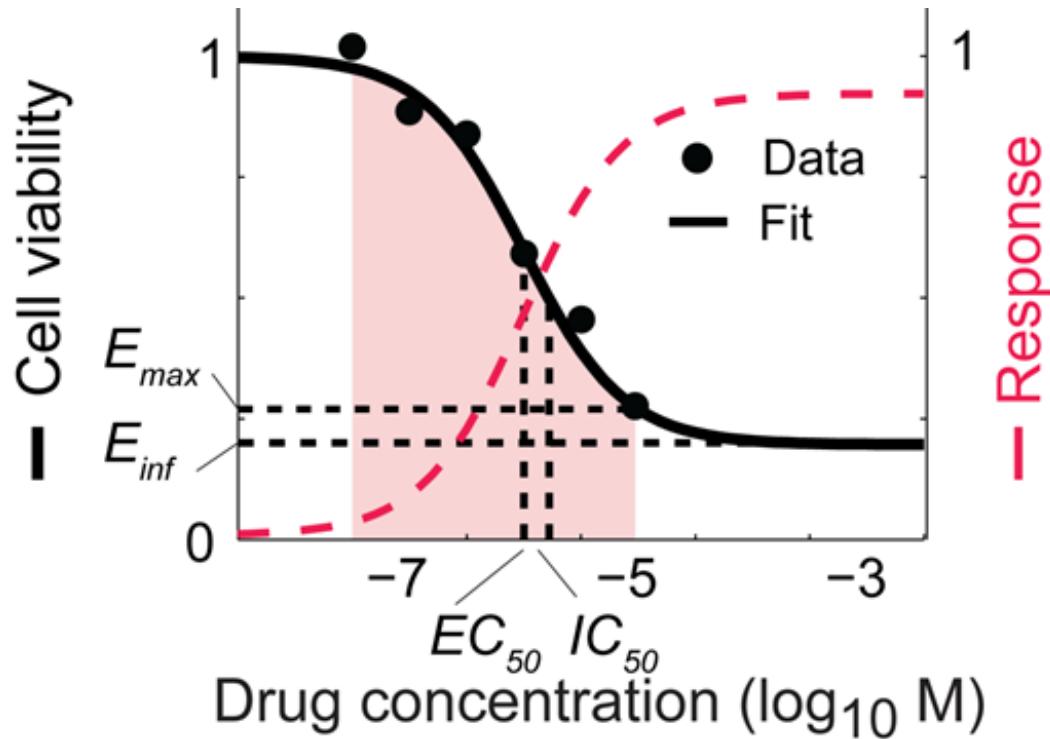
## Analysis of Cell Line Sensitivity

Relative sensitivity of MCF7



<http://www.cancerrxgene.org/>

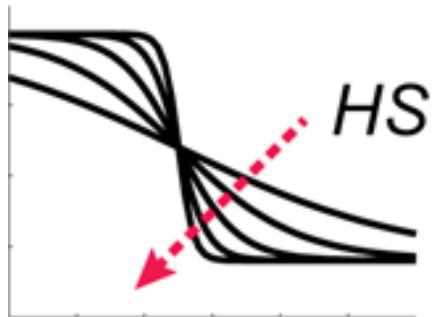
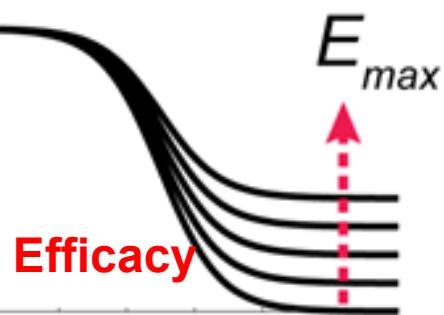
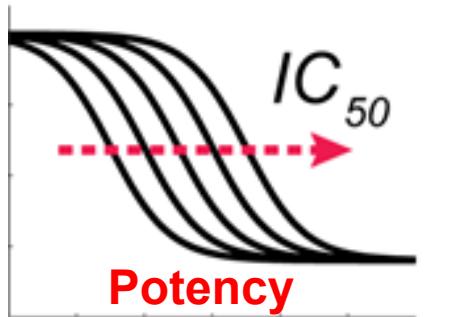
# Rethinking what really varies in dose-response relationships



