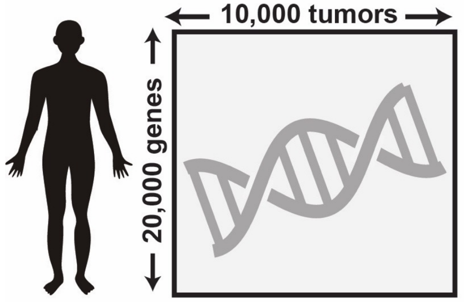
Combining mechanism and clinical data to explain chemotherapy efficacy

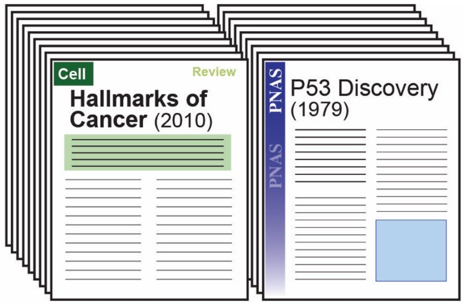
Eugene F Douglass Jr
October 15, 2021
Assistant Professor
Pharmaceutical and Biomedical Sciences
College of Pharmacy
University of Georgia

Clinical "Big Data" + Experiment = **Precision Medicine**

Genomic vs Experimental "Big Data:" *challenges and opportunities*



Sequencing Tech



Scientific Literature

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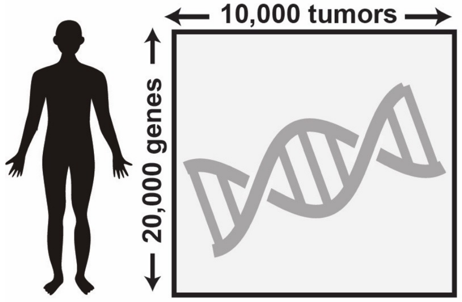

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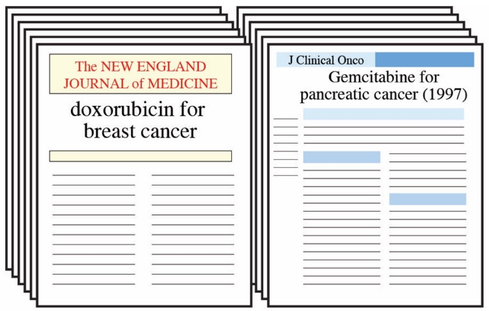

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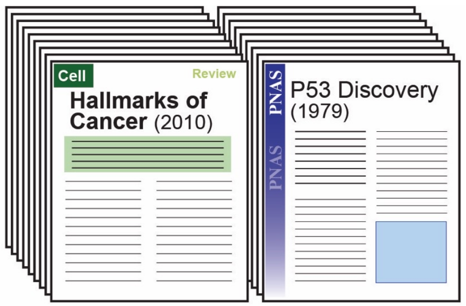

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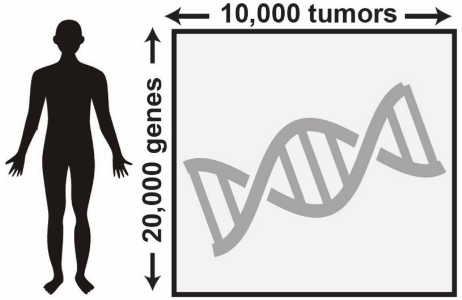
Onco-gene



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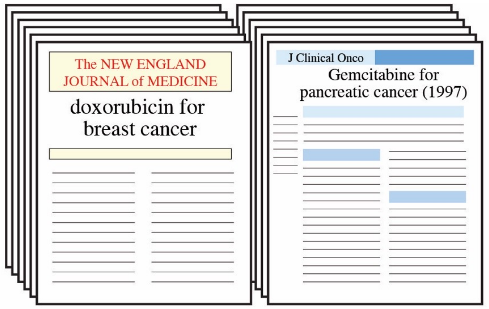

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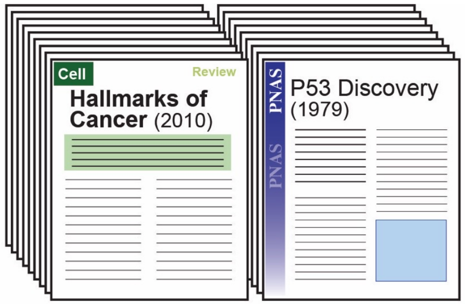

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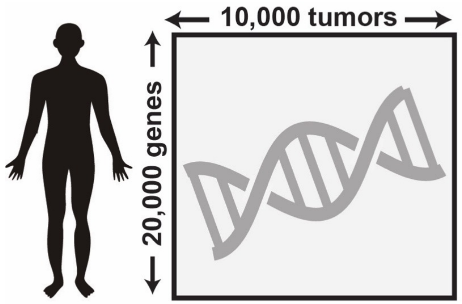

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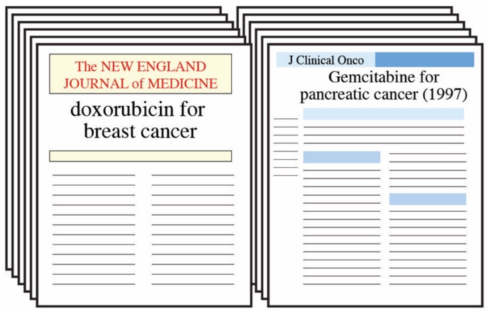

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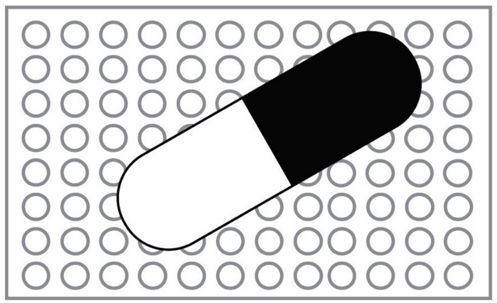
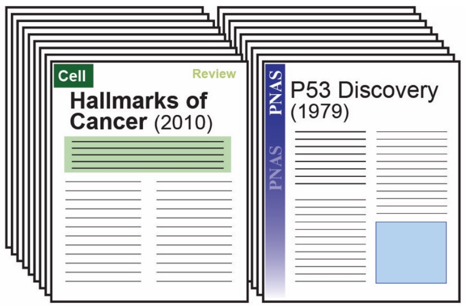

Screening Technology



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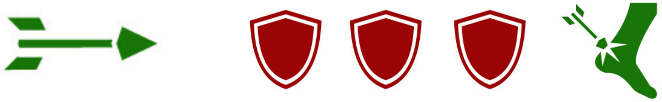

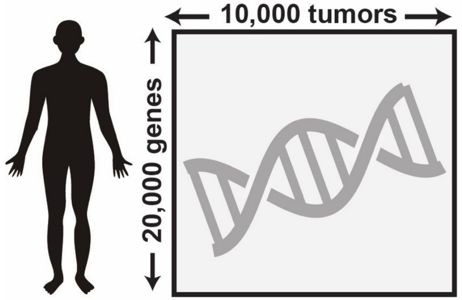

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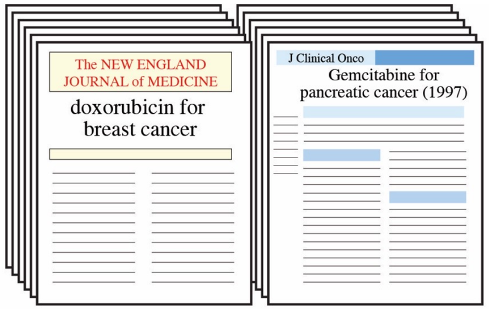

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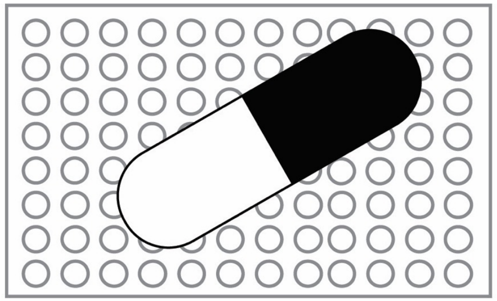
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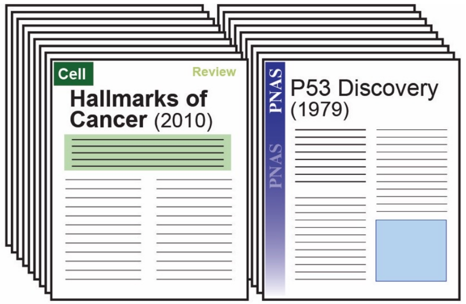

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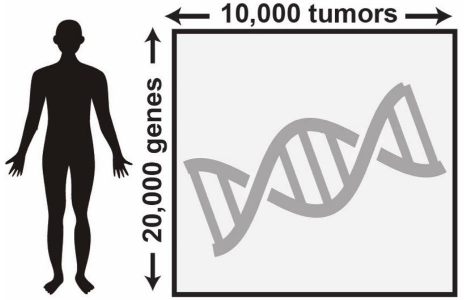

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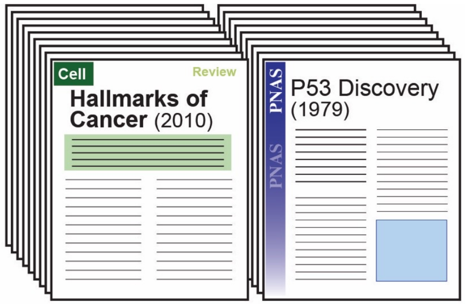


Scientific Literature

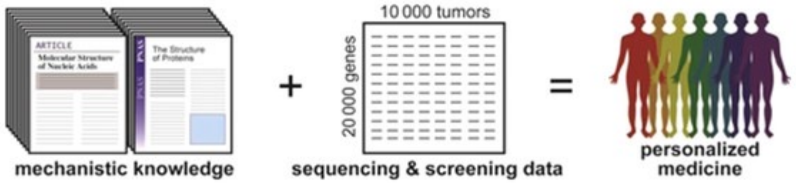
Sequencing/Screening vs Experimental "Big Data"

ChemBioChem
Combining Chemistry and Biology

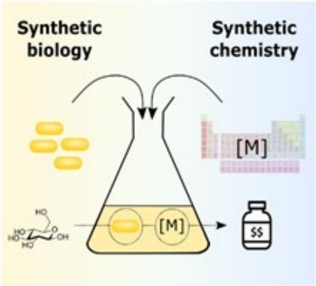
Chemistry Europe
European Chemical Societies Publishing

Chemical Translational Biology – Early-Career Award Winners

Eugene Douglass
University of Georgia
Bridging "Big Data" and Mechanistic Insight To Enable Precision Medicine



Joanna Sadler
University of Edinburgh
The Bipartisan Future of Synthetic Chemistry and Synthetic Biology

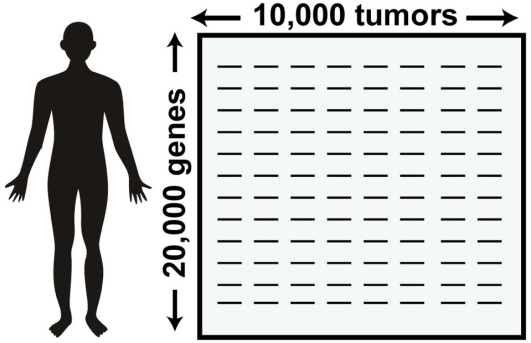


Special Award

ChemBioChem, **2020**, 21, 3047-3050

Sequencing/Screening vs Experimental "Big Data"

Clinical Tumor Sequencing "Big Data"



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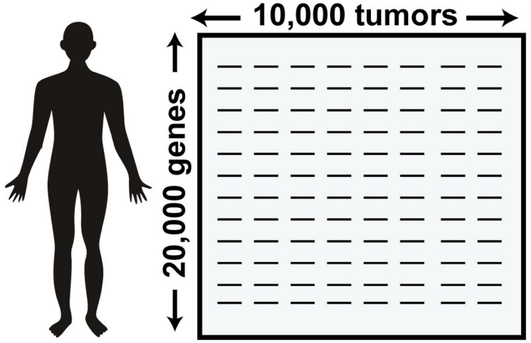
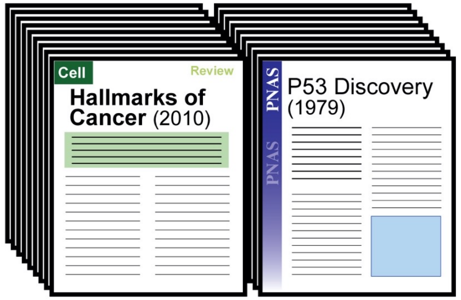


Experimental Literature "Big Data"

3,000,000 cancer-papers



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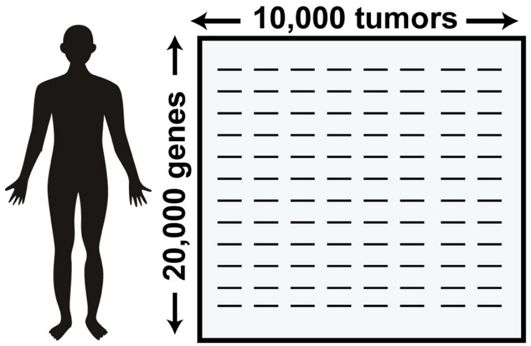

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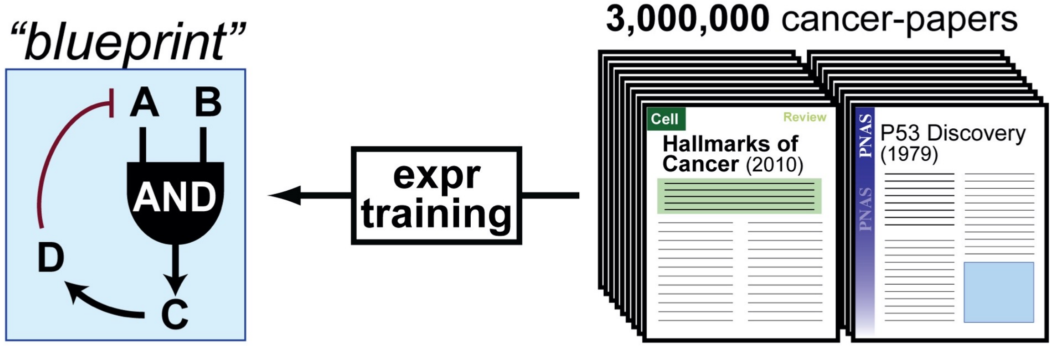

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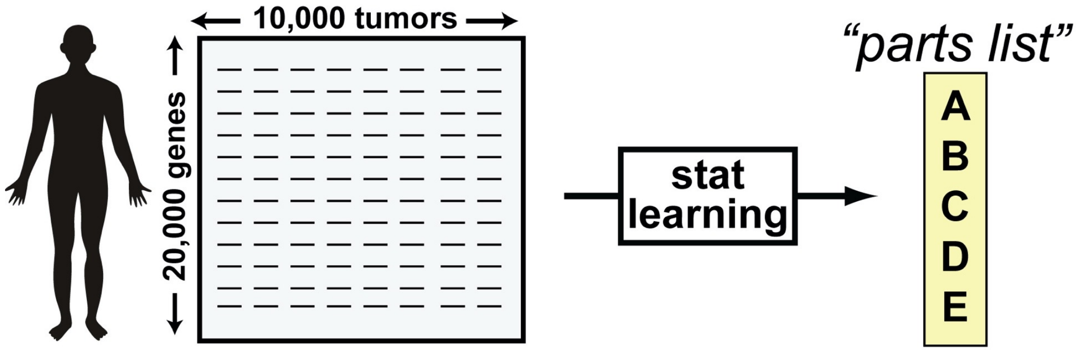

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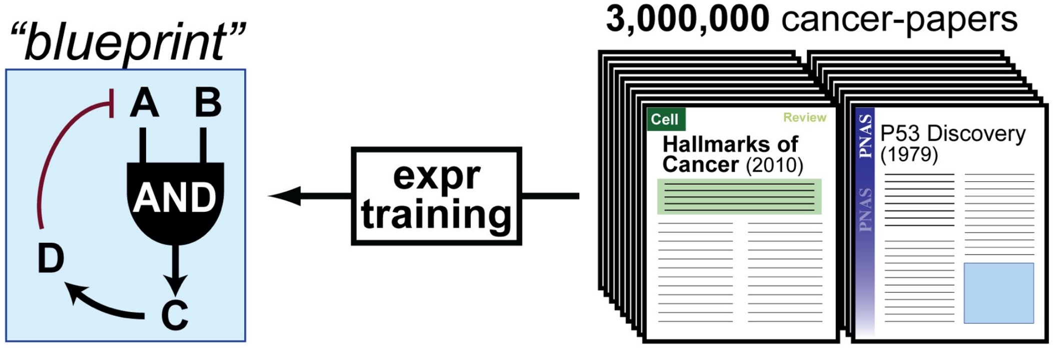
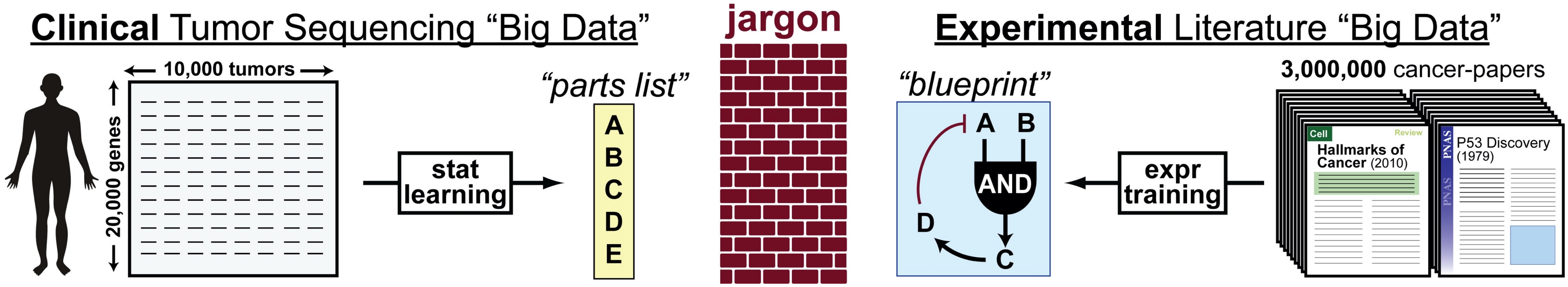


Communication Barriers prevent Big Data Synergy



Different Definitions of Proof: *Correlation* vs *Causation*

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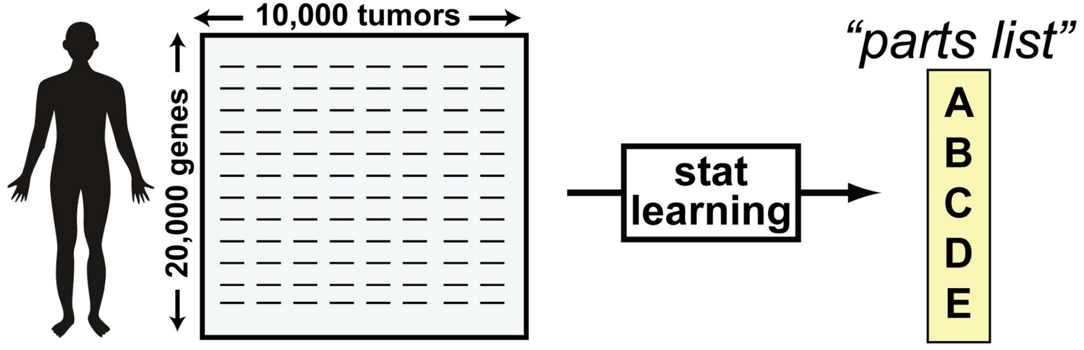

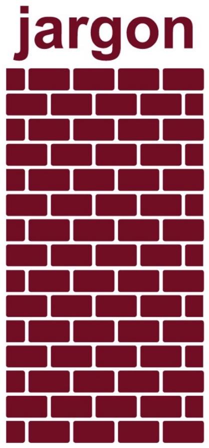

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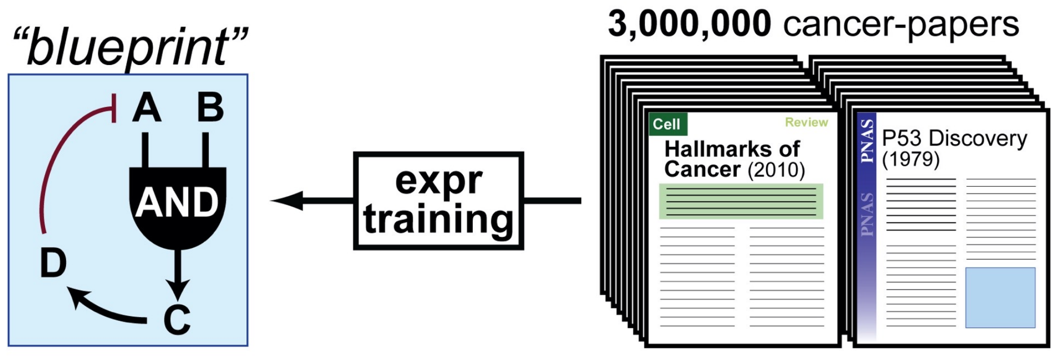

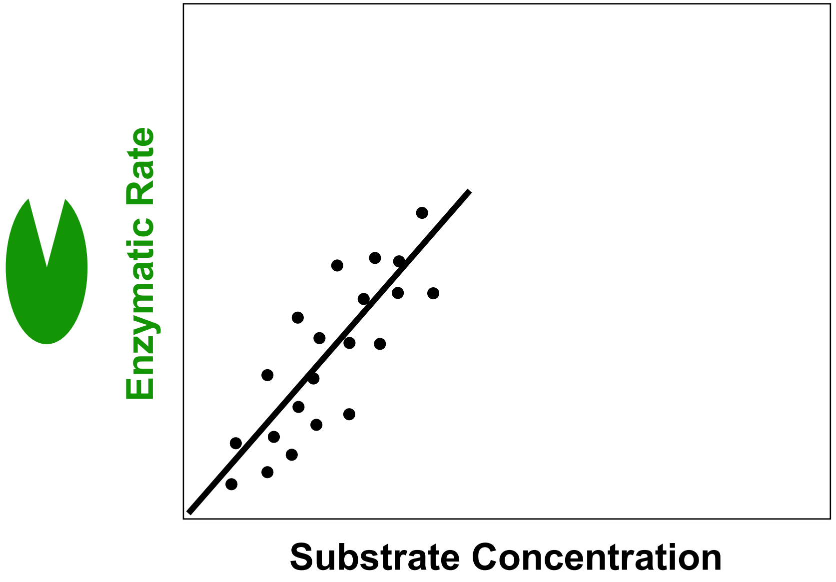

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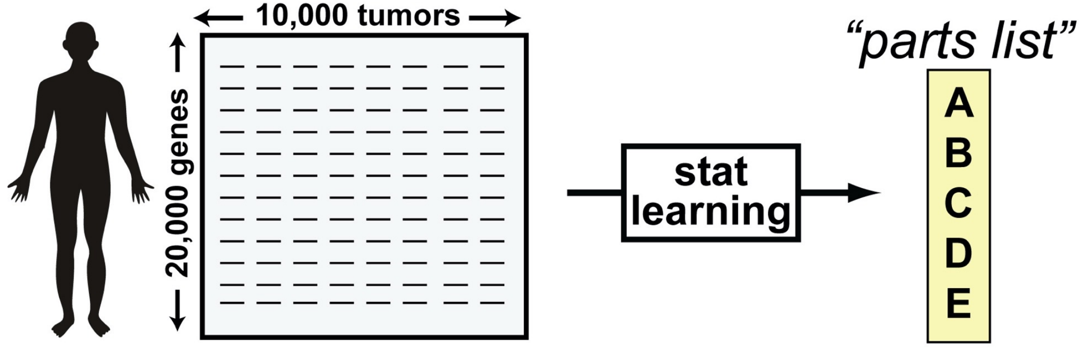

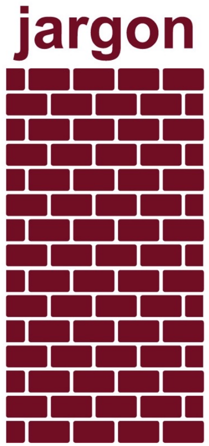

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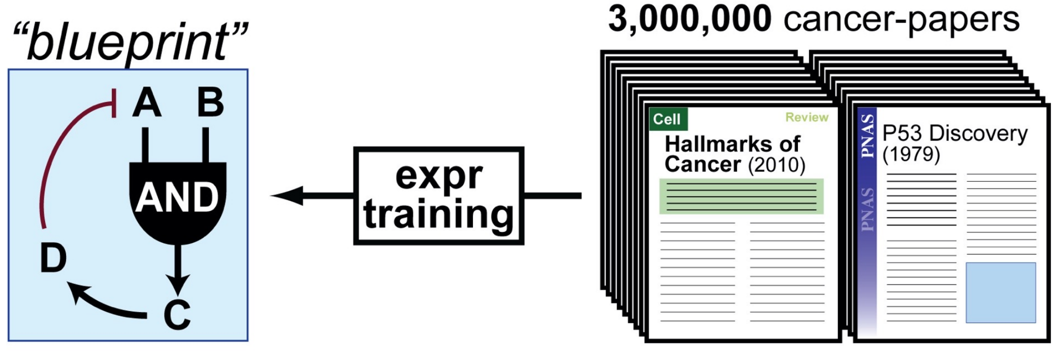

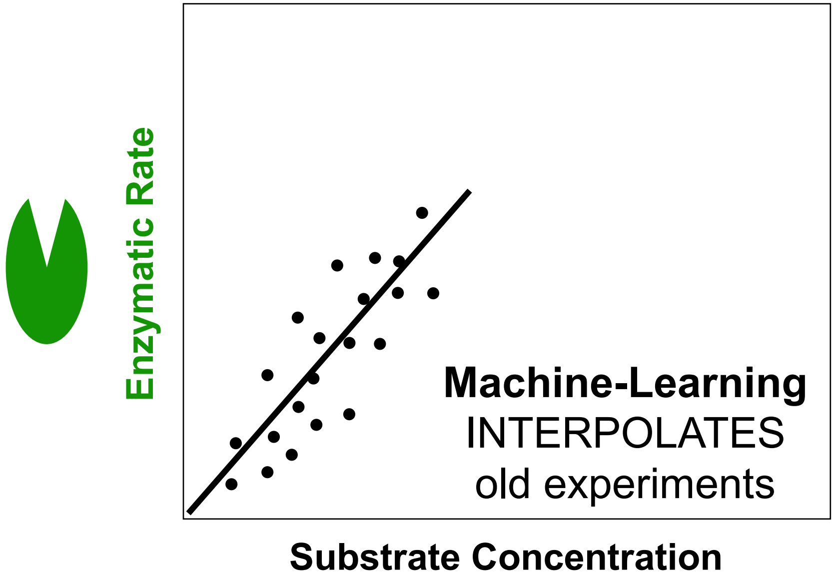

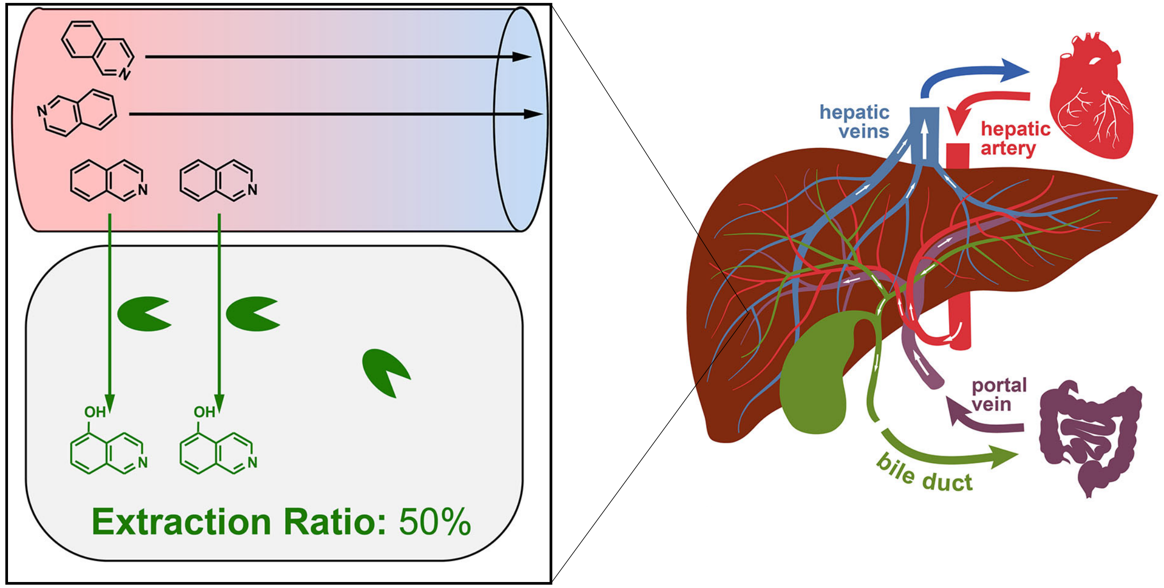

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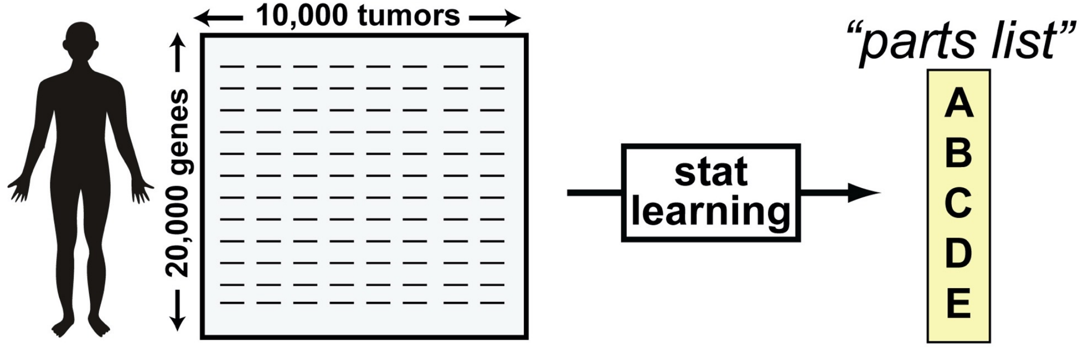

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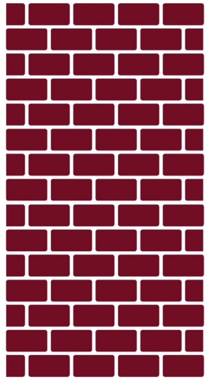

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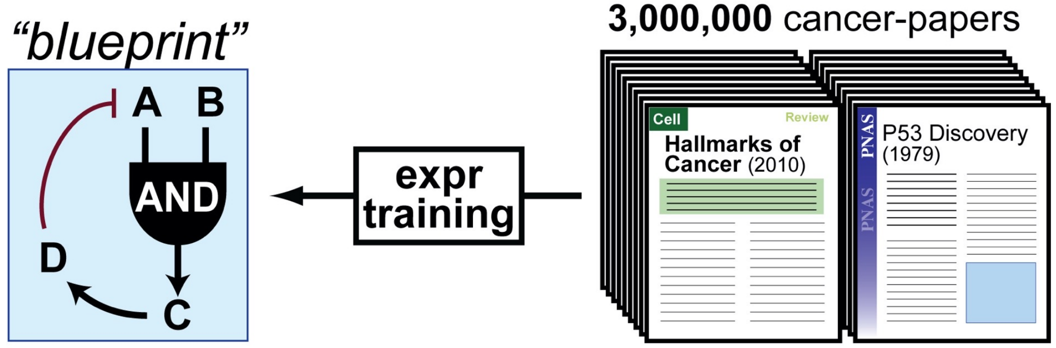

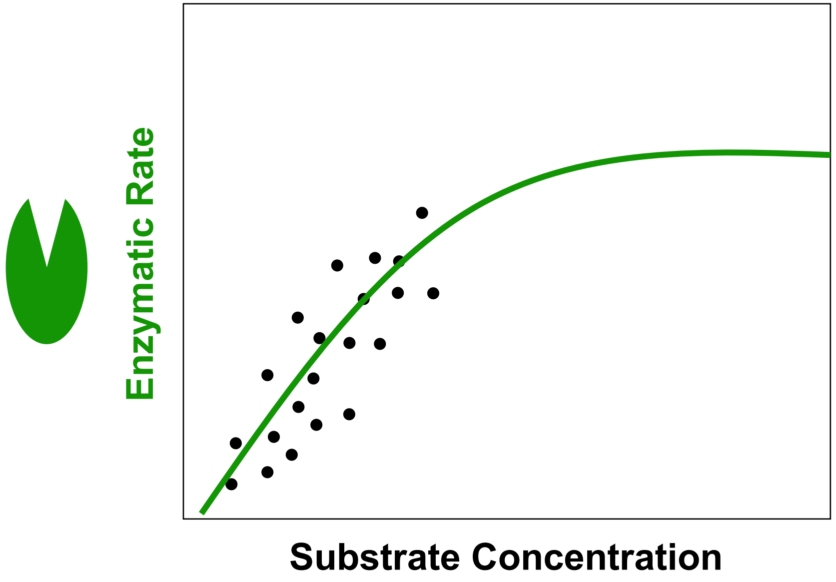

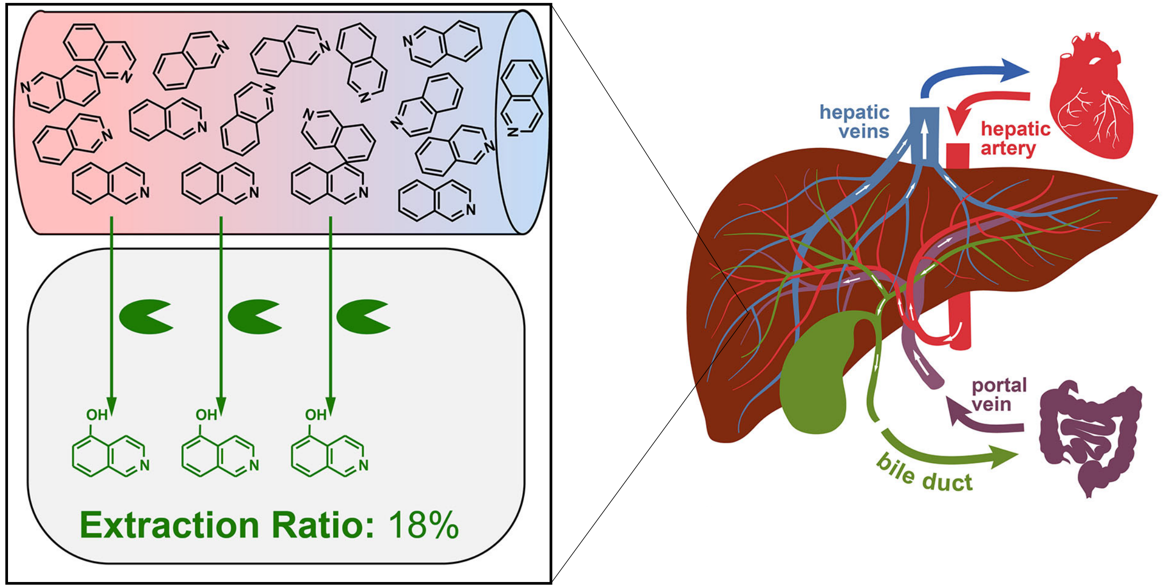

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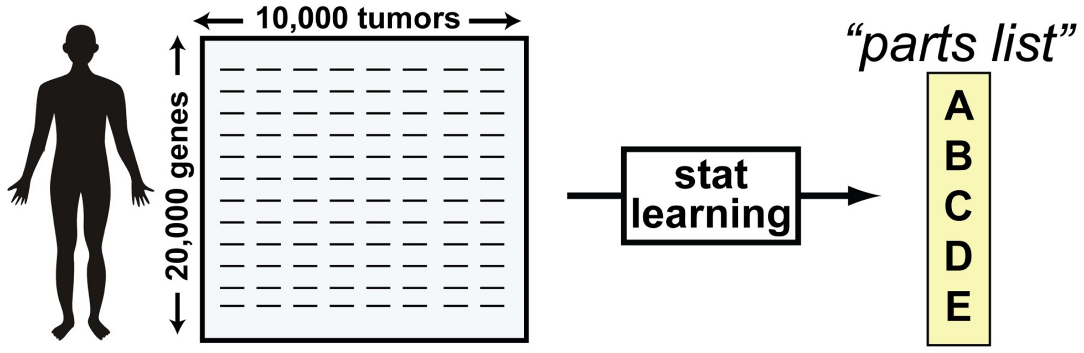

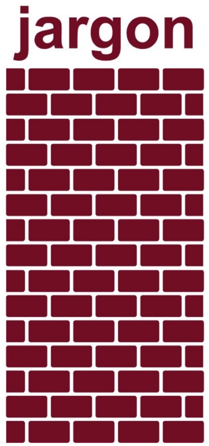

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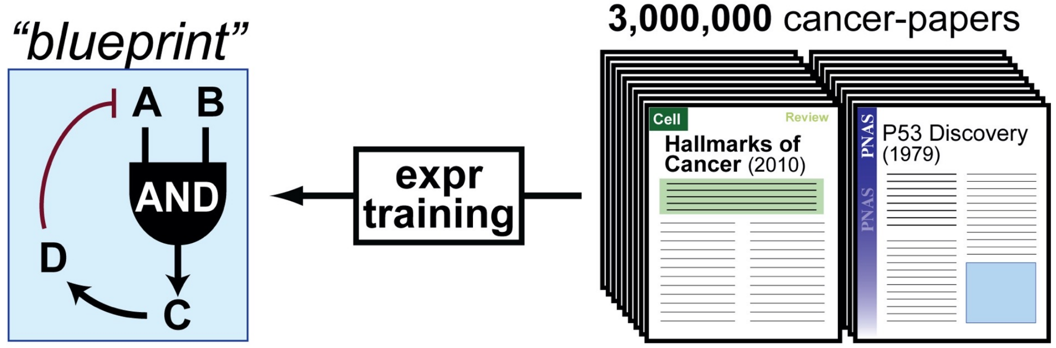
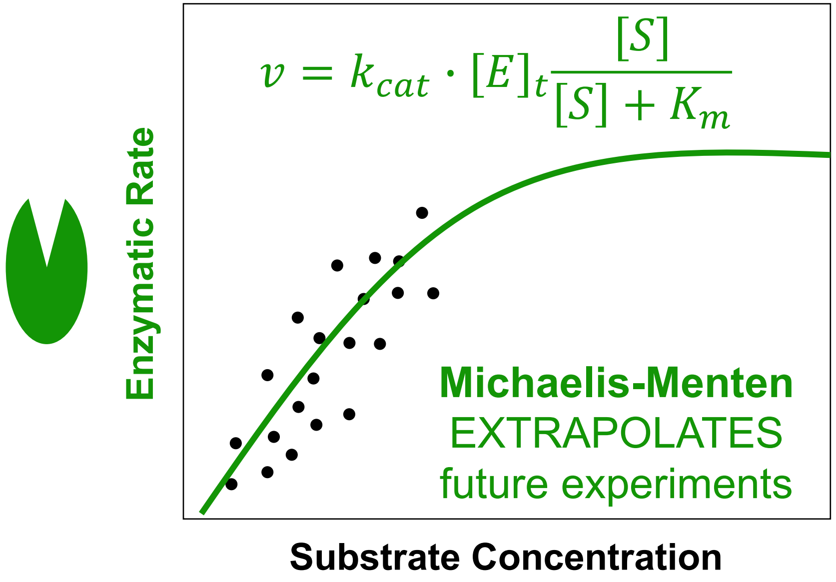
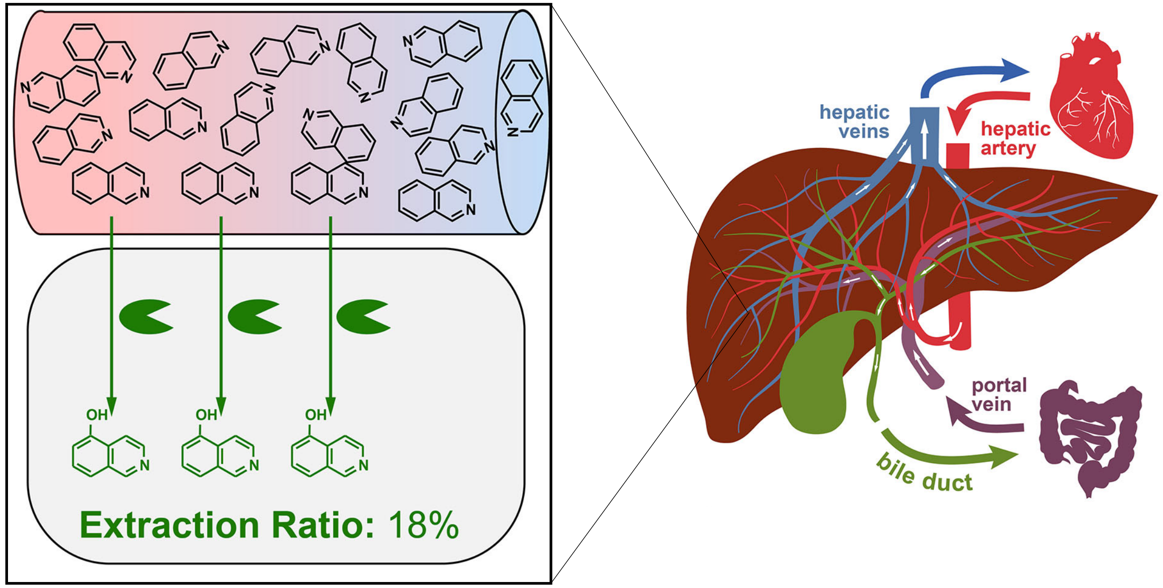
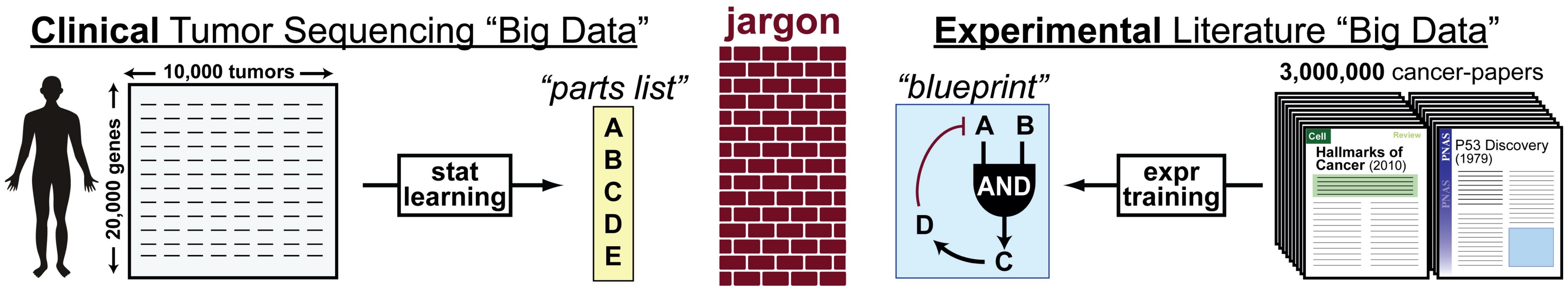






Precedents for “Big Data” driving paradigm shifts



Spectroscopy: Black Body Radiation → **Empirical Models:** Wien Approximation (1896) → **First Principles:** Plank’s Law (1901) → **New Paradigm:** Quantum Mechanics

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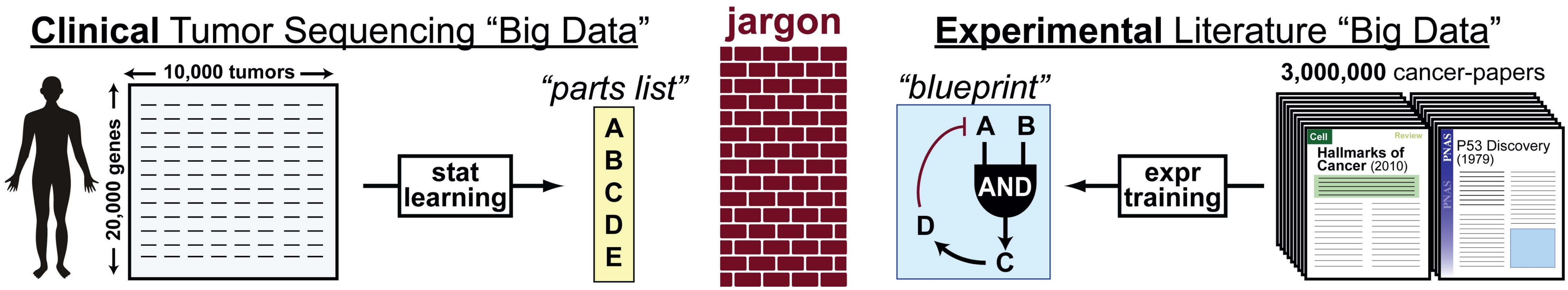


New Big Data:
Black Body Radiation

→

Empirical Models:
Wien Approximation (1896)

→

First Principles:
Plank's Law (1901)

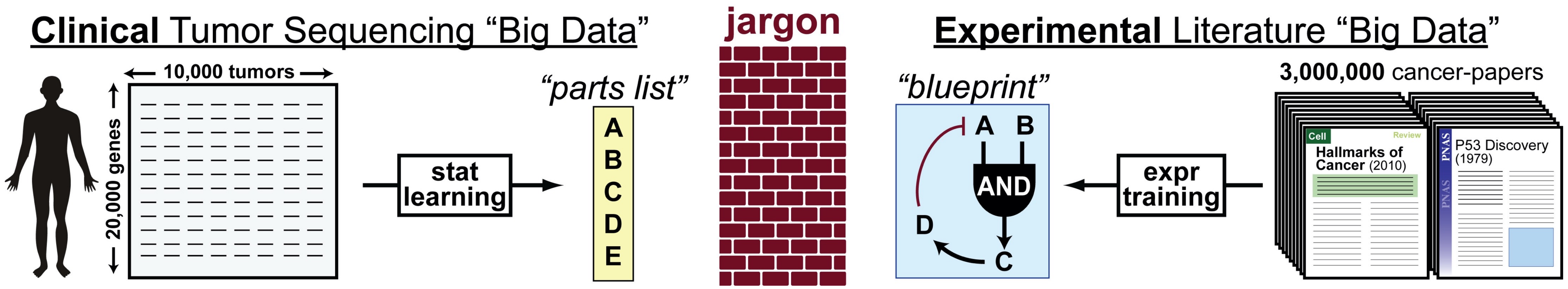
→

New Paradigm:
Quantum Mechanics

*"The year was **1903**...It was an ideal moment for an aspiring young man to enter the field. Half a century of laboratory research had generated an **unparalleled backlog of data** that demanded understanding."*

- Niels Bohr's Times, Clarendon Press 1991

Precedents for “Big Data” driving paradigm shifts

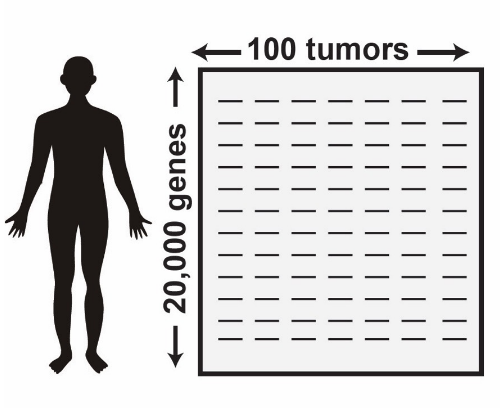


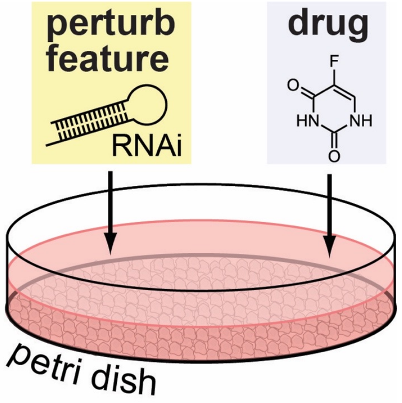
New Big Data: Spectroscopy → **Empirical Models:** Wien Approximation (1896) → **First Principles:** Plank’s Law (1901) → **New Paradigm:** Quantum Mechanics

New Big Data: Tumor genomics → **Empirical Models:** *Machine learning* → **First Principles:** ?? → **New Paradigm:** Precision Medicine

Doctoral Student Educational Approach:
computational scientists

Student Training Experience: *Columbia University*





<u>Computational Laboratory</u>:
skeleton crew

<u>Experimental Laboratory</u>:
fully staffed

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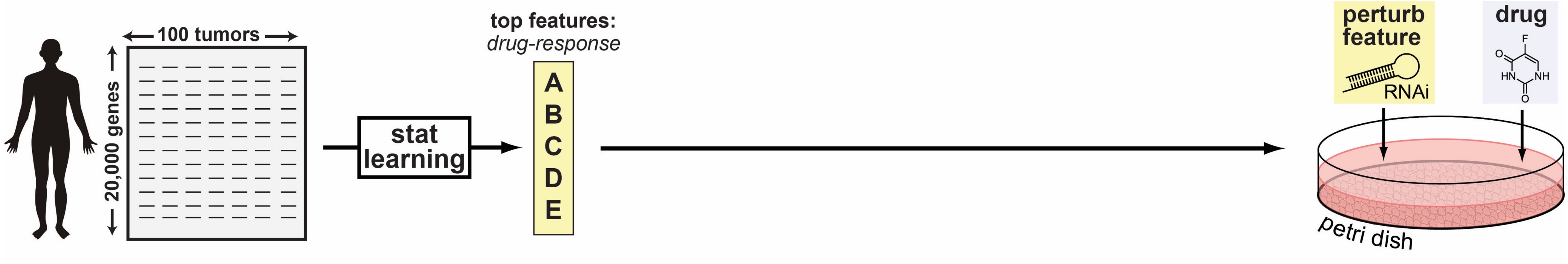

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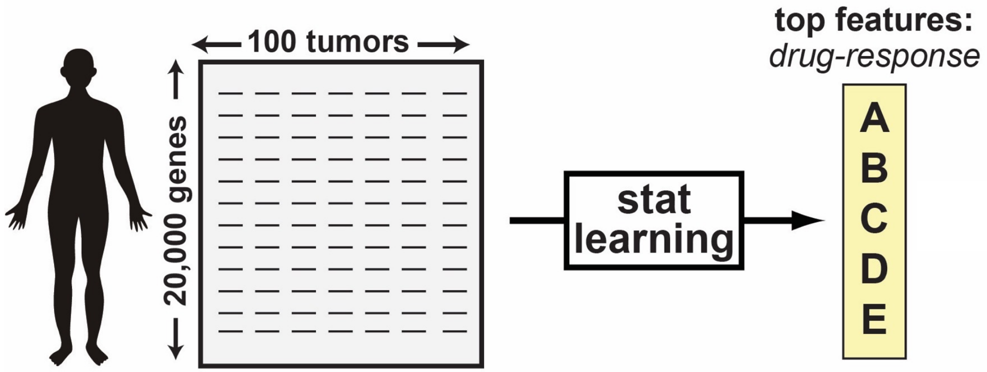

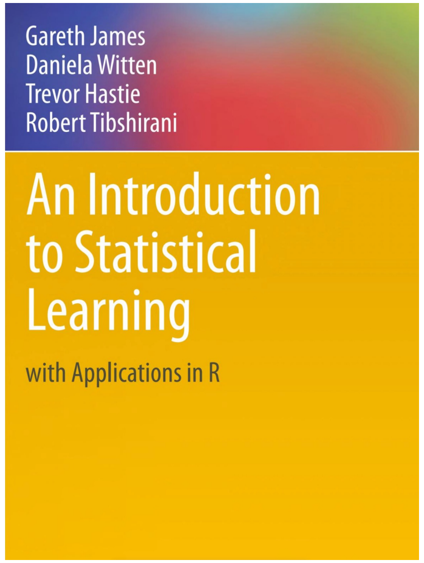

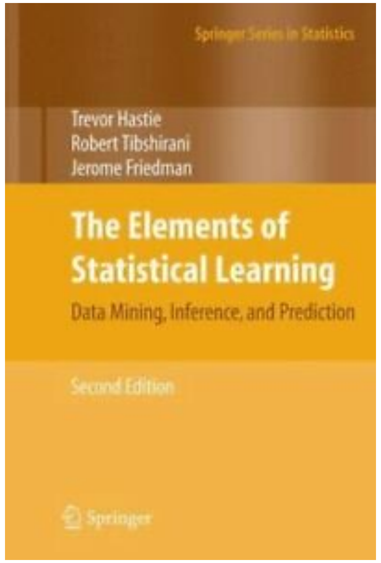

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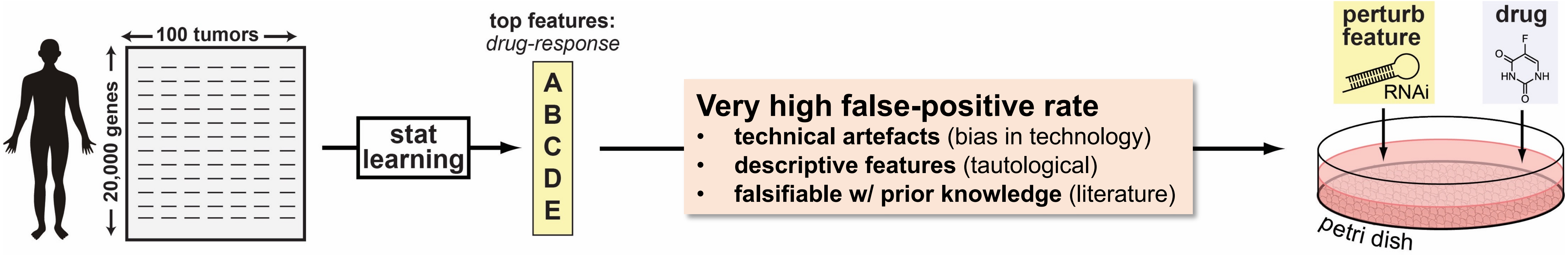

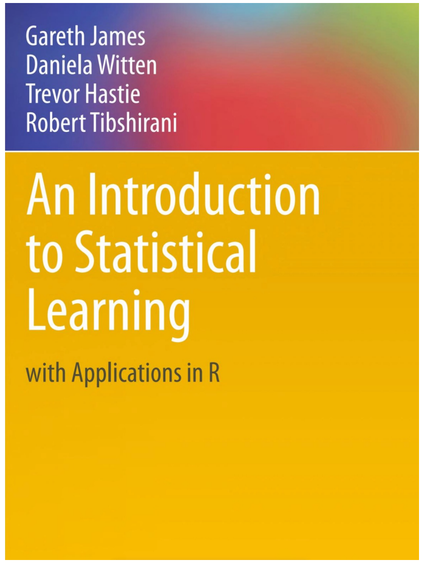

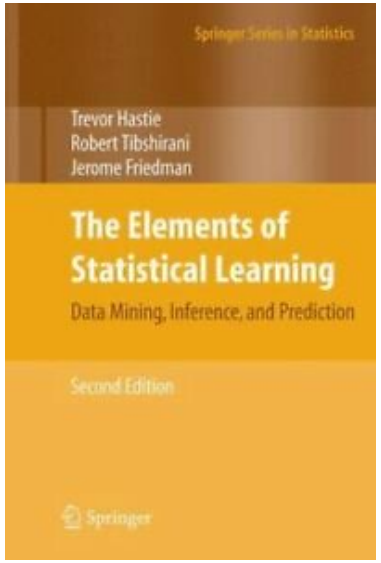

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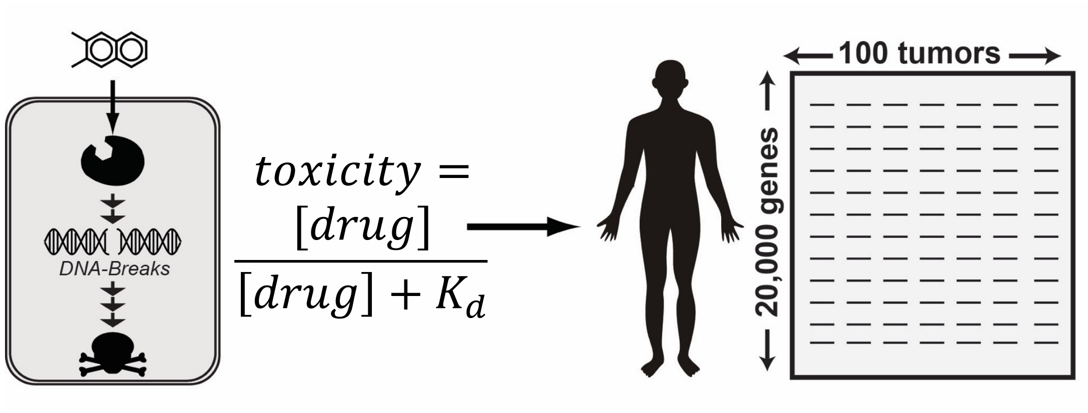

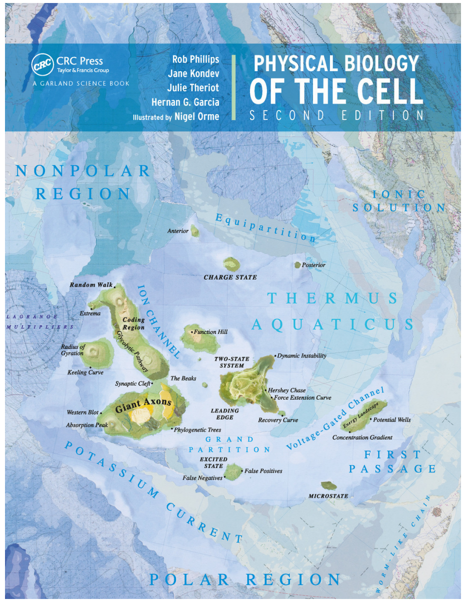

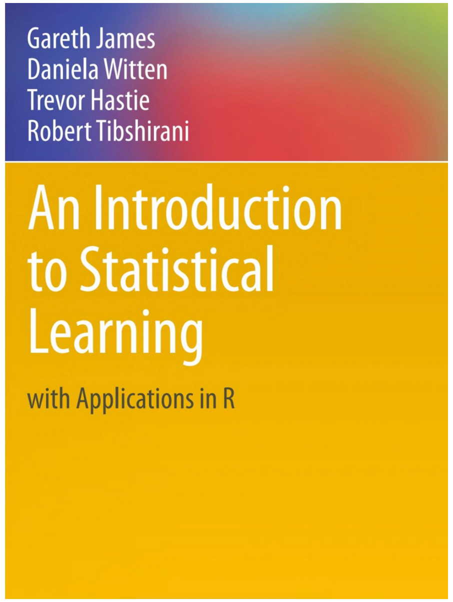

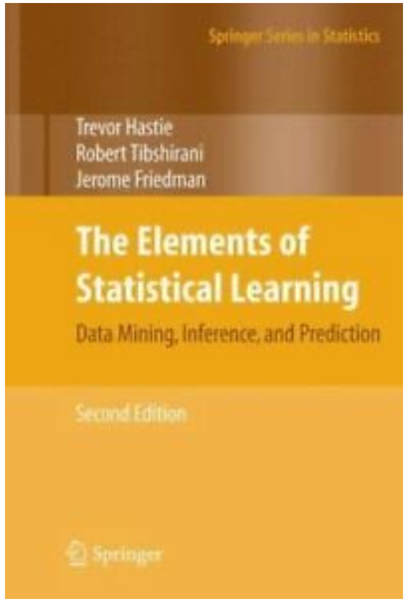

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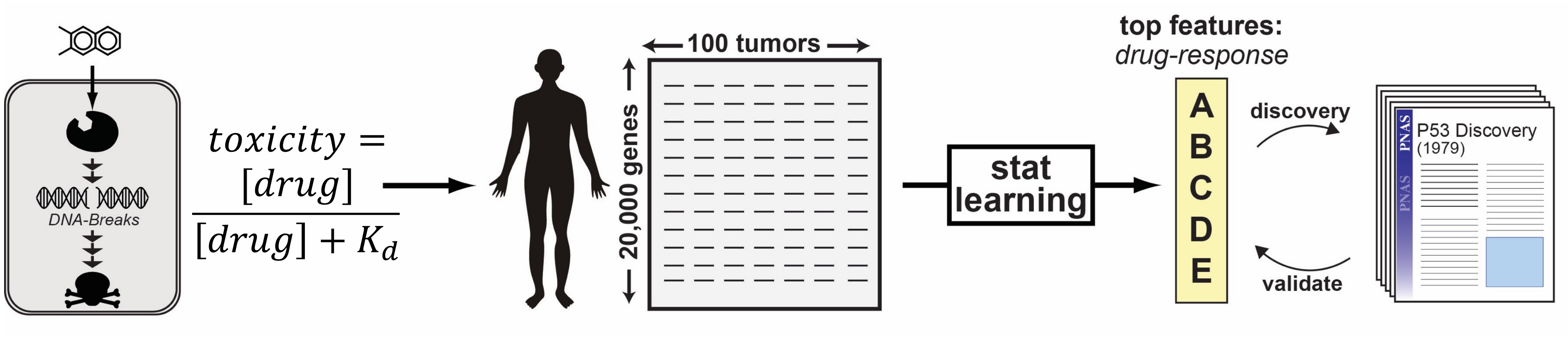
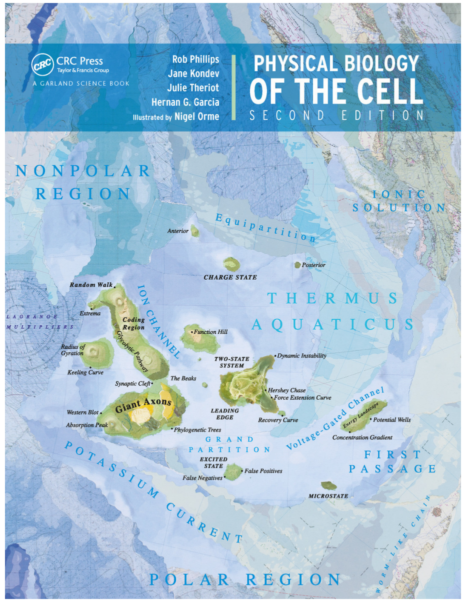
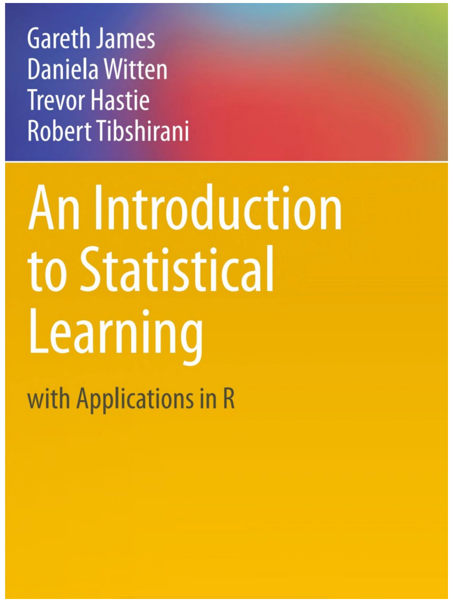
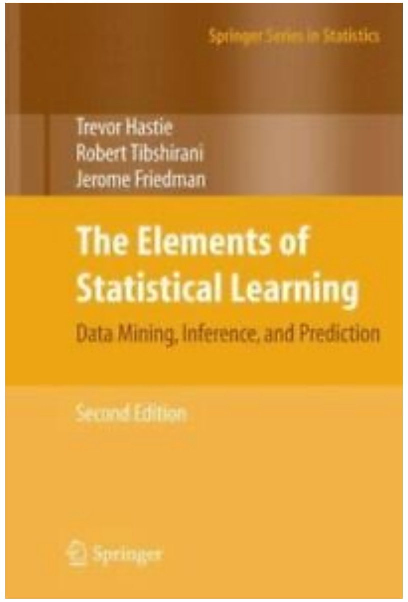
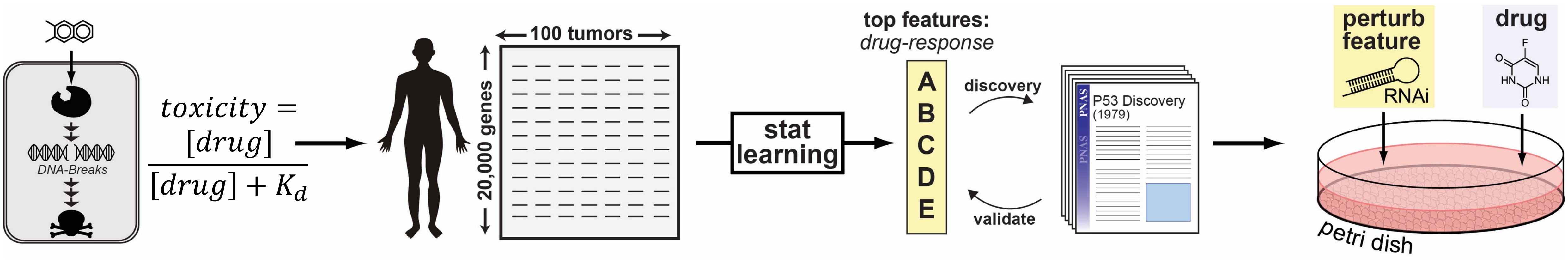


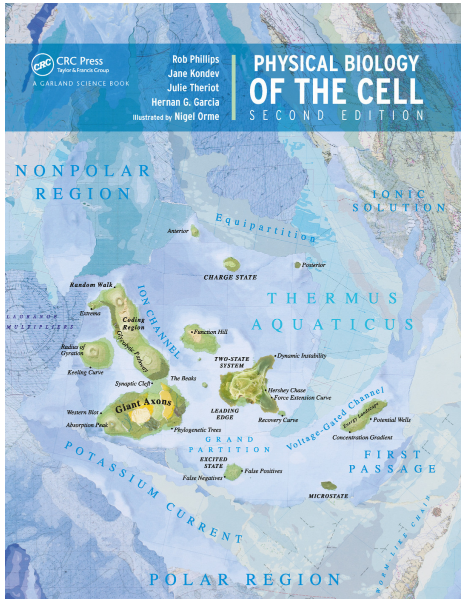


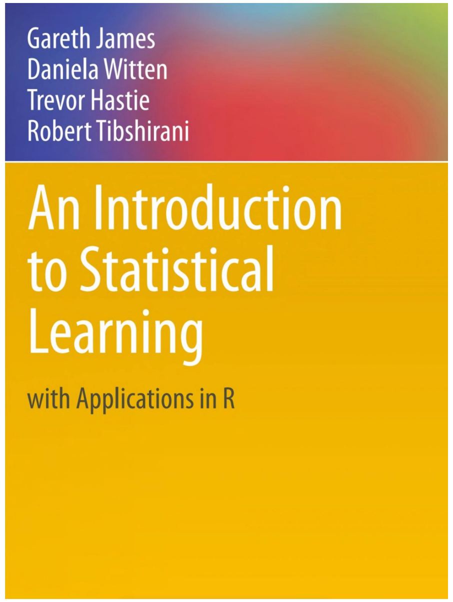


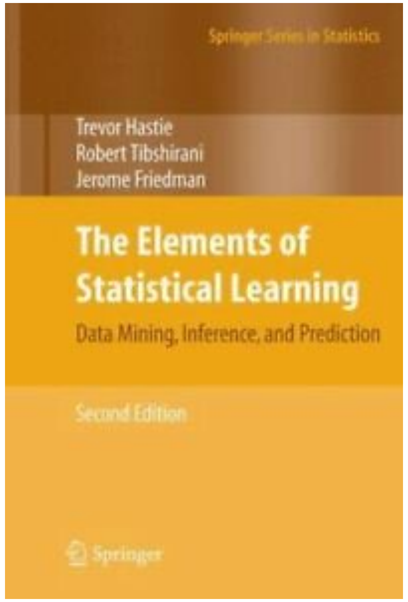


Doctoral Training Philosophy: *Columbia University*

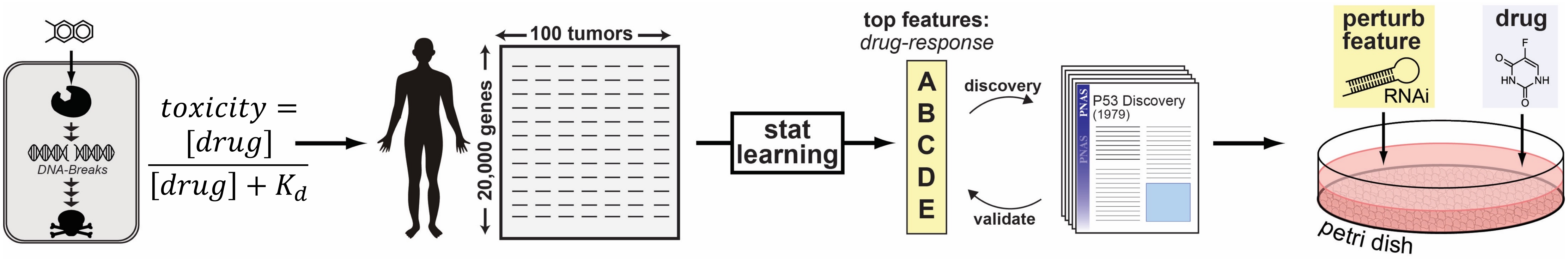








Doctoral Training Philosophy: Columbia University



50 years of Data Science

David Donoho

Sept. 18, 2015
Version 1.00

Abstract

More than 50 years ago, John Tukey called for a reformation of academic statistics. In 'The Future of Data Analysis', he pointed to the existence of an as-yet unrecognized *science*, whose subject of interest was learning from data, or 'data analysis'. Ten to twenty years ago, John Chambers, Bill Cleveland and Leo Breiman independently once again urged academic statistics to expand its boundaries beyond the classical domain of theoretical statistics; Chambers called for more emphasis on data preparation and presentation rather than statistical modeling; and Breiman called for emphasis on prediction rather than inference. Cleveland even suggested the catchy name "Data Science" for his envisioned field.

<u>FIELD SPECIFIC:</u>

1. **Data Preparation:** data-QC and organizing/cleaning
2. **Data Transformation:** emphasize meaningful info (Fourier)
3. **Data Visualization**: effective communication

<u>FIELD AGNOSTIC:</u>

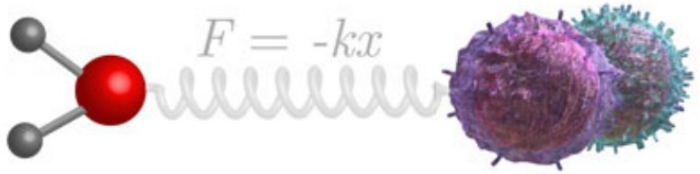
4. **Computing:** languages, cluster computing
5. **Machine Learning:** "Adequate Stat Model"
6. **Mathematics:** Deterministic Modeling or "True Model"

J. Comput. Graphic. Stat., **2017**, 26, 745

Original Teaching Material: practicallyscience.com

MATH COMPUTING PHYSICS CHEMISTRY BIOLOGY TIMELINES RUNNING

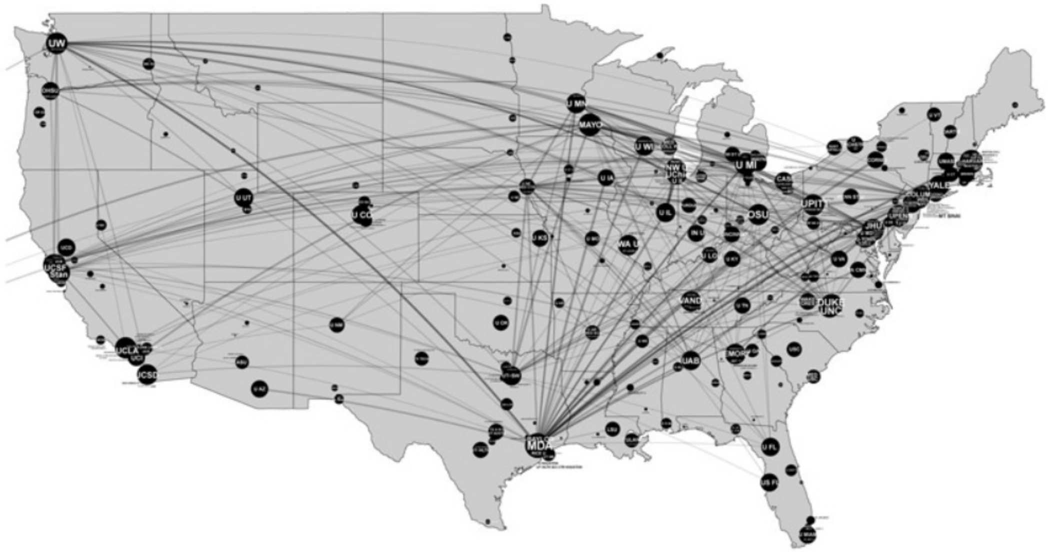
Practically Science



conceptual infographics for interdisciplinary scientists

Cancer Research in the USA

Posted on October 28, 2018 | Comments Off



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ABOUT US

Practically Science was started by two Yale PhD students in 2012. Its goal is to make single-sheet summaries of common interdisciplinary methods, ideas, etc.
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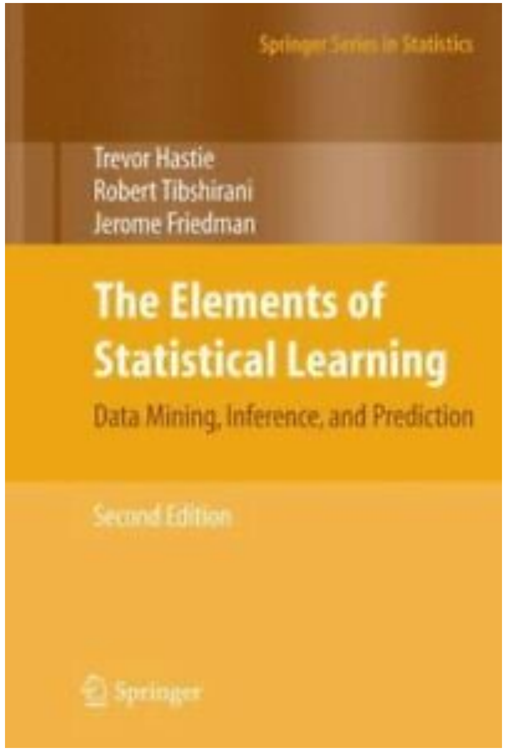
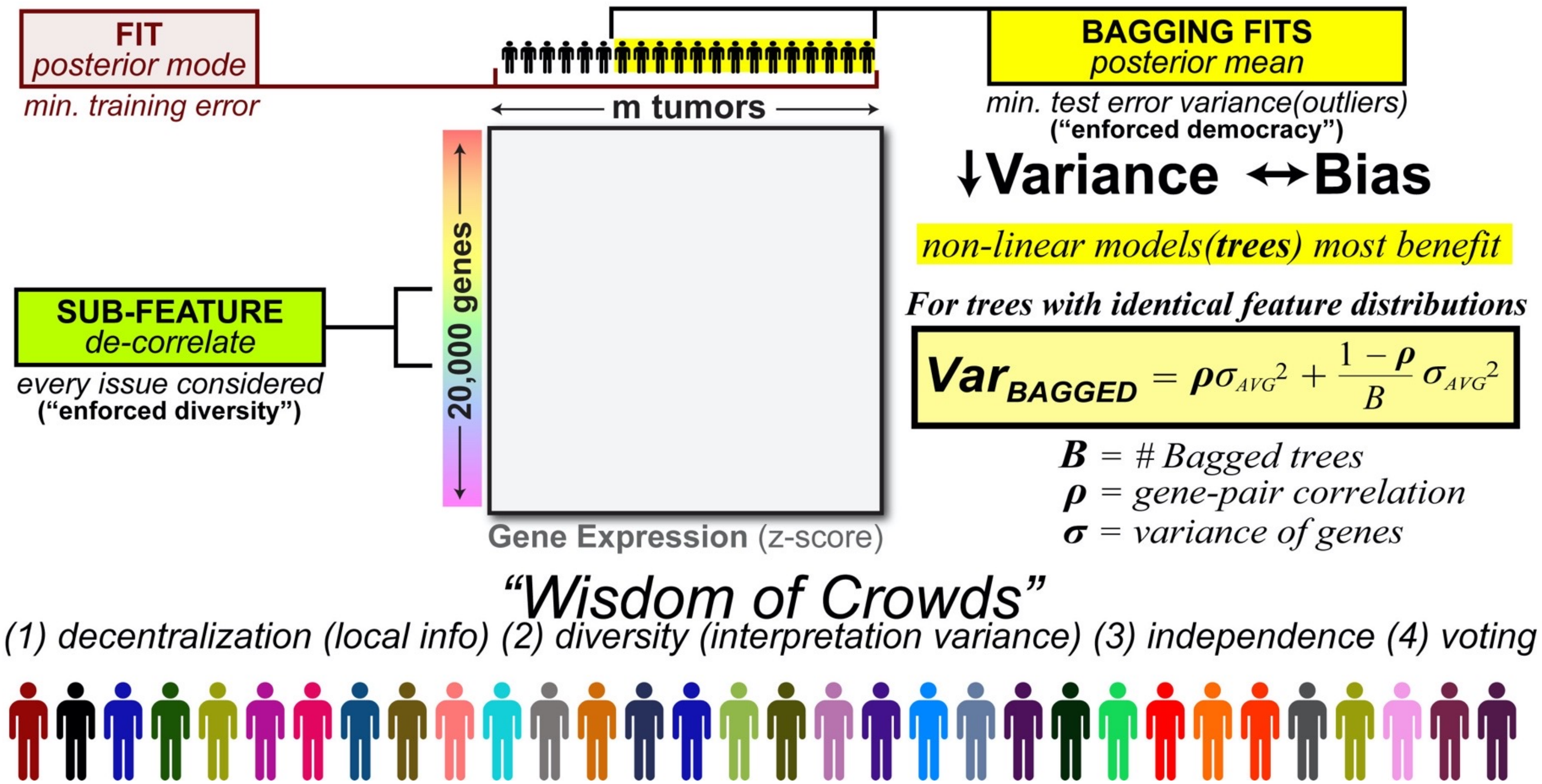
BLOGROLL

Original Teaching Material: *graphical summaries*



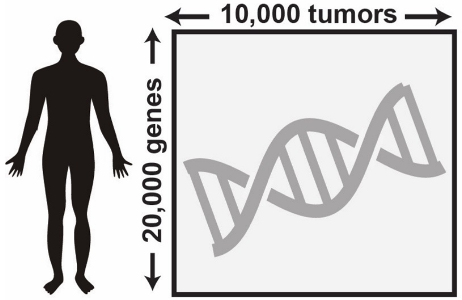


Clinical "Big Data" + Experiment = **Precision Medicine**

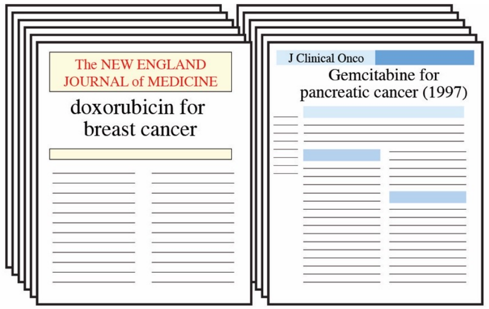
Genomic vs Experimental "Big Data:" *challenges and opportunities*

History & Current Status of Cancer Therapy: *1 drug / 1 target paradigm*

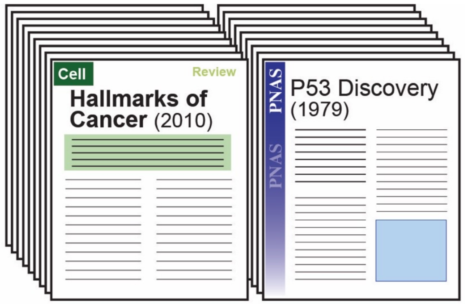
Reconciling Clinical & Laboratory "Big Data": *1 drug / N-biomarkers*



Sequencing Tech



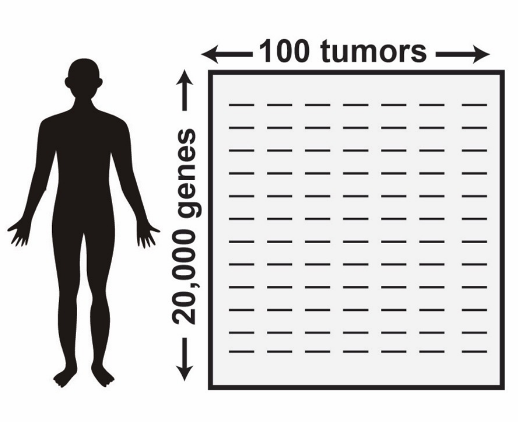
Clinical Literature

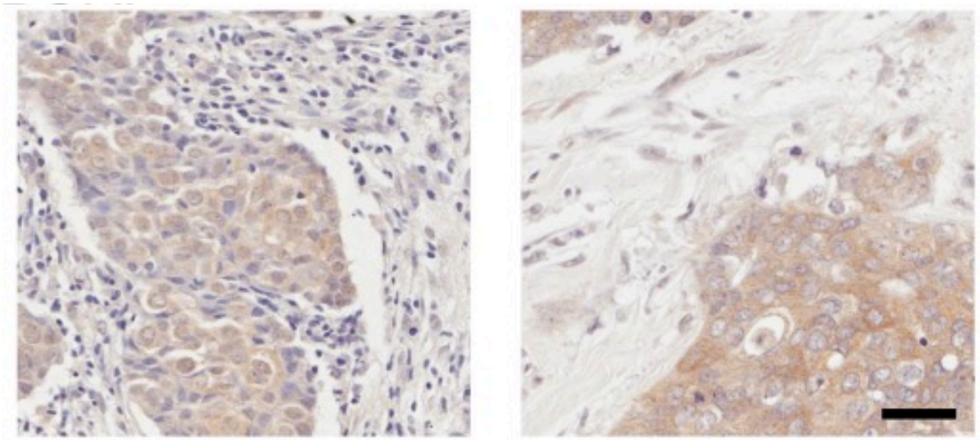


Scientific Literature

Emory Collaboration: *Kevin Kalinsky & Bill Li*

EMORY
WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center





pre-NAC post-NAC

PLOS One **2013**, 8, e62766

Emory Collaboration: *Kevin Kalinsky & Bill Li*

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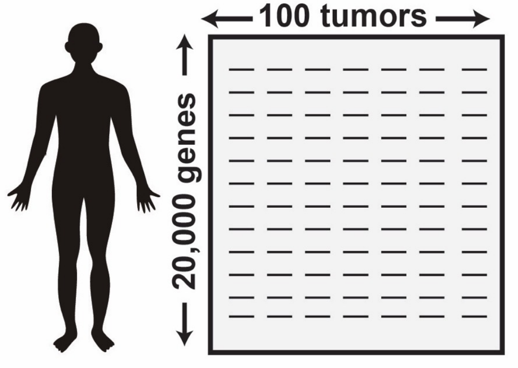
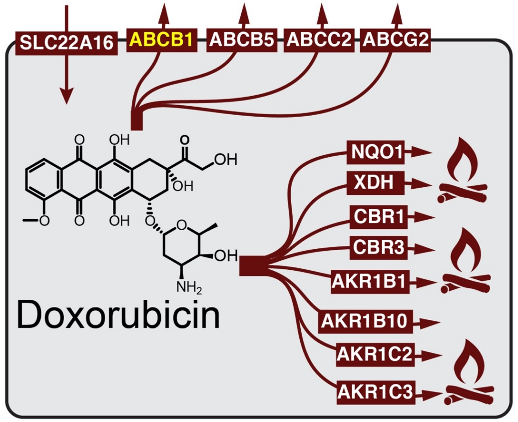
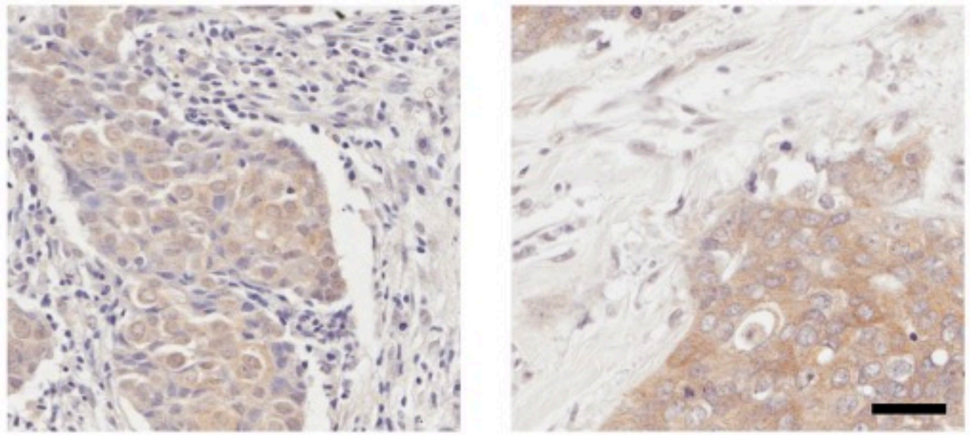


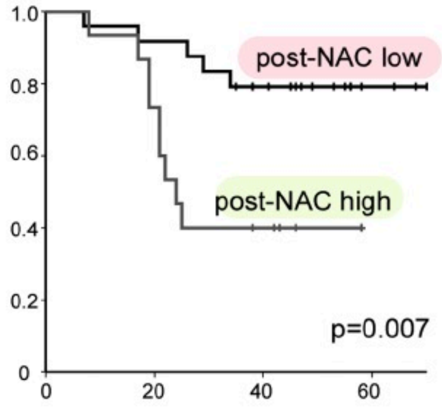
GEORGIA
Pharmacy



Prognostic
Gene-signatures



pre-NAC post-NAC



PLOS One **2013**, 8, e62766

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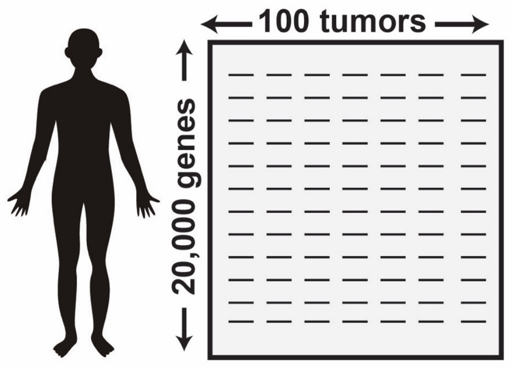
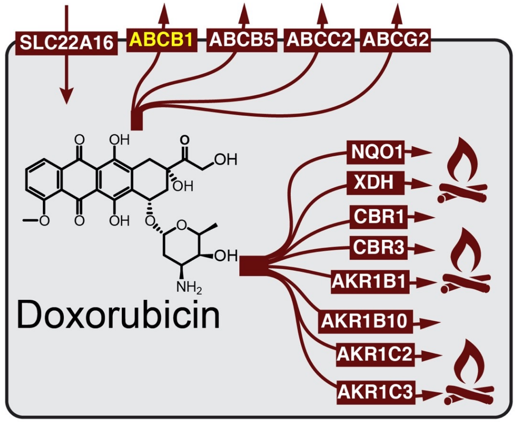


GEORGIA Pharmacy



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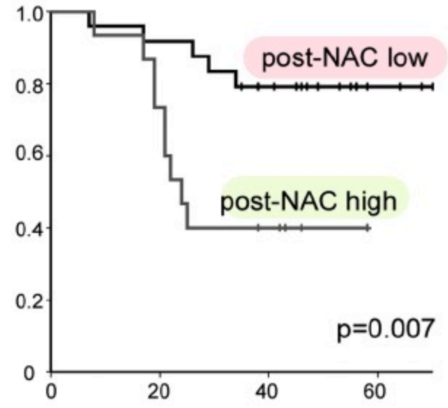
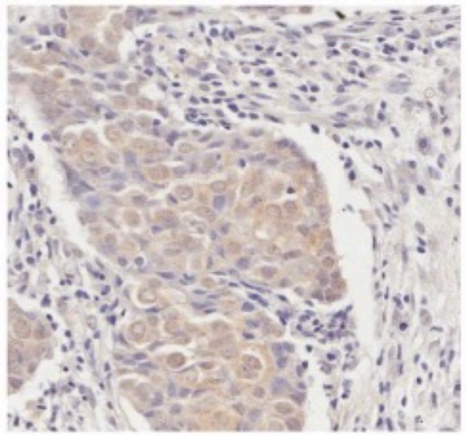
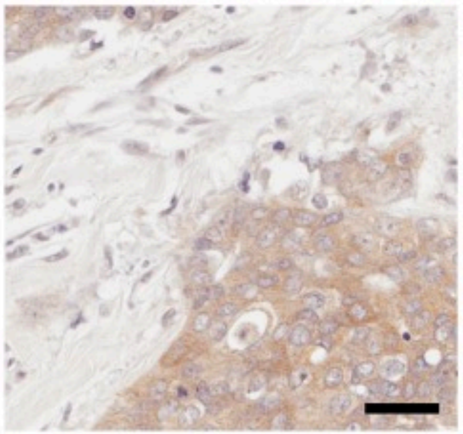




pre-NAC

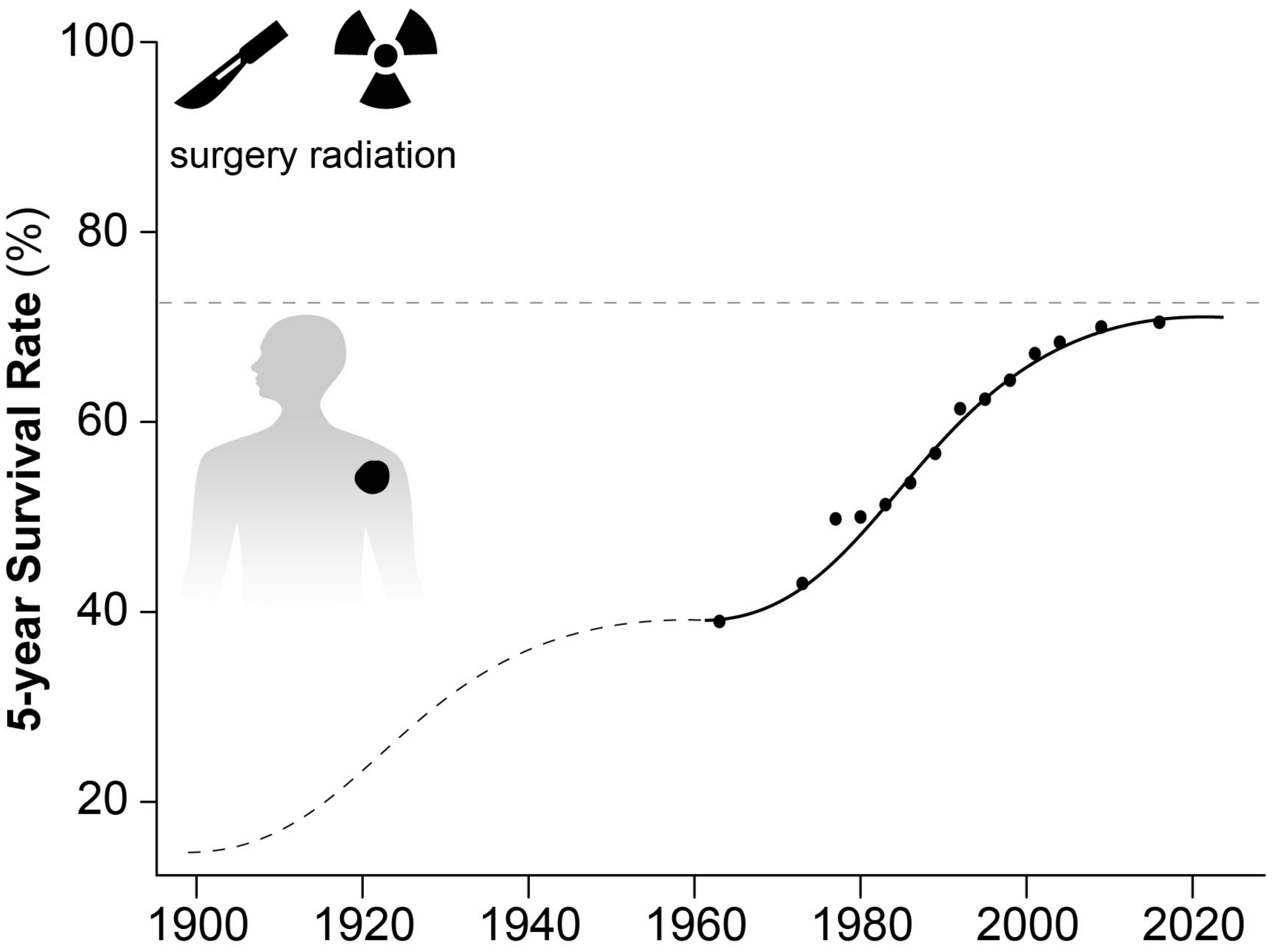


post-NAC

Predict drug-response
Identify drugs to overcome resistance

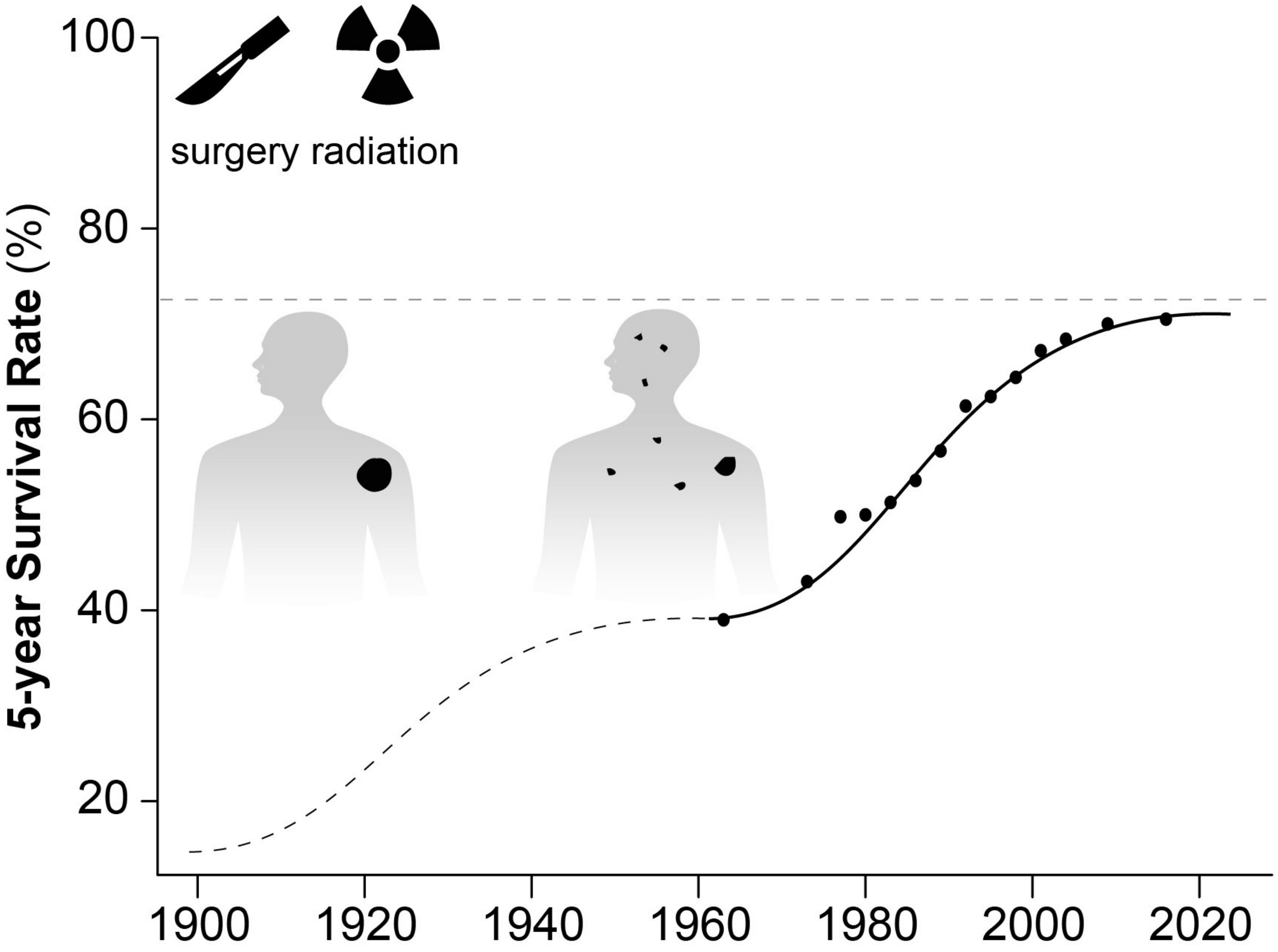
PLOS One **2013**, 8, e62766

History of Cancer Treatment: *localized cancers*



V. DeVita *The Death of Cancer*, **2016**, Sarah Crichton Books
SEER Cancer Statistics Review, **1975-2017**, National Cancer Institute

History of Cancer Treatment: *metastatic cancer*



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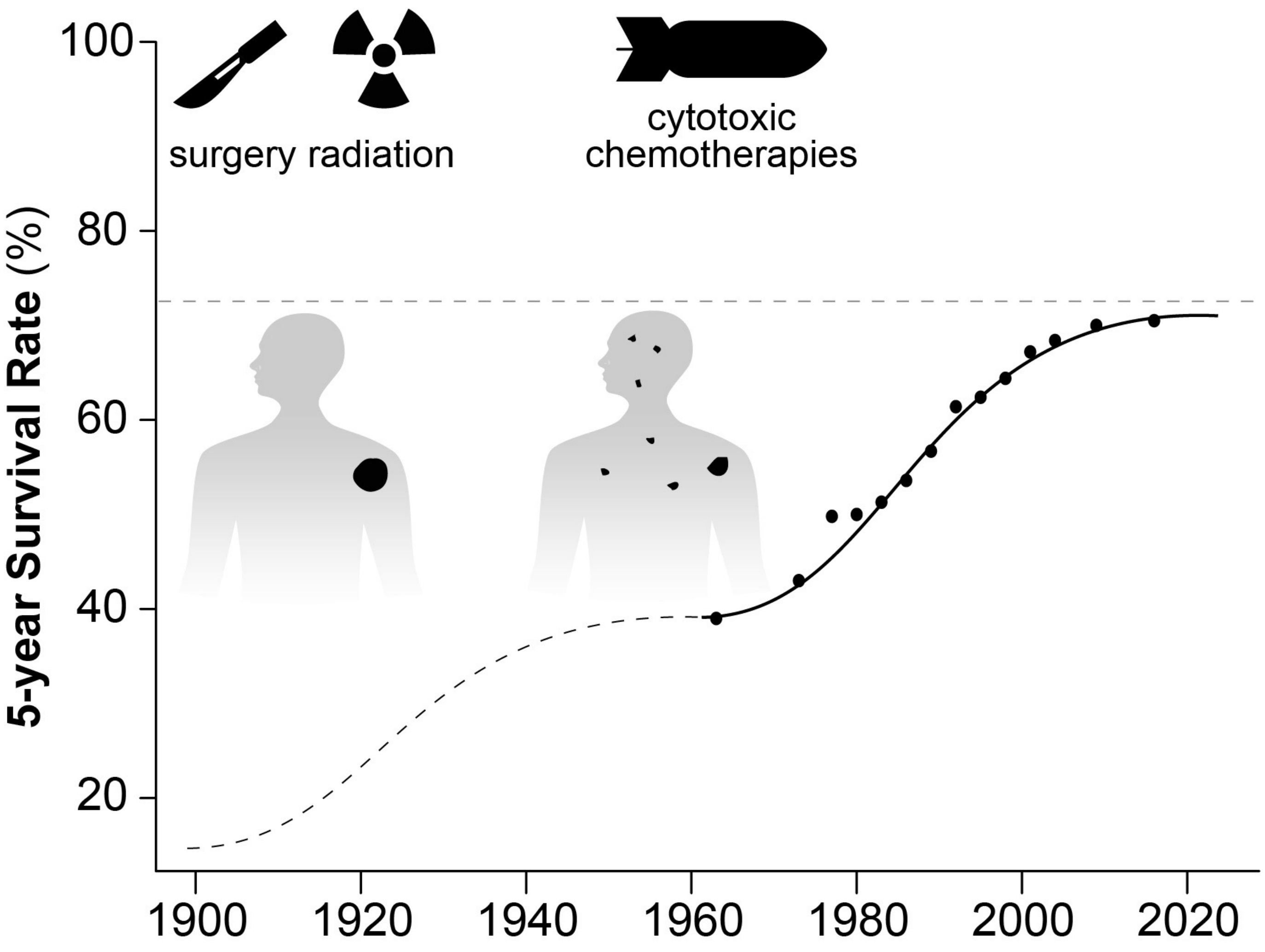

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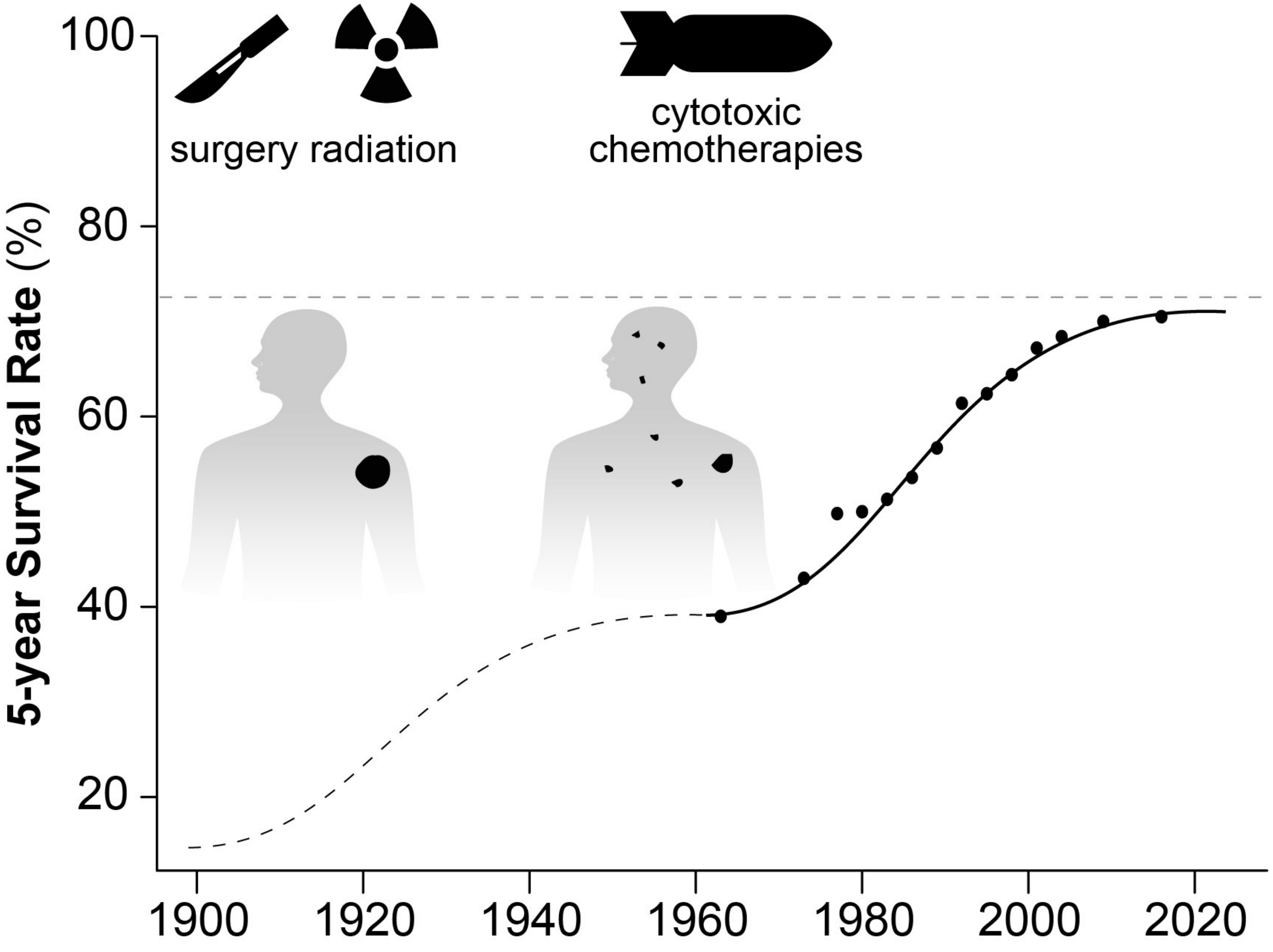
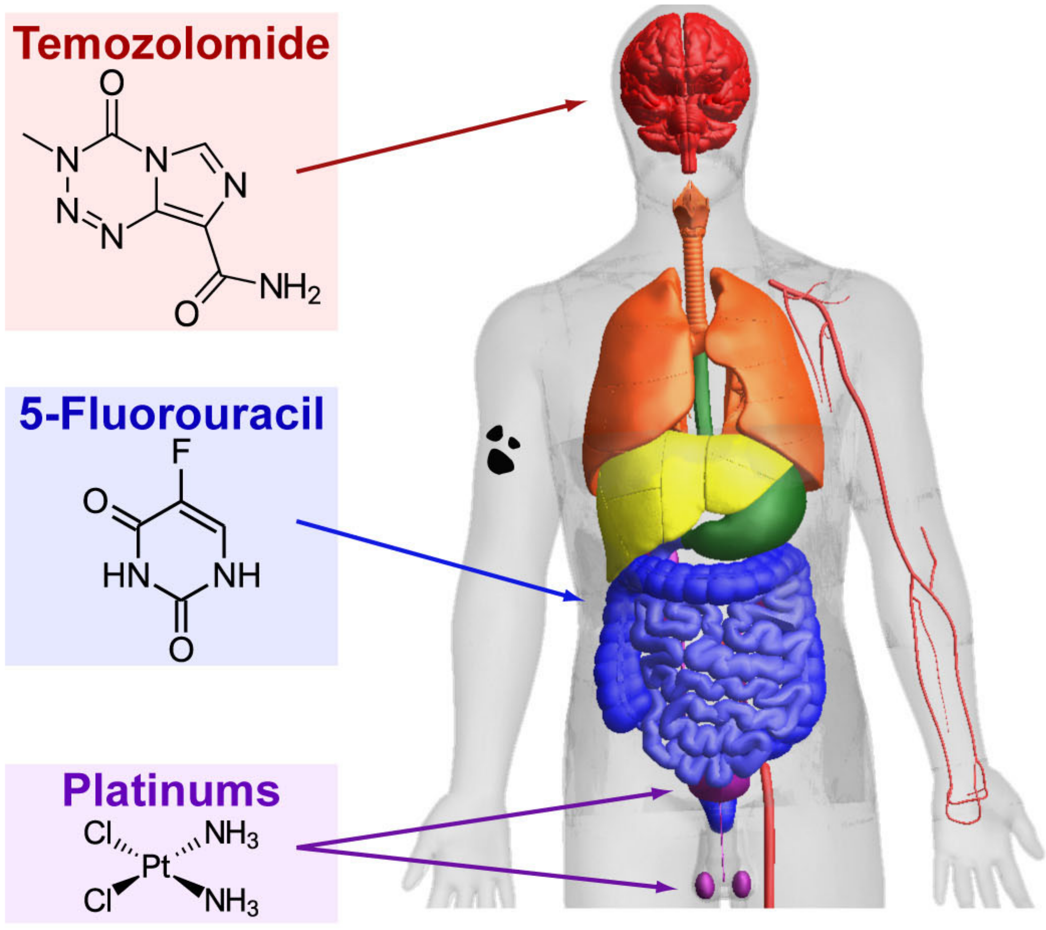
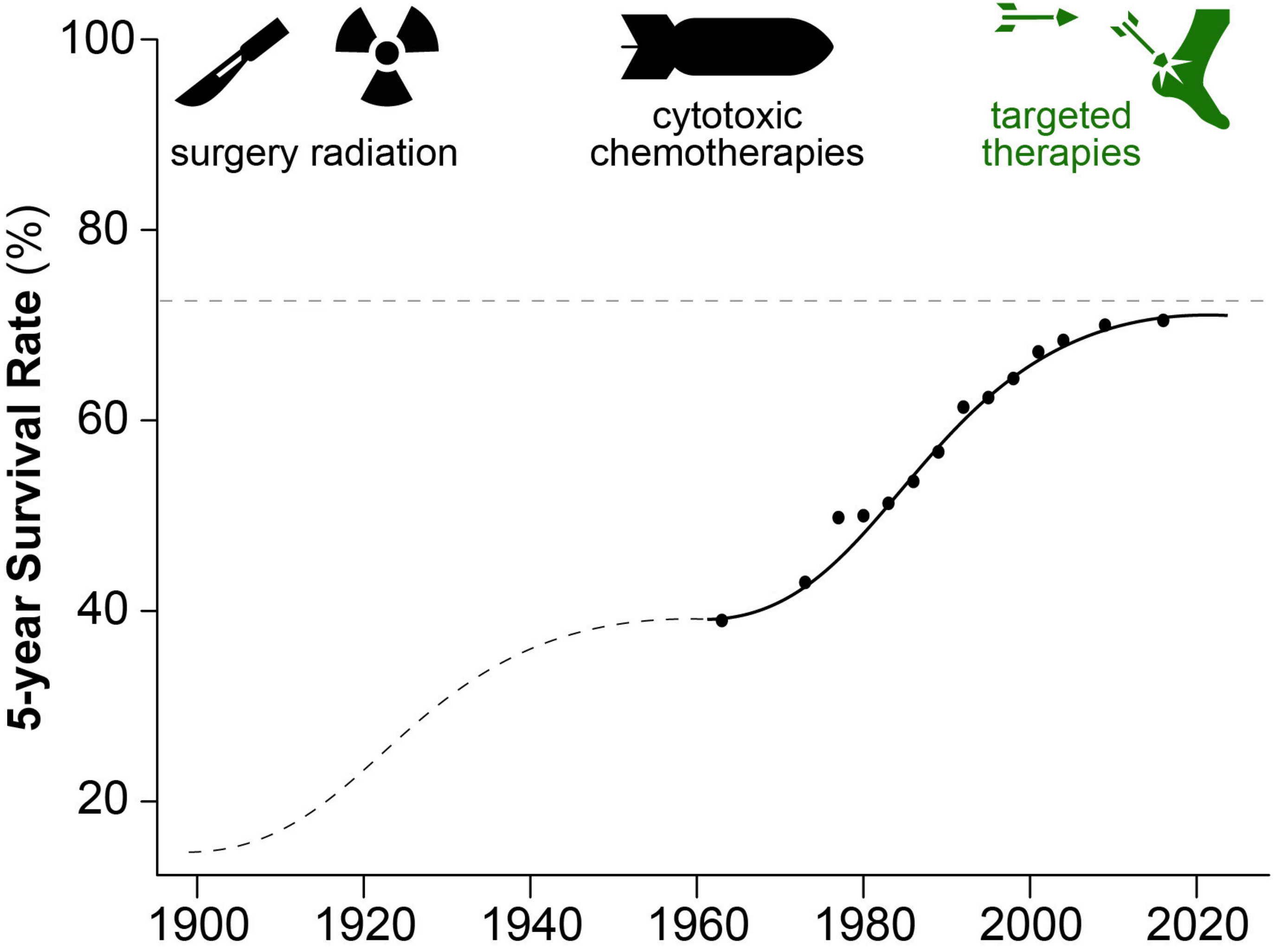