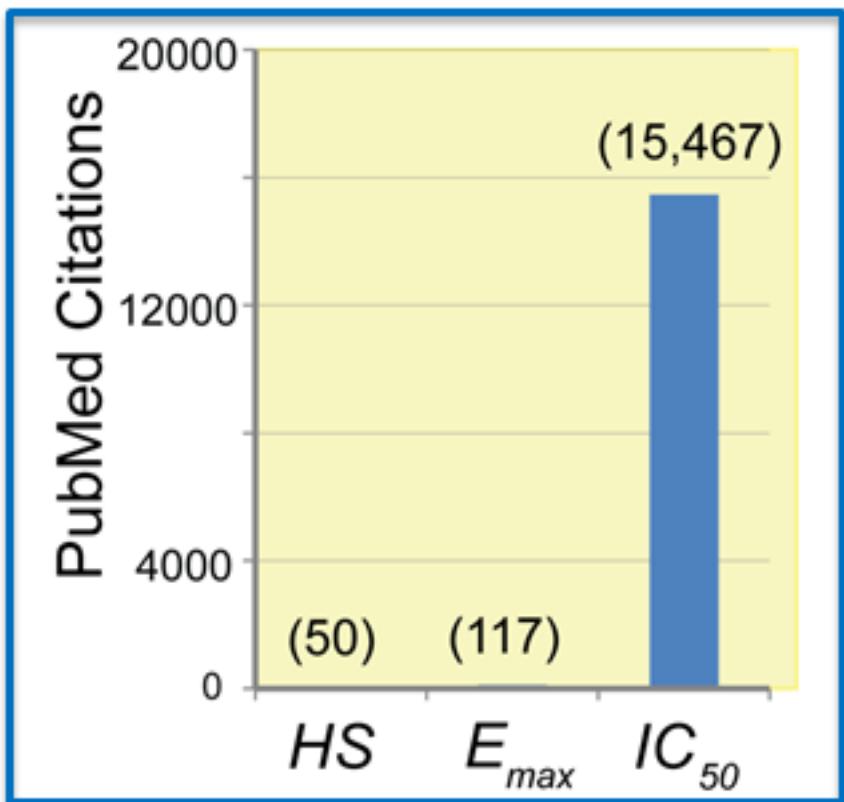
$$y = E_{inf} + \left[ \frac{E_0 - E_{inf}}{1 + \left( \frac{D}{EC_{50}} \right)^{HS}} \right]$$