V. DeVita *The Death of Cancer*, **2016**, Sarah Crichton Books
SEER Cancer Statistics Review, **1975-2017**, National Cancer Institute

History of Cancer Treatment: *targeted therapies?*



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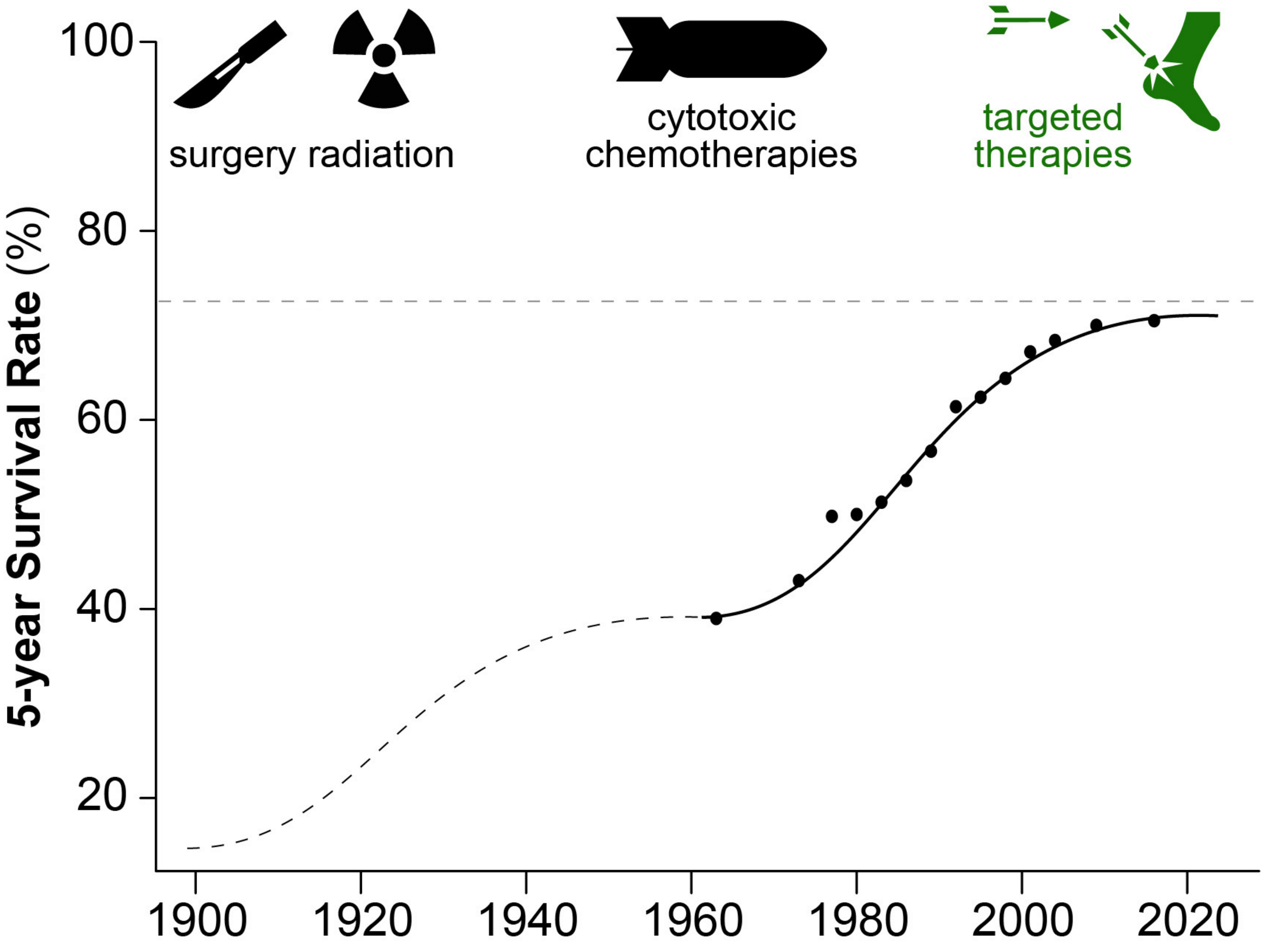
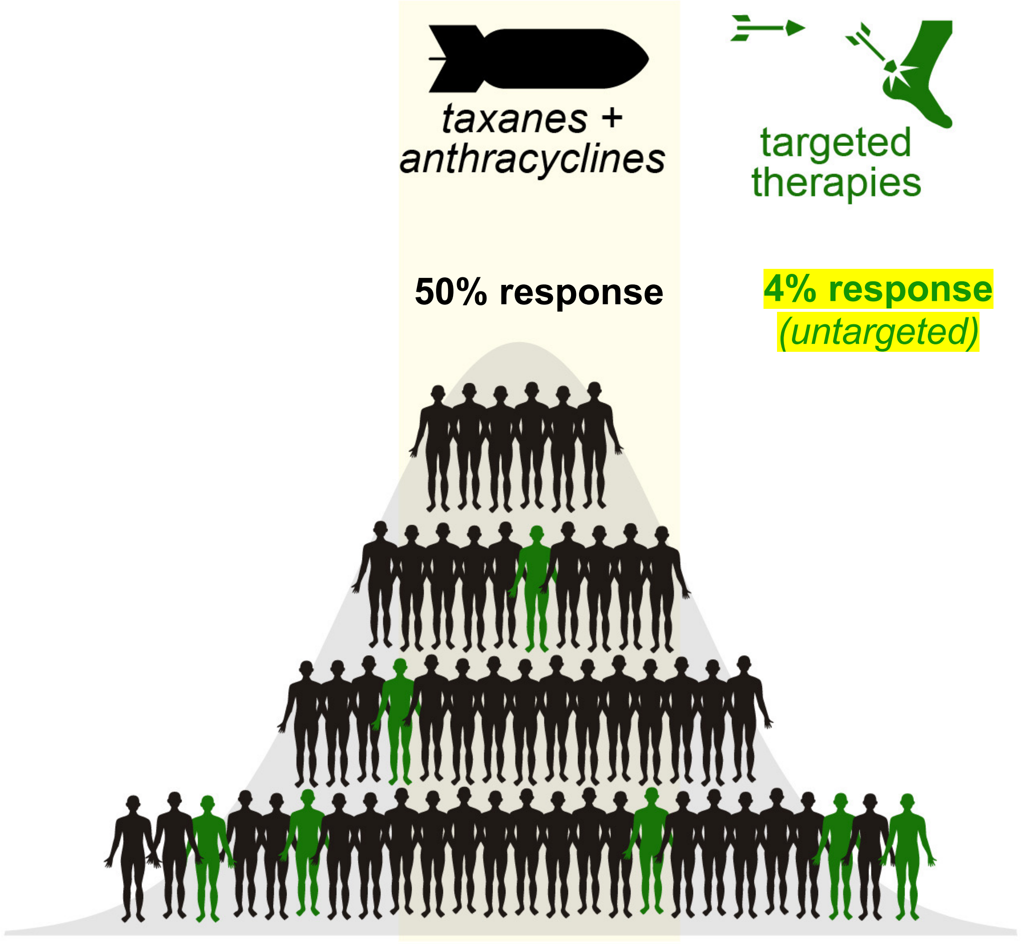
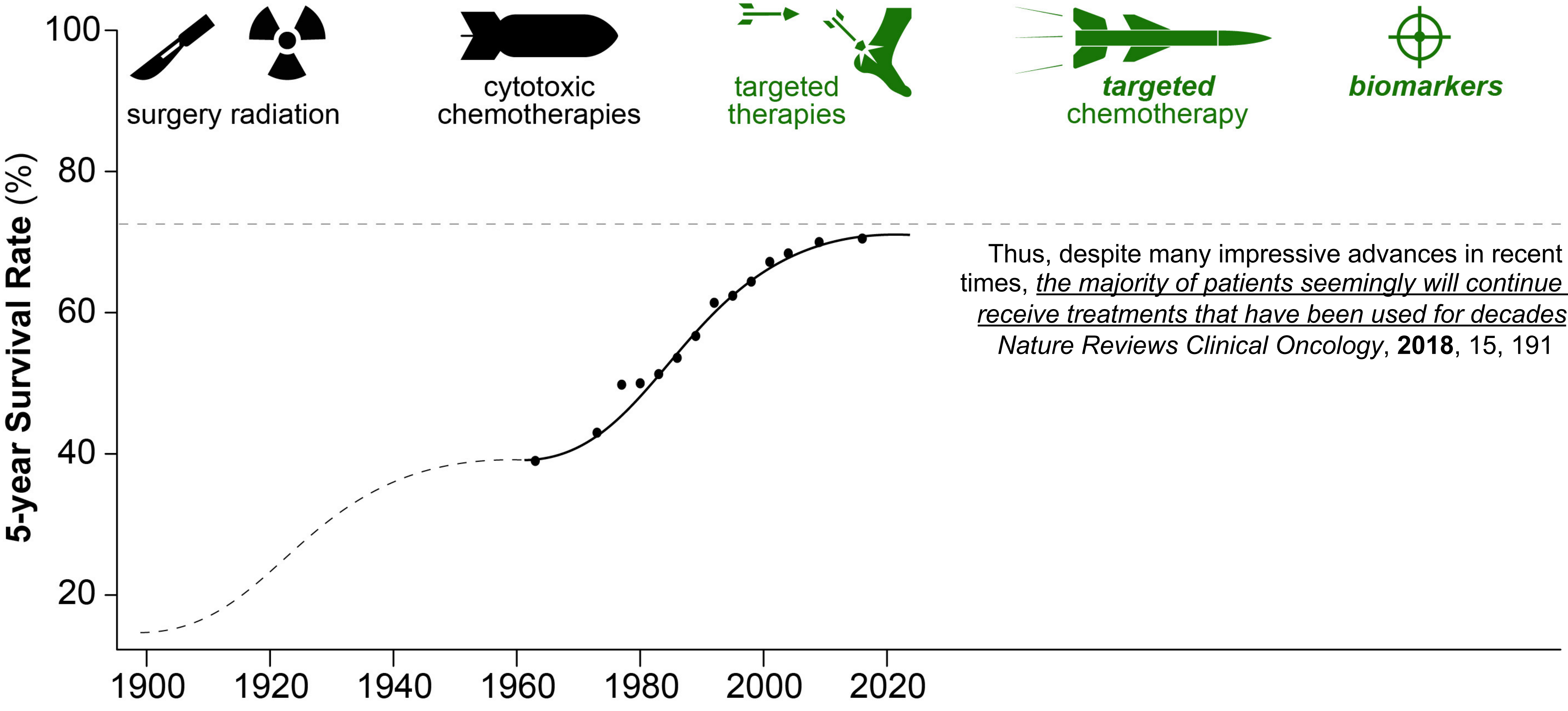




J. Clin. Oncol., **2015**, 33, 3817
V. DeVita *The Death of Cancer*, **2016**, Sarah Crichton Books
SEER Cancer Statistics Review, **1975-2017**, National Cancer Institute

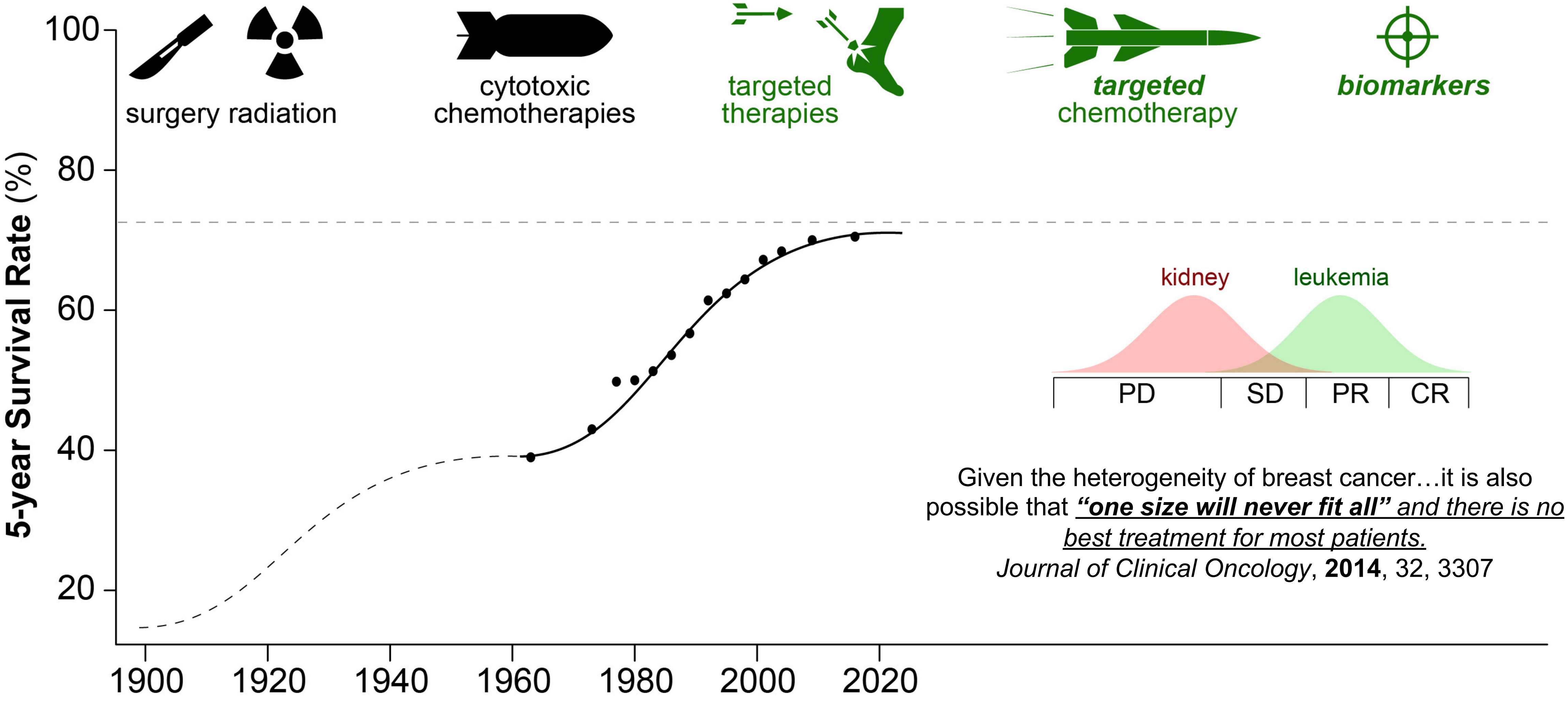
History of Cancer Treatment: *targeted chemotherapies?*



Thus, despite many impressive advances in recent times, *the majority of patients seemingly will continue to receive treatments that have been used for decades*.
Nature Reviews Clinical Oncology, **2018**, 15, 191

V. DeVita *The Death of Cancer*, **2016**, Sarah Crichton Books
SEER Cancer Statistics Review, **1975-2017**, National Cancer Institute

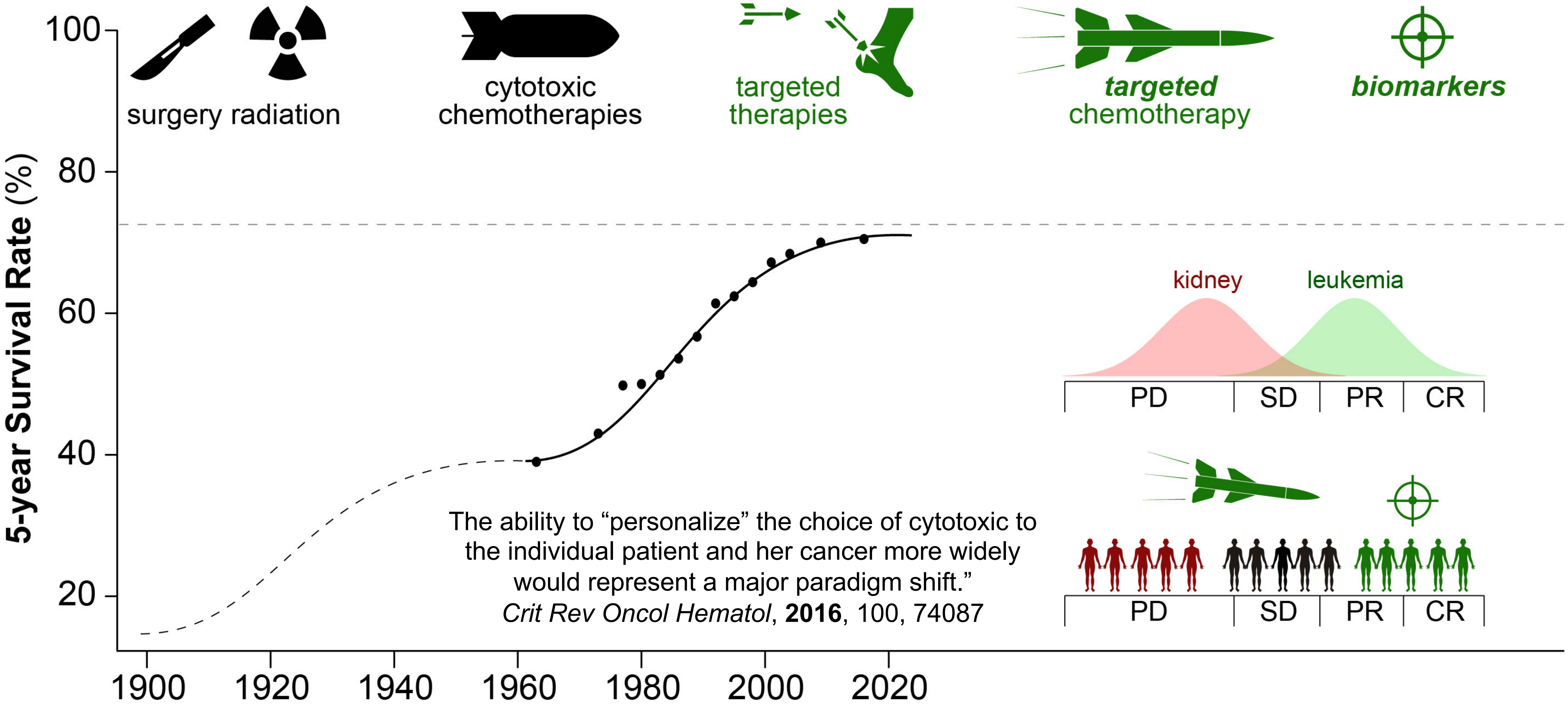
History of Cancer Treatment: *targeted chemotherapies?*



Given the heterogeneity of breast cancer…it is also possible that ***"one size will never fit all"*** *and there is no best treatment for most patients.*
Journal of Clinical Oncology, **2014**, 32, 3307

PNAS, **2019**, 116, 10494
V. DeVita *The Death of Cancer*, **2016**, Sarah Crichton Books
SEER Cancer Statistics Review, **1975-2017**, National Cancer Institute

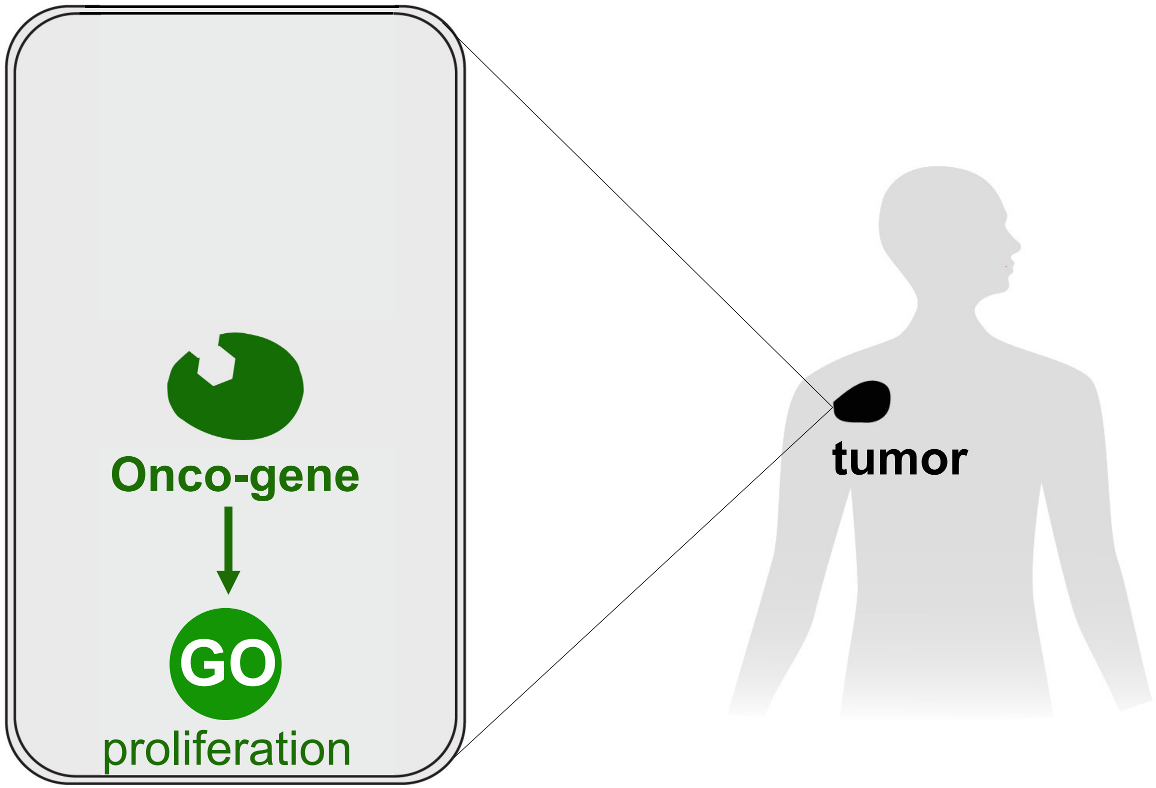
History of Cancer Treatment: *targeted chemotherapies?*



The ability to “personalize” the choice of cytotoxic to the individual patient and her cancer more widely would represent a major paradigm shift.”
Crit Rev Oncol Hematol, **2016**, 100, 74087

PNAS, **2019**, 116, 10494
V. DeVita *The Death of Cancer*, **2016**, Sarah Crichton Books
SEER Cancer Statistics Review, **1975-2017**, National Cancer Institute

Laboratory Drug-sensitivity: *dose-response curves*



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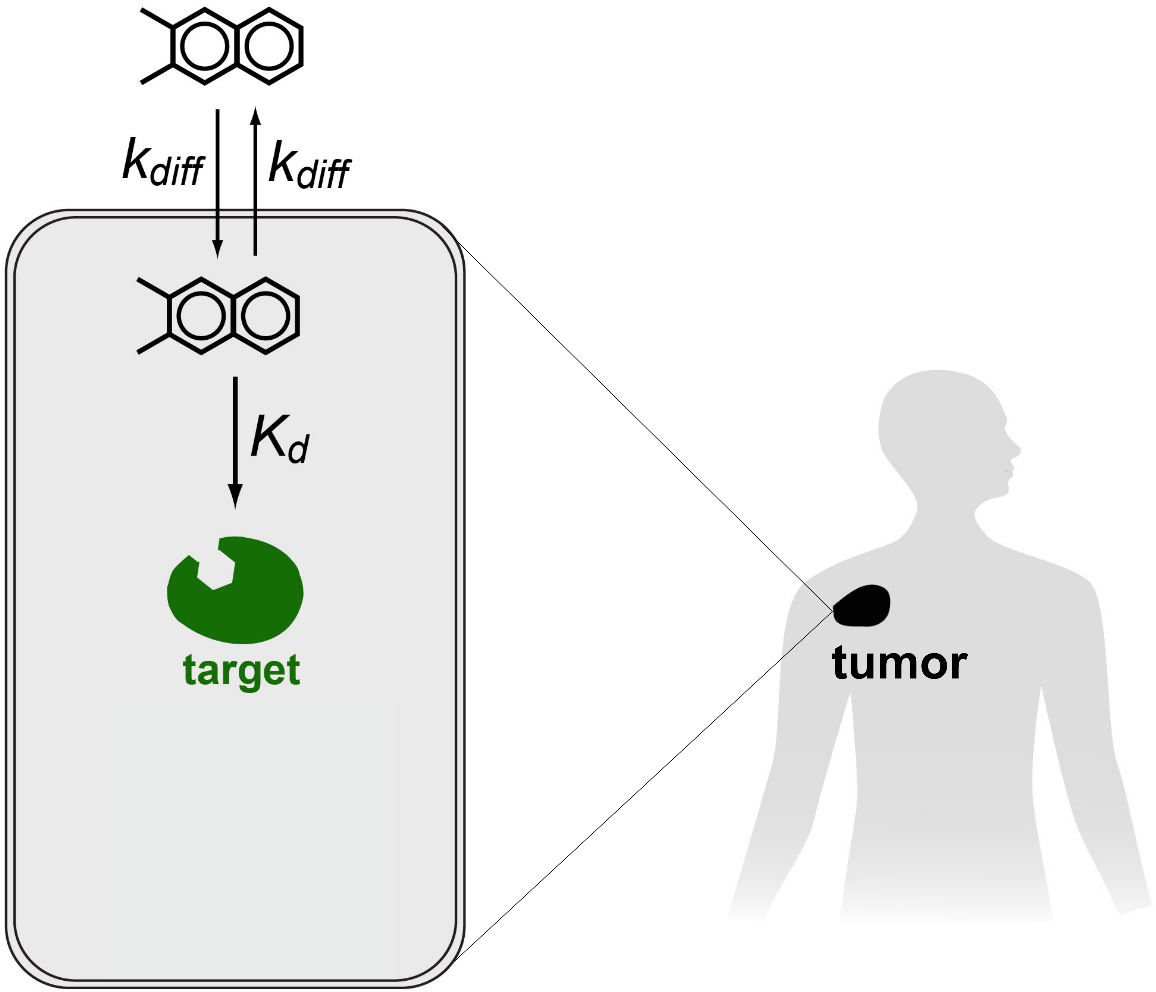

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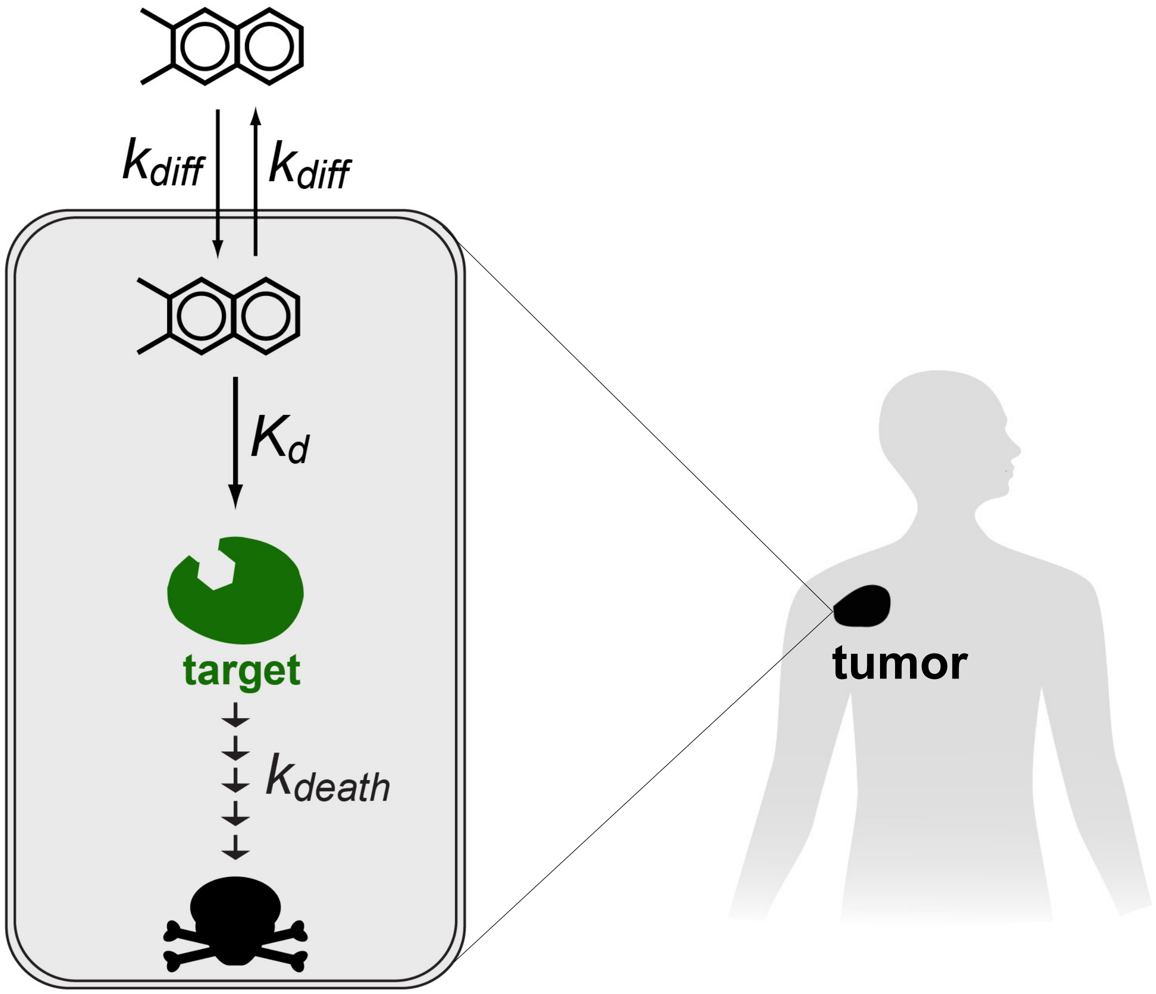

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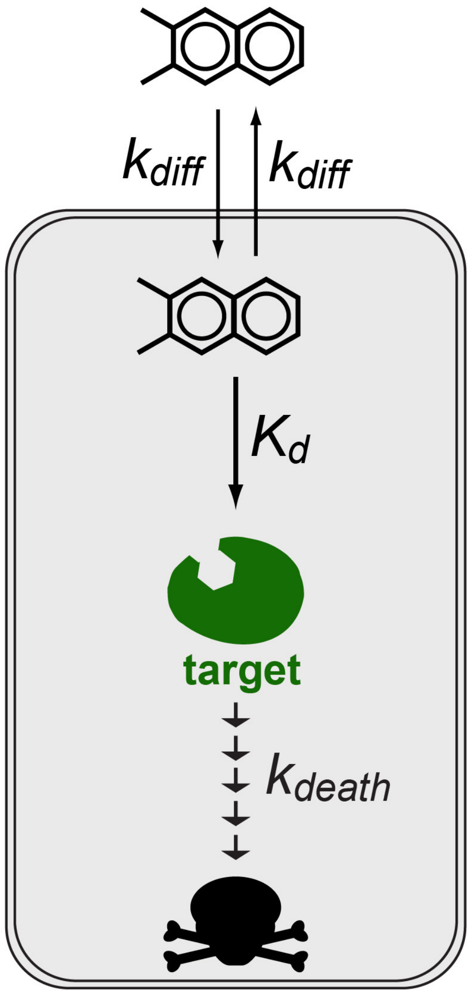

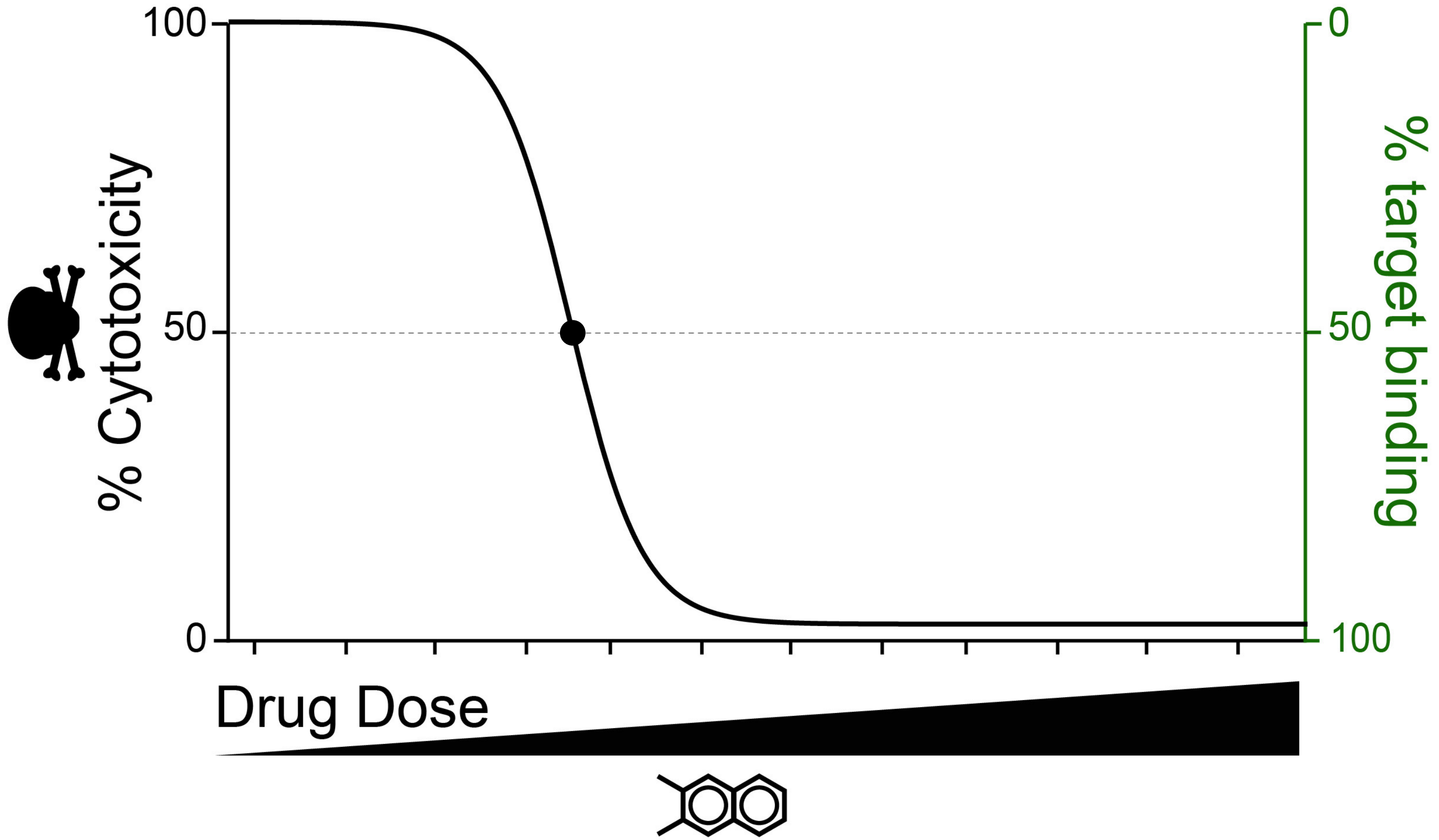

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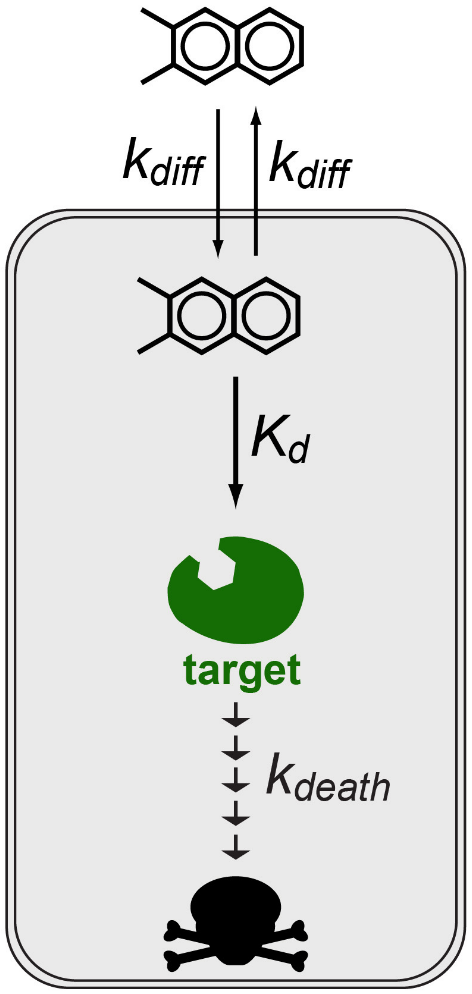
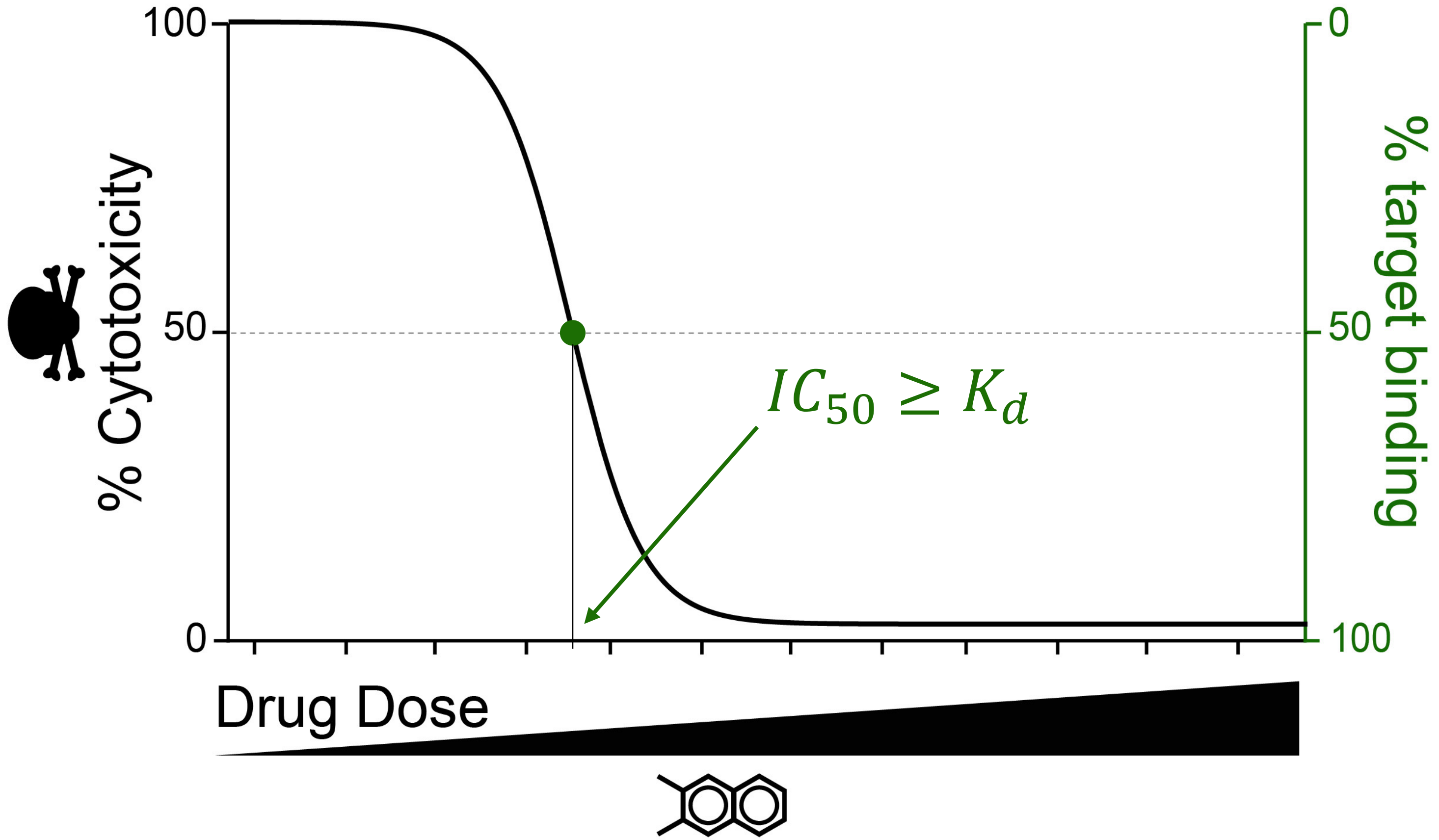
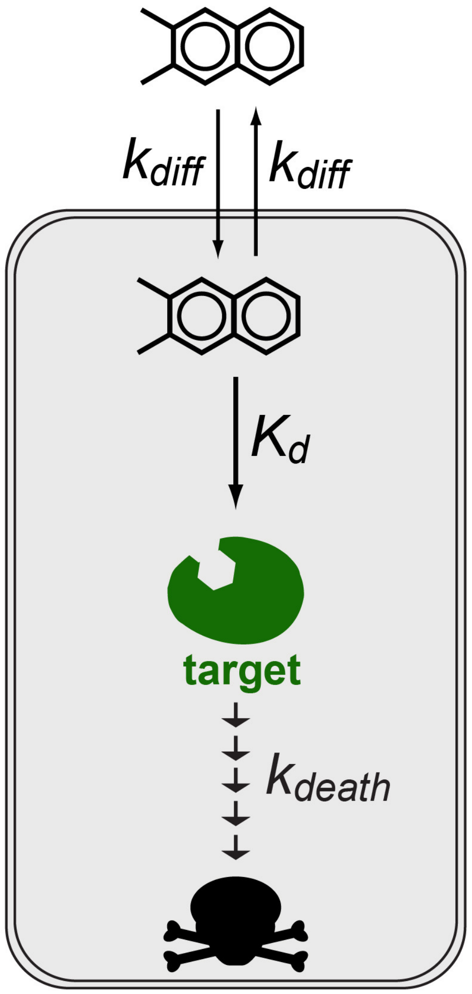
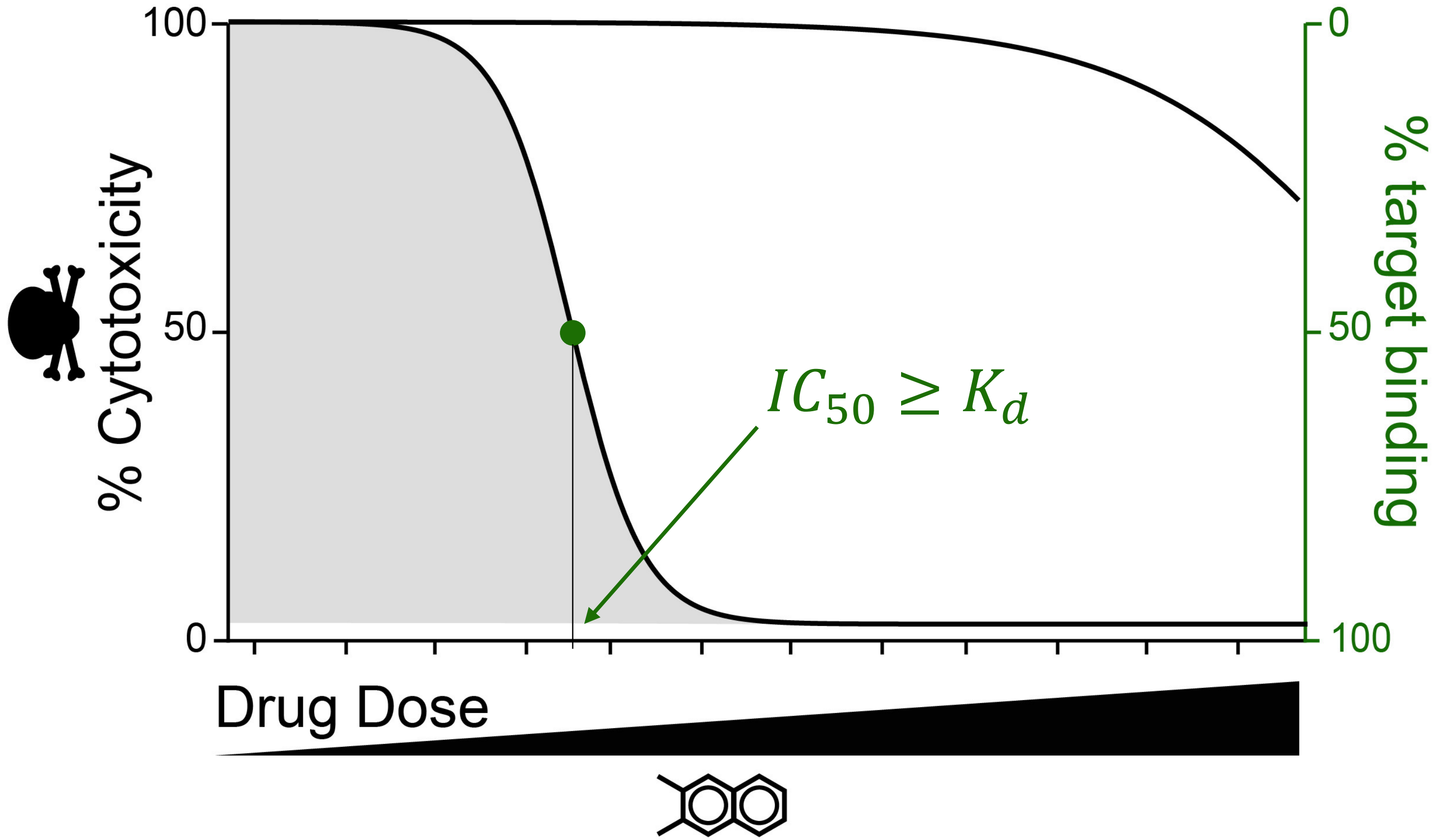




Biochemical Pharmacology, **1973**, 22, 3099-3108

Laboratory Drug-sensitivity: *dose-response curves*





Biochemical Pharmacology, **1973**, 22, 3099-3108

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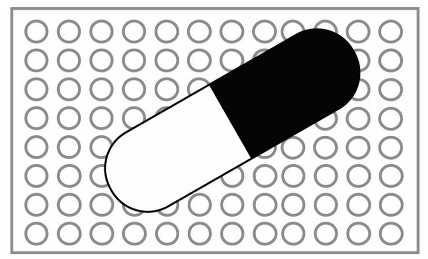
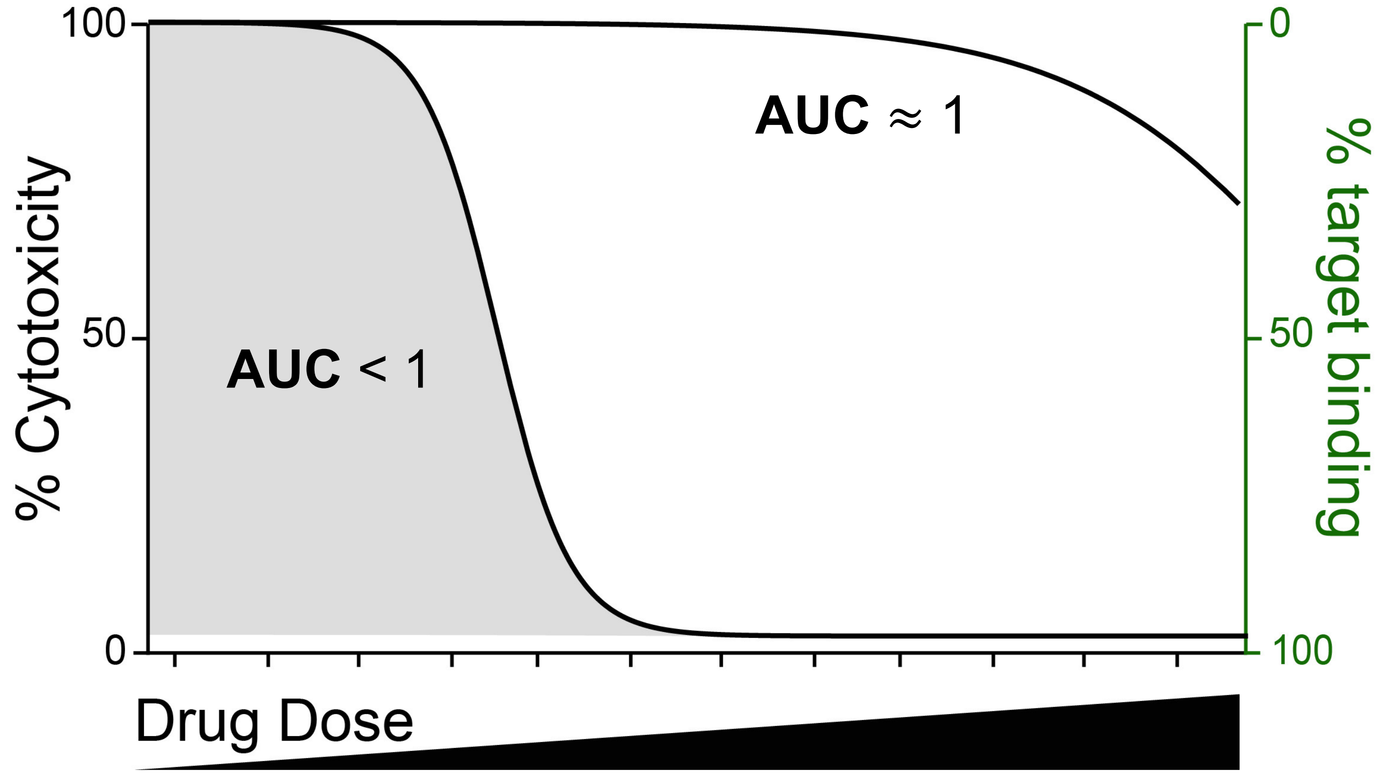
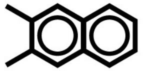


Screening Technology





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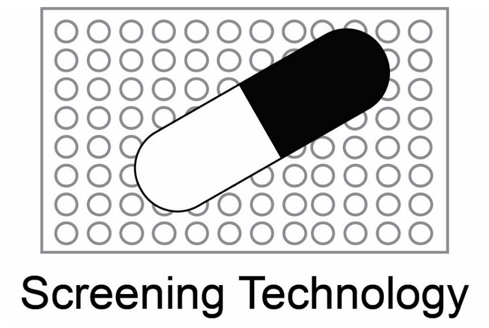
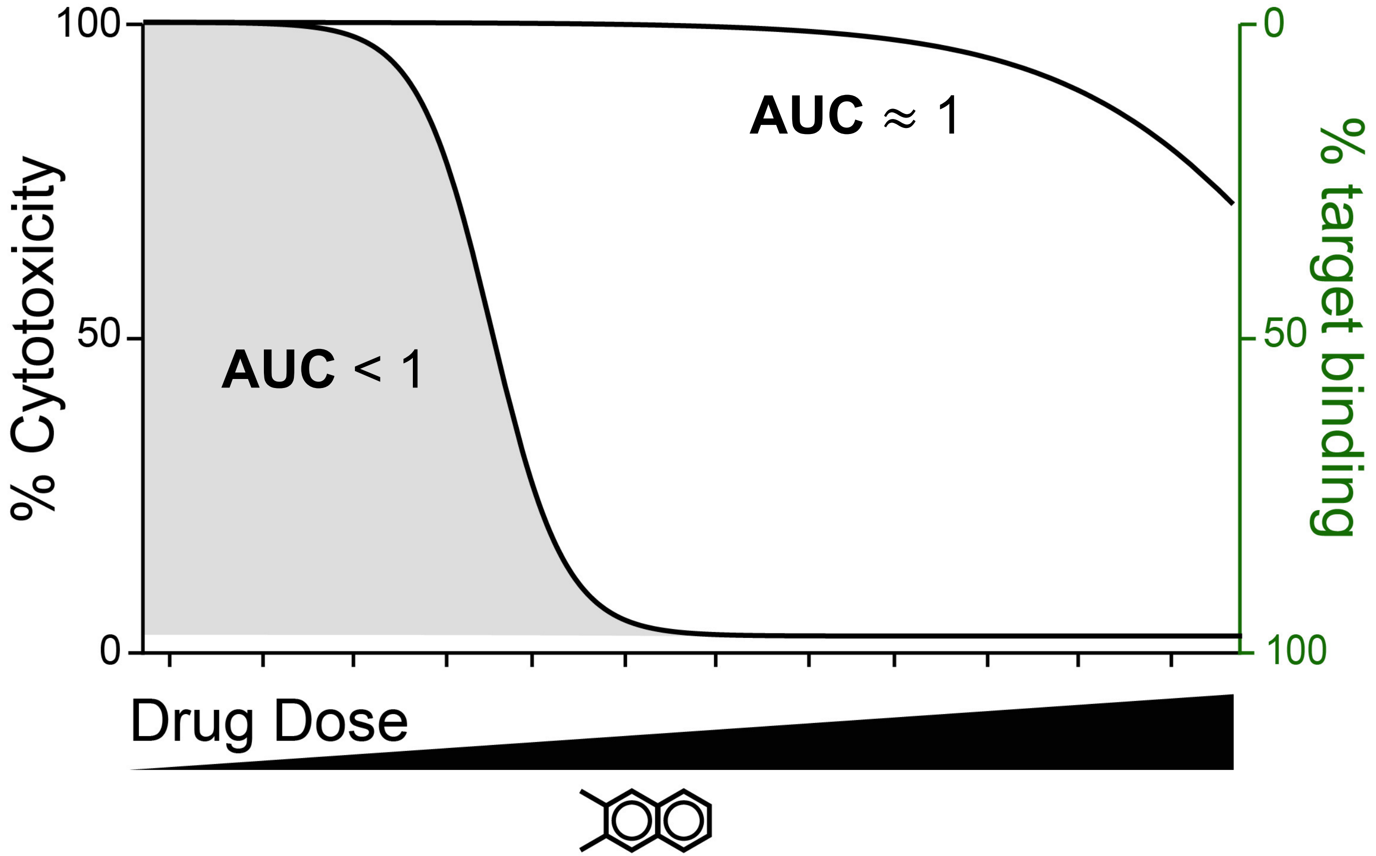
Laboratory Drug-sensitivity: *dose-response curves*



Cancer Therapeutic Response Portal (CTRP)
545 drugs x 887 cell-lines
Cell, **2013**, 154, 1151

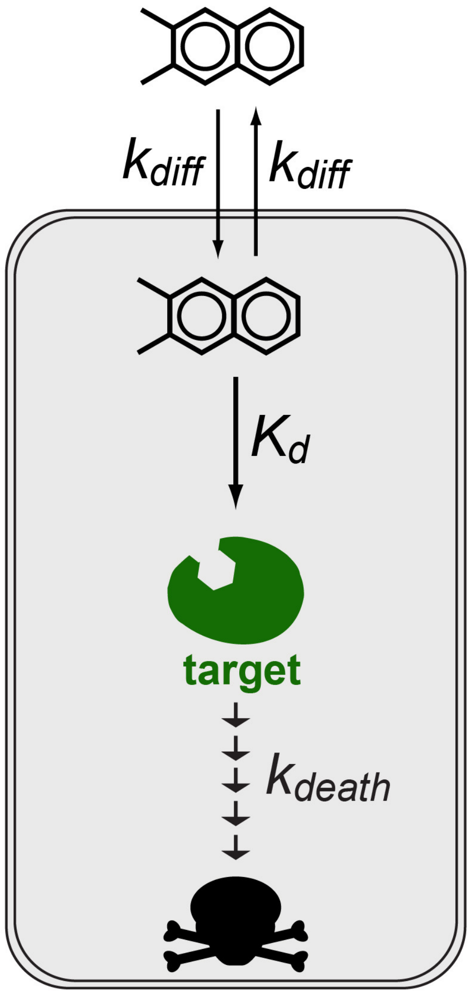
Genomics of Drug Sensitivity (GDSC)
473 drugs x 972 cell-lines
Cell, **2016**, 166, 740

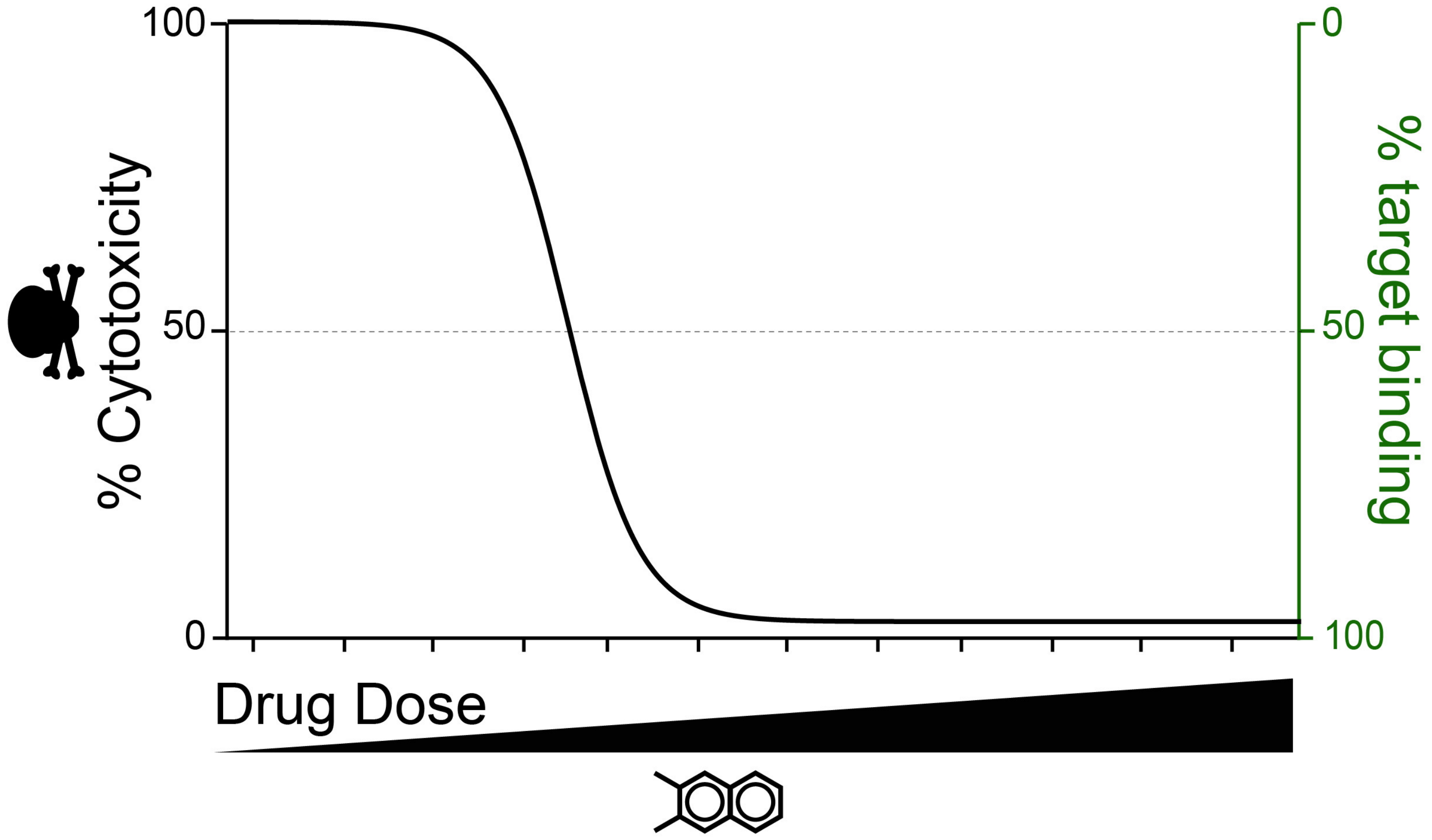
Profiling Relative Inhibition Simultaneously in Mixtures(PRISM)
1,448 drugs x 480 cell-lines
Nature Cancer, **2020**, 1, 235



Biochemical Pharmacology, **1973**, 22, 3099-3108

Drug Resistance: *Laboratory Data*





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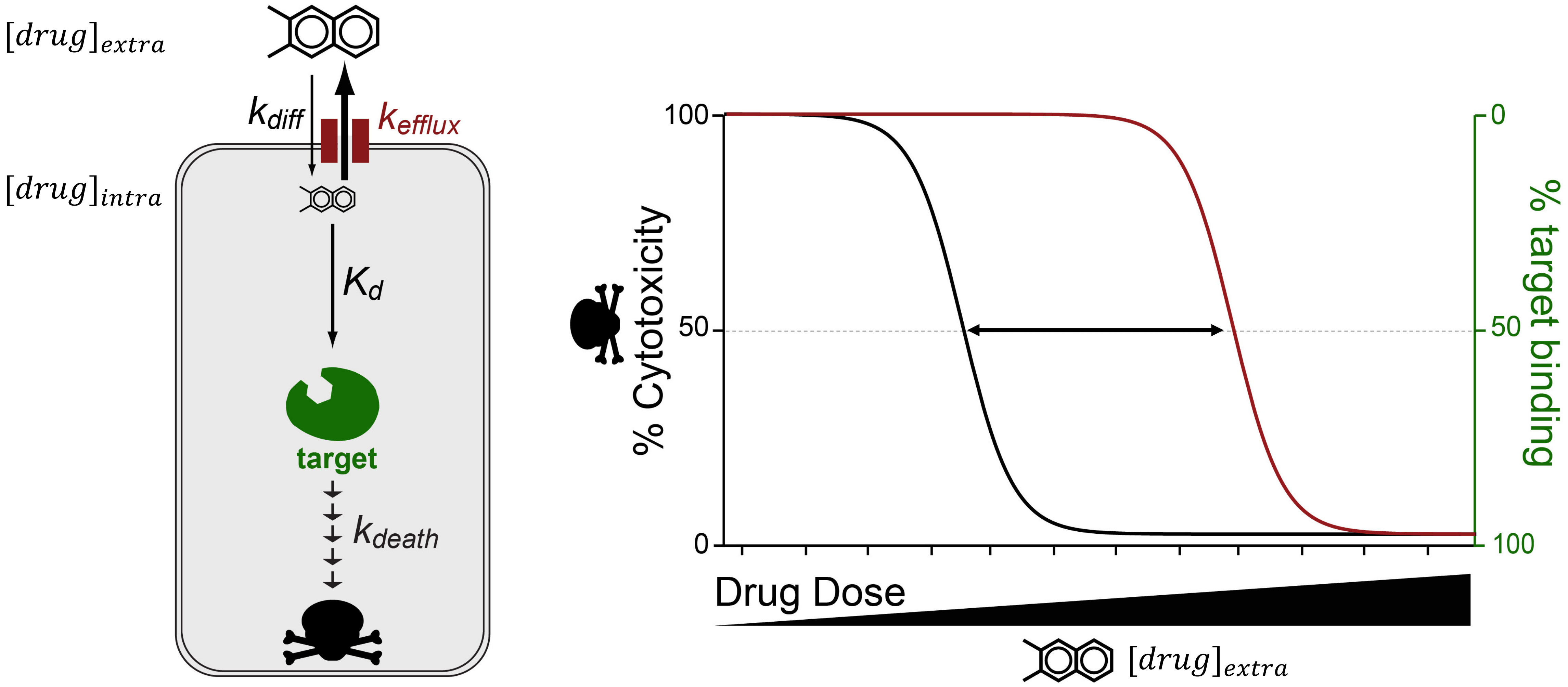

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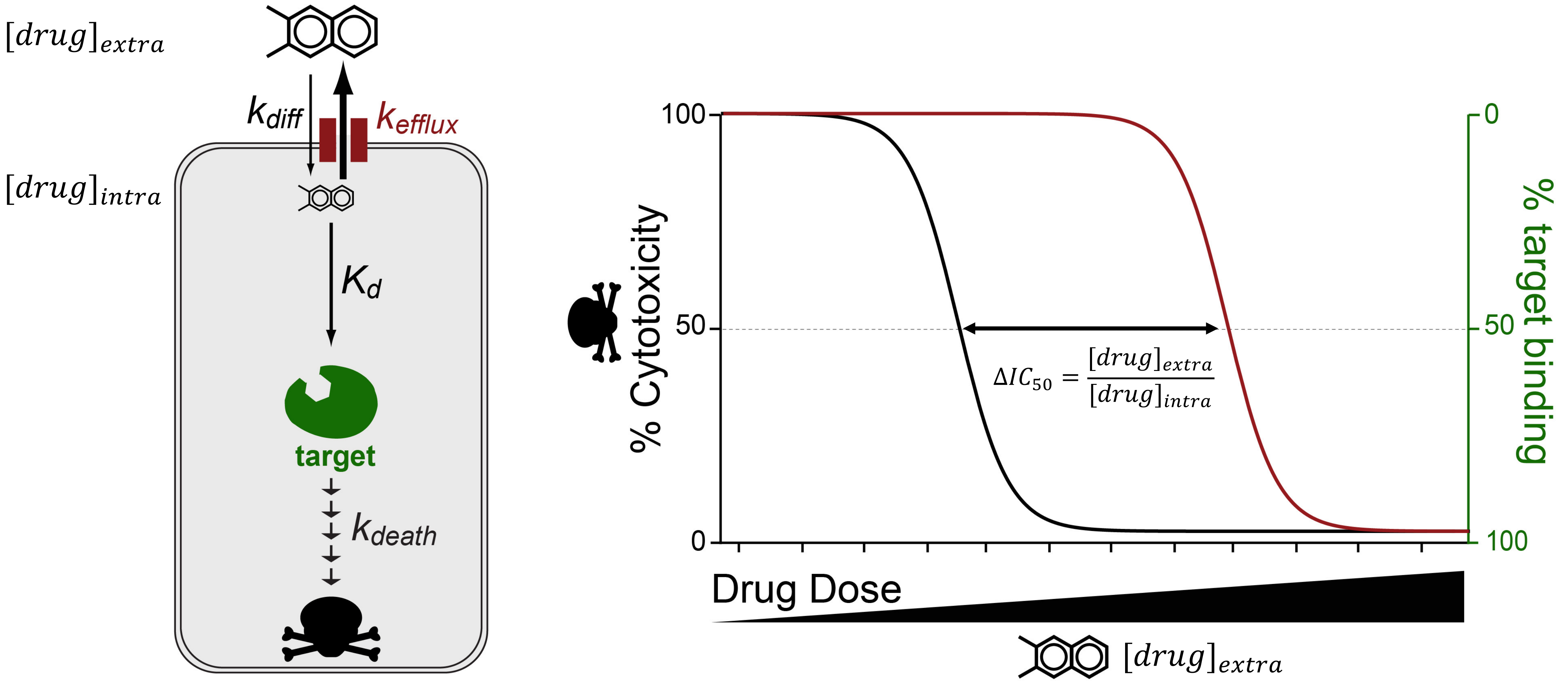
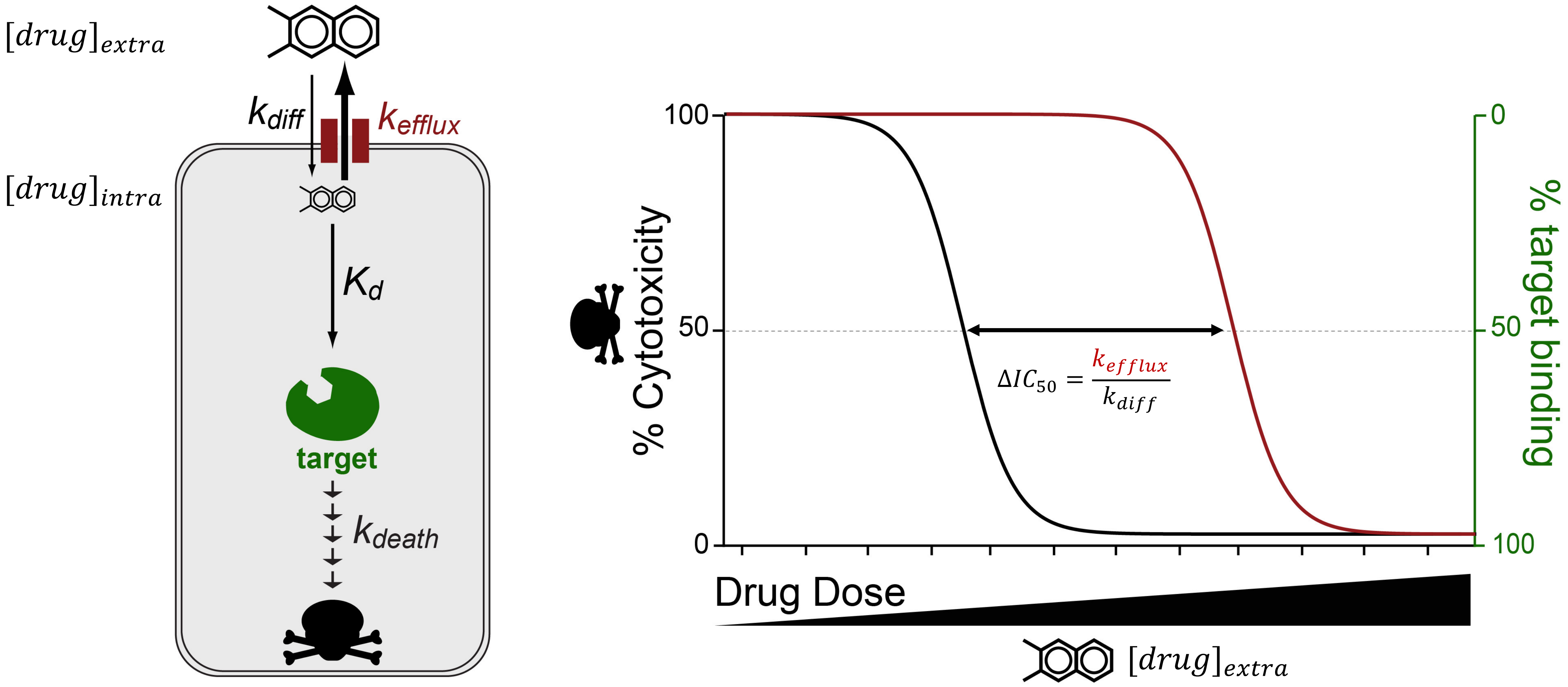
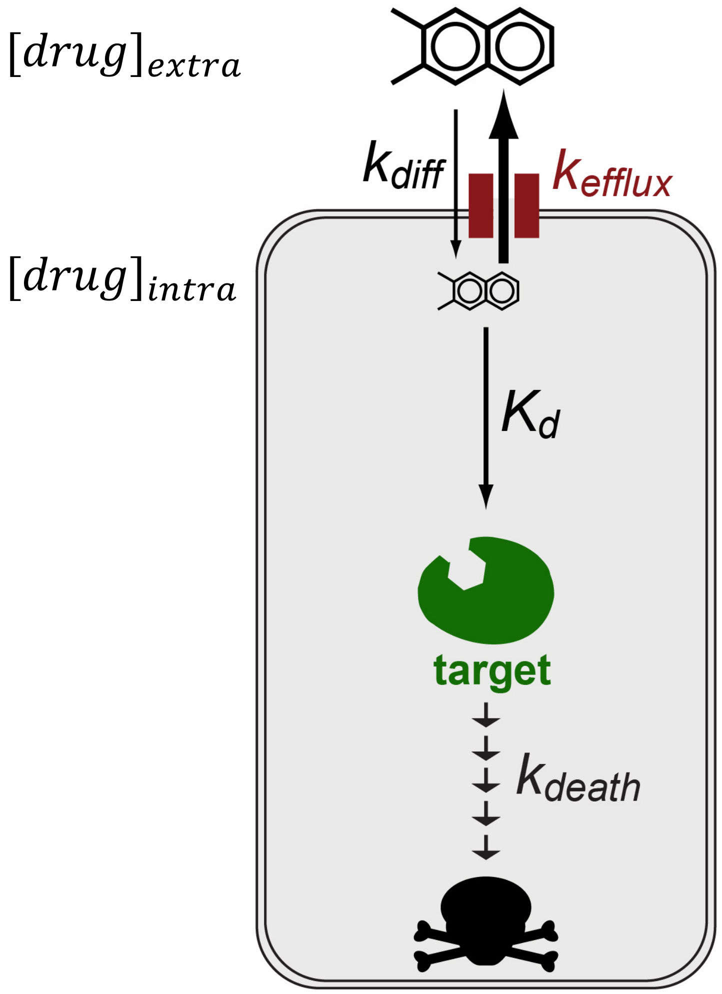
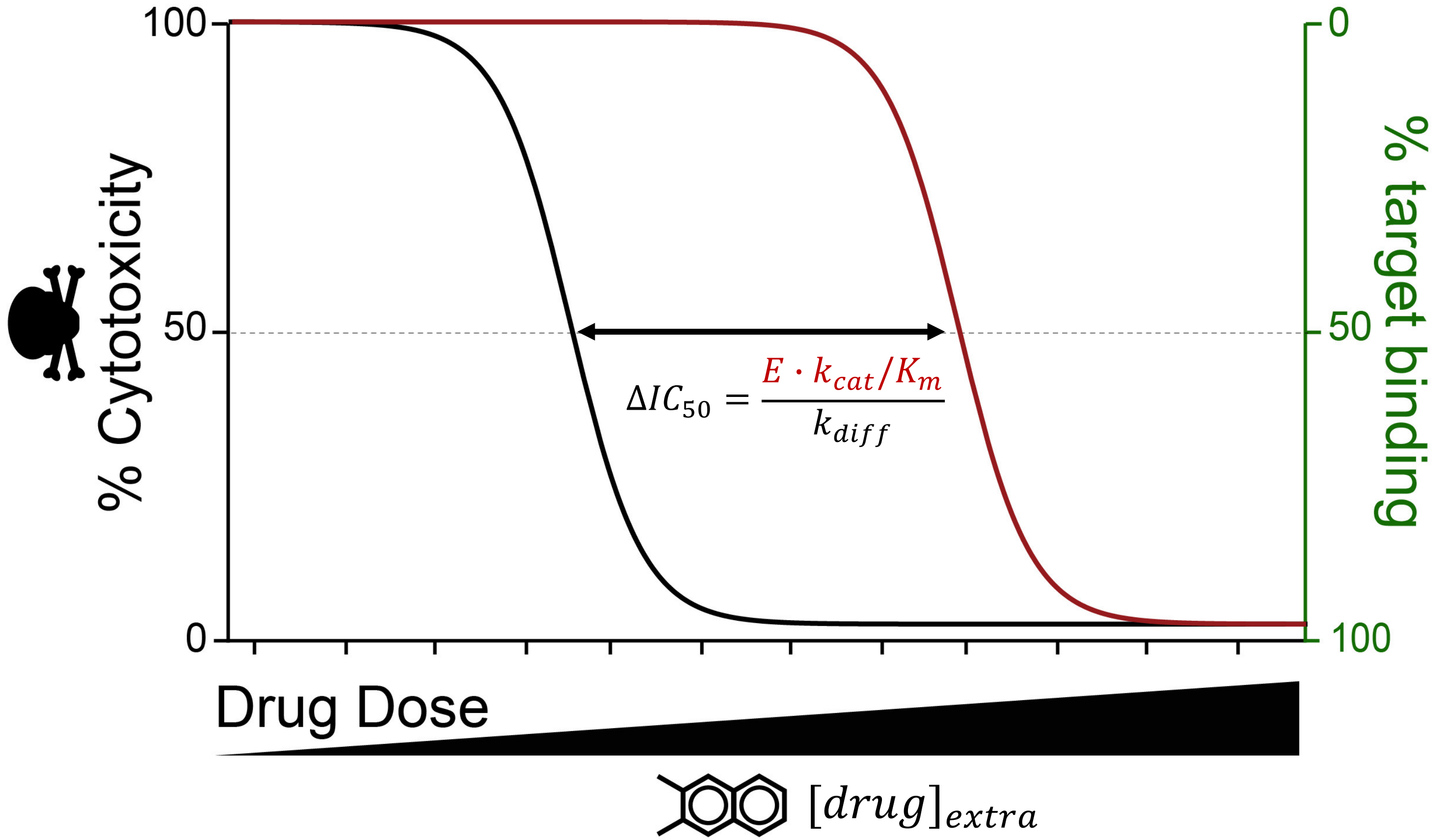


Drug Resistance: *Laboratory Data*

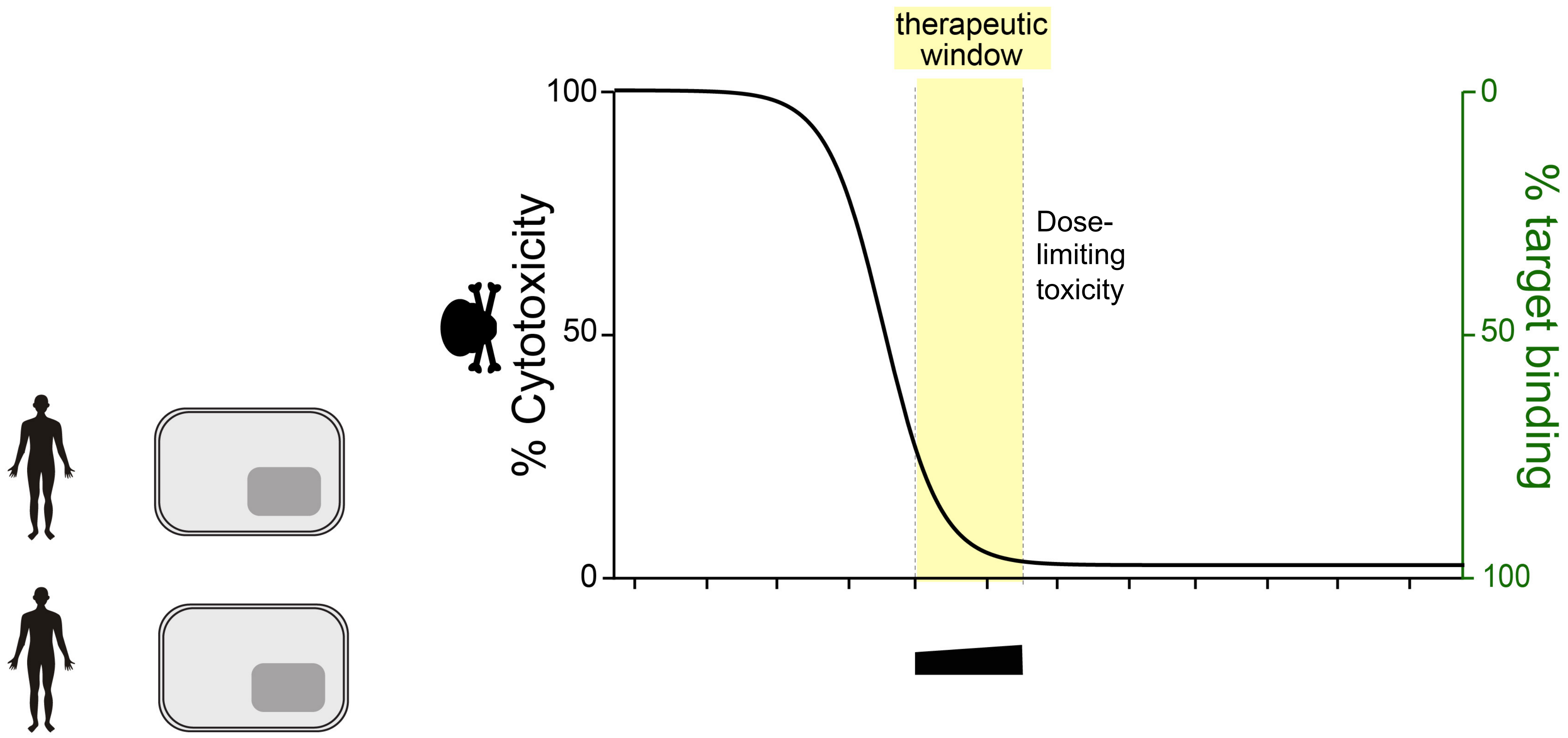


Drug Resistance: *Laboratory Data*



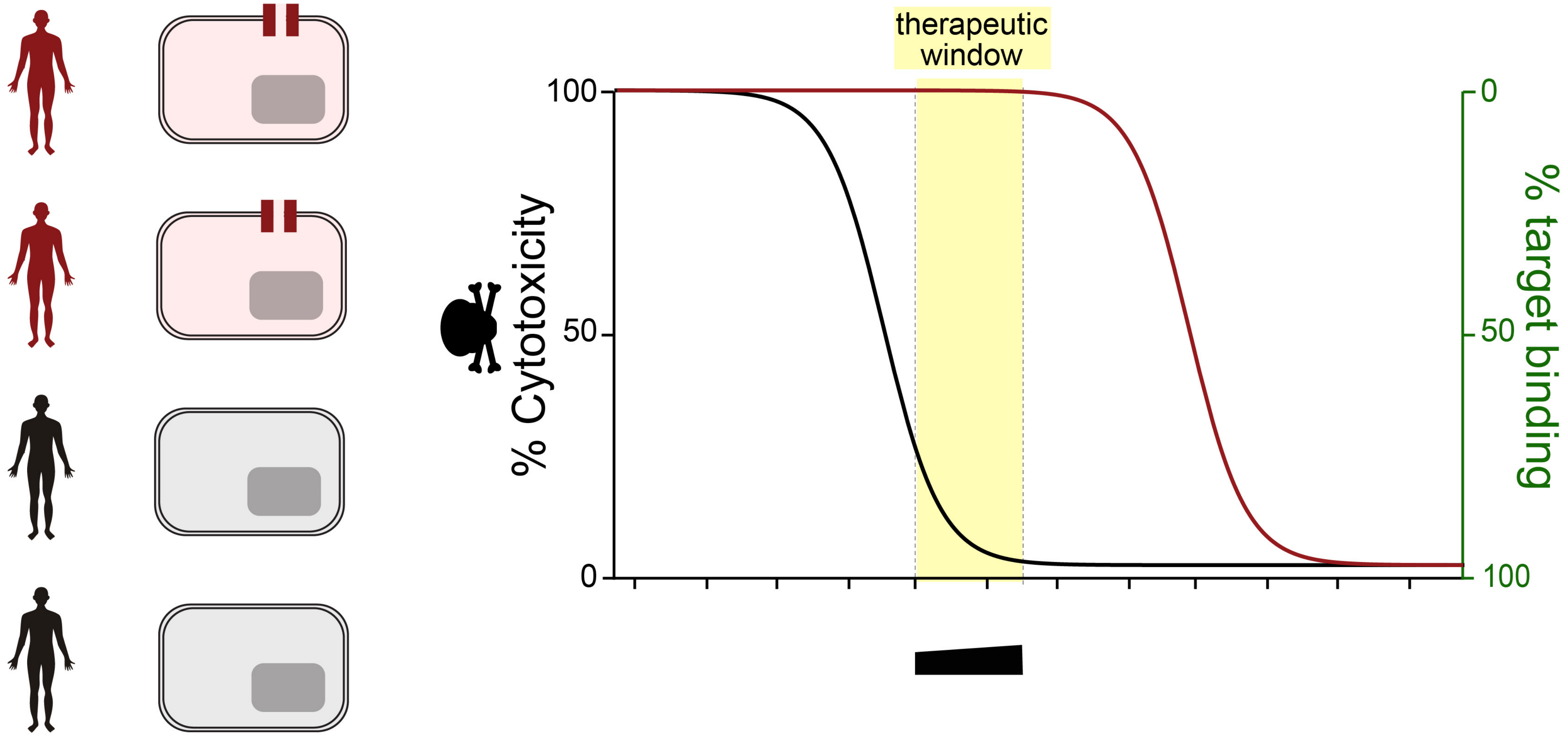


Drug Resistance: *clinical response rates*



Clinical Pharmacokinetics and Pharmacodynamics 5th ed, **2020**, Wolters Kluwer

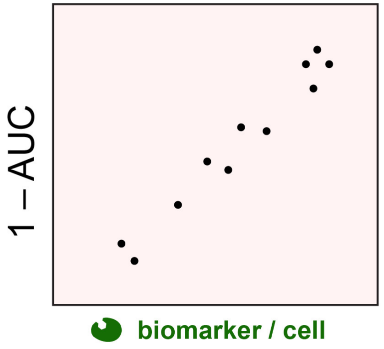
Drug Resistance: *clinical response rates*



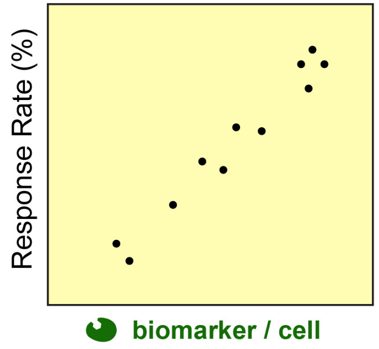
Clinical Pharmacokinetics and Pharmacodynamics 5th ed, **2020**, Wolters Kluwer

Laboratory vs Clinical Biomarker analysis:

in vitro data sets

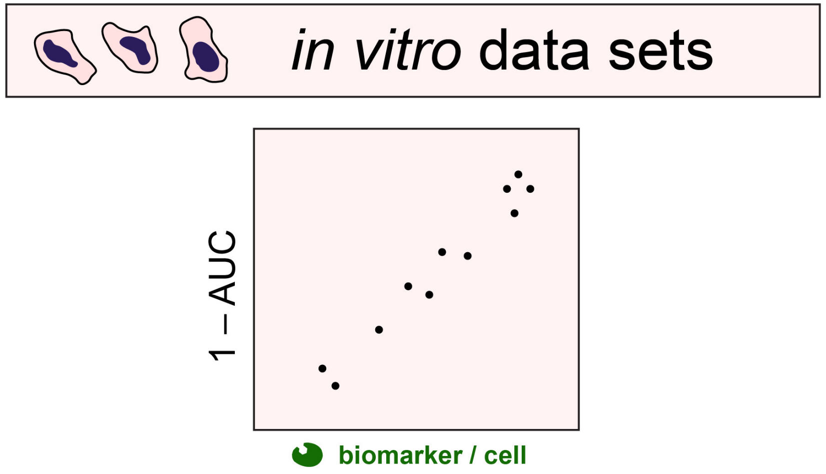


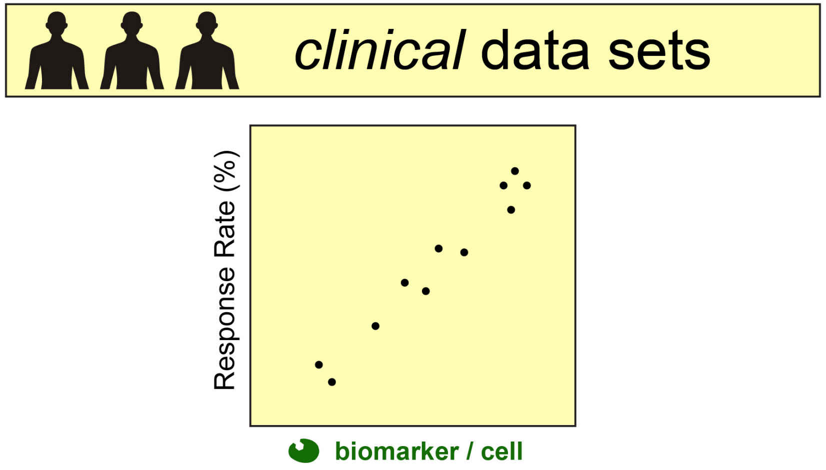
clinical data sets

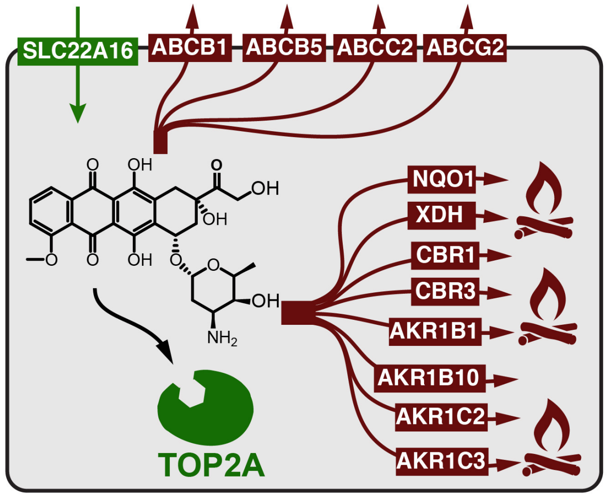


Annals of Oncology, **2016**, 27, 2004-2016

Cytotoxic chemotherapies: *1-drug / N-biomarkers*







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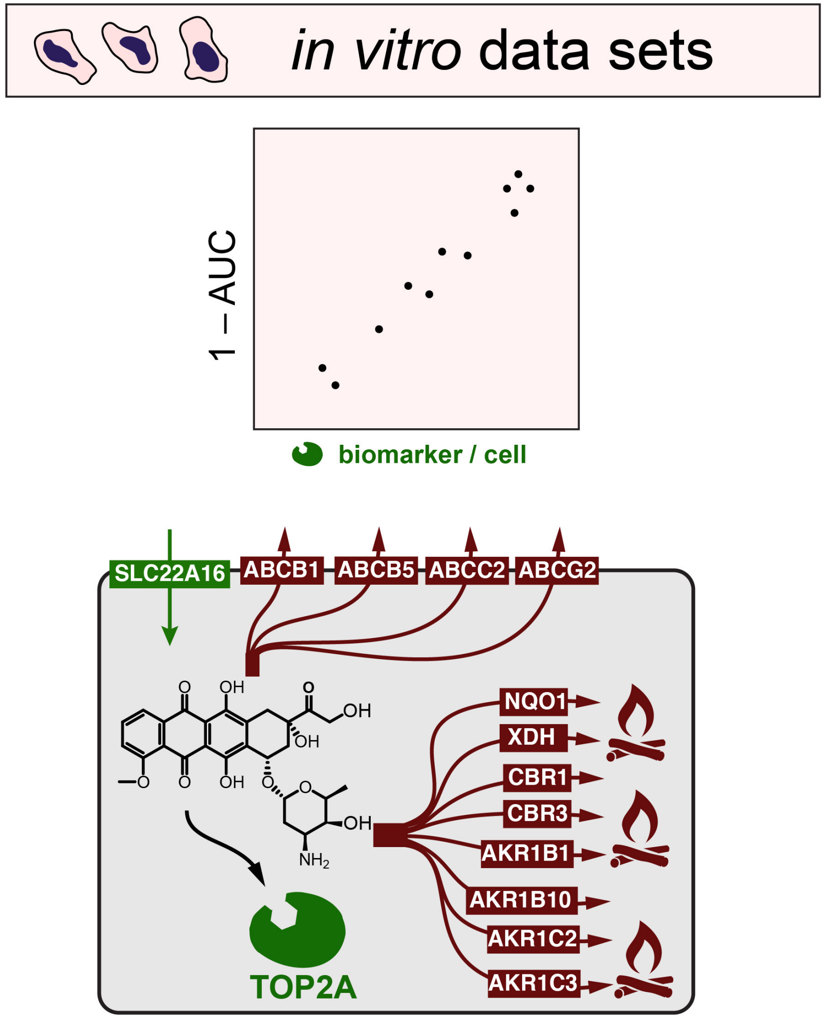

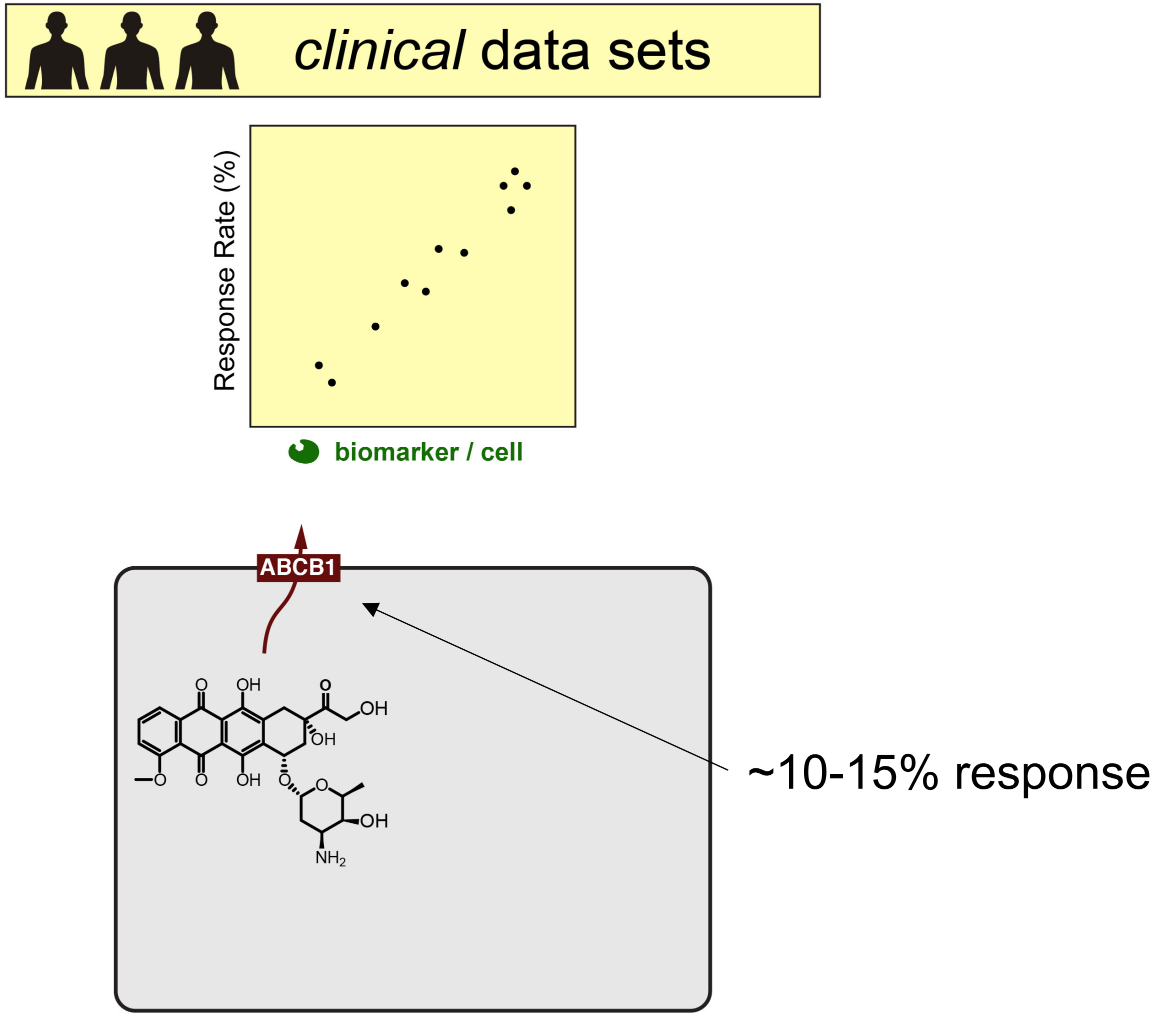

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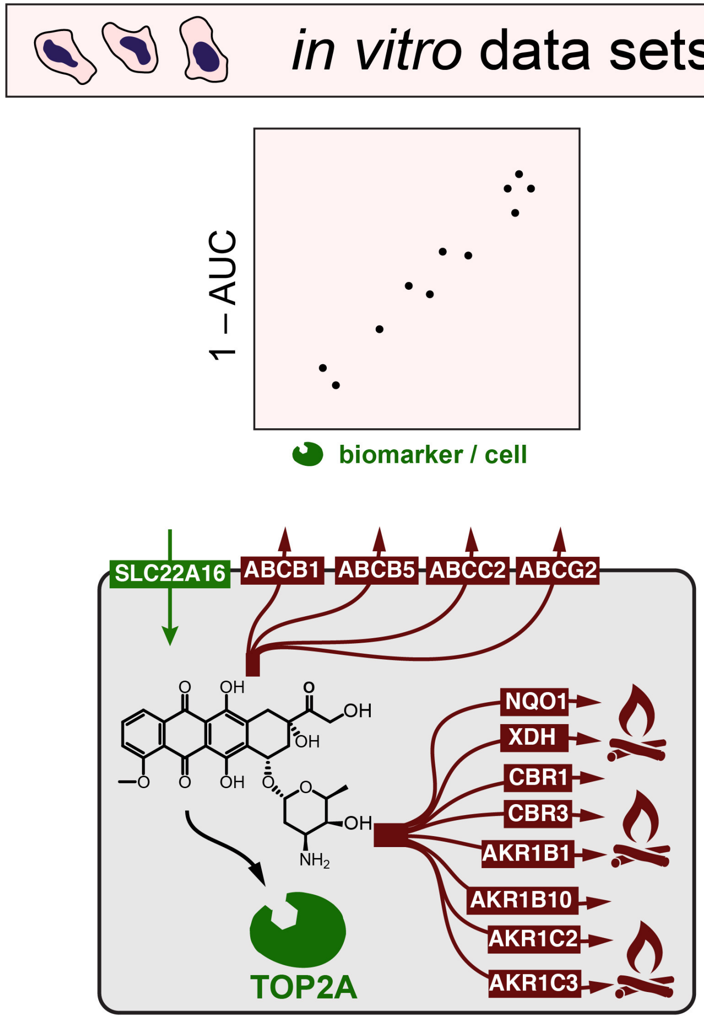
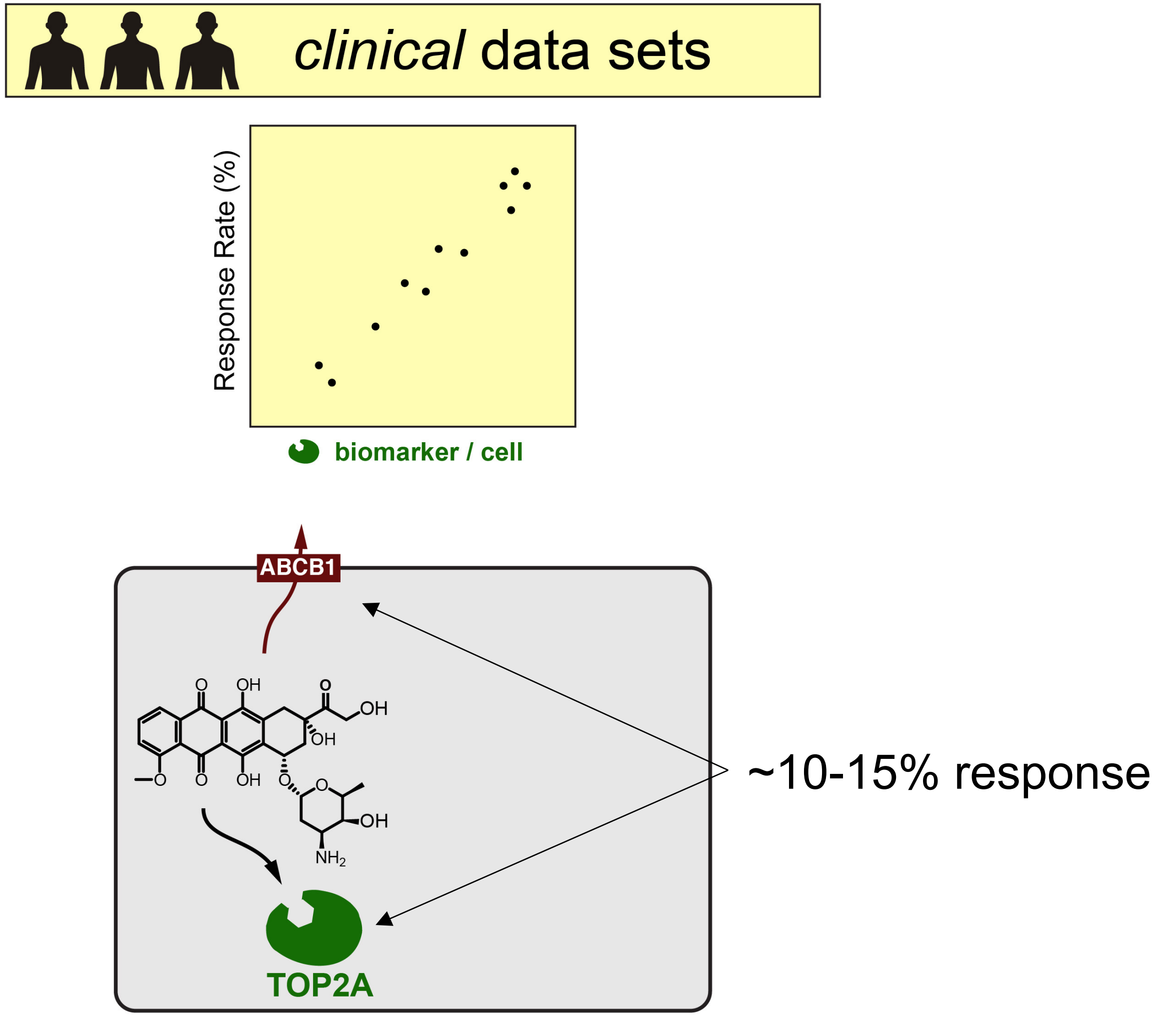
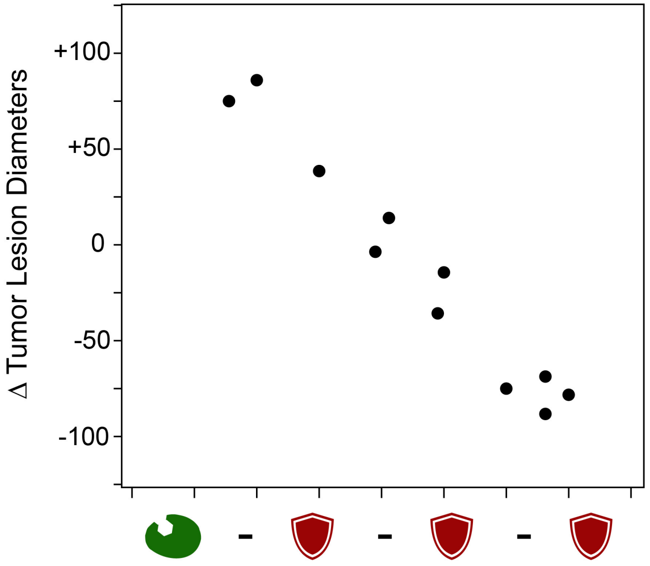
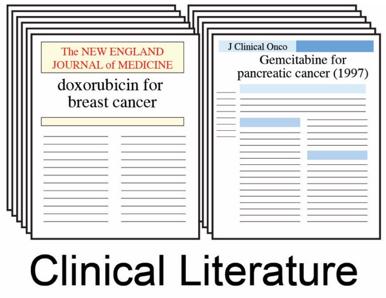




Annals of Oncology, **2016**, 27, 2004-2016

How do you combine N-biomarkers?