# What does the literature say?

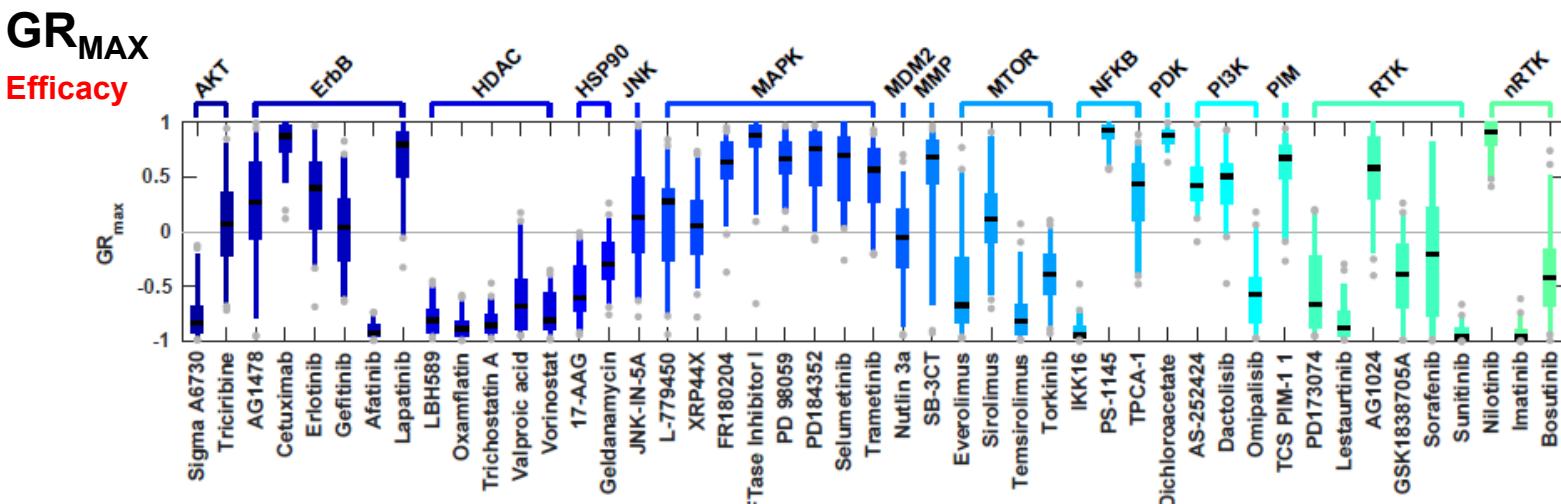
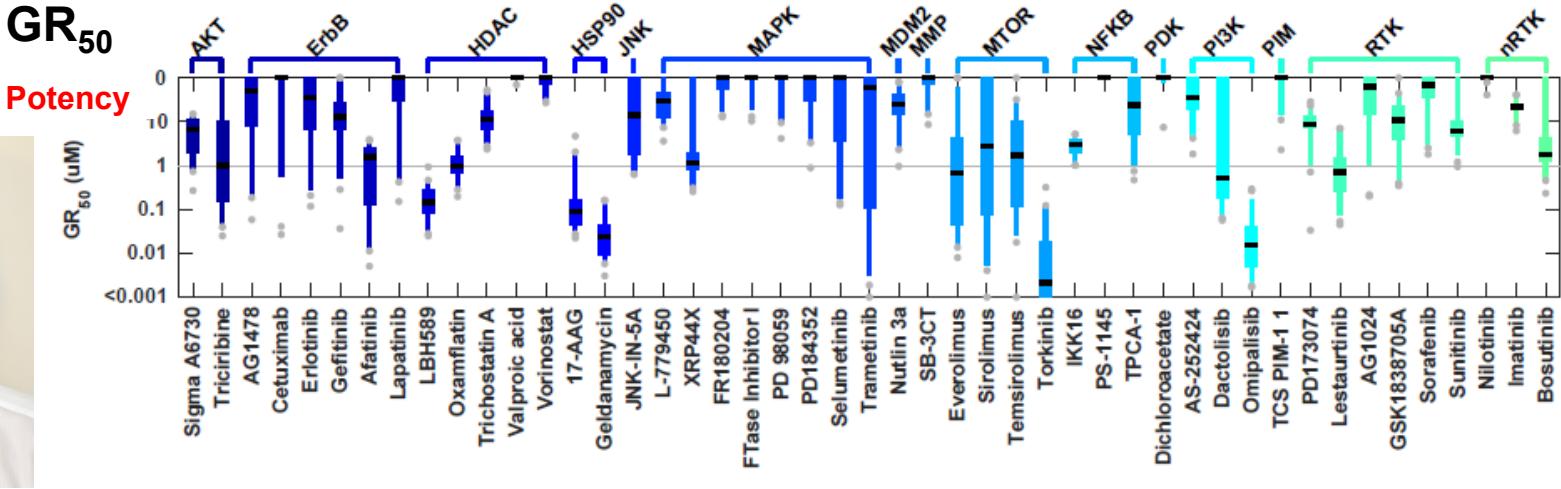
## Theory