Bandord, C.H. **Comprehensive Chemical Kinetics.** p. 32-35

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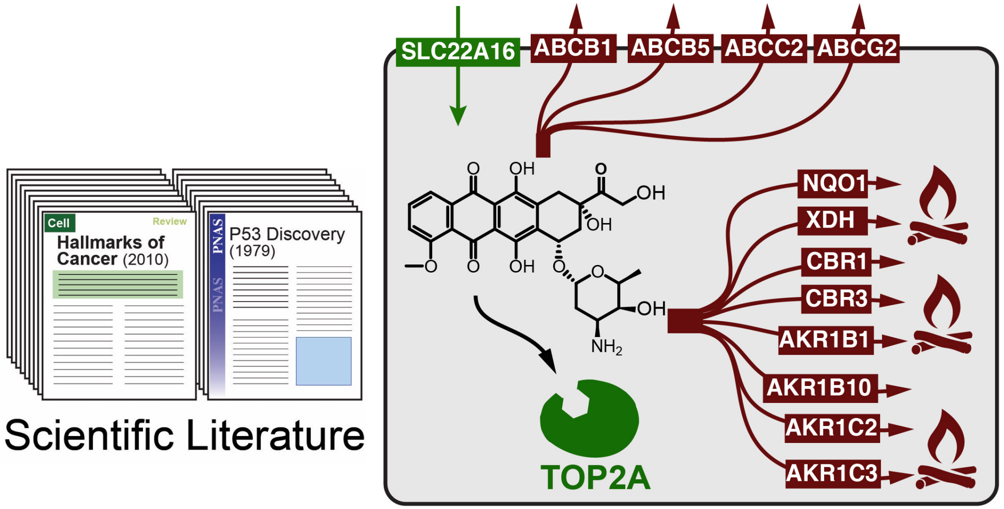

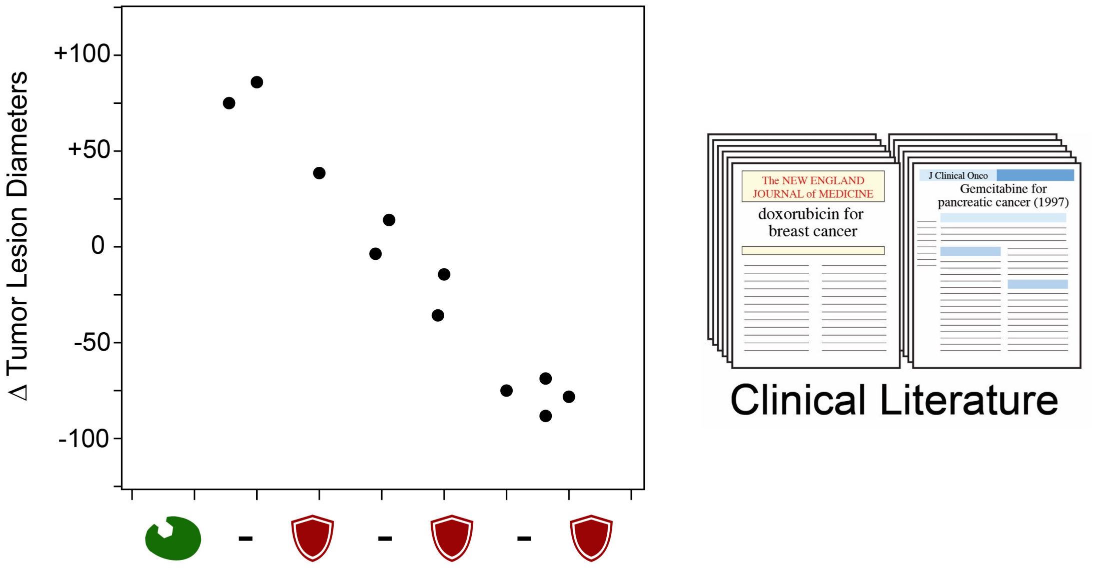

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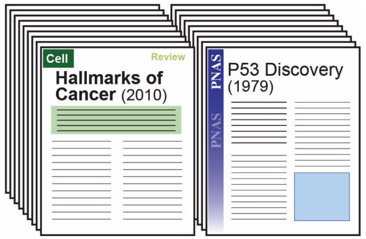
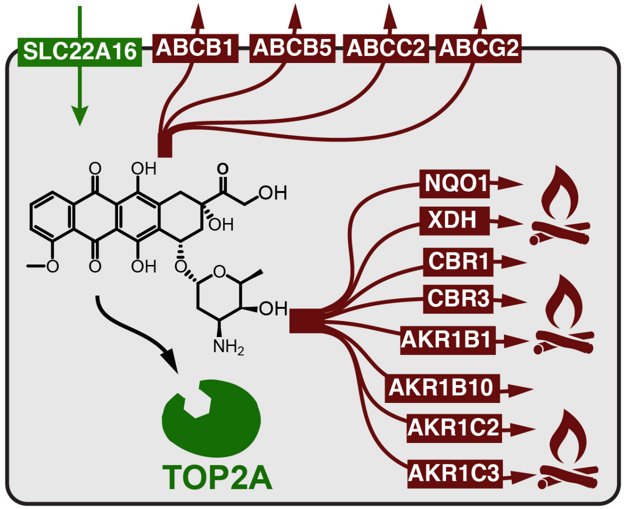
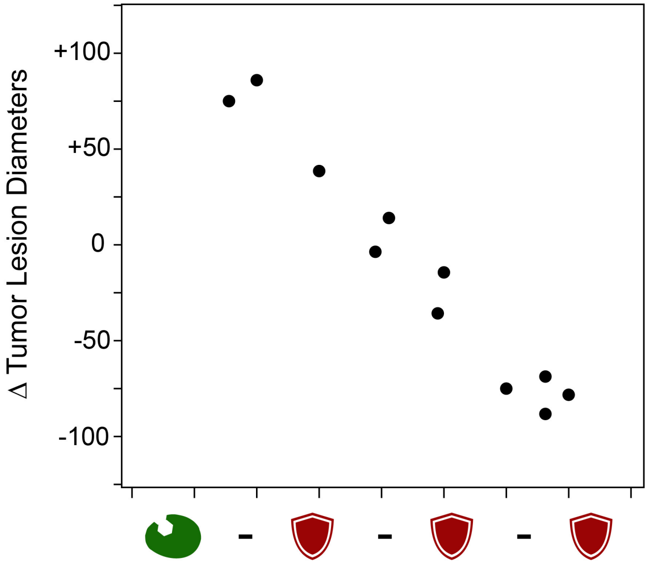
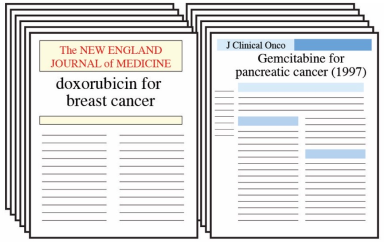


Scientific Literature







Clinical Literature

$$efflux = \sum_{i=1}^{N} k_{cat}[E]_t \frac{[drug]_{intra}}{[drug]_{intra} + K_m}$$

Segel, I. **Enzyme Kinetics**, Wiley, p 64
Bandord, C.H. **Comprehensive Chemical Kinetics.** p. 32-35

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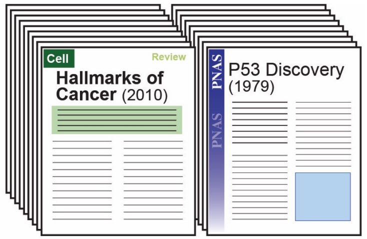

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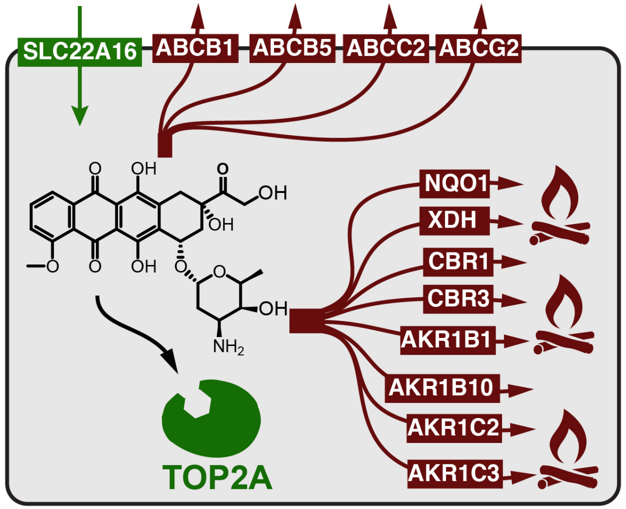

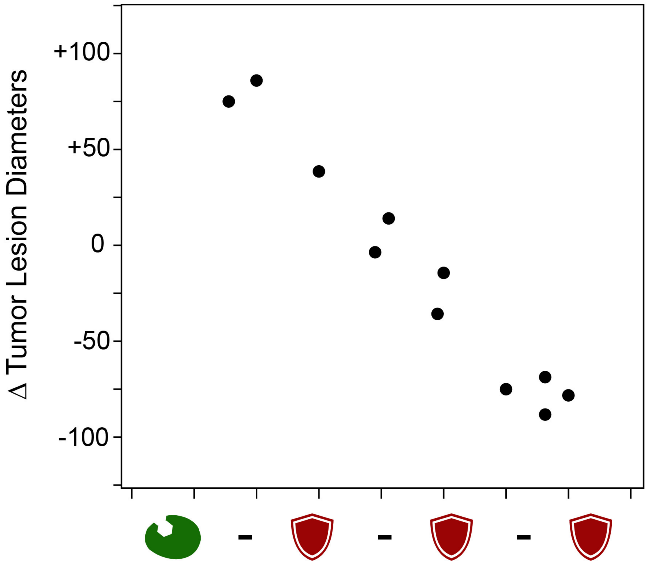

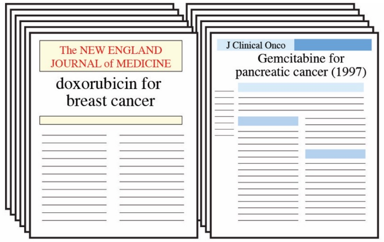

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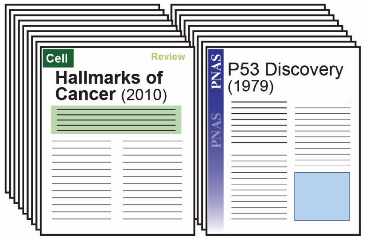

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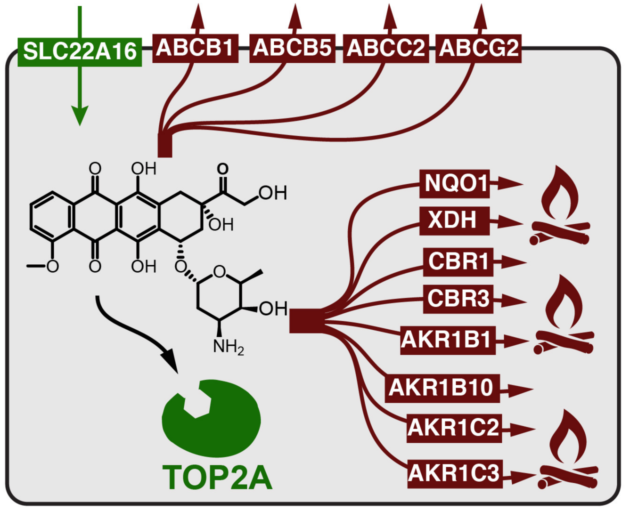

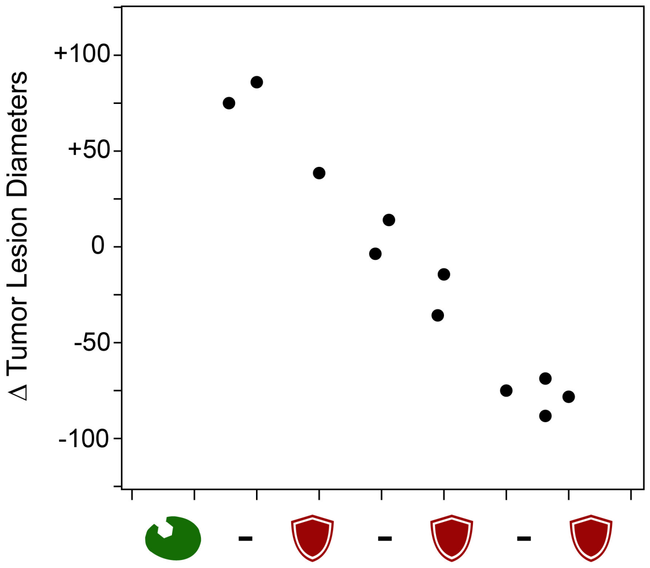

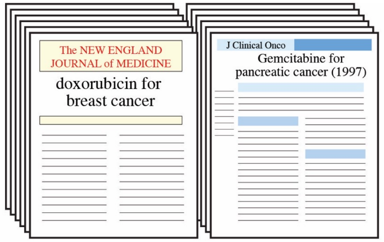

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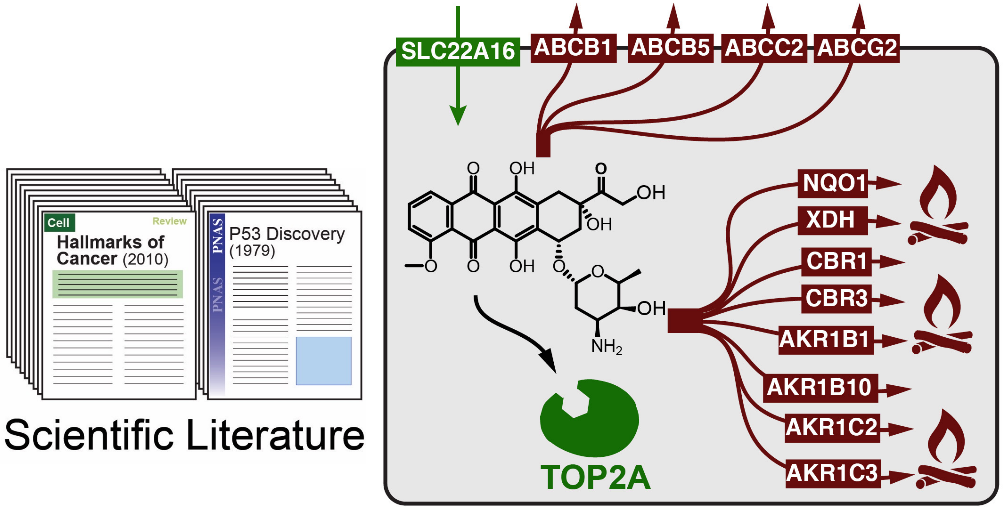

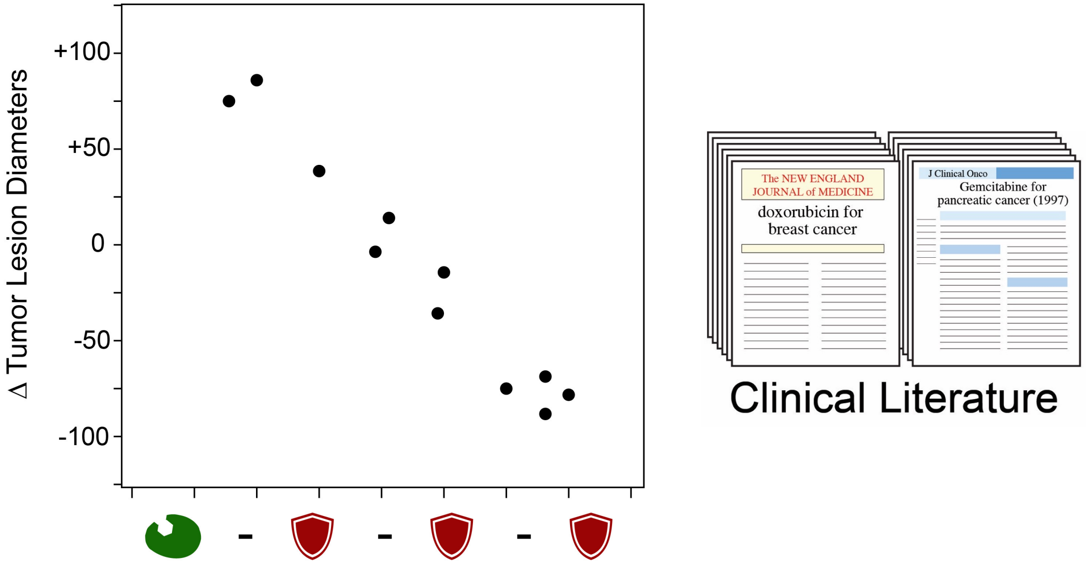

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$$k_{diff}[drug]_{extra} = k_{resist}[drug]_{intra}$$

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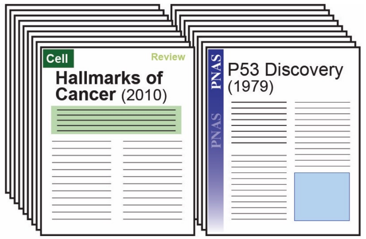

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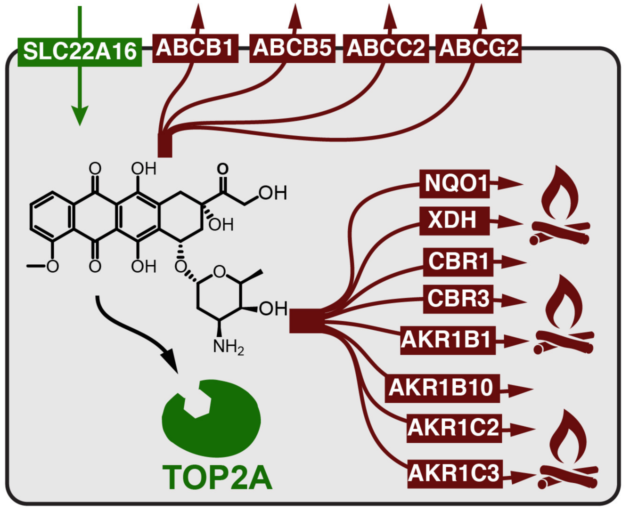

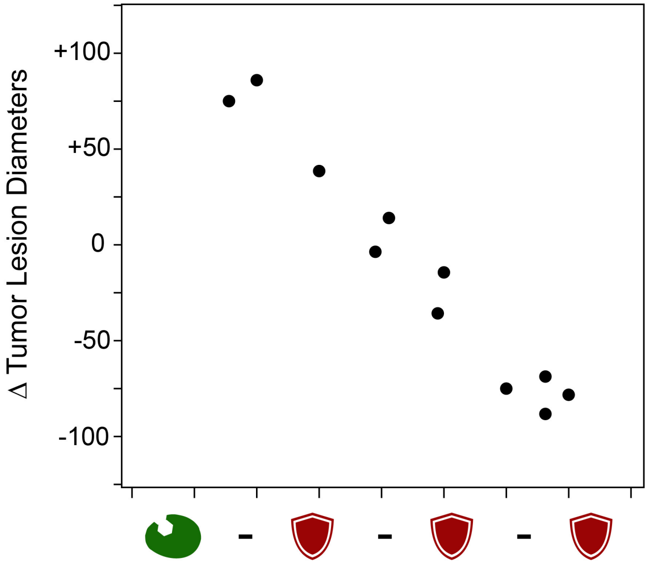

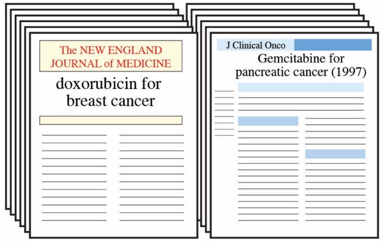

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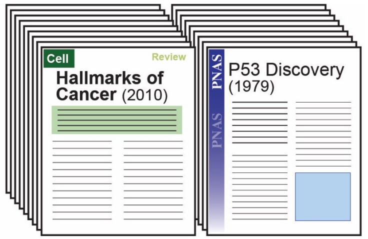

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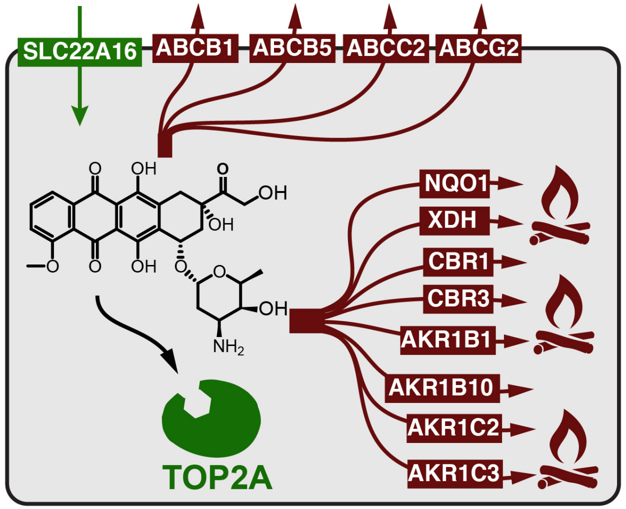

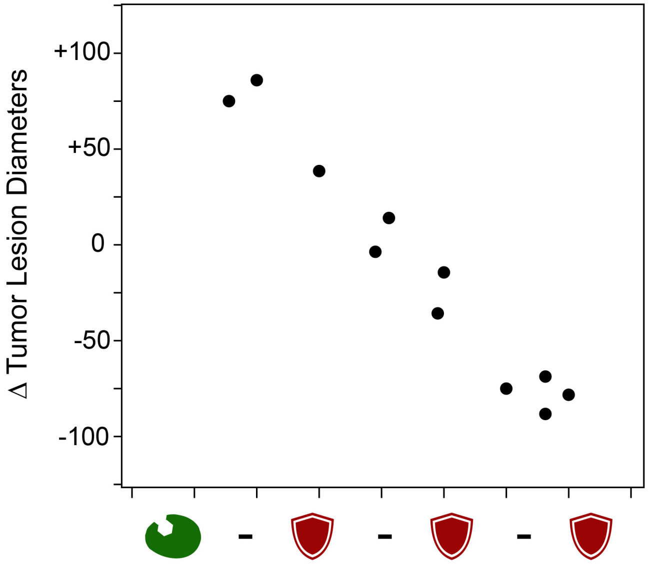

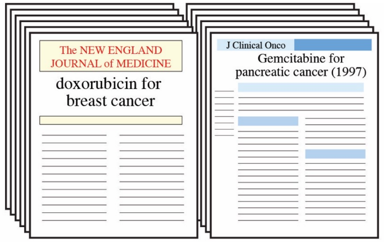

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$$\Delta IC_{50} = \frac{[drug]_{extra}}{[drug]_{intra}} = \frac{k_{resist}}{k_{diff}}$$

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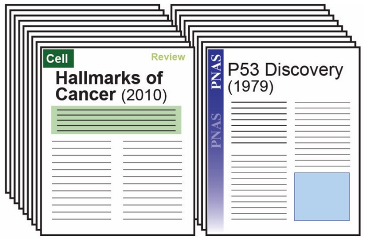

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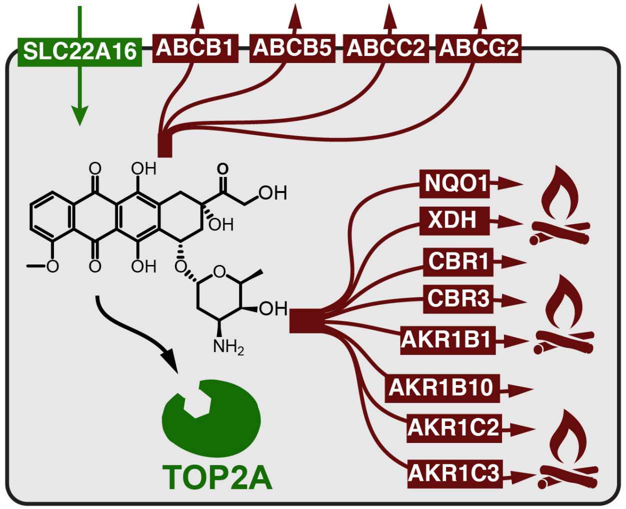
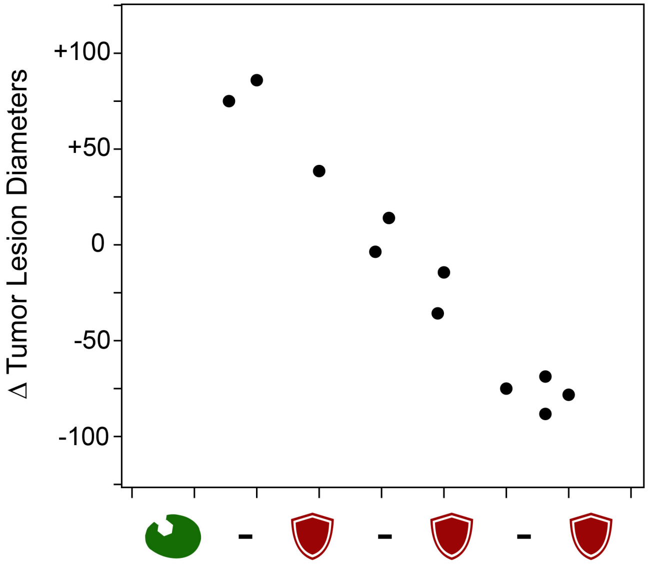
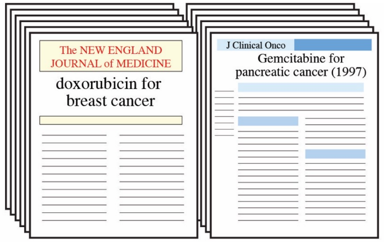




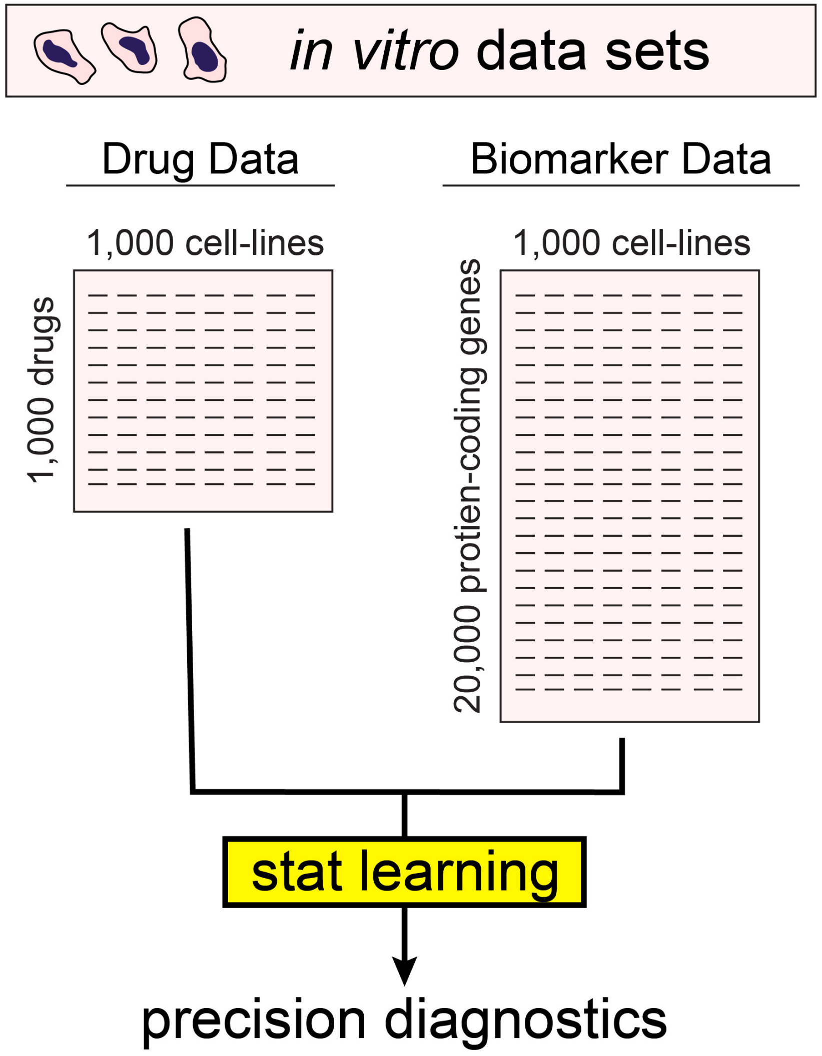


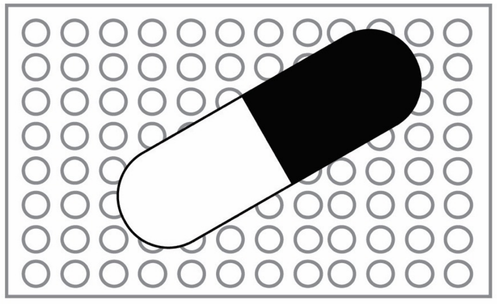
Clinical Literature

$$\Delta IC_{50} = \frac{k_{cat}/K_m}{k_{diff}} [ABCB1] + \frac{k_{cat}/K_m}{k_{diff}} [ABCG2] \ldots$$

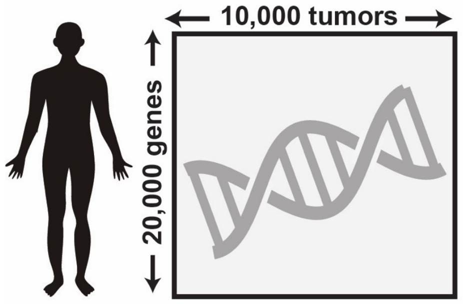
$$\Delta IC_{50} = \frac{k_{resist}}{k_{diff}} = \sum_{i=1}^{N} \frac{k_{cat}/K_m}{k_{diff}} [E]_t$$

Previous Pharmacogenomic Learning:





Screening Technology



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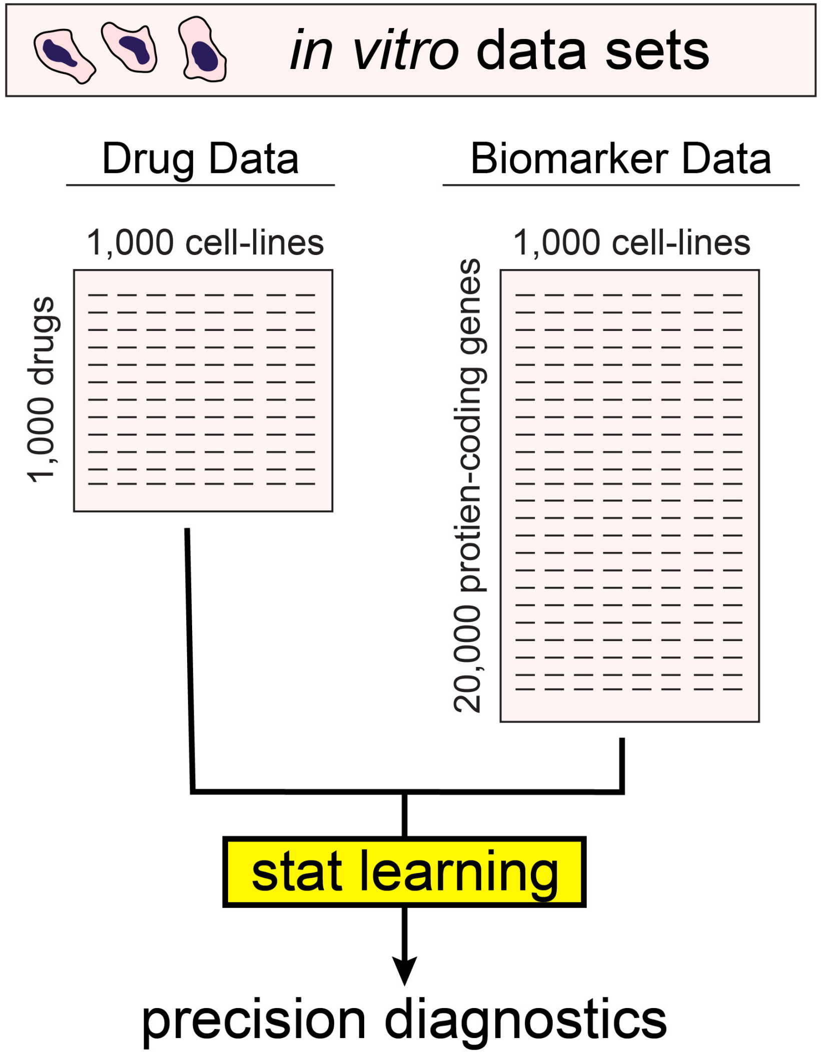

In a pan-cancer analysis, the most predictive data type was gene expression, closely followed by the tissue of origin of the cell lines. By comparison, genomic features performed poorly.

Cell, **2016**, 166, 740–754

Cell, **2016**, 166, 740
Cell, **2013**, 154, 1151

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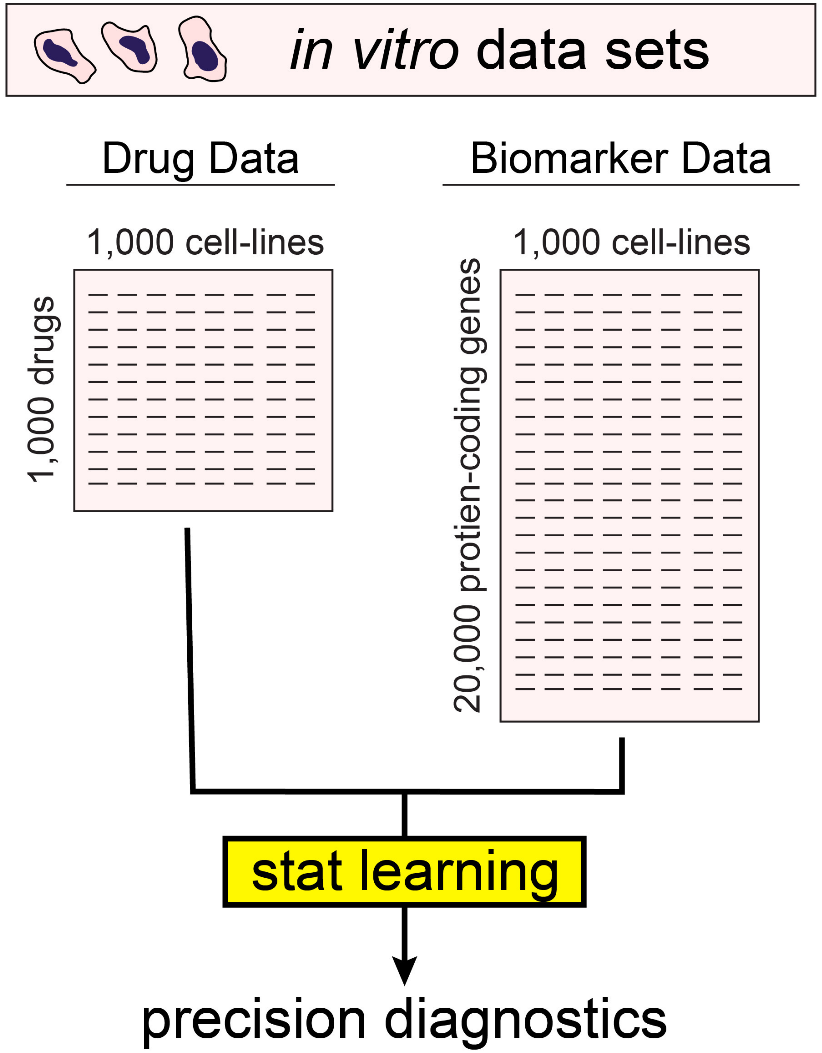

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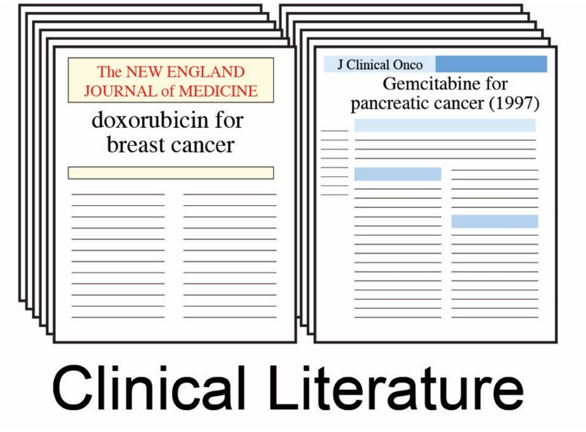

Drug Sensitivity(GDSC): *Cell*, **2016**, 166, 740
Drug Sensitivity(CTRP): *Cell*, **2013**, 154, 1151

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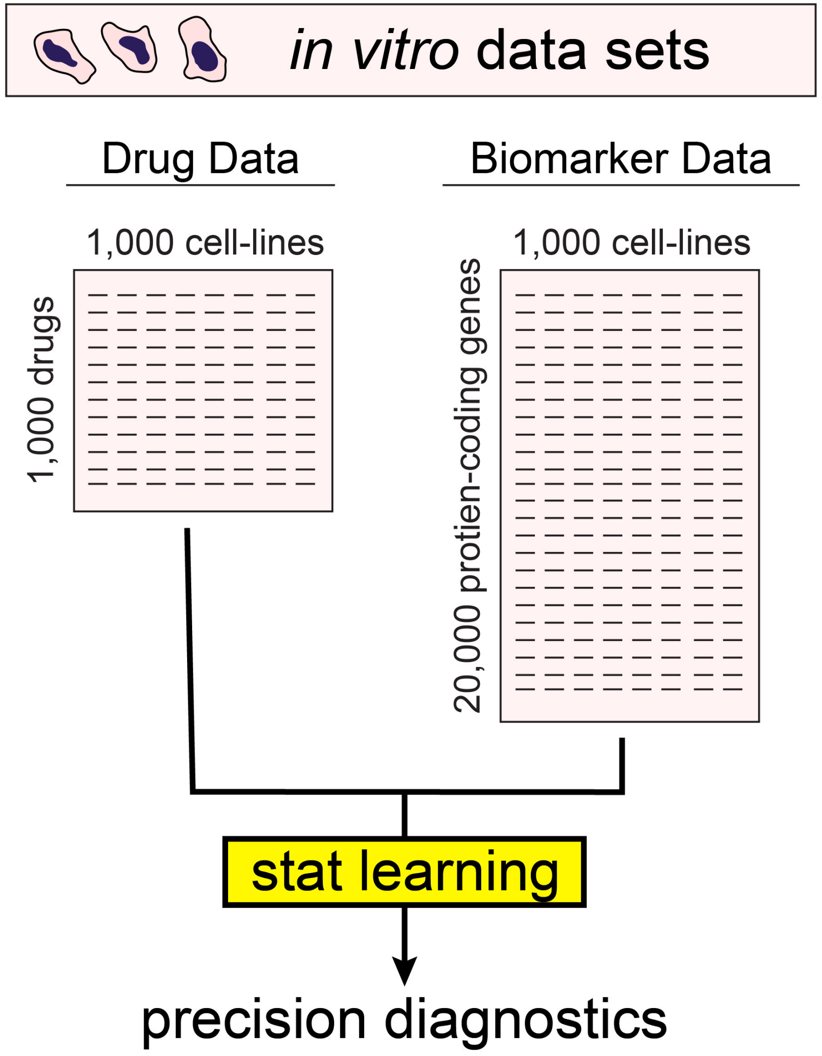

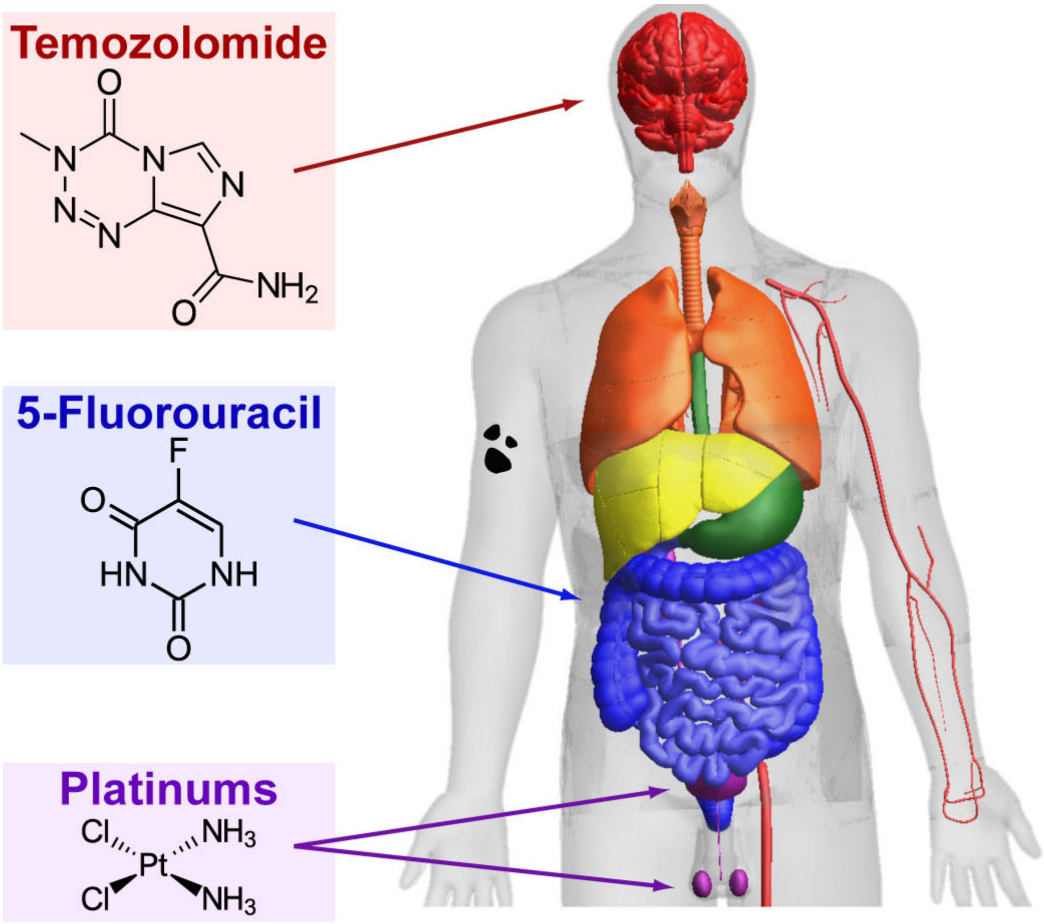

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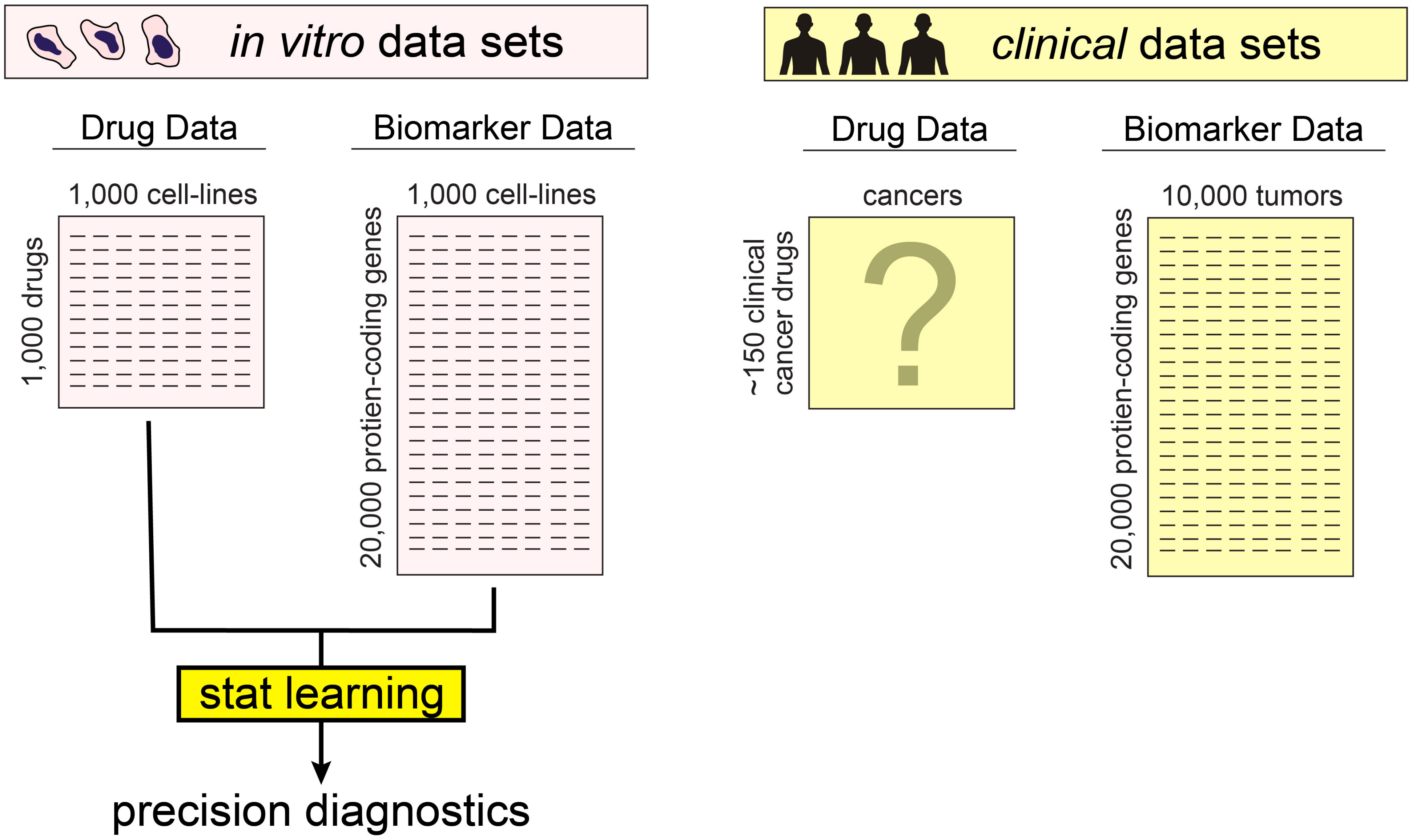
Data-gap within clinical literature:



Biomarker Expression(TCGA): *Nat. Genet.* **2013**, 45, 1113
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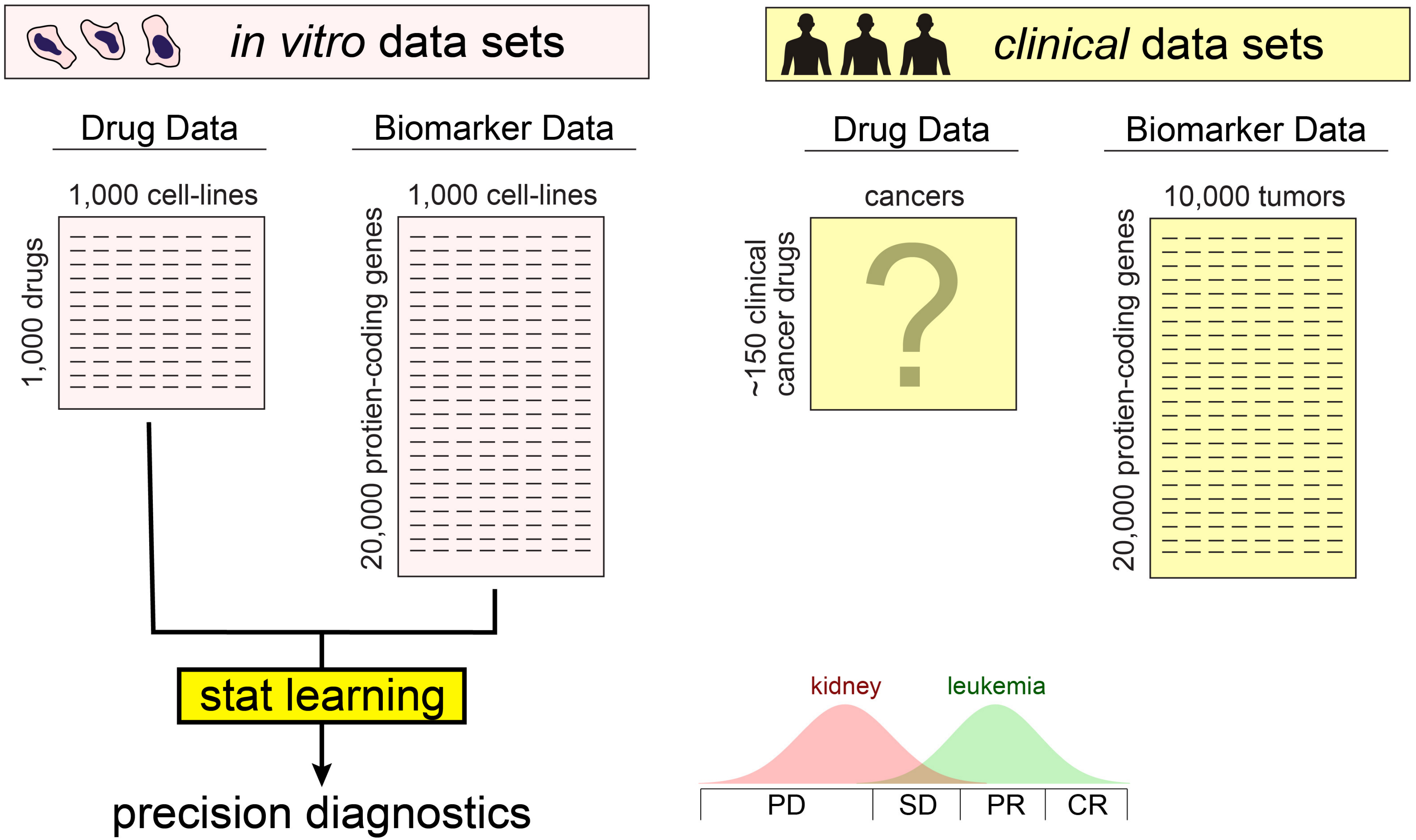

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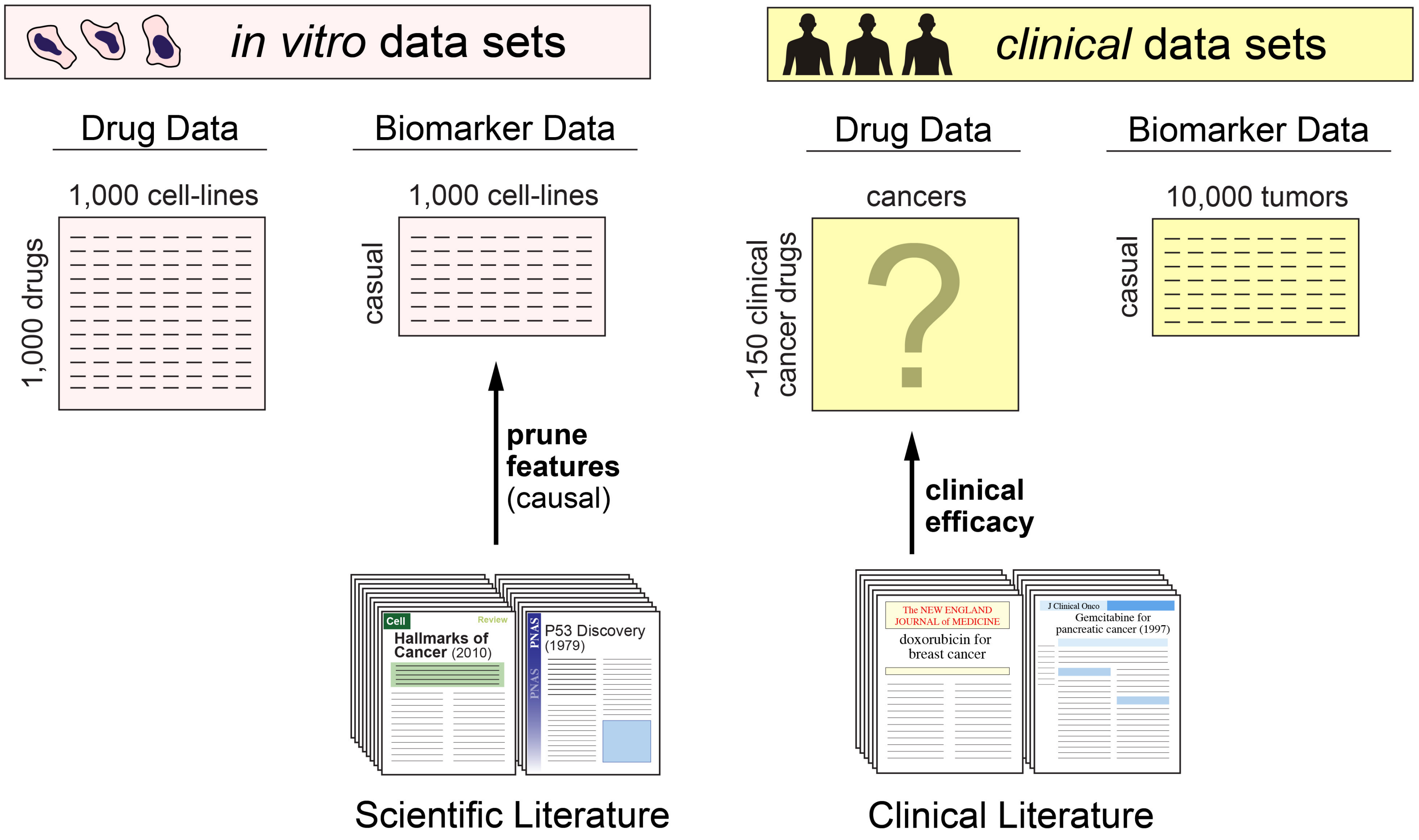
Douglass Lab Approach: *prune features & build database*

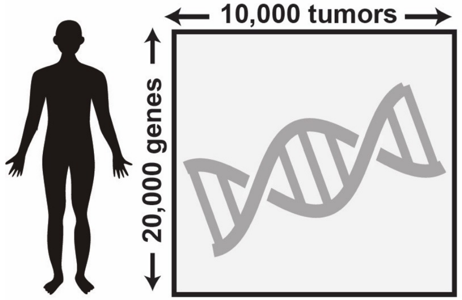


Clinical “Big Data” + Experiment = **Precision Medicine**

Genomic vs Experimental “Big Data:” *challenges and opportunities*

History & Current Status of Cancer Therapy: *1 drug / 1 target paradigm*

Reconciling Clinical & Laboratory “Big Data”: *1 drug / N-biomarkers*



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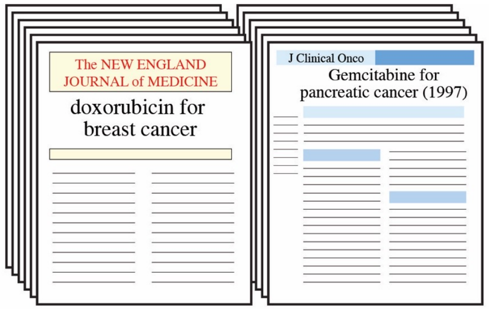
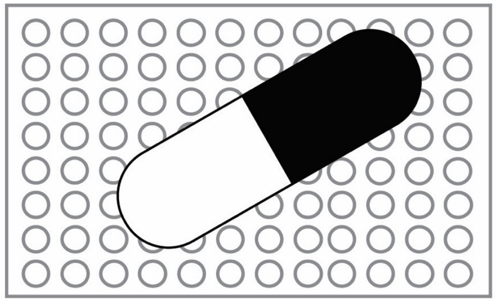


Clinical Literature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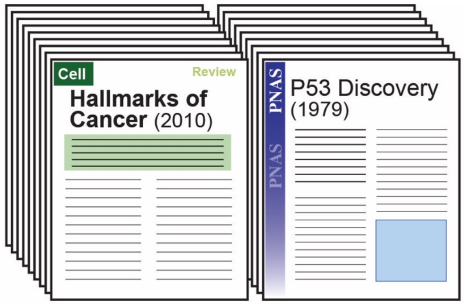
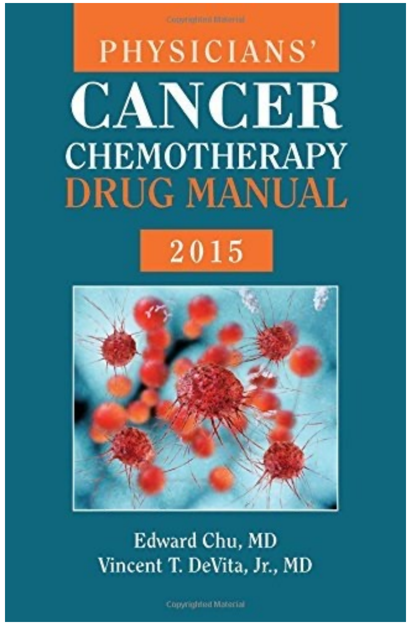
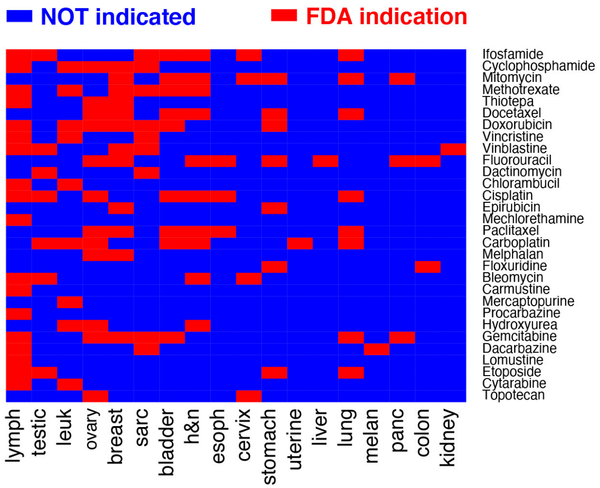


Scientific Literature

Douglass Lab Approach: *prune features & build database*

Define Top Clinical Chemotherapies





Chu, E.; et al. *Physicians' Cancer Chemotherapy Drug Manual 2015*, **2016**, Jones and Bartlett

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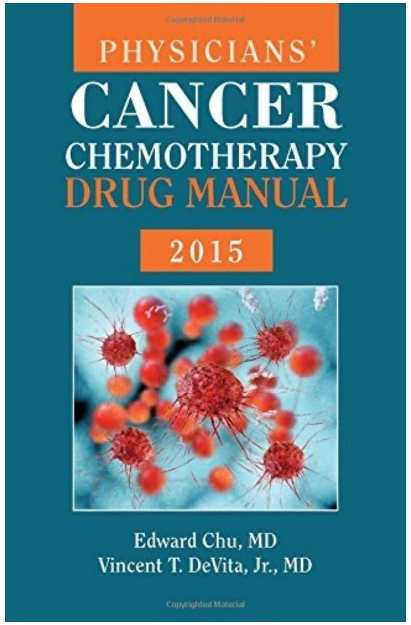
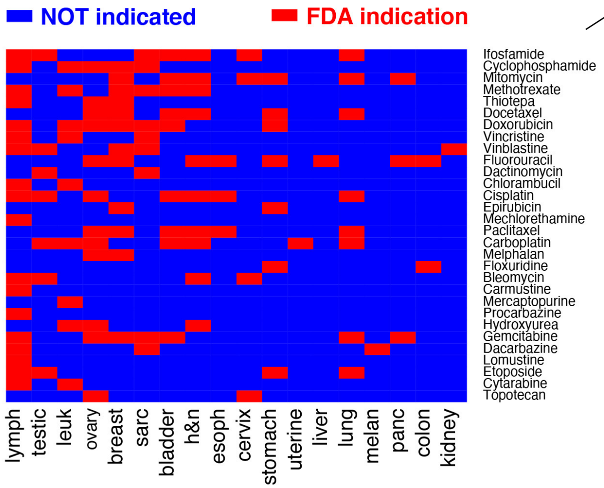
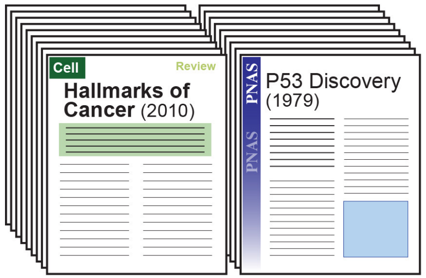
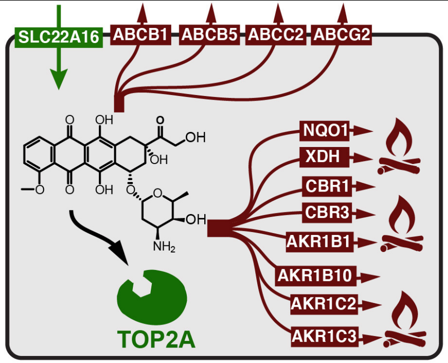






Scientific Literature

Causal Biomarker Lists



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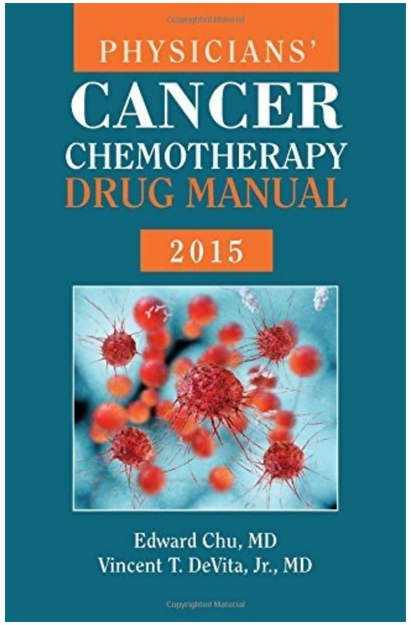
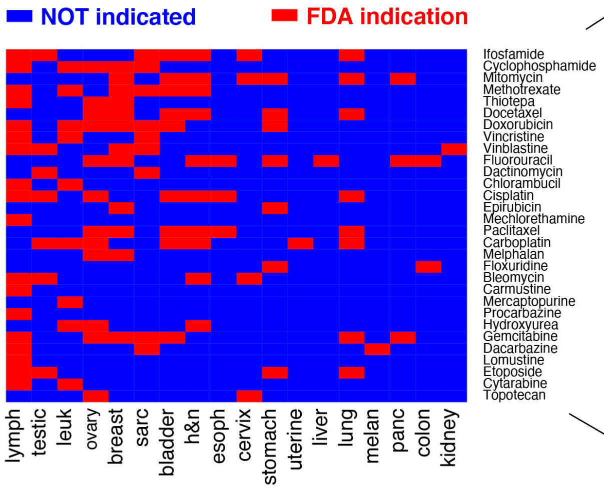
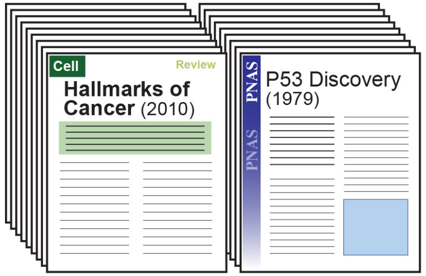
Douglass Lab Approach: *prune features & build database*

Define Top Clinical Chemotherapies

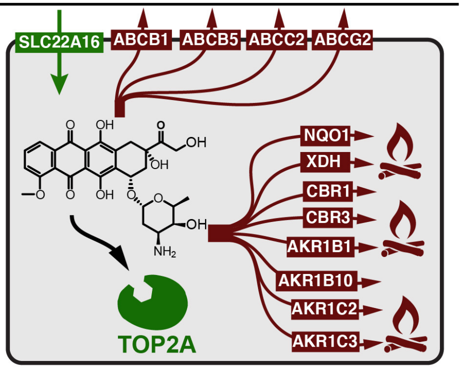


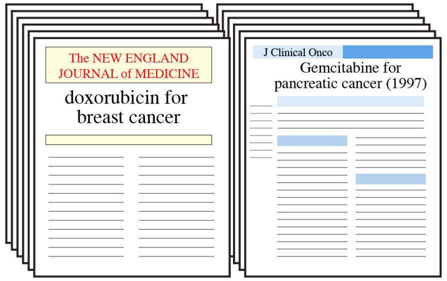




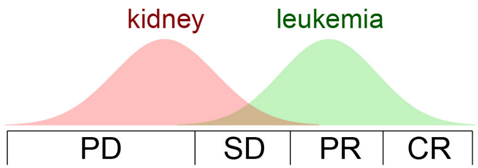
Scientific Literature

Causal Biomarker Lists





Clinical Literature

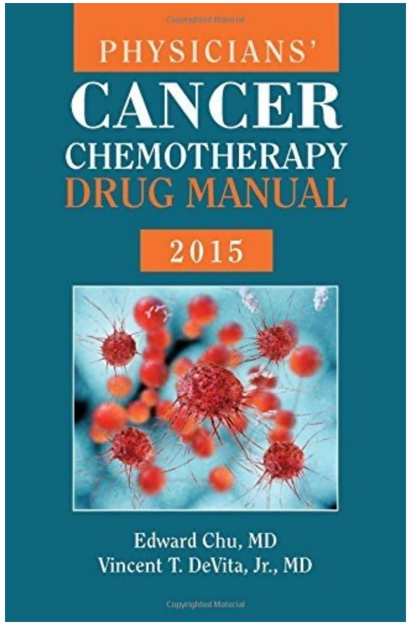


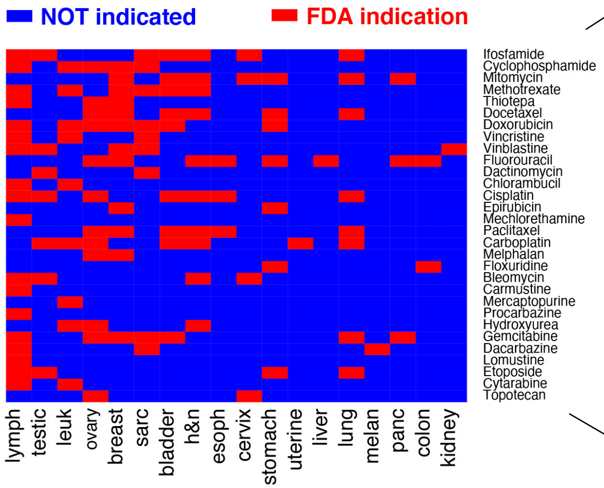
Pooled Clinical Trials

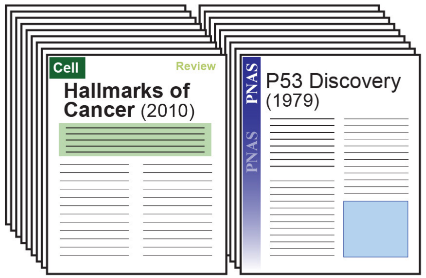
Chu, E.; et al. *Physicians' Cancer Chemotherapy Drug Manual 2015*, **2016**, Jones and Bartlett

Douglass Lab Approach: *build clinical database*

Define Top Clinical Chemotherapies

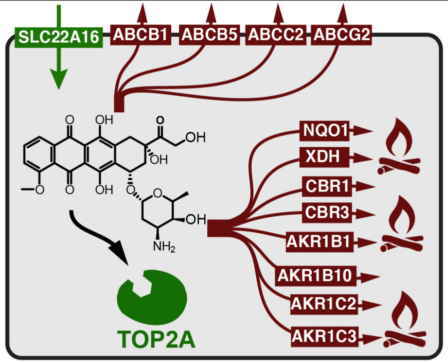


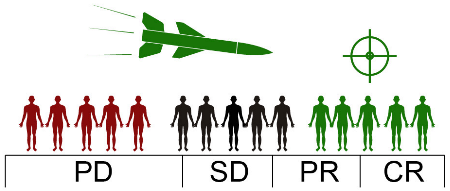


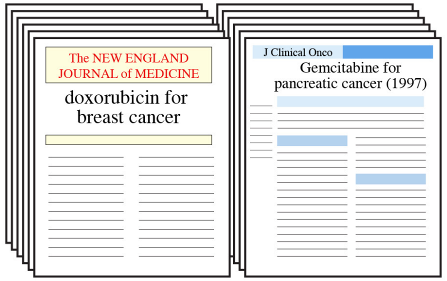


Scientific Literature

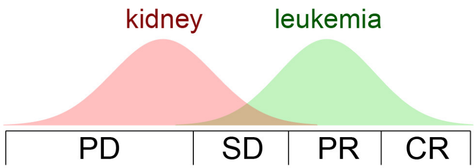
Causal Biomarker Lists







Clinical Literature

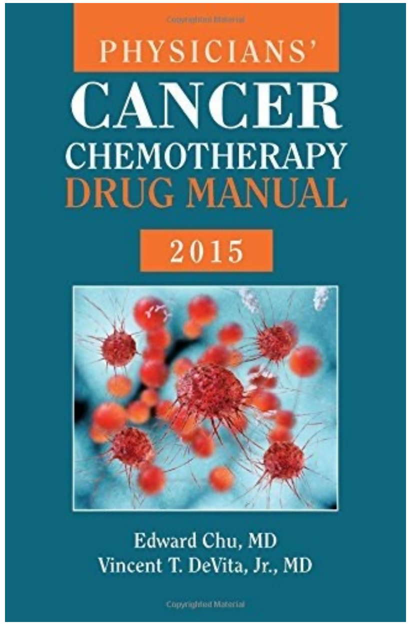


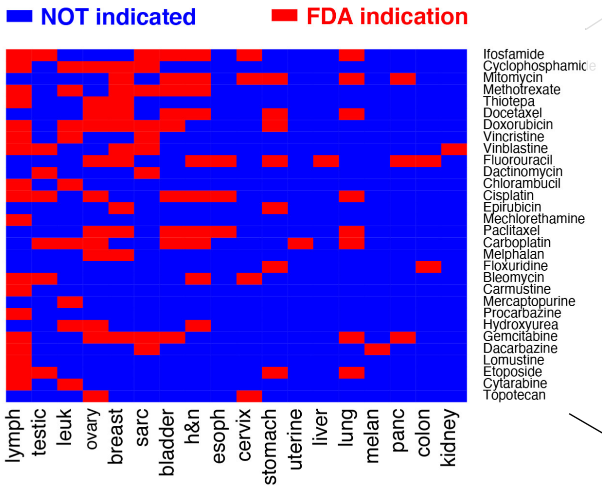
Pooled Clinical Trials

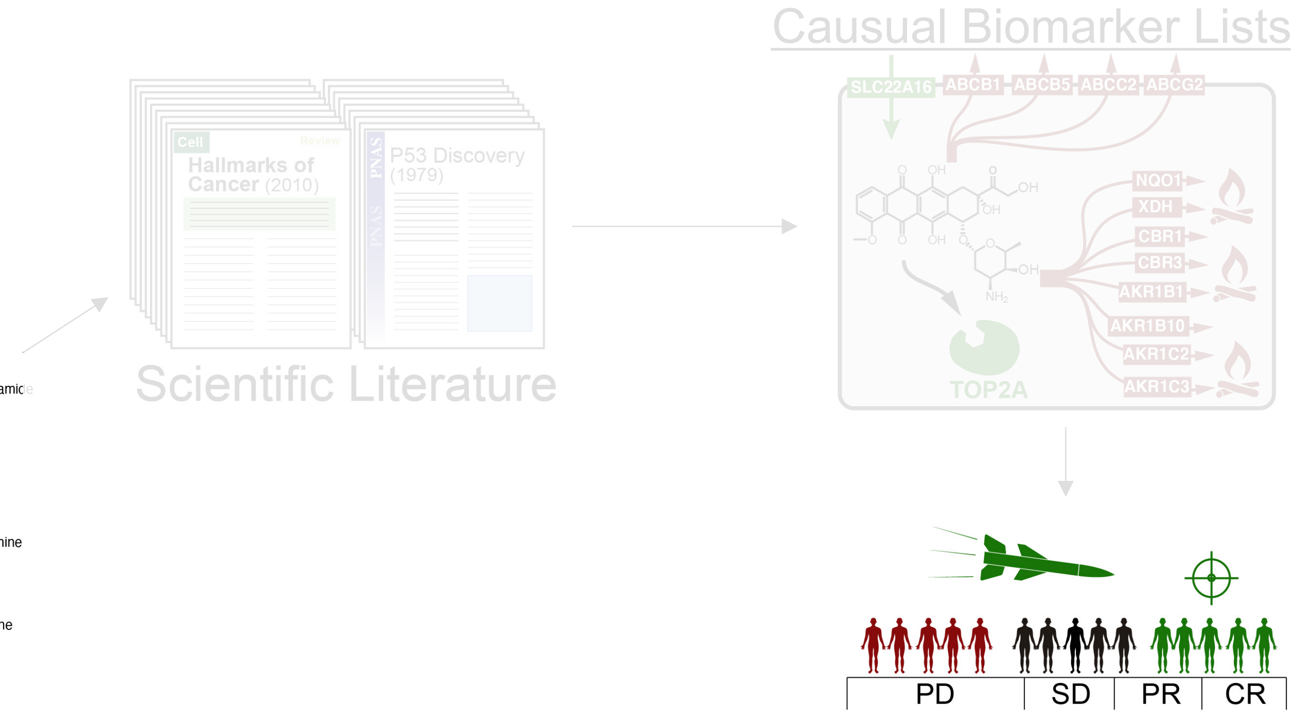
Chu, E.; et al. *Physicians' Cancer Chemotherapy Drug Manual 2015*, **2016**, Jones and Bartlett

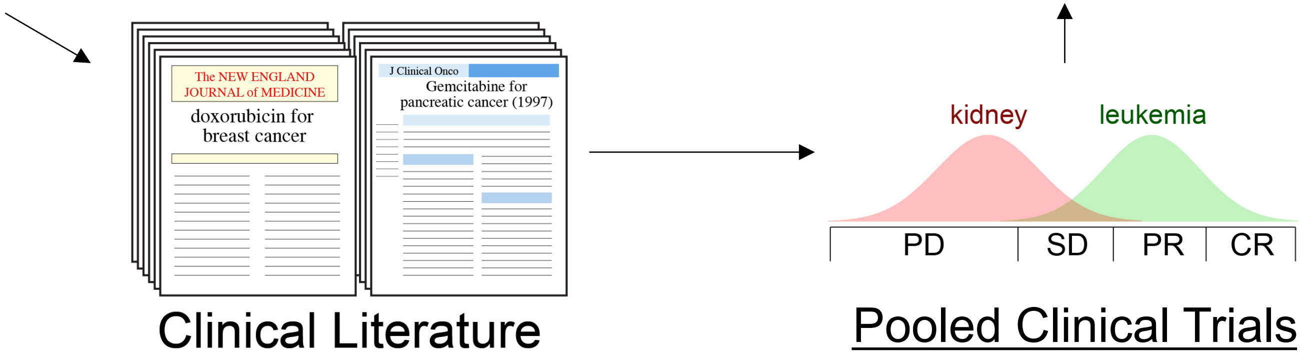
Douglass Lab Approach: *build clinical database*

Define Top Clinical Chemotherapies







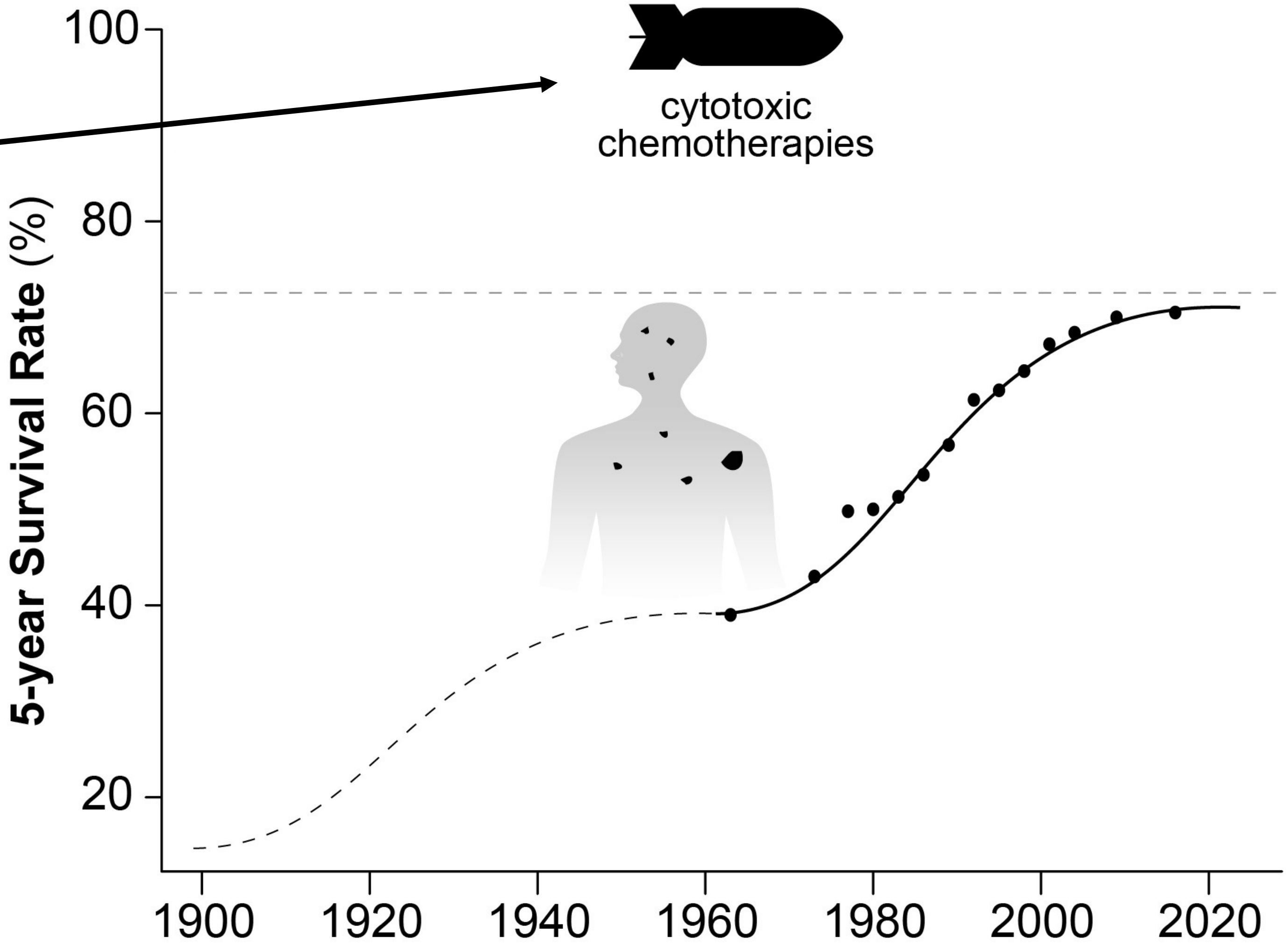


Pooled Clinical Trials

Chu, E.; et al. *Physicians' Cancer Chemotherapy Drug Manual 2015*, **2016**, Jones and Bartlett

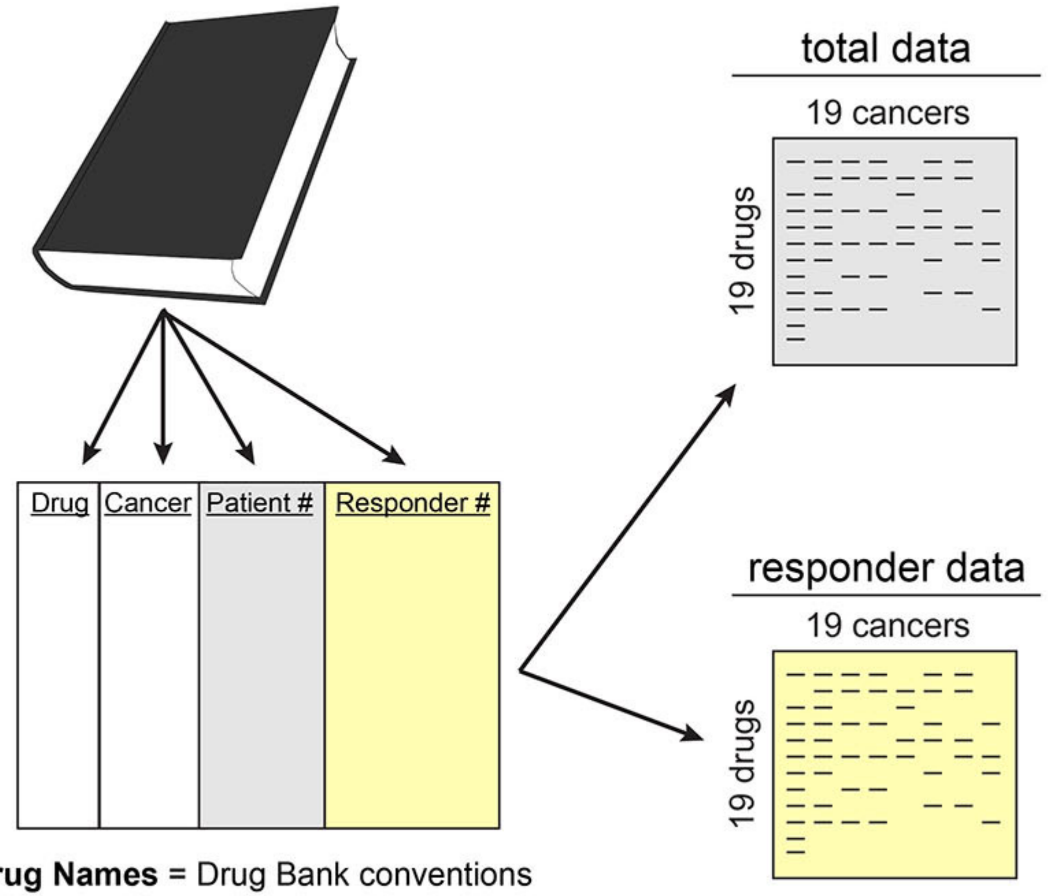
Douglass Lab Approach: *build clinical database*

NCI Clinical Trial Database (1970)
786 clinical trials
19,958 evaluable patients



Livingston & Carter, *Single-Agents in Cancer Chemotherapy*, **1970**, National Cancer Institute

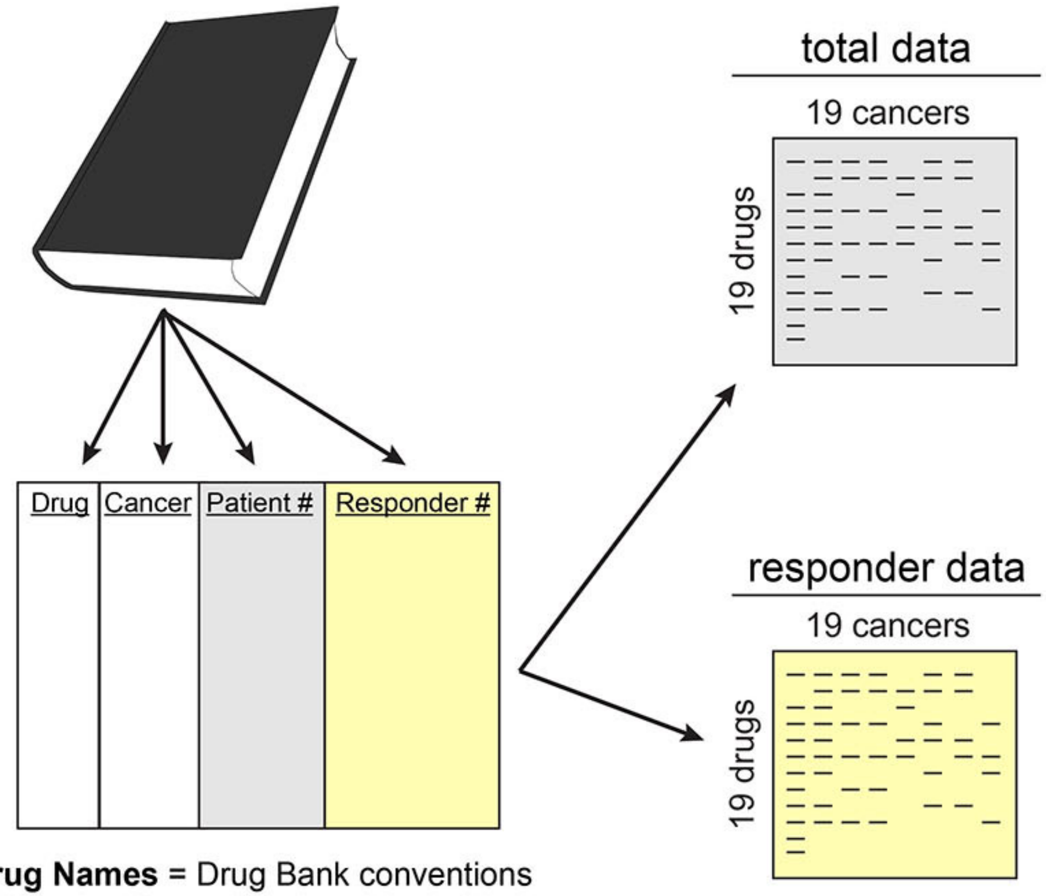
Douglass Lab Approach: *build clinical database*



Drug Names = Drug Bank conventions
Cancer Names = TCGA abbreviations
Patient # = total evaluatable patients
Responder # = WHO definitions

Livingston & Carter, *Single-Agents in Cancer Chemotherapy*, **1970**, National Cancer Institute

Douglass Lab Approach: *build clinical database*



Drug Names = Drug Bank conventions
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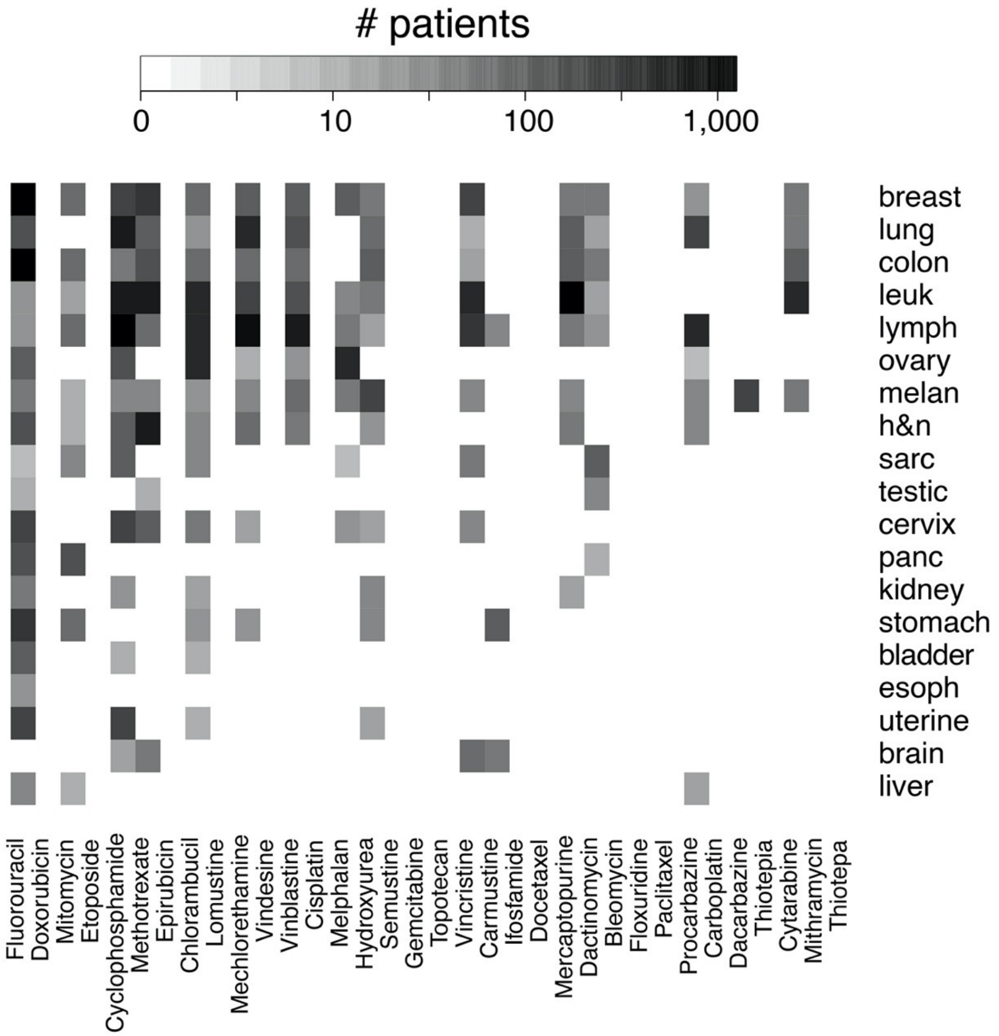
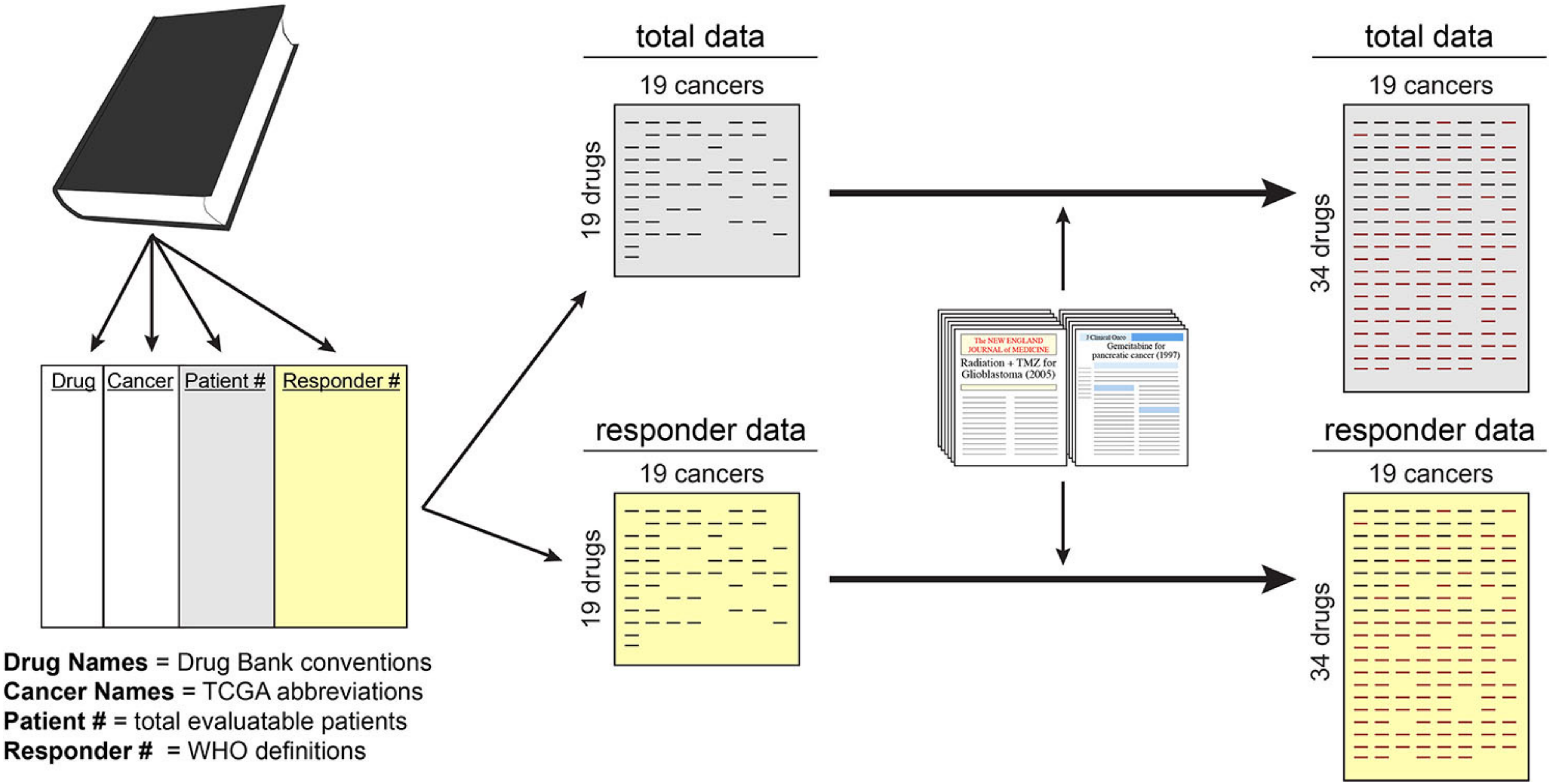


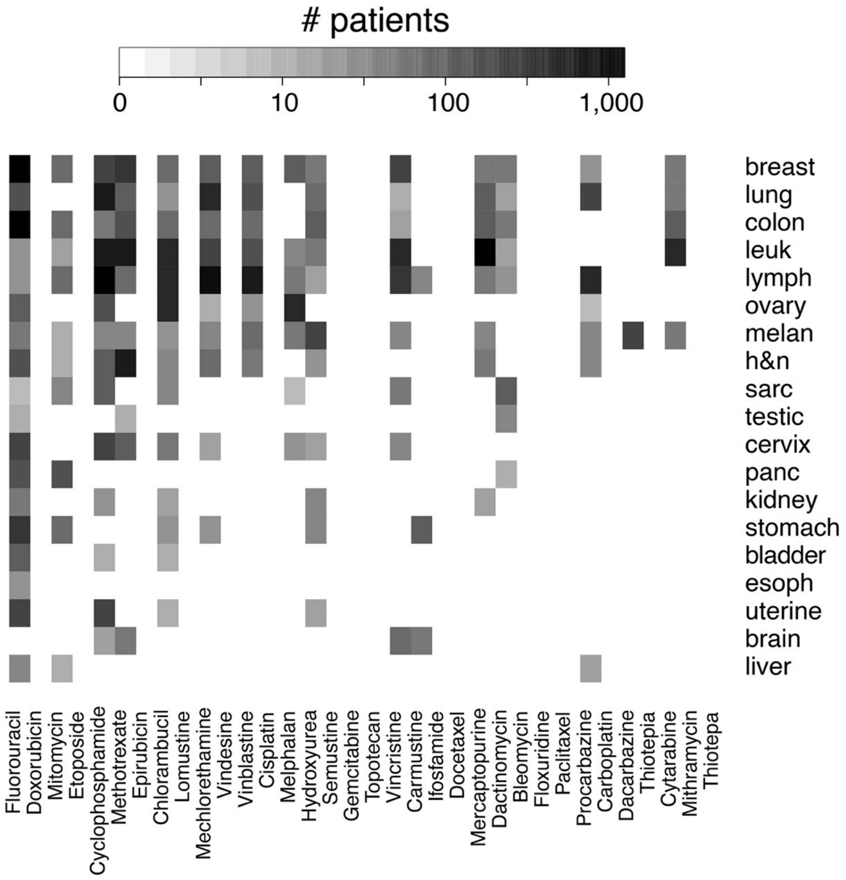
Livingston & Carter, *Single-Agents in Cancer Chemotherapy*, **1970**, National Cancer Institute

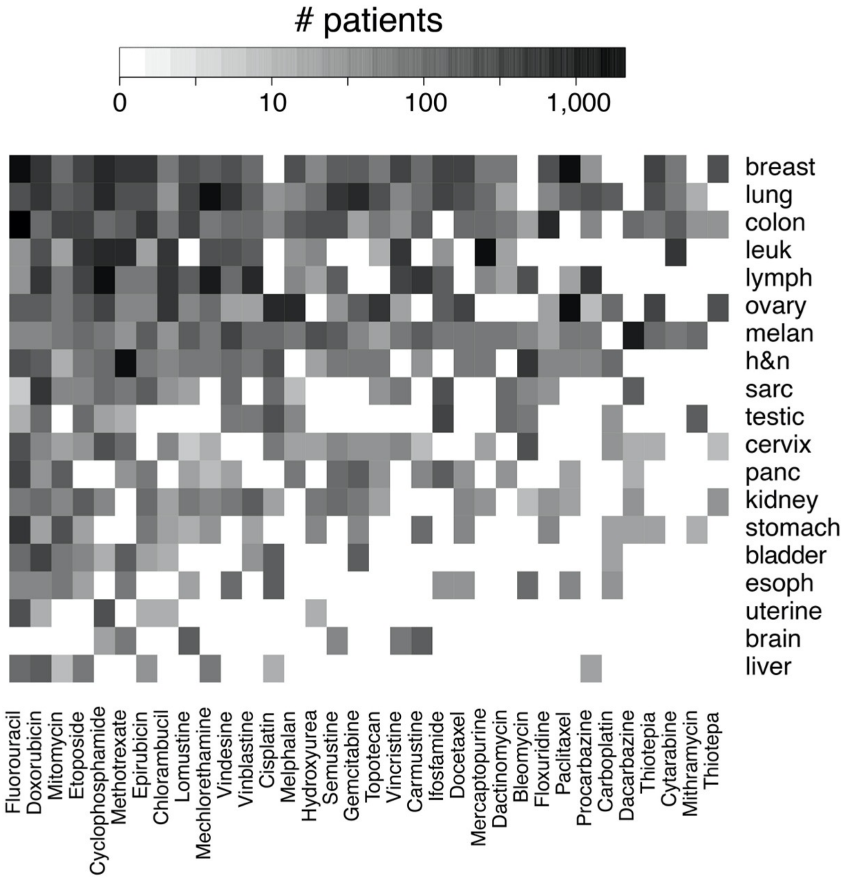
Douglass Lab Approach: *build clinical database*



Livingston & Carter, *Single-Agents in Cancer Chemotherapy*, **1970**, National Cancer Institute

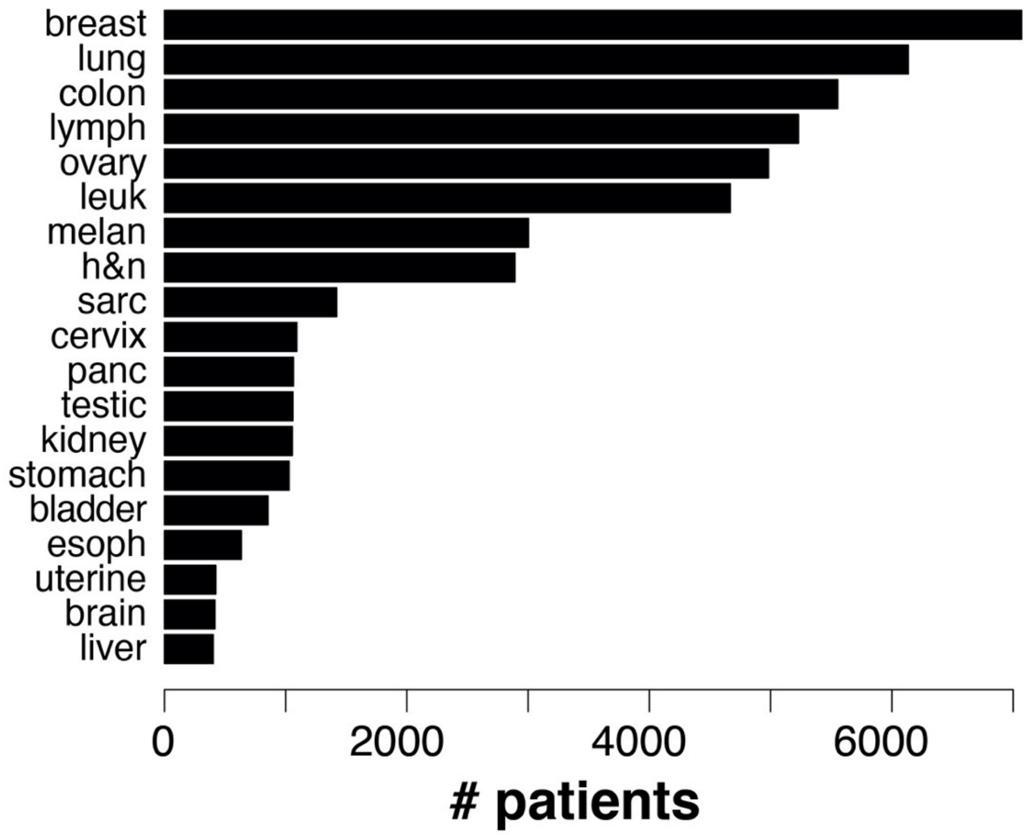
Cancer-Type bias in clinical data:

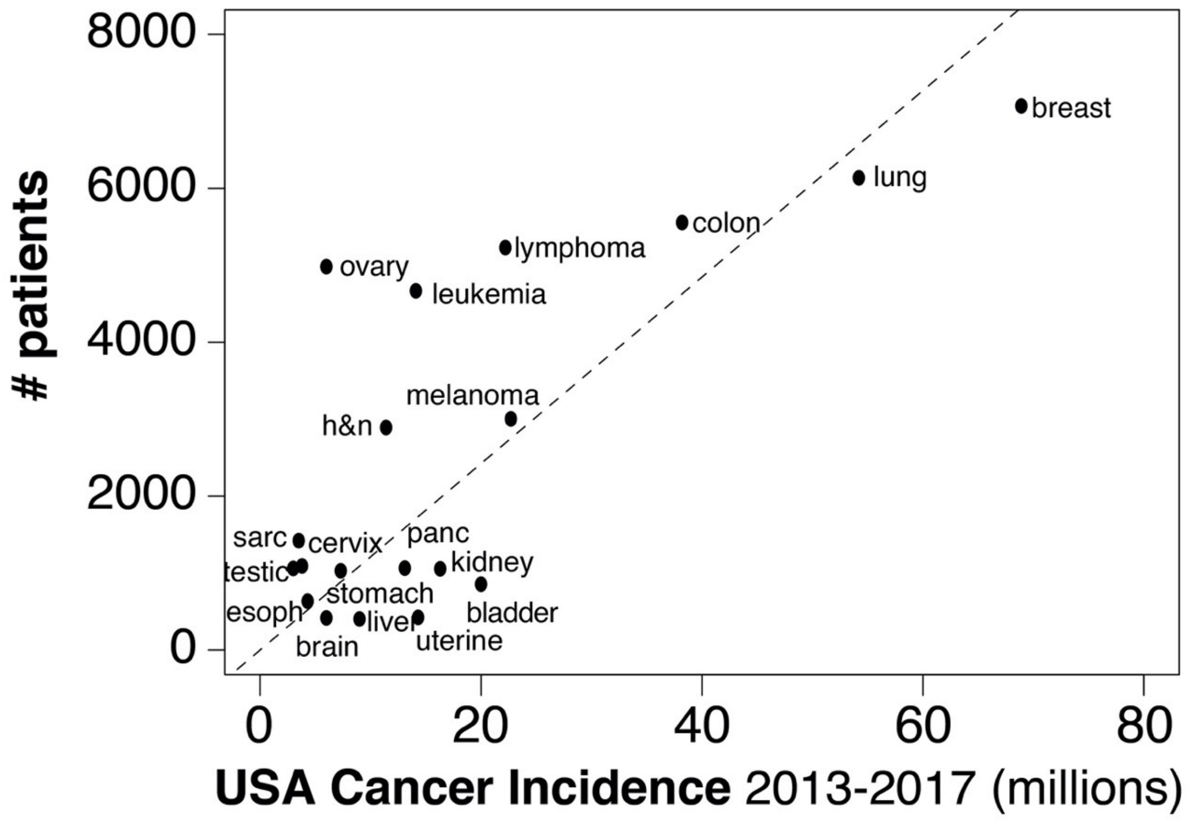




Livingston & Carter, *Single-Agents in Cancer Chemotherapy*, **1970**, National Cancer Institute

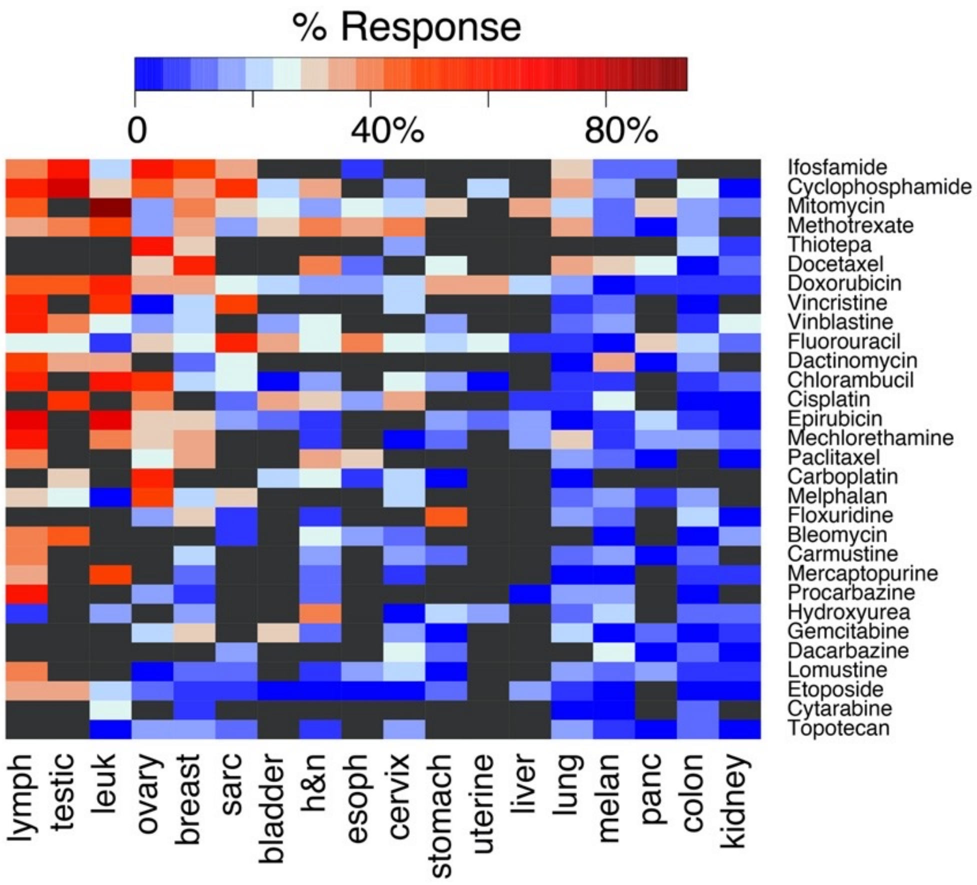
Cancer-Type bias in clinical data: *cancer incidence*