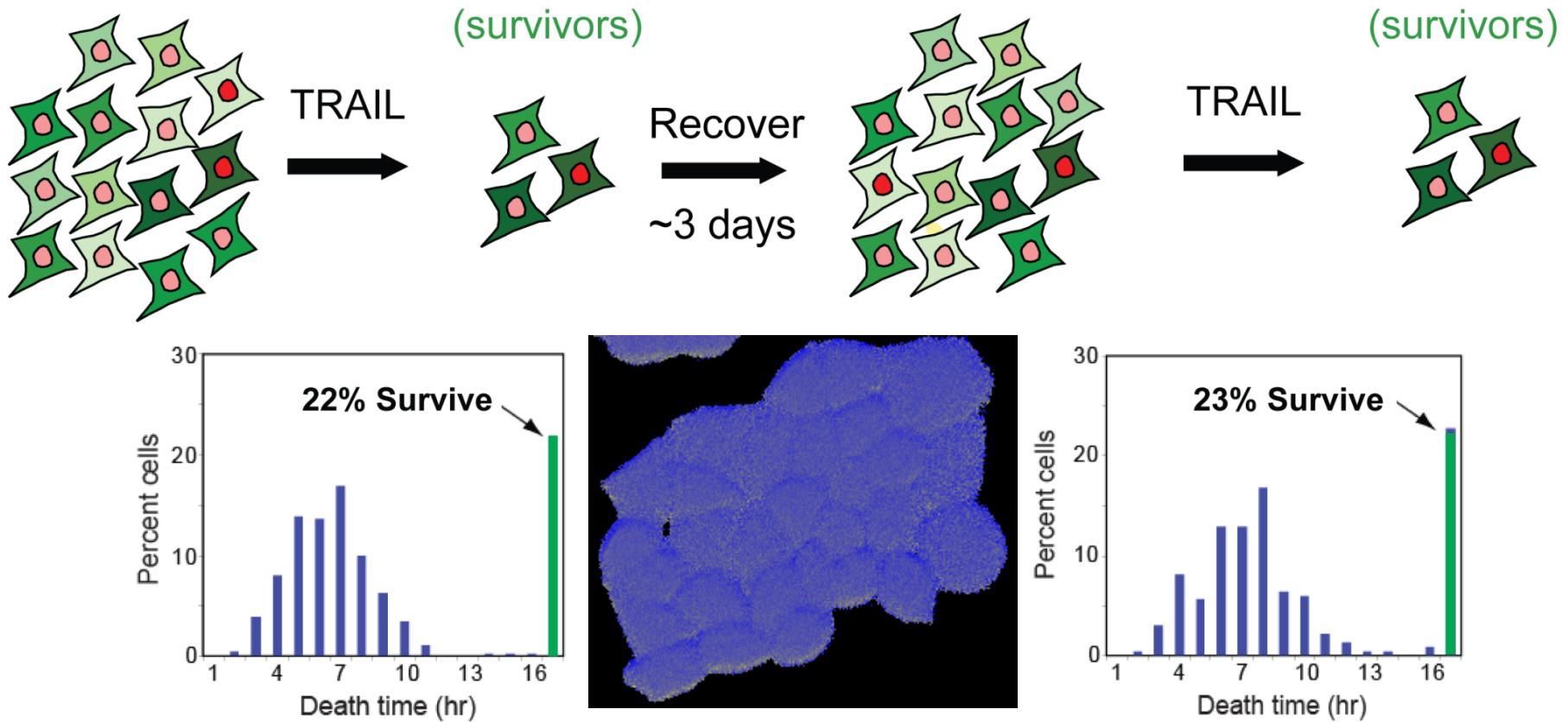
## Literature



# Extensive variation in potency and efficacy

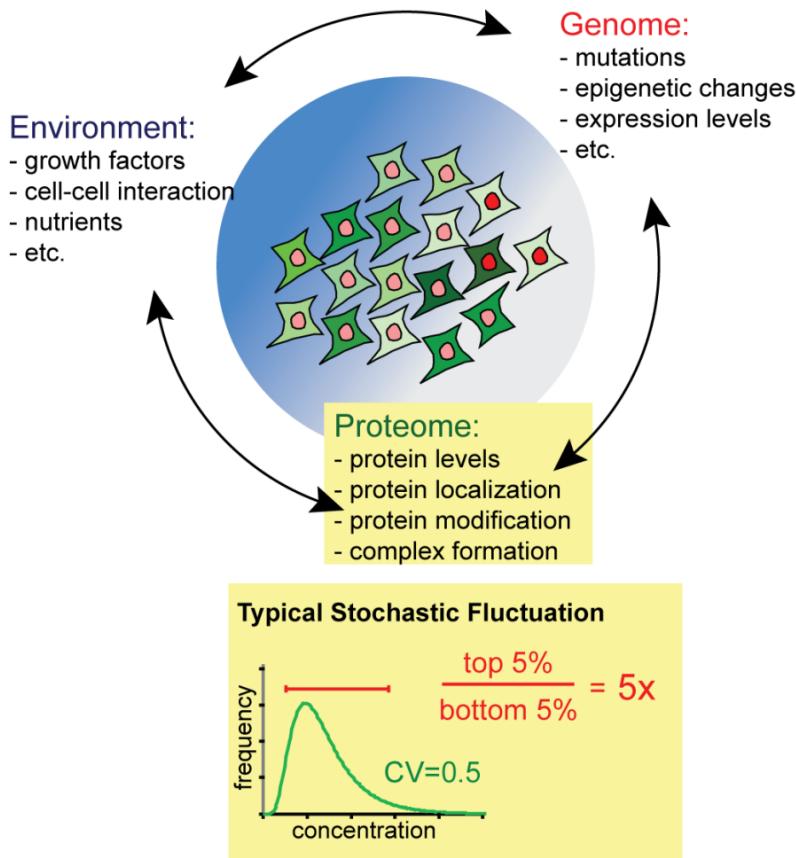


# Fractional response (to TRAIL) is a stable property of cell populations

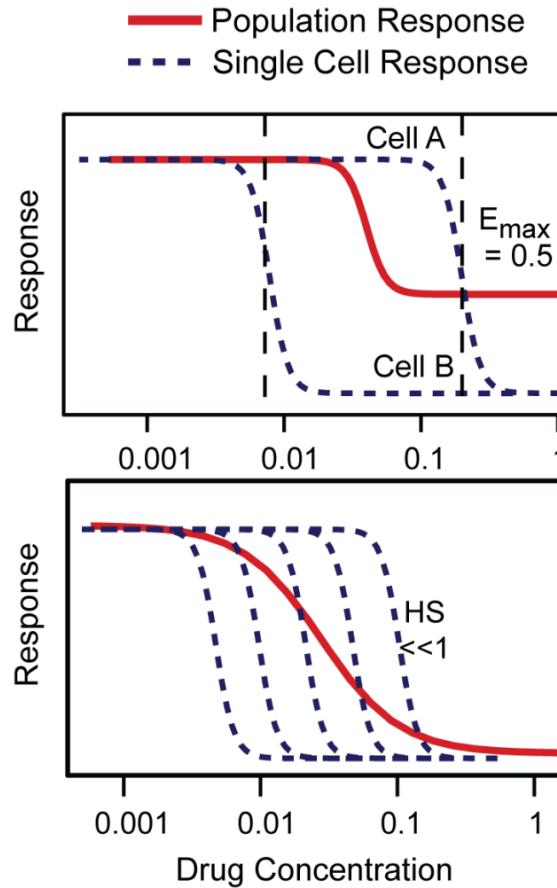