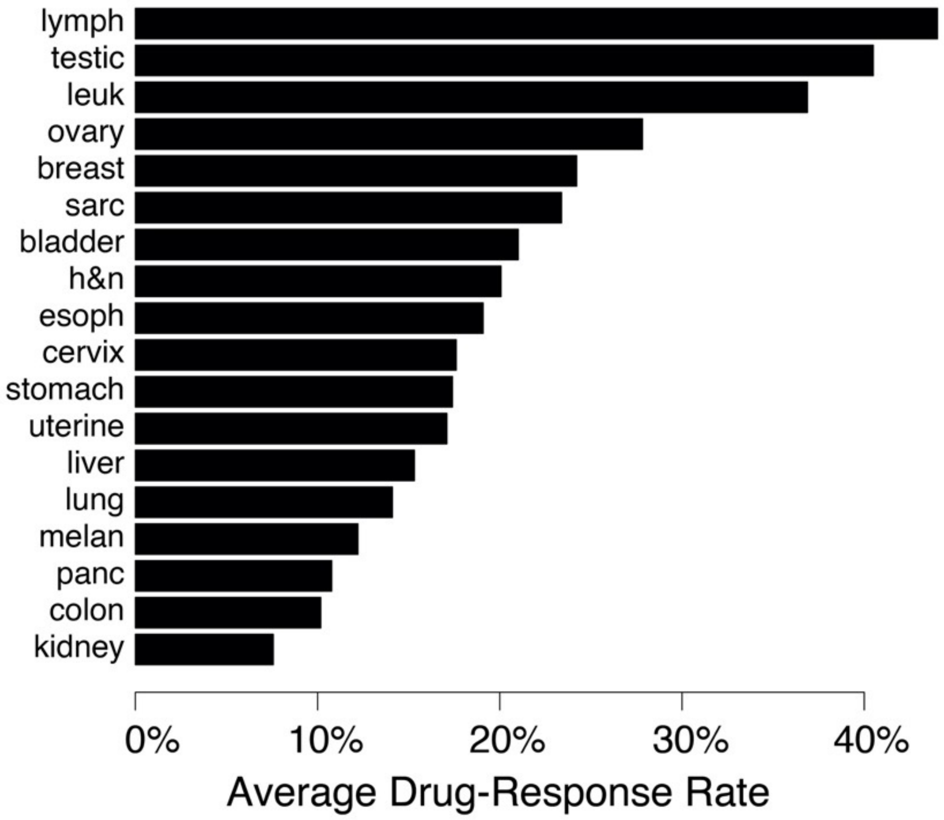




SEER Cancer Statistics Review, **1975-2017**, National Cancer Institute

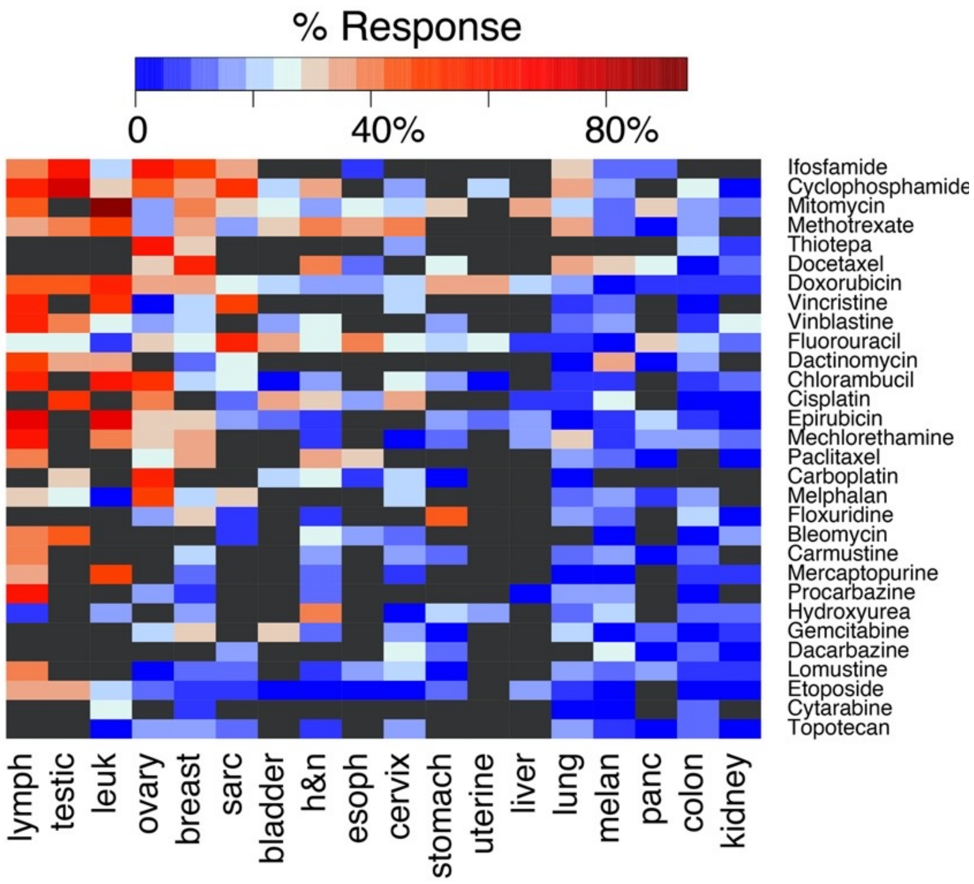
Average chemo-sensitivity of different cancers

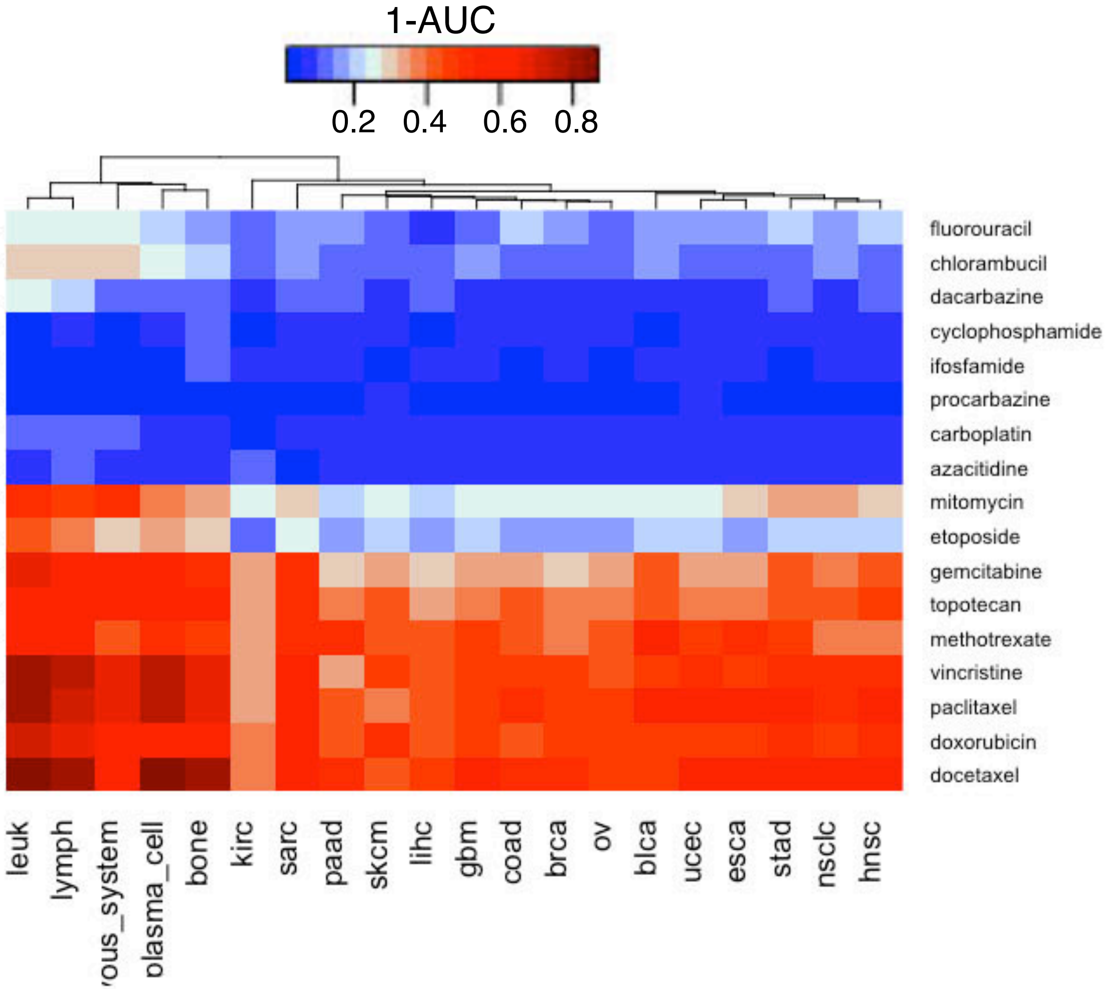




DeVita, V.; *et al.* **Cancer: Principles & Practice of Oncology** p. 823, 858, 1035

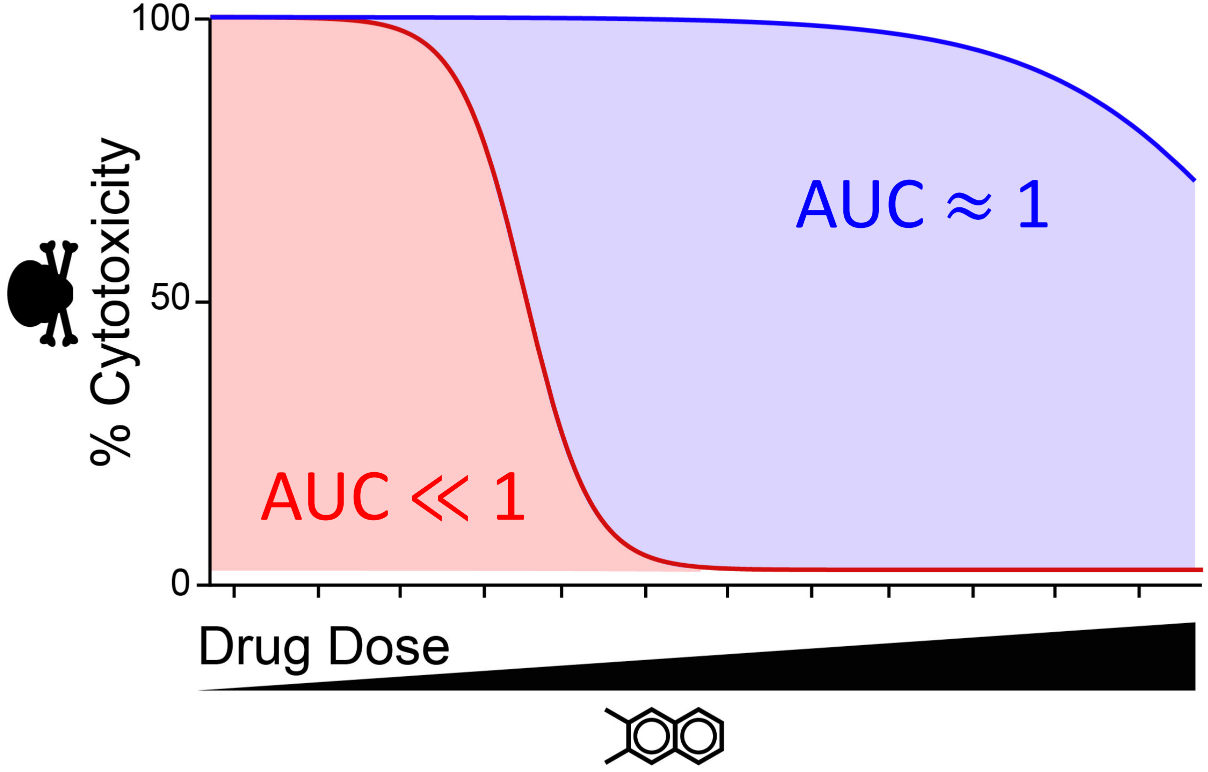
Laboratory-Clinical Agreement: *laboratory artifacts*

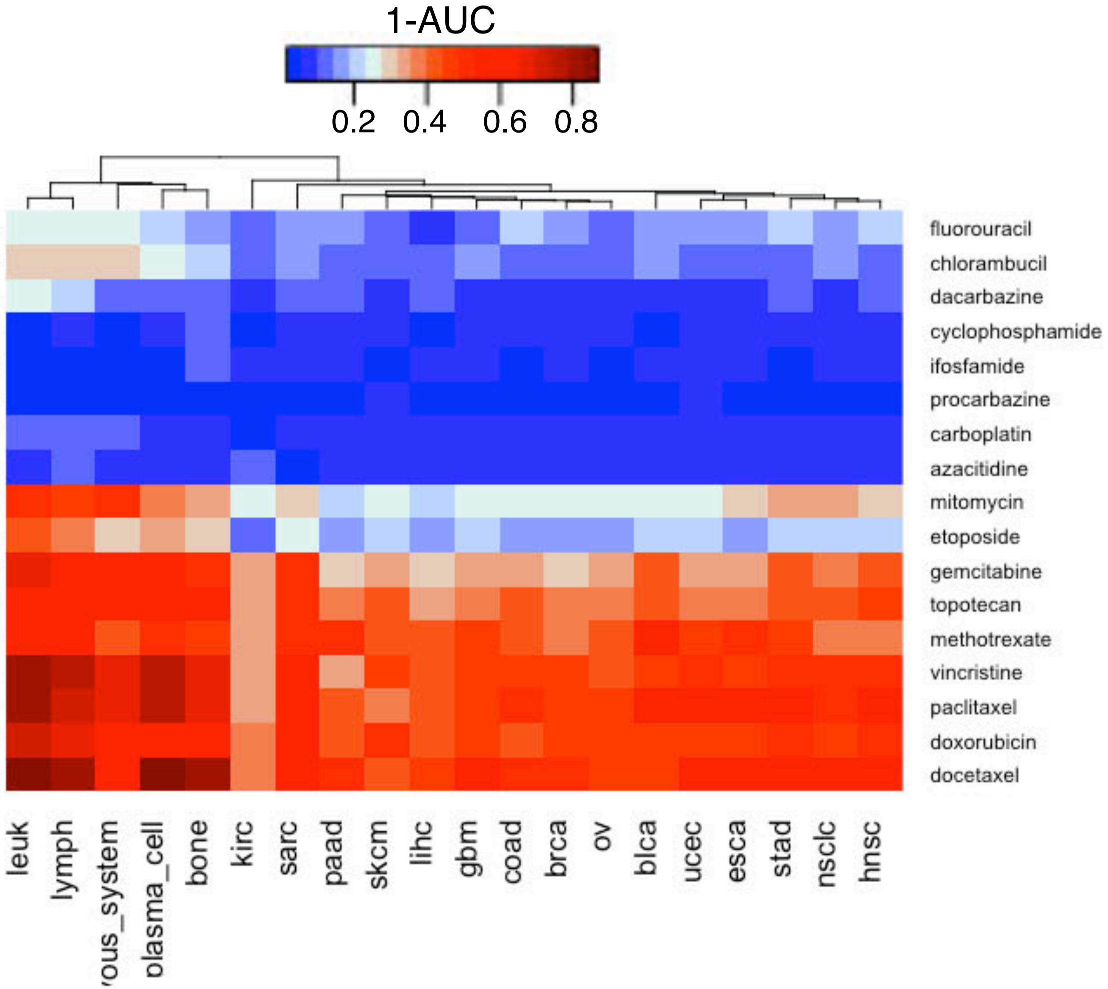




Cell, **2016**, 166, 740
Cell, **2013**, 154, 1151

Laboratory-Clinical Agreement: *laboratory artifacts*





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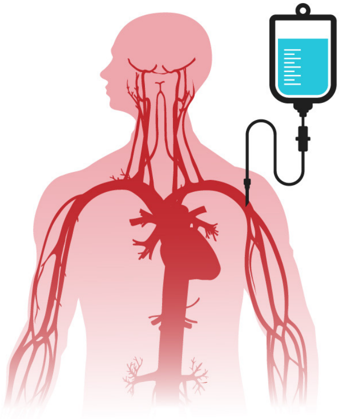
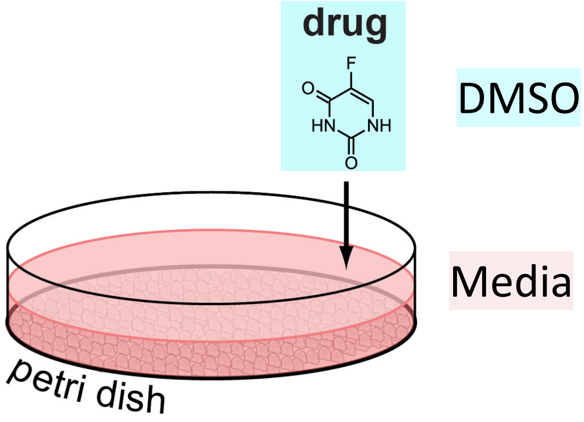
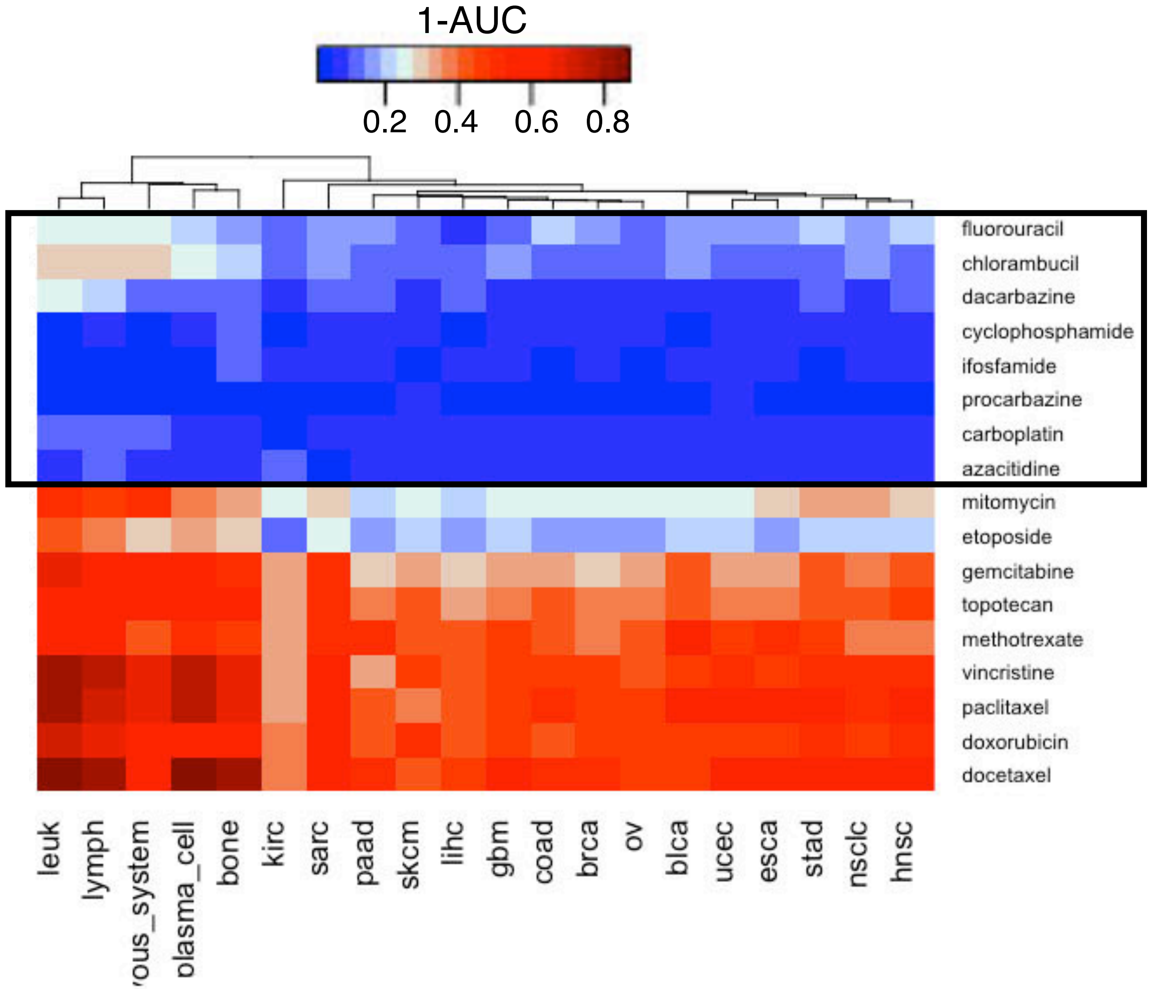
Laboratory-Clinical Agreement: *laboratory artifacts*



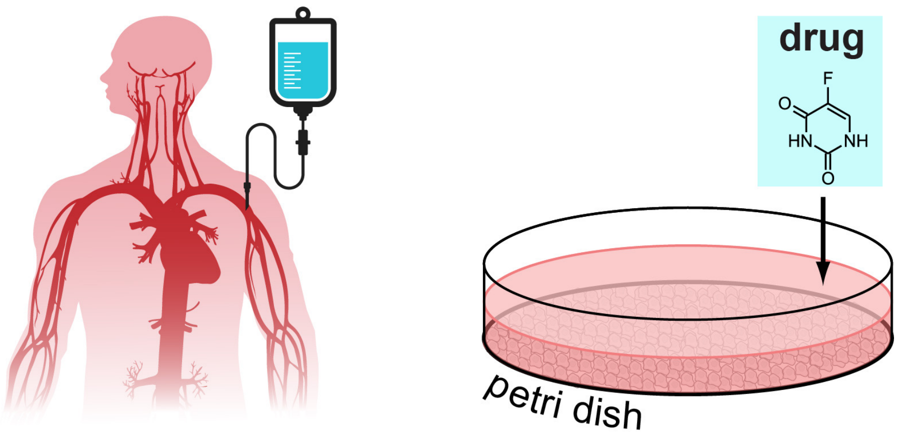


laboratory artifacts

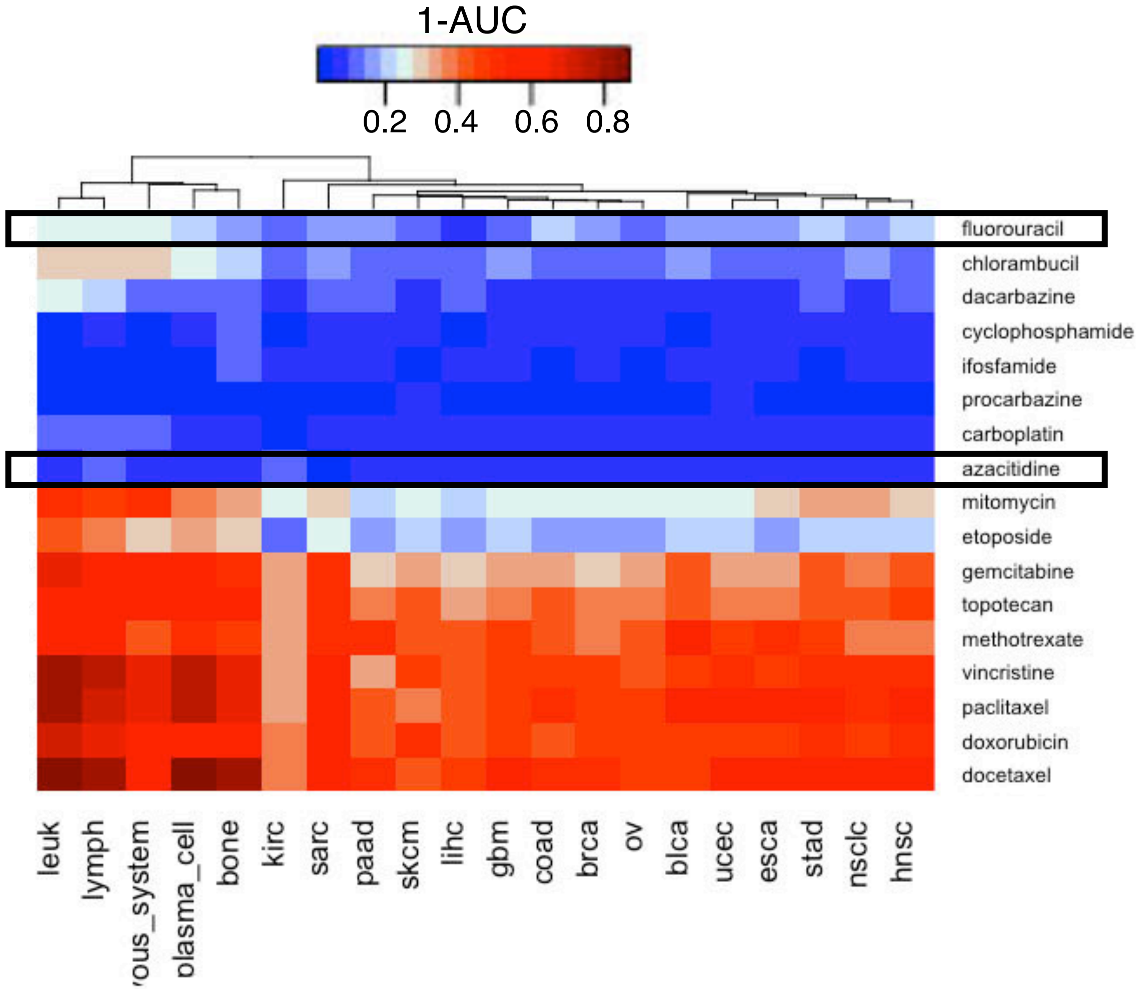


Cell, **2016**, 166, 740
Cell, **2013**, 154, 1151

Laboratory-Clinical Agreement: *laboratory artifacts*



anti-metabolite
chemotherapies



Cell

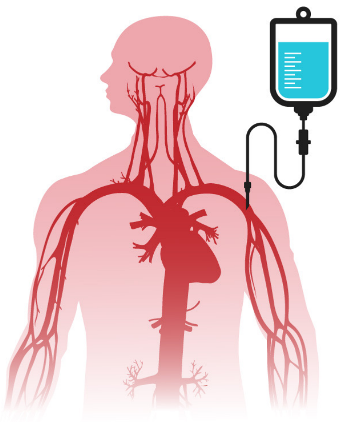
Article

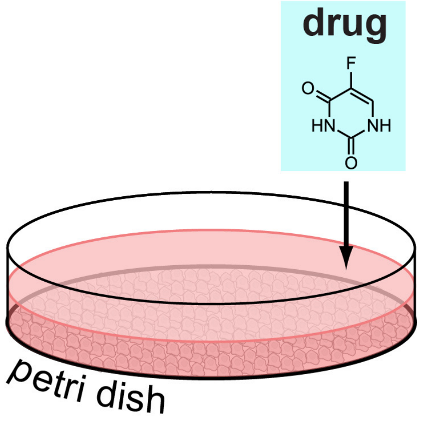
Physiologic Medium Rewires Cellular Metabolism and Reveals Uric Acid as an Endogenous Inhibitor of UMP Synthase

We find that uric acid directly inhibits UMP synthase and consequently reduces the sensitivity of cancer cells to the chemotherapeutic agent 5-fluorouracil.
Cell, **2017**, 169, 258

Cell, **2016**, 166, 740
Cell, **2013**, 154, 1151

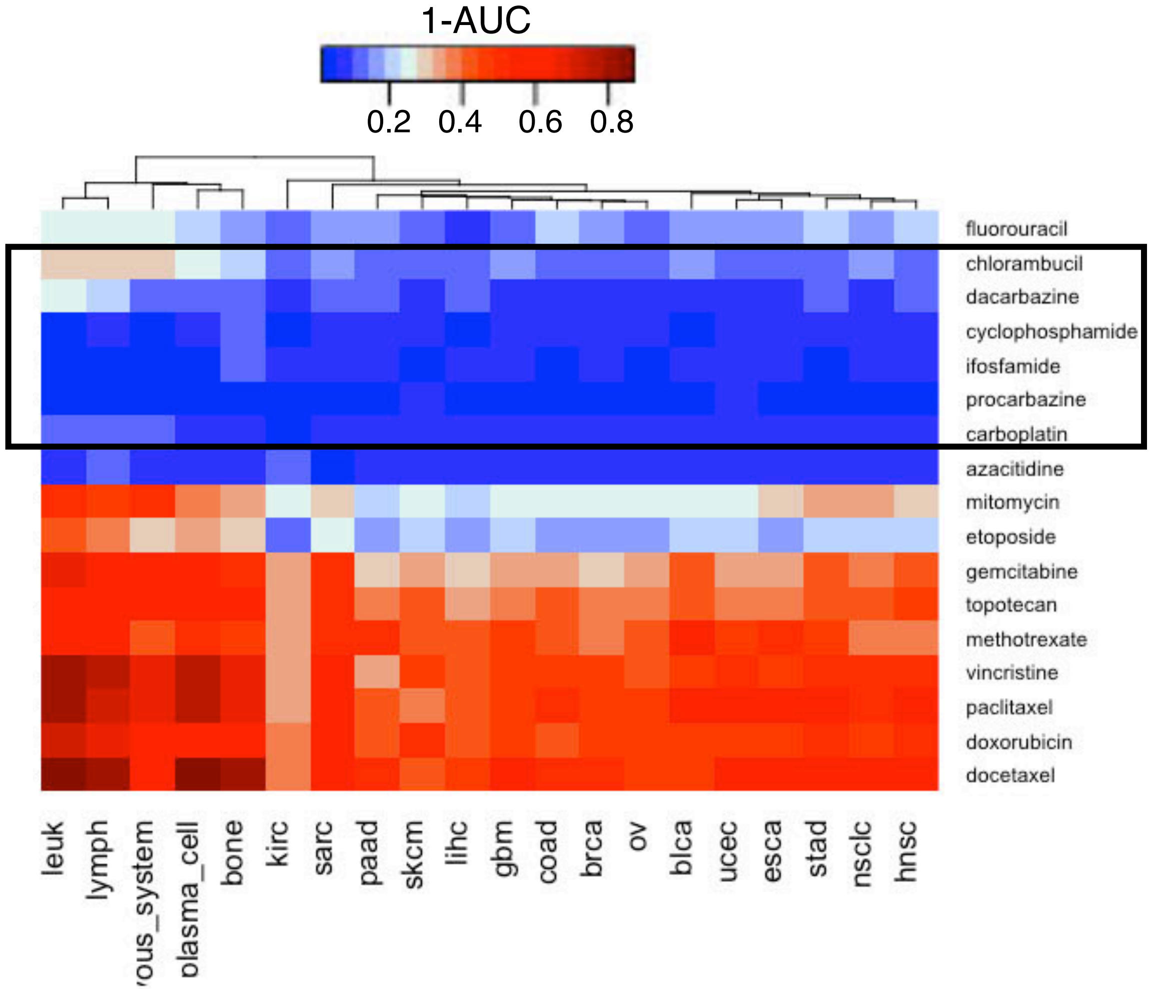
Laboratory-Clinical Agreement: *laboratory artifacts*





DMSO

electrophilic
chemotherapies



Therapeutics, Targets, and Chemical Biology

Cancer Research

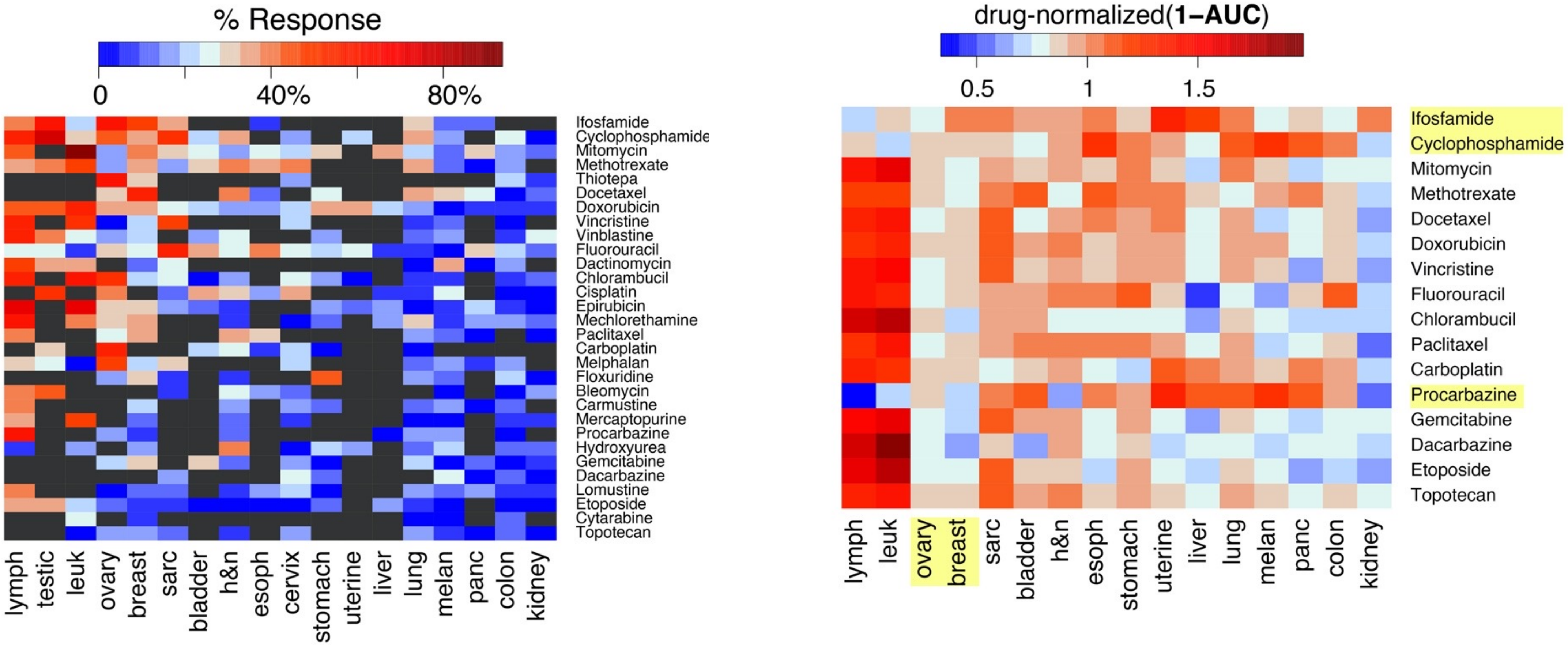
Say No to DMSO: Dimethylsulfoxide Inactivates Cisplatin, Carboplatin, and Other Platinum Complexes

Matthew D. Hall[1], Katherine A. Telma[1], Ki-Eun Chang[1], Tobie D. Lee[1], James P. Madigan[1], John R. Lloyd[2], Ian S. Goldlust[3], James D. Hoeschele[4], and Michael M. Gottesman[1]

Cancer Res, **2014**,74, 3913

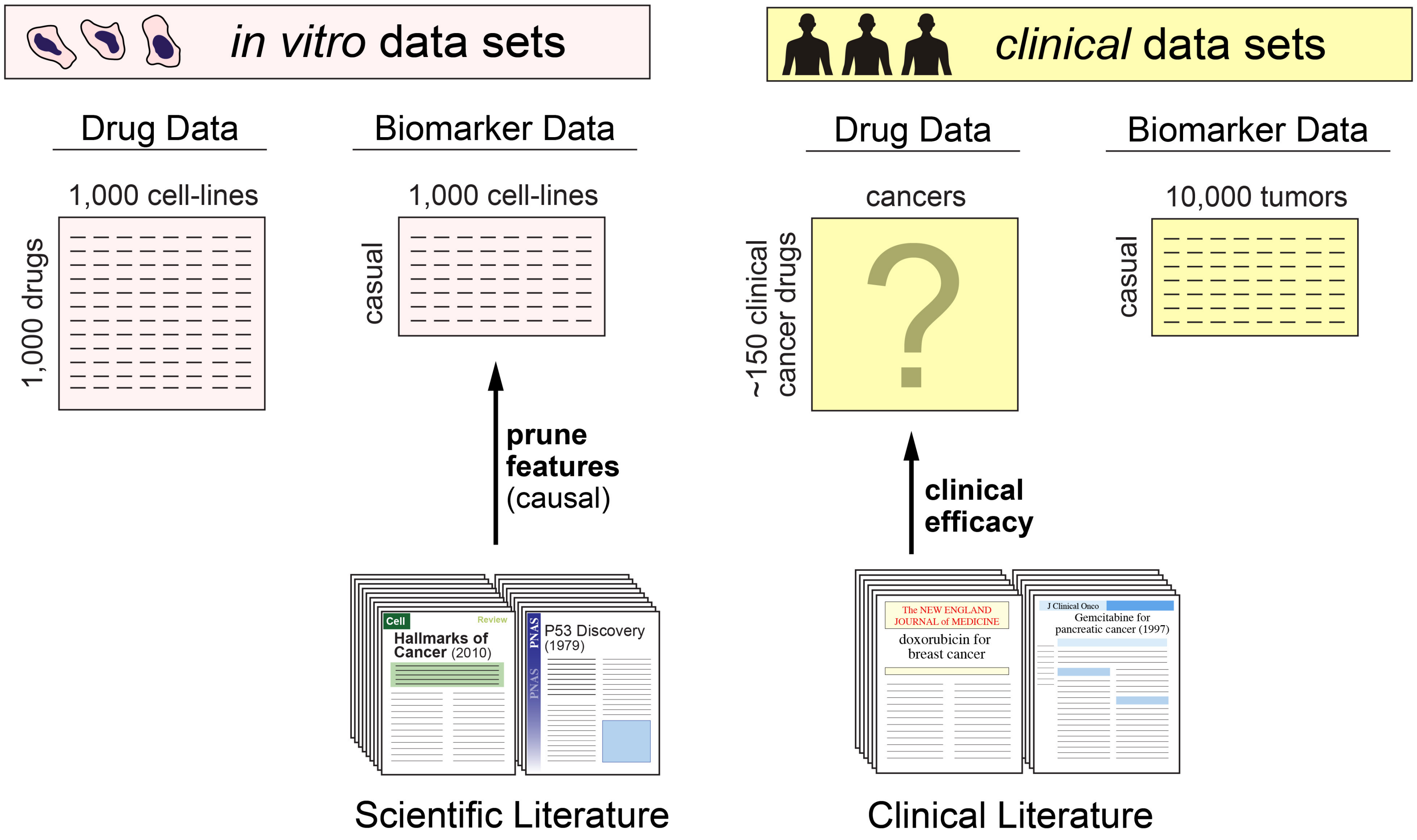
Cell, **2016**, 166, 740
Cell, **2013**, 154, 1151

Laboratory-Clinical Agreement: *normalize by drug*



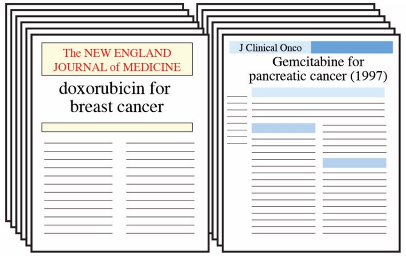
Cell, **2016**, 166, 740
Cell, **2013**, 154, 1151

Douglass Lab Approach: *prune features & build database*

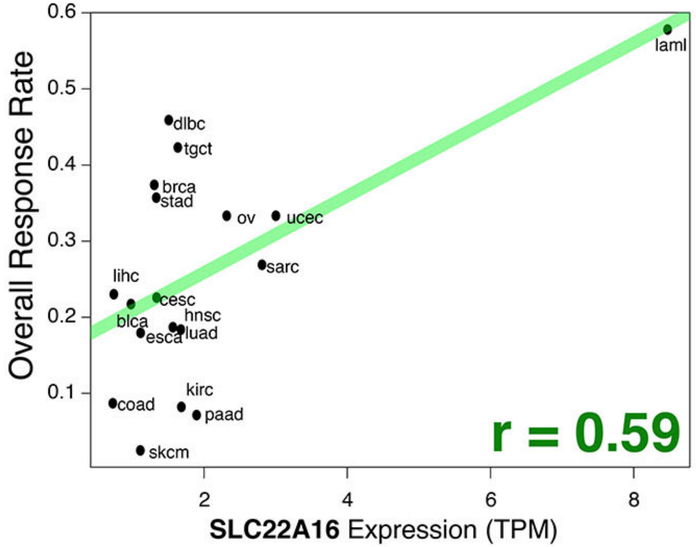


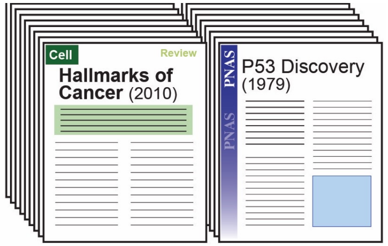
Evaluate Clinical Validity of each biomarker:

clinical data sets

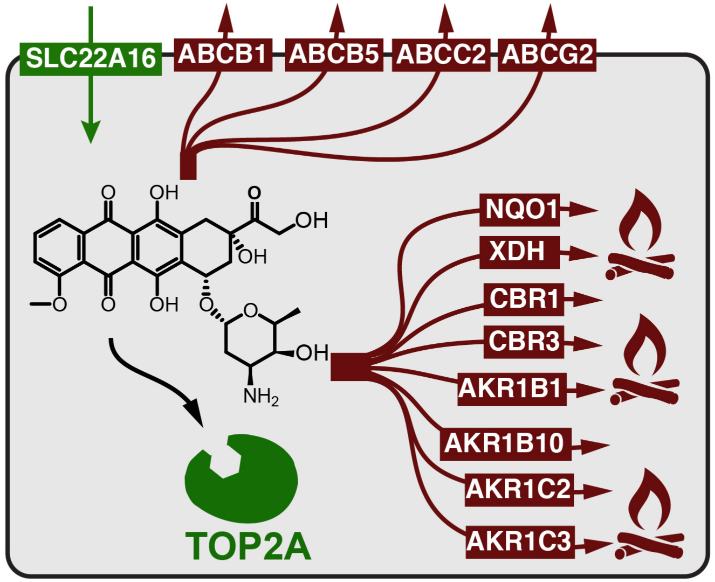


Clinical Literature





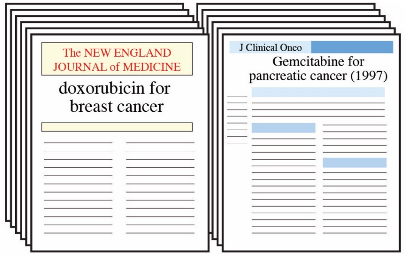
Scientific Literature



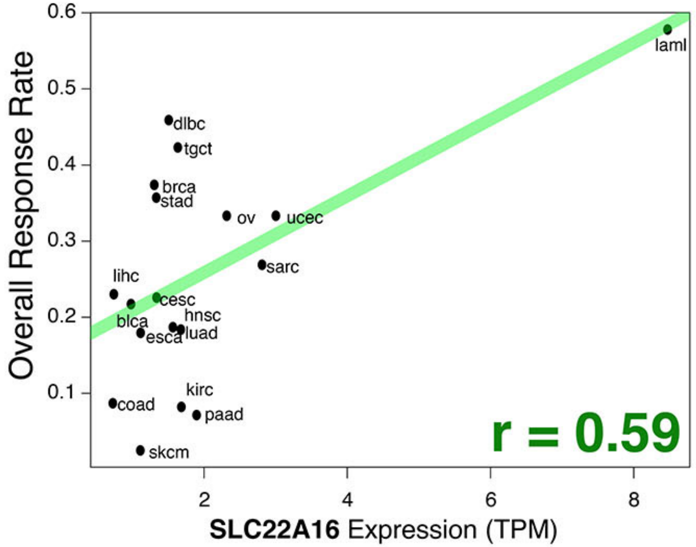
Biomarker Expression (TCGA): *Nat. Genet.* **2013**, 45, 1113

Evaluate Clinical Validity of each biomarker:

clinical data sets

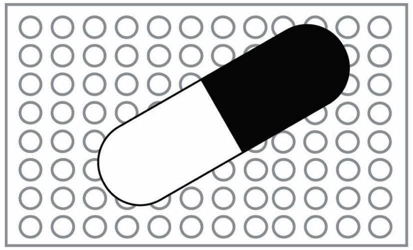


Clinical Literature

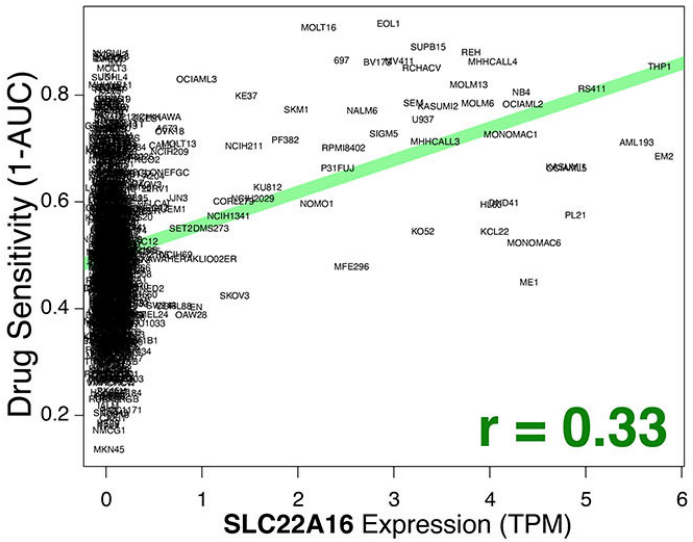


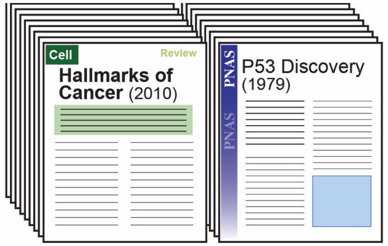
+

in vitro data sets

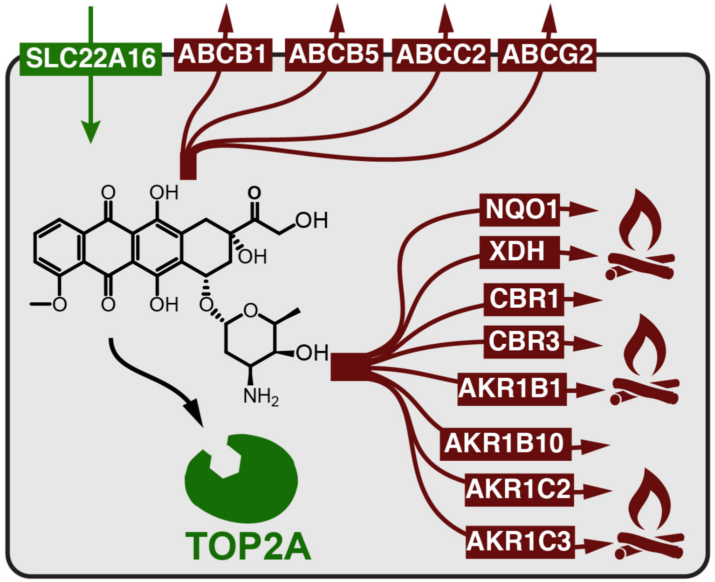


Screening Technology





Scientific Literature

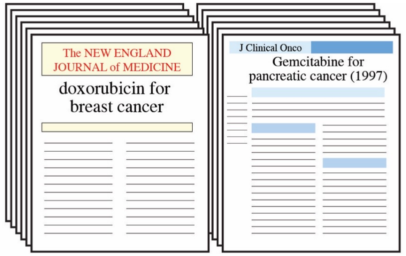


Drug Sensitivity(CTRP): *Cell,* **2013**, 154, 1151
Biomarker Expression (CCLE): *Nature,* **2019**, 569, 503

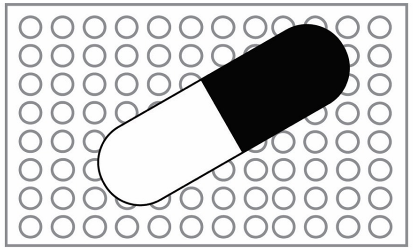
Evaluate Clinical Validity of each biomarker:

clinical data sets

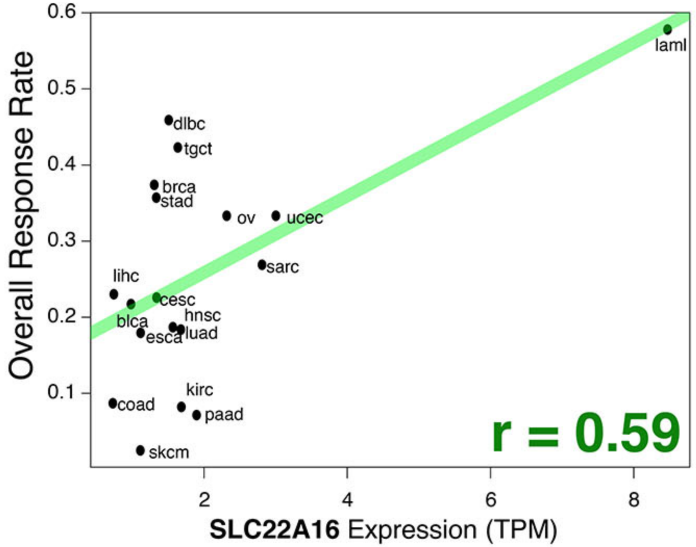
in vitro data sets



Clinical Literature



Screening Technology



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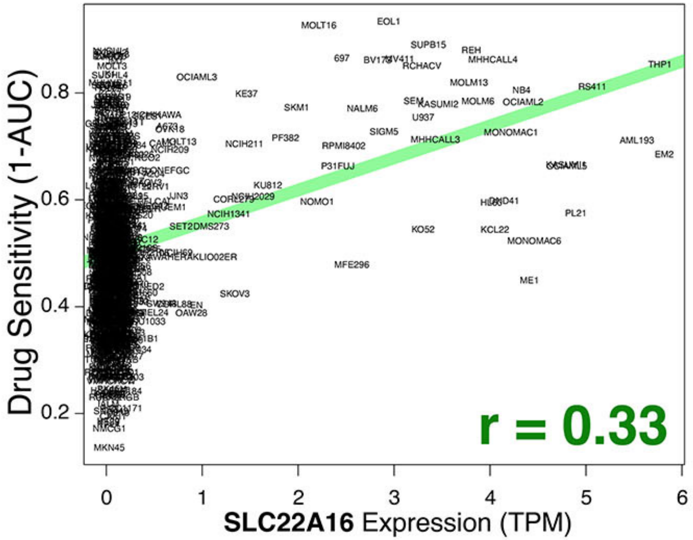

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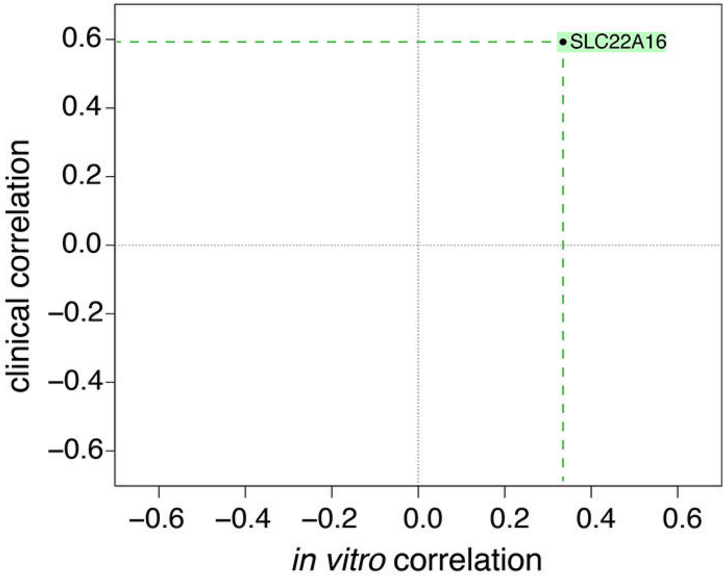
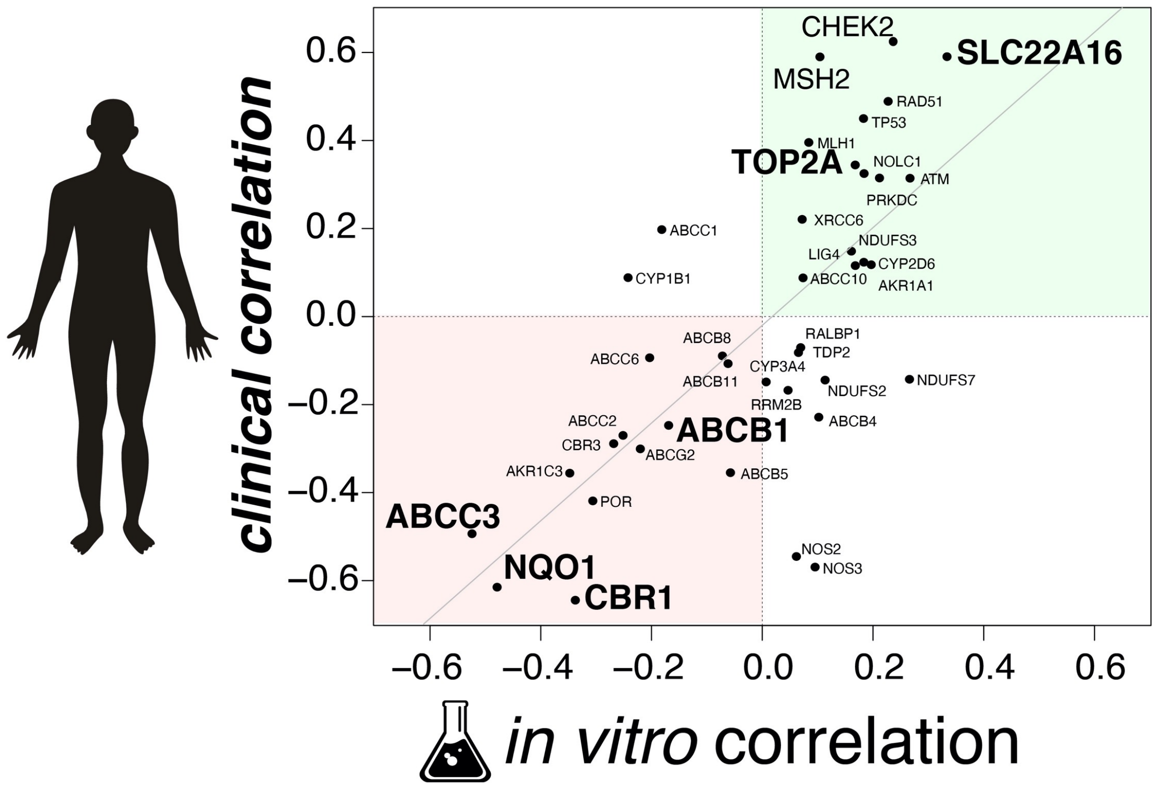


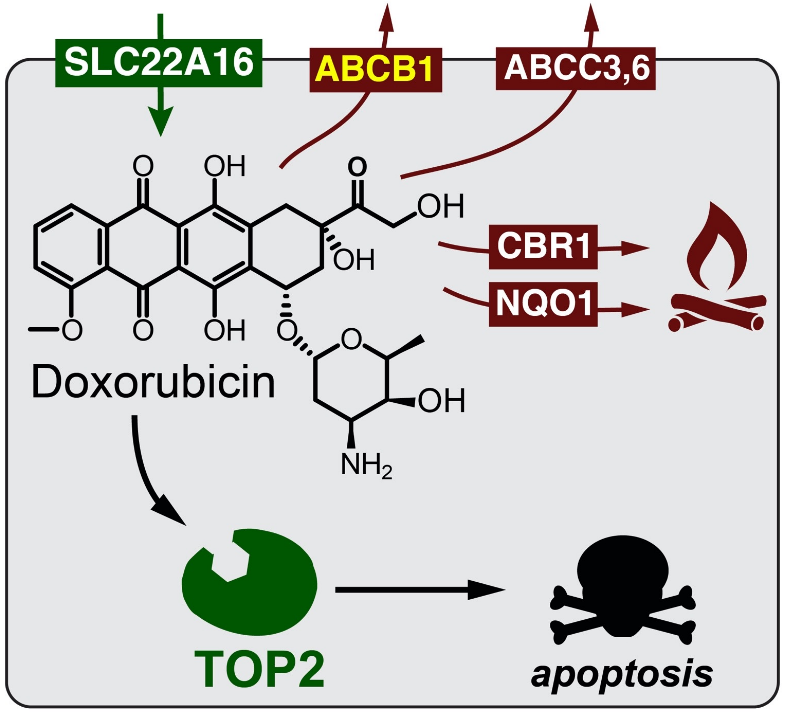
Drug Sensitivity(CTRP): *Cell*, **2013**, 154, 1151
Biomarker Expression (CCLE): *Nature*, **2019**, 569, 503