# Cell-to-cell variability and its impact on dose response at a population level

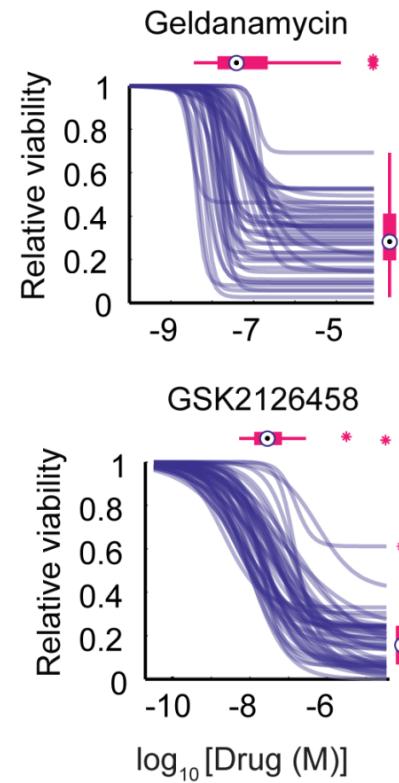
## Sources of Variation



## Theory



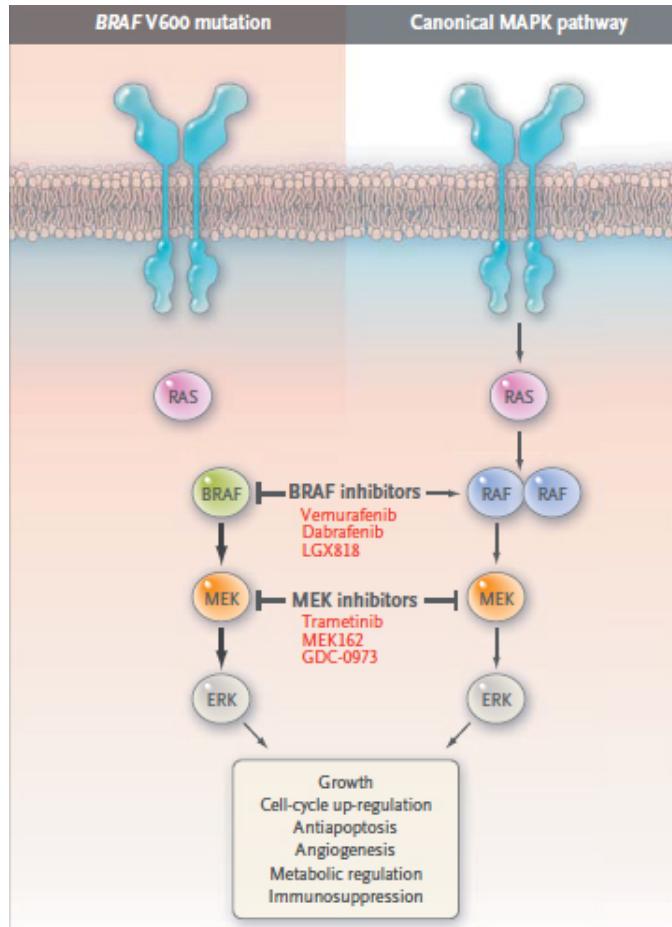
## Real Data



# Application to a targeted therapy ( $BRAF^{V600E/K}$ melanoma)



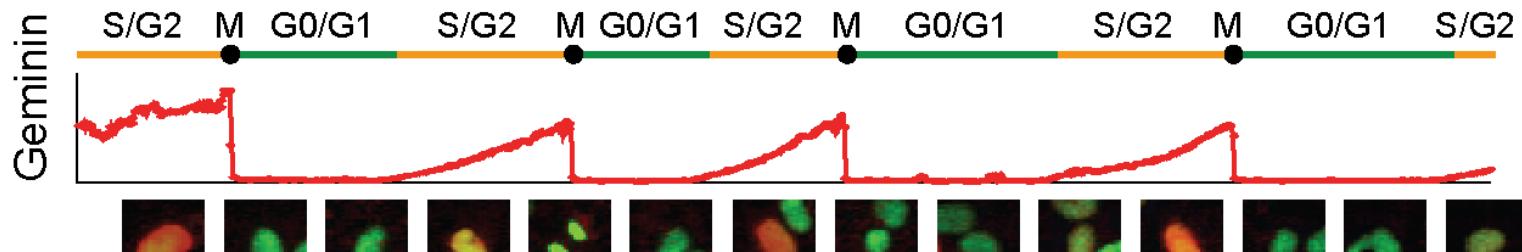
The NEW ENGLAND  
JOURNAL of MEDICINE



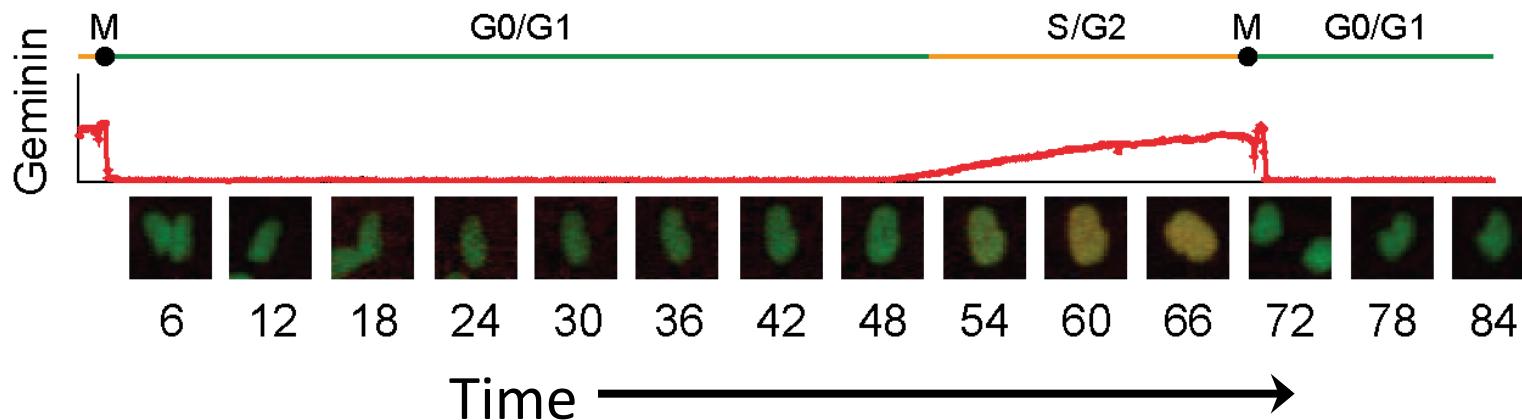
# Understanding residual disease: drug response in single $BRAF^{V600E}$ melanoma cells

**Control**

Live cell imaging using cell-cycle reporter



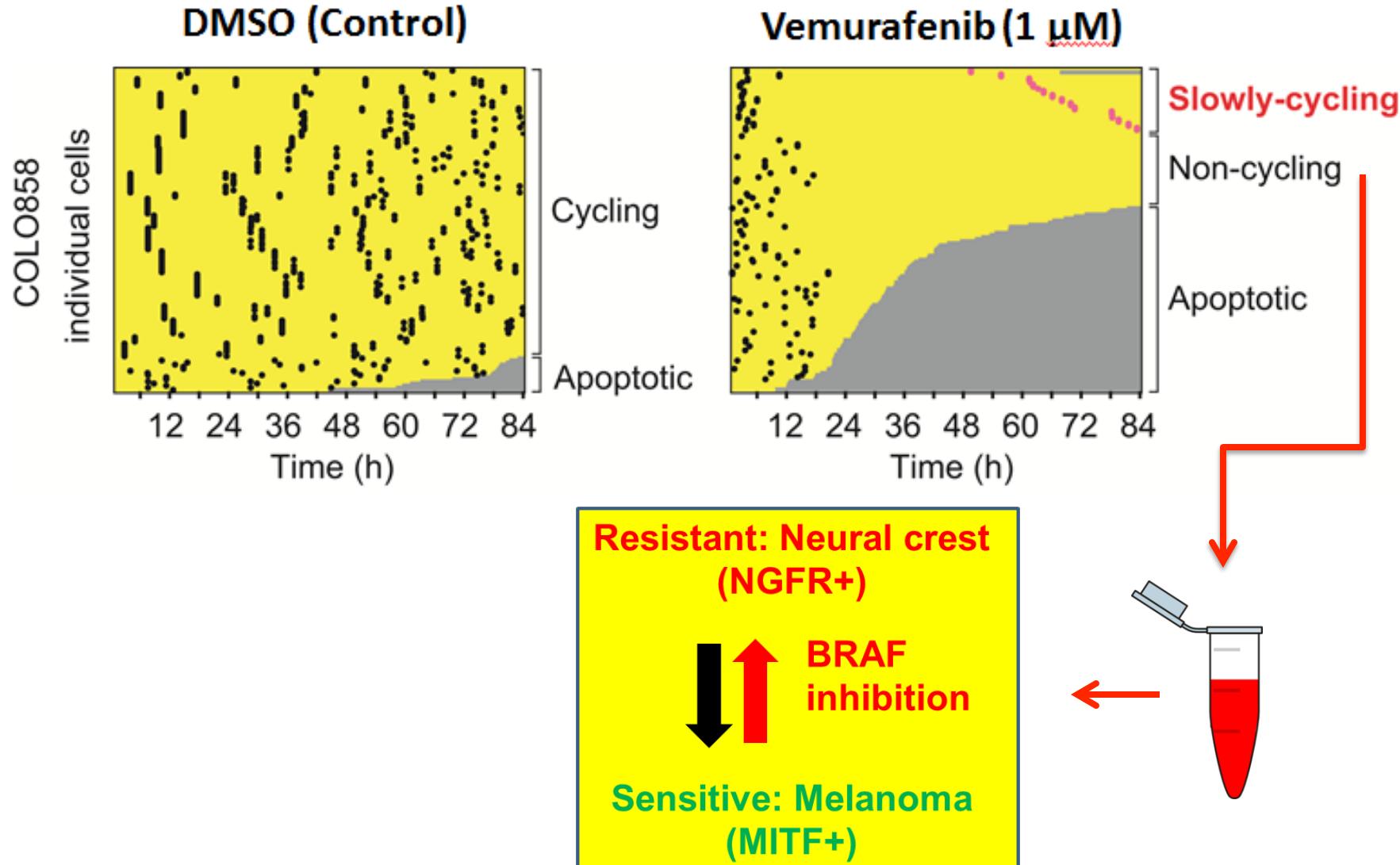
**+Vemurafenib -**



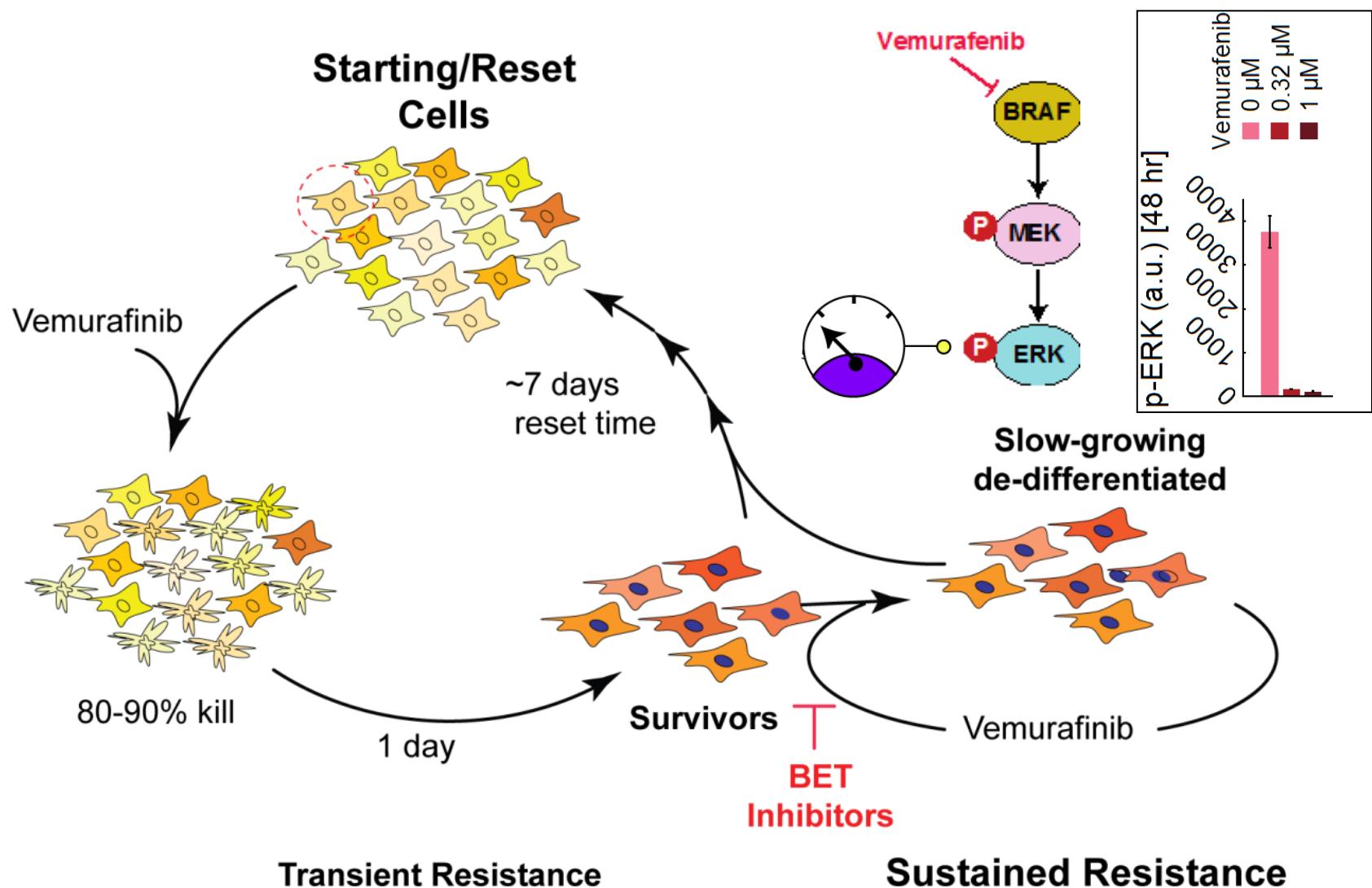
*H2B-Venus → tracks nuclear morphology*

*mCherry-geminin → tracks cell cycle progression*

# Live-cell imaging to monitor single-cell phenotypes



# Single-cell effects and the time-dependence of response



# Typical dose-response curves for anti-cancer drugs (LINCS-optimized protocols)