Comprehensive evaluation of anthracycline biomarkers

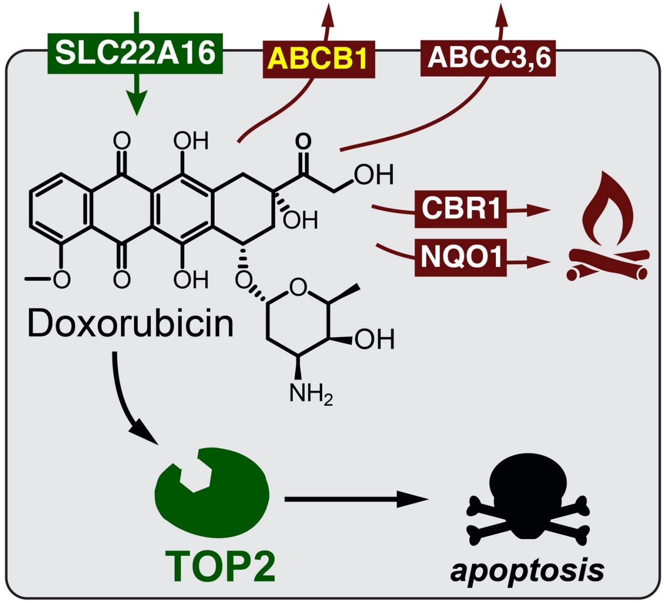
A. Clinical Benchmark: Anthracycline Biomarkers



B. Clinical Hypothesis: Anthracyclines



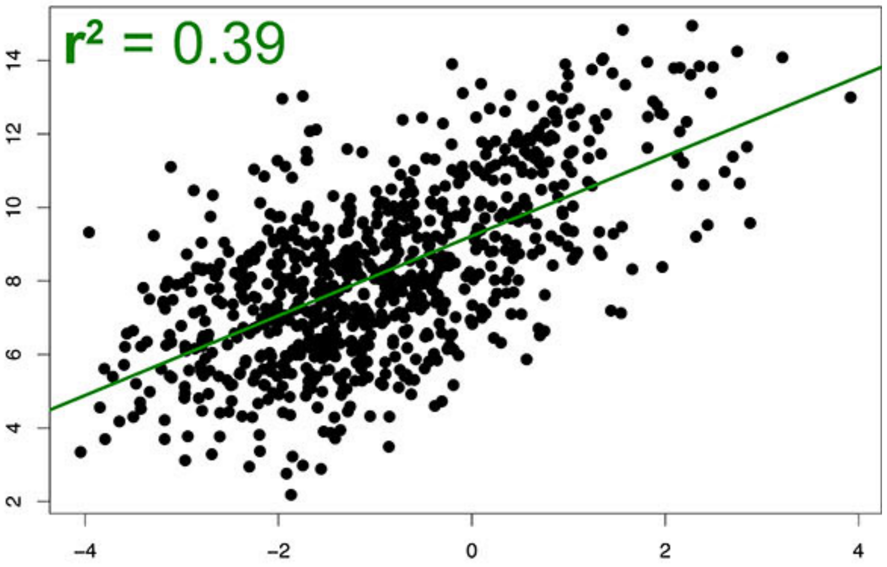
Multi-Linear Regression: *N-biomarker working hypothesis*



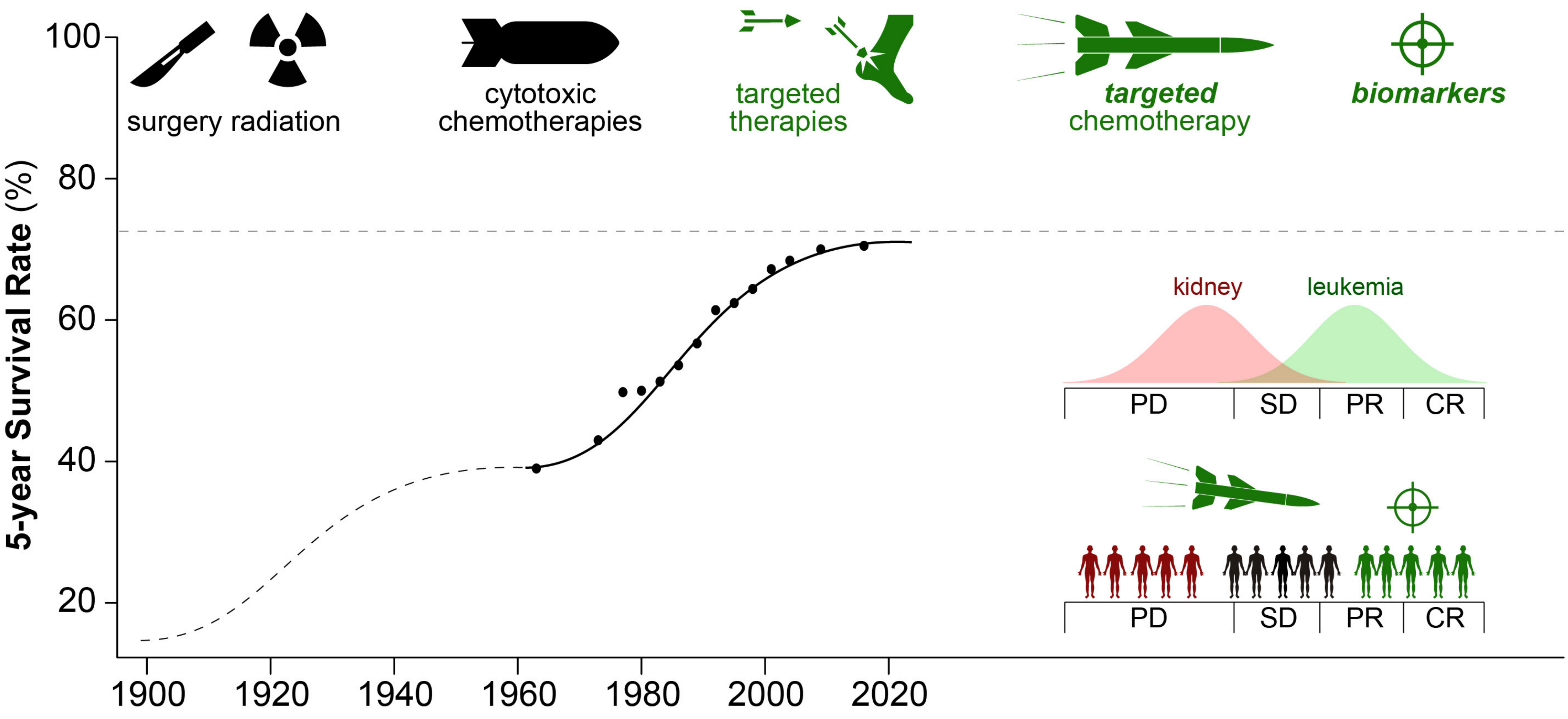
multi-linear model

+0.44 · SLC22A16
+0.25 · NDUFS7
+0.11 · TOP2A
+0.11 · TP53

–0.10 · CBR1
–0.11 · NQO1
–0.16 · ABCB1
–0.17 · ABCC6
–0.22 · ABCC3
–0.22 · ABCC1

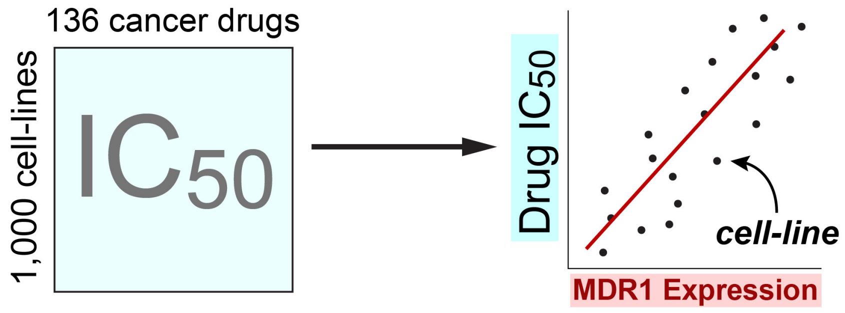


History of Cancer Treatment: *targeted chemotherapies?*



Douglass Laboratory: *computational program*

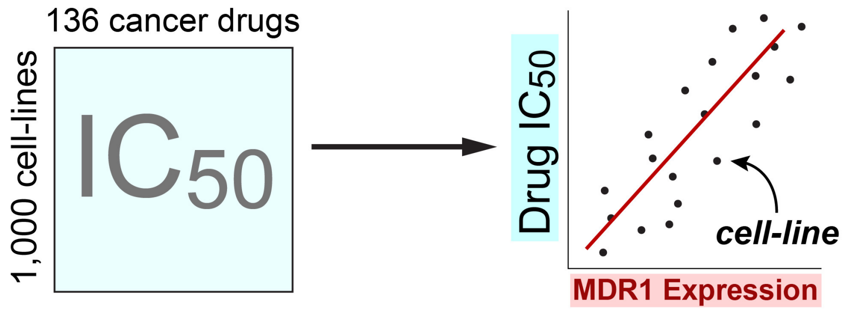
Computational Cancer Resistance Program: deconvolute N-biomarker phenotype



$$\Delta IC_{50} = \frac{k_{cat}/K_m}{k_{diff}}[ABCB1] + \frac{k_{cat}/K_m}{k_{diff}}[ABCG2] \ldots$$

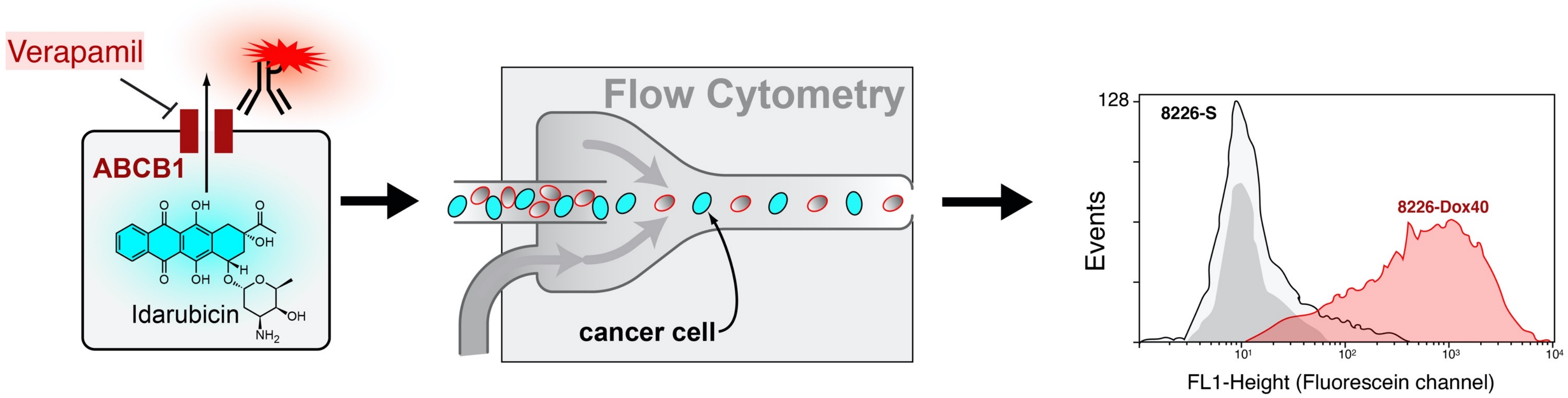
Douglass Laboratory: *experimental program*

Computational Cancer Resistance Program: deconvolute N-biomarker phenotype



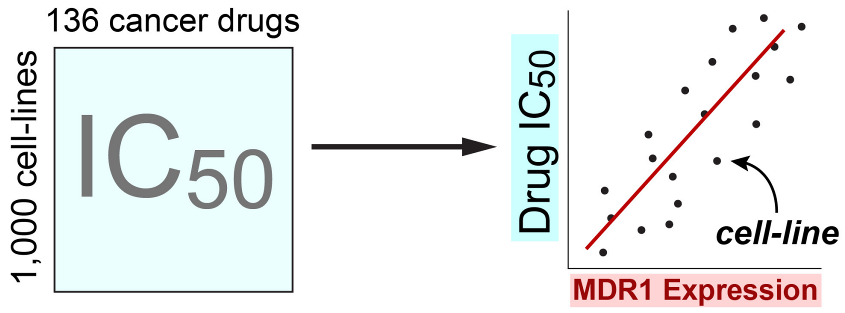
$$\Delta IC_{50} = \frac{k_{cat}/K_m}{k_{diff}}[ABCB1] + \frac{k_{cat}/K_m}{k_{diff}}[ABCG2]\ldots$$

Experimental Cancer Resistance Program: deconvolute physical constants of resistance



Douglass Laboratory: *experimental program*

Computational Cancer Resistance Program: deconvolute N-biomarker phenotype



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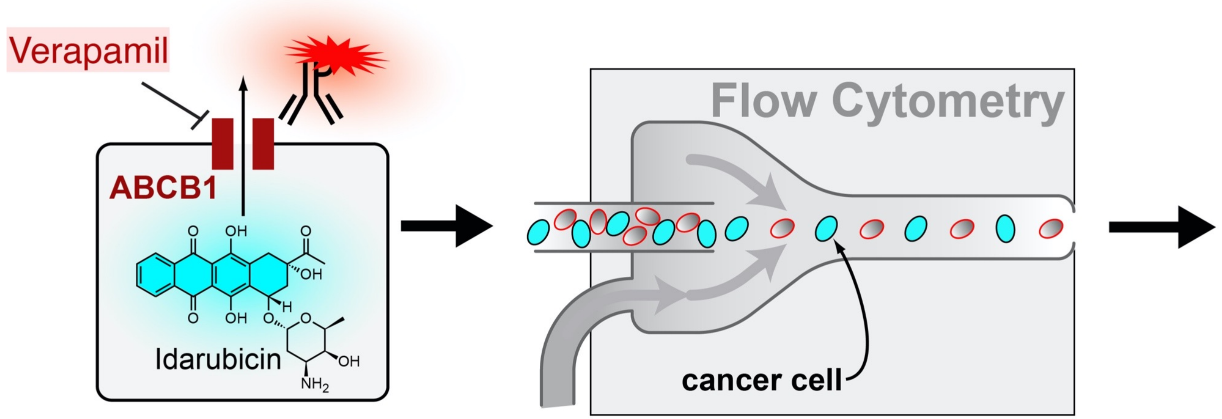
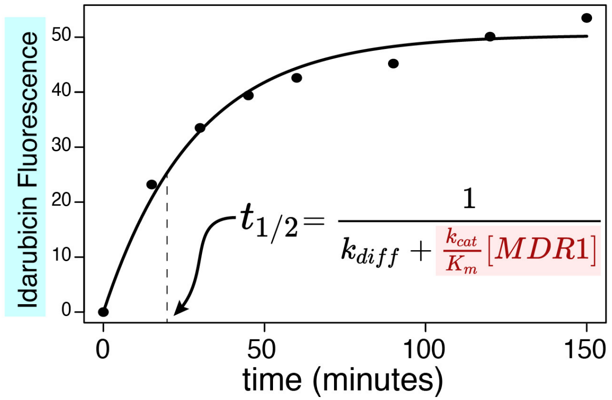
Experimental Cancer Resistance Program: deconvolute physical constants of resistance

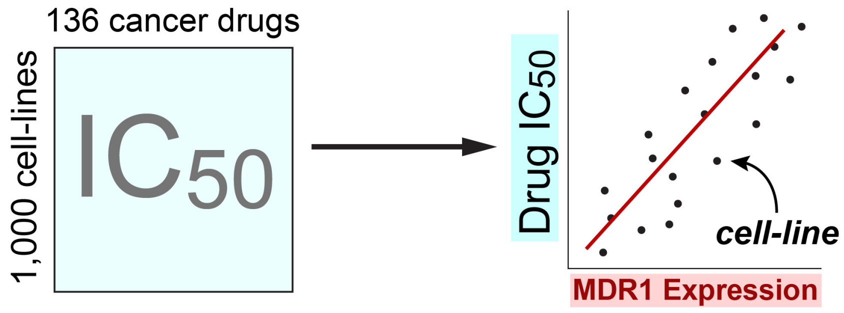




$$t_{1/2} = \frac{1}{k_{diff} + \frac{k_{cat}}{K_m}[MDR1]}$$

Douglass Laboratory: *experimental program*

Computational Cancer Resistance Program: deconvolute N-biomarker phenotype



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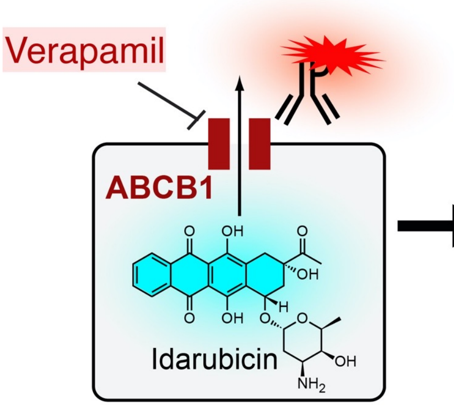
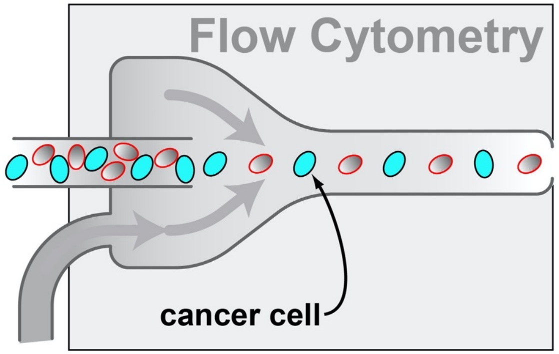
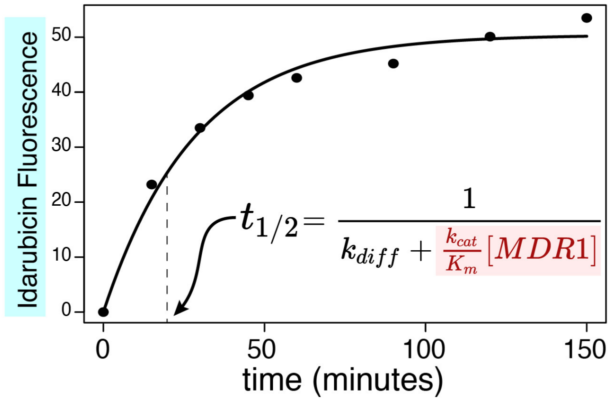
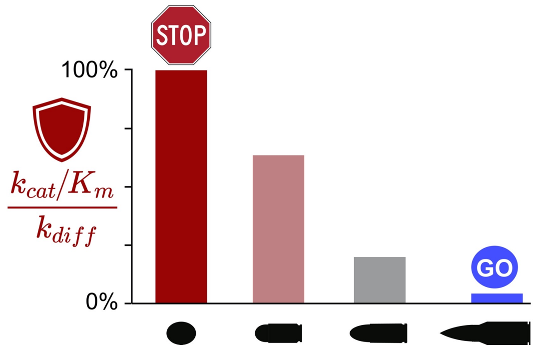
Experimental Cancer Resistance Program: deconvolute physical constants of resistance

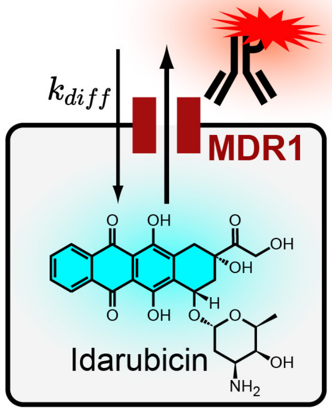




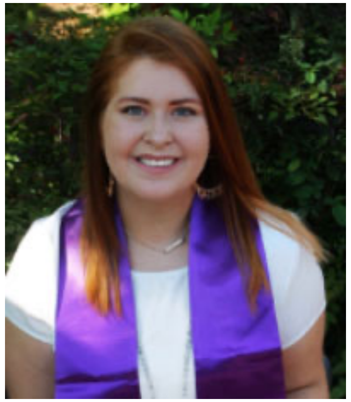




Acknowledgements:

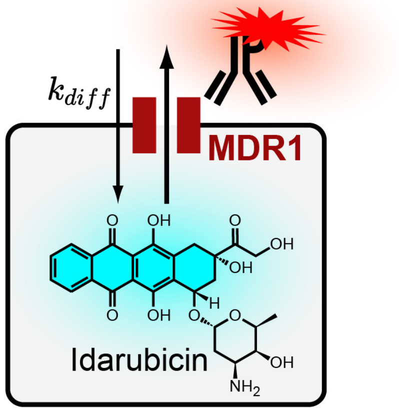



Ashley Ray


Elizabeth Hughes


George Johnson

Acknowledgements:



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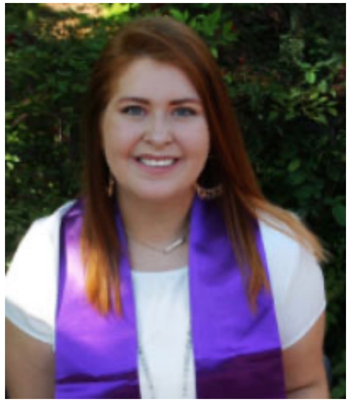

Elizabeth Hughes

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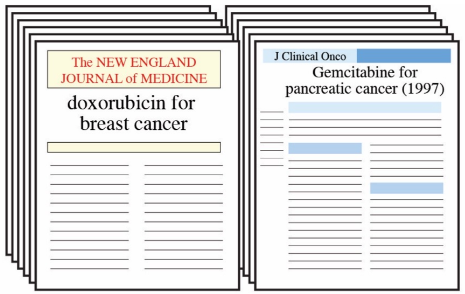
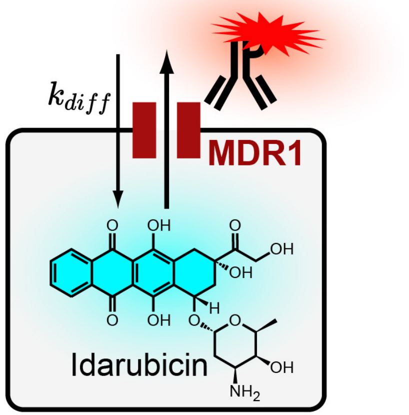


Clinical Literature

Tobin Paez

Emily Hannan

Acknowledgements:

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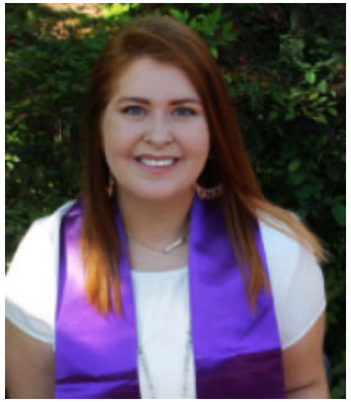
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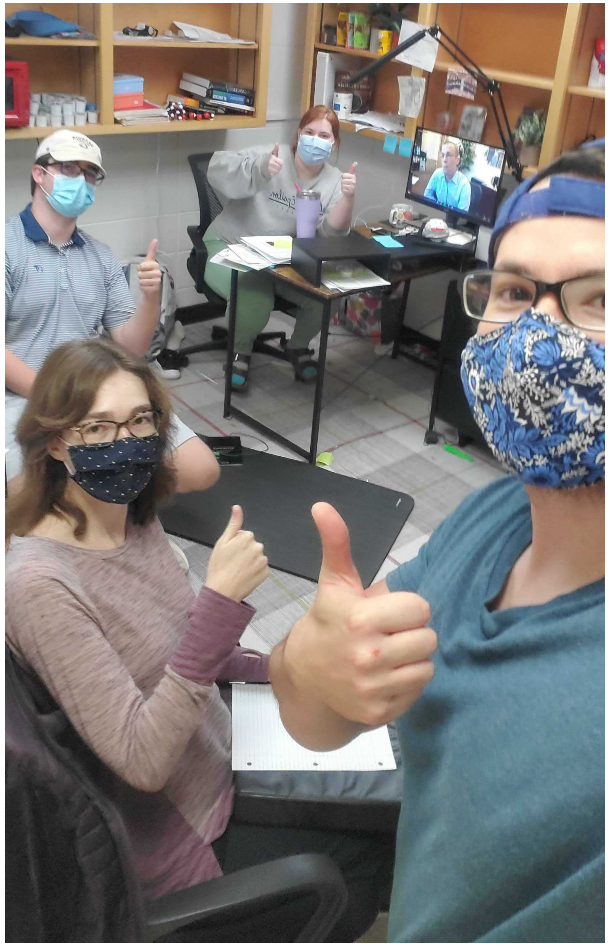
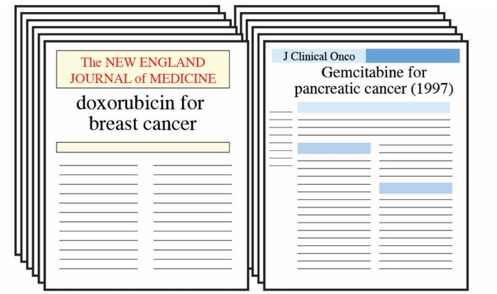




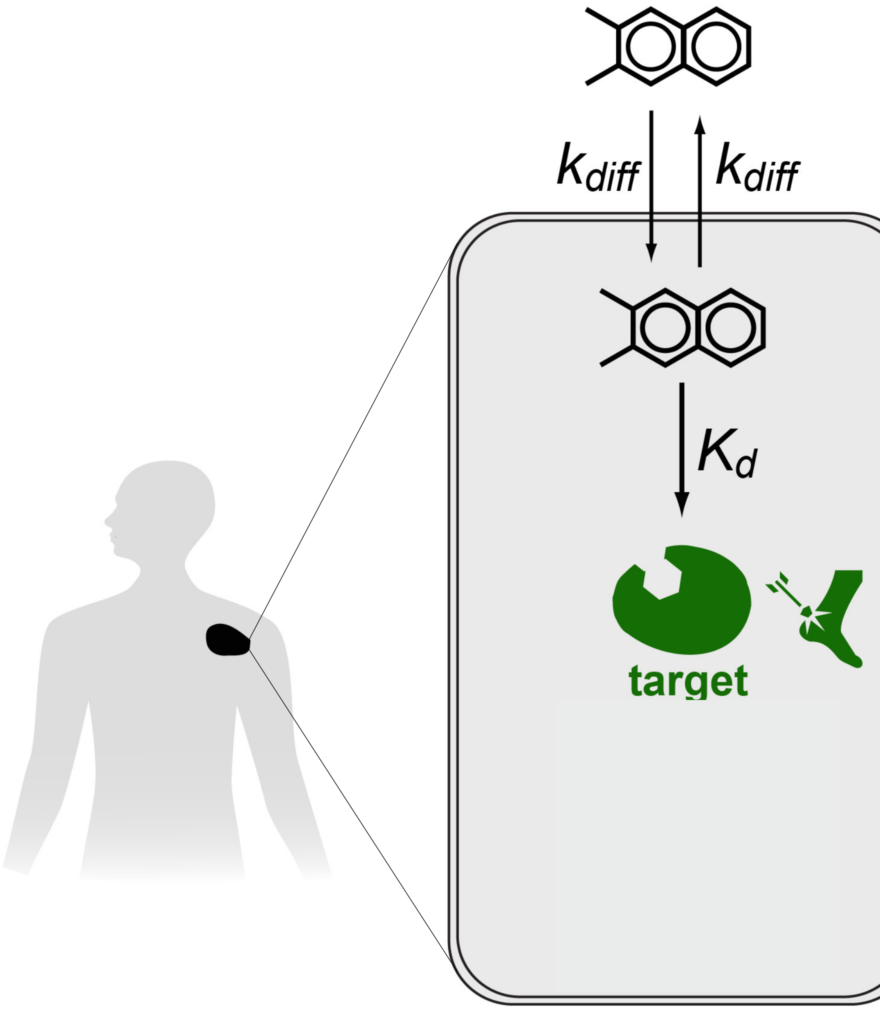
Clinical Literature


Tobin Paez

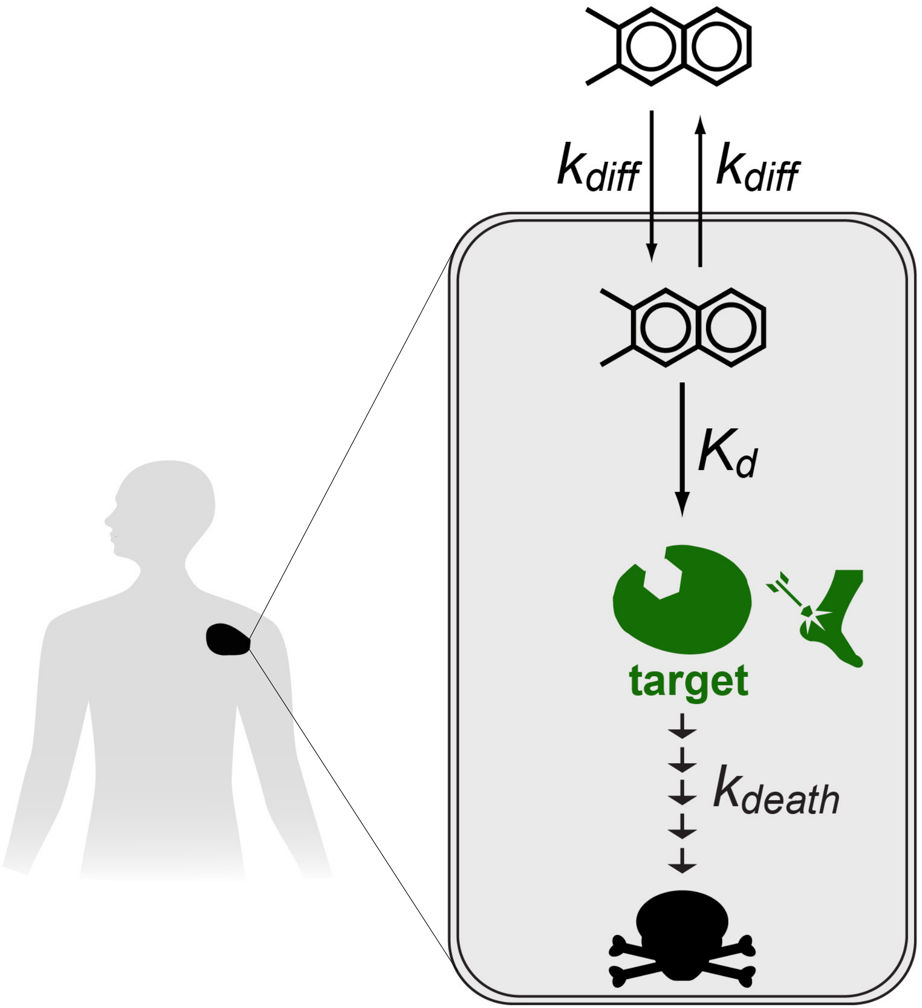

Emily Hannan

CLINICAL MEASUREMENT INTRO

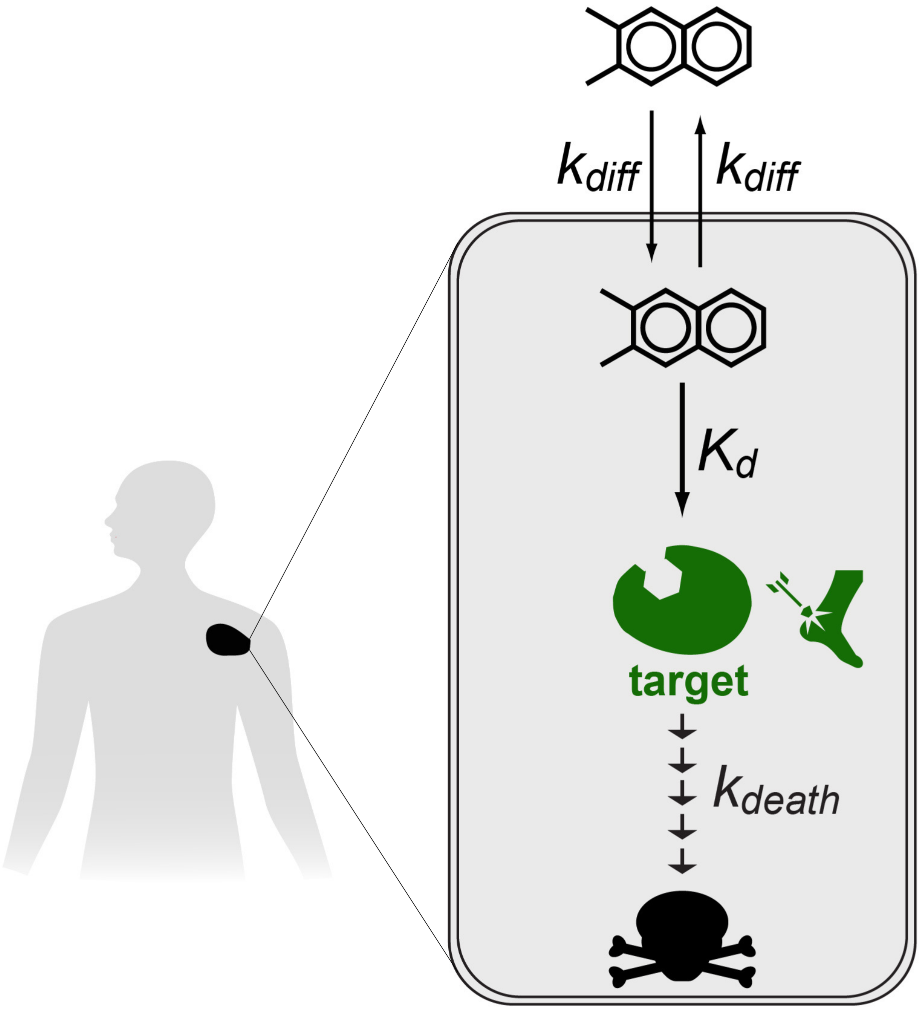
1-drug / 1 target paradigm: *historical artifact*

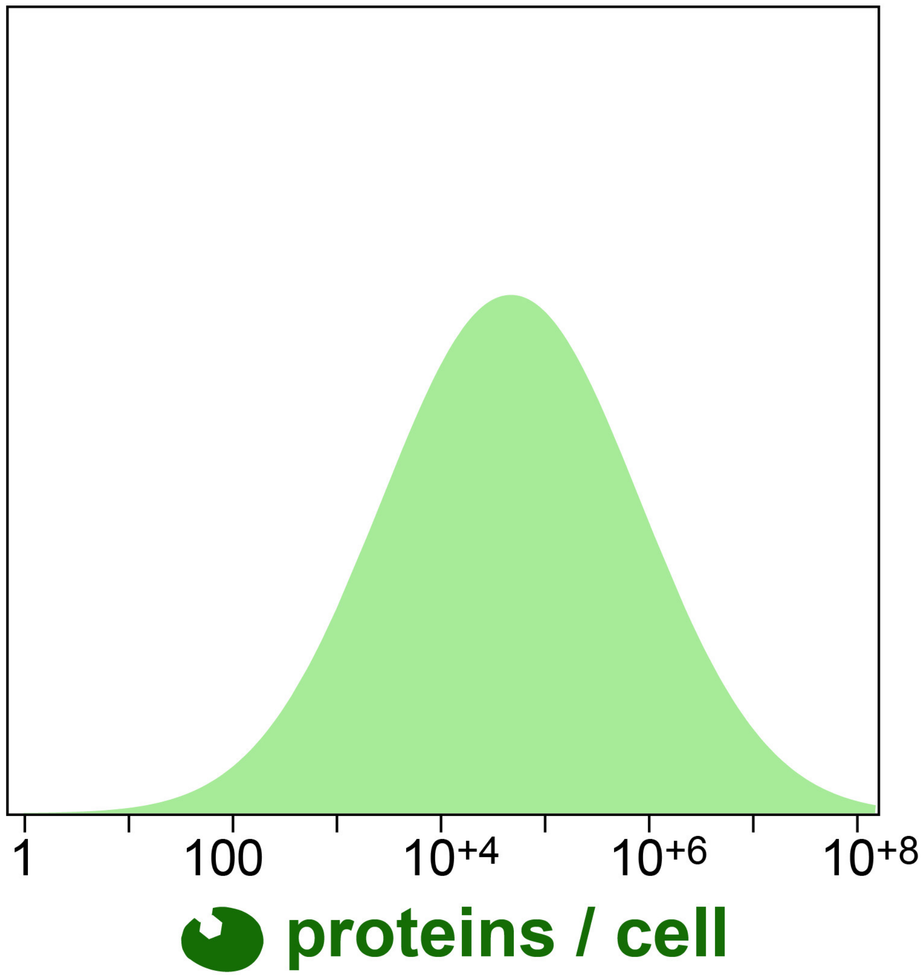


1-drug / 1 target paradigm: *historical artifact*



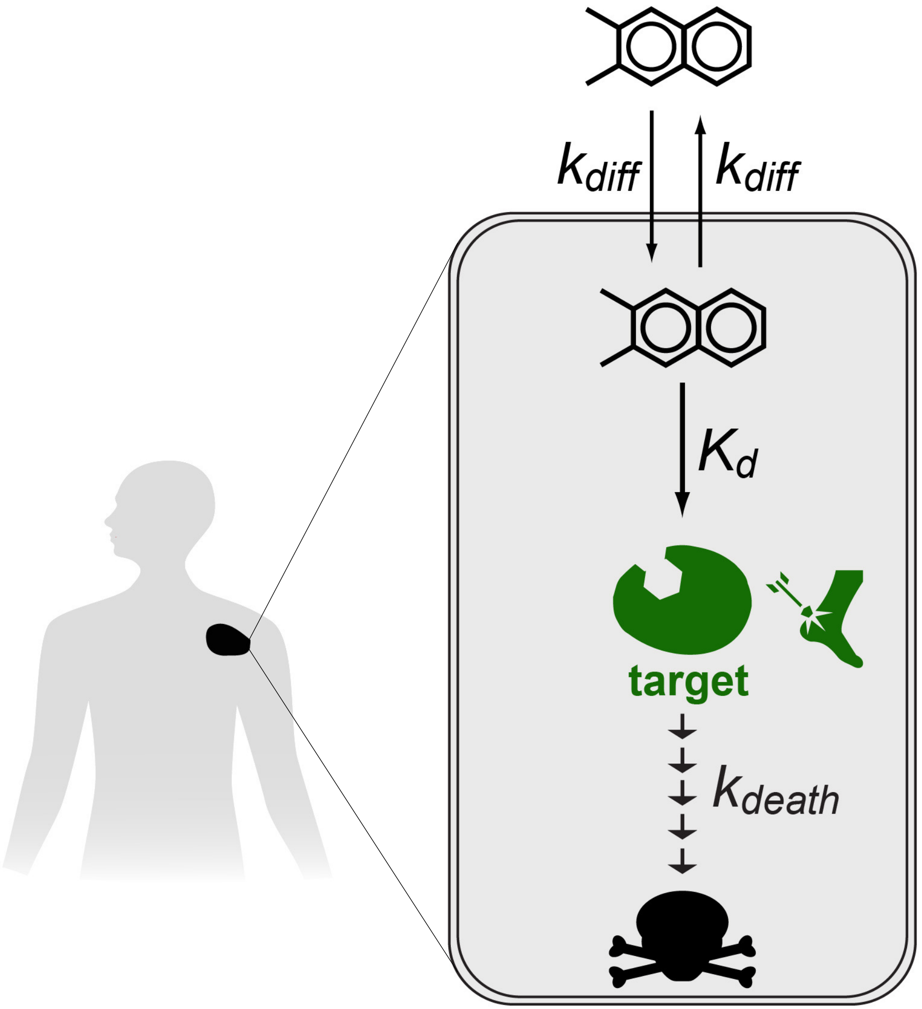
Biomarker Expression: *log-normal distribution*

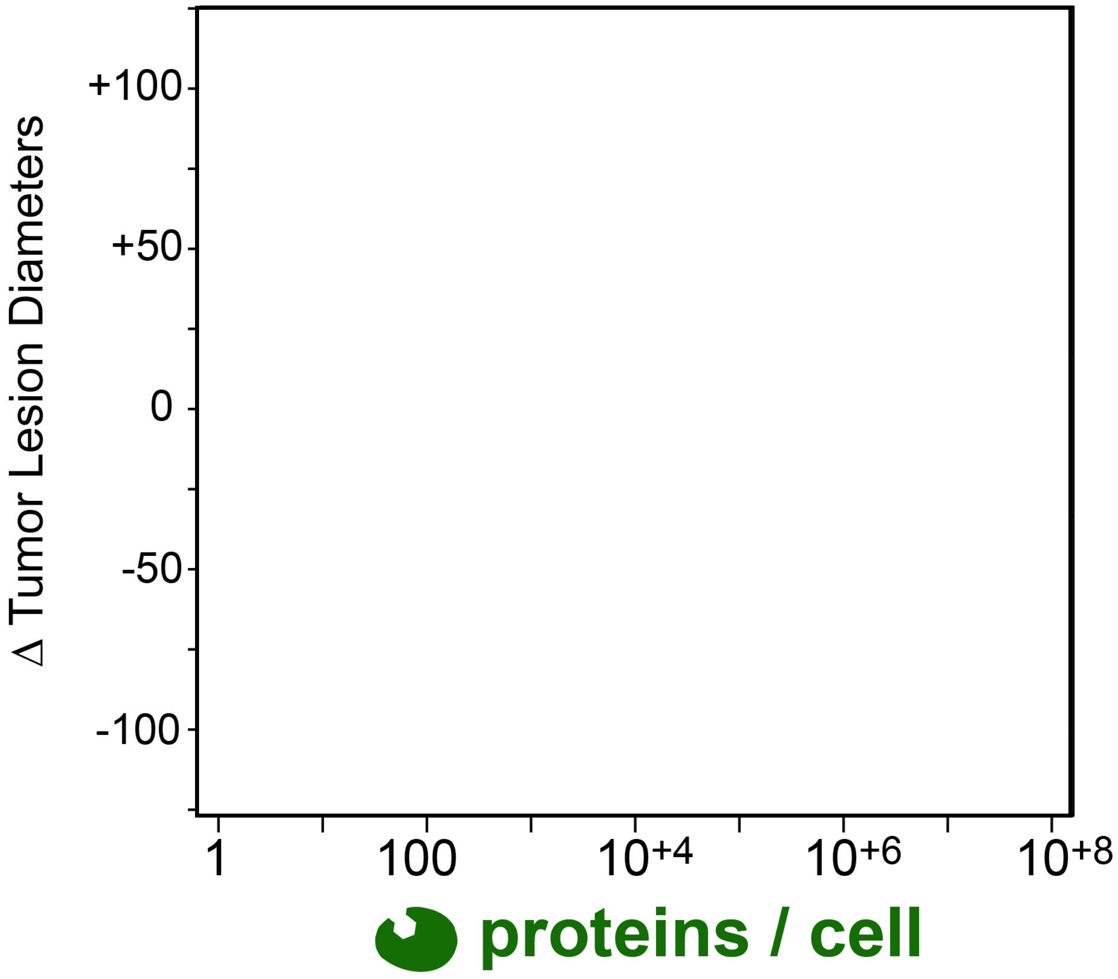




Nature, **2011**, 474, 337-342

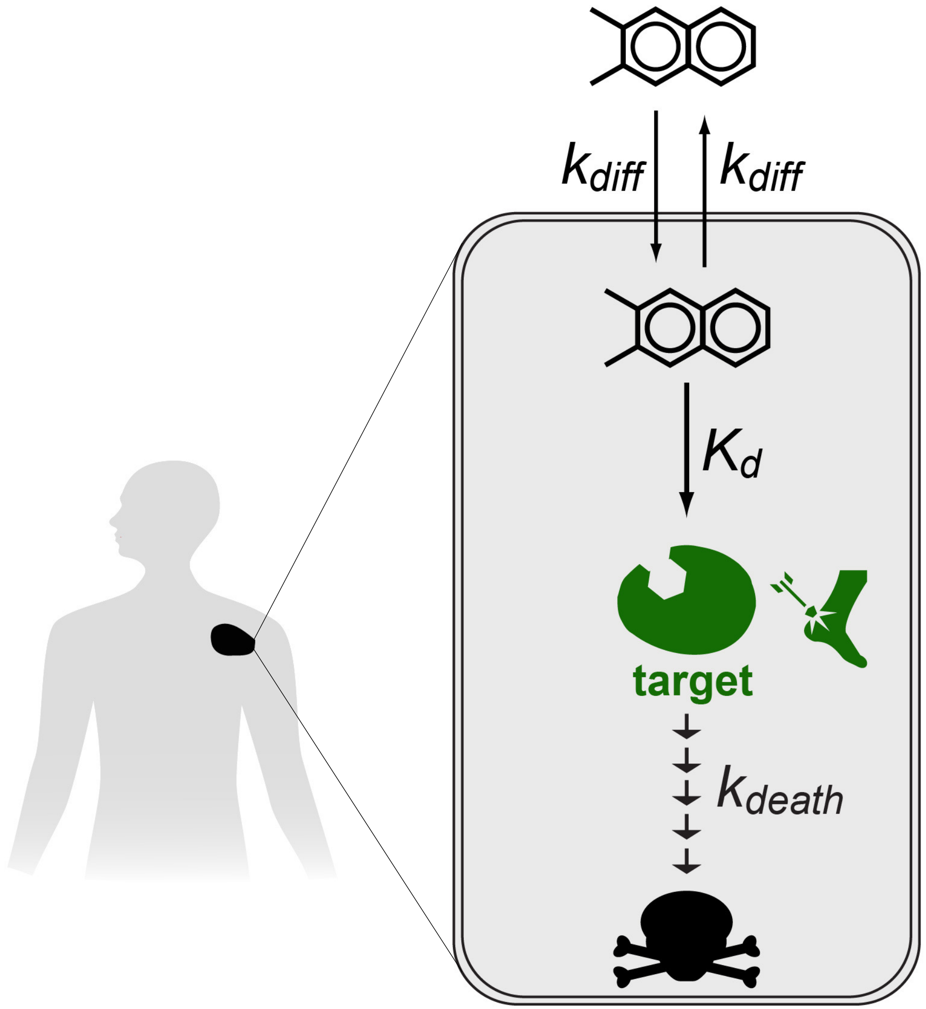
Clinical Response Definitions: lesion diameter

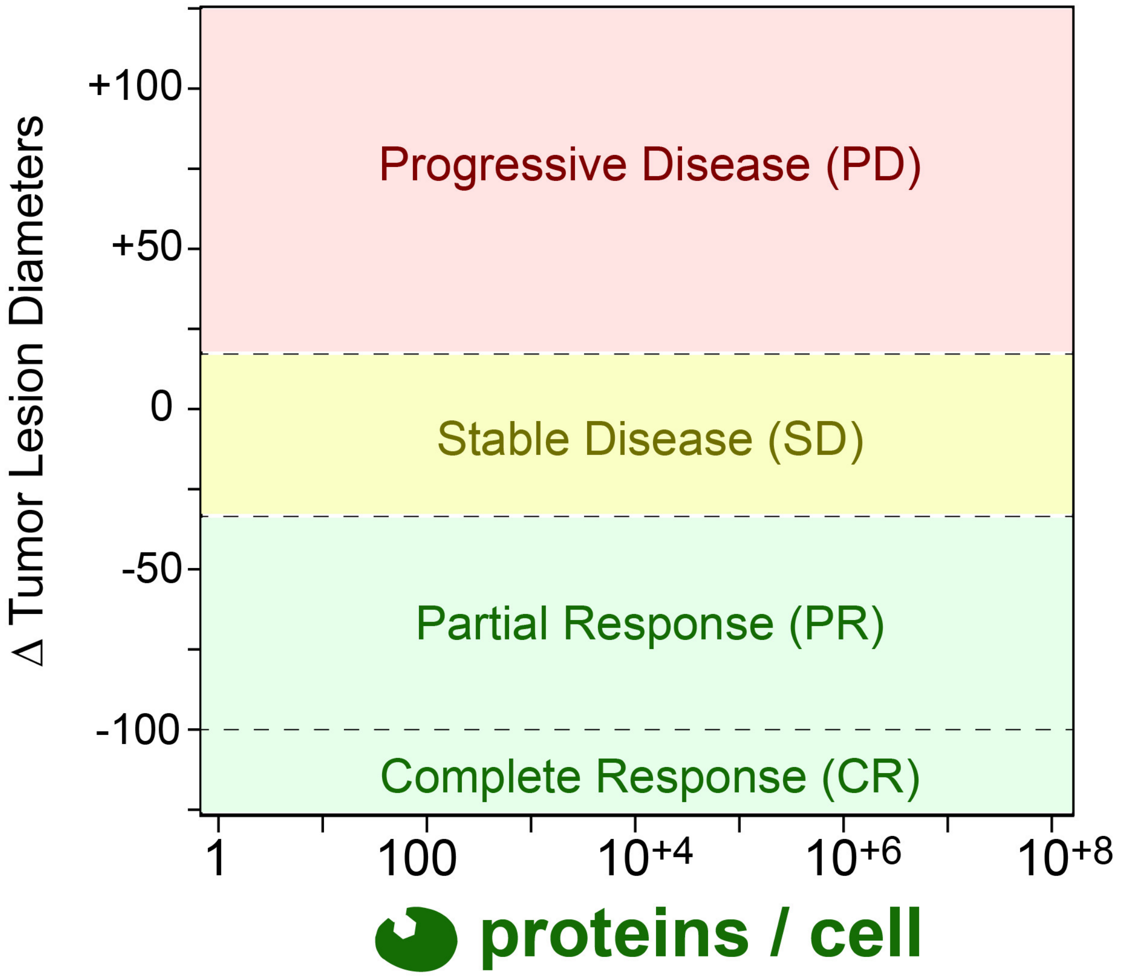




Cancer Res Treat., **2005**, 37, 290-293

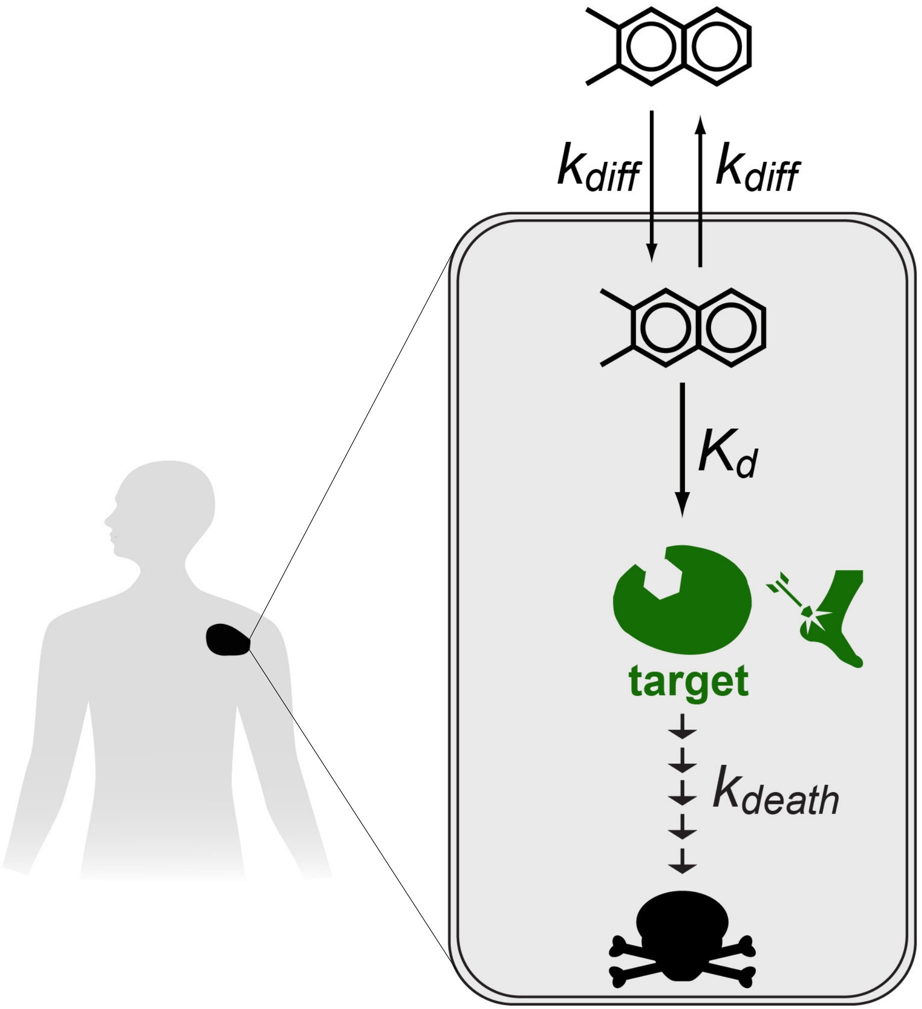
Clinical Response Definitions: lesion diameter

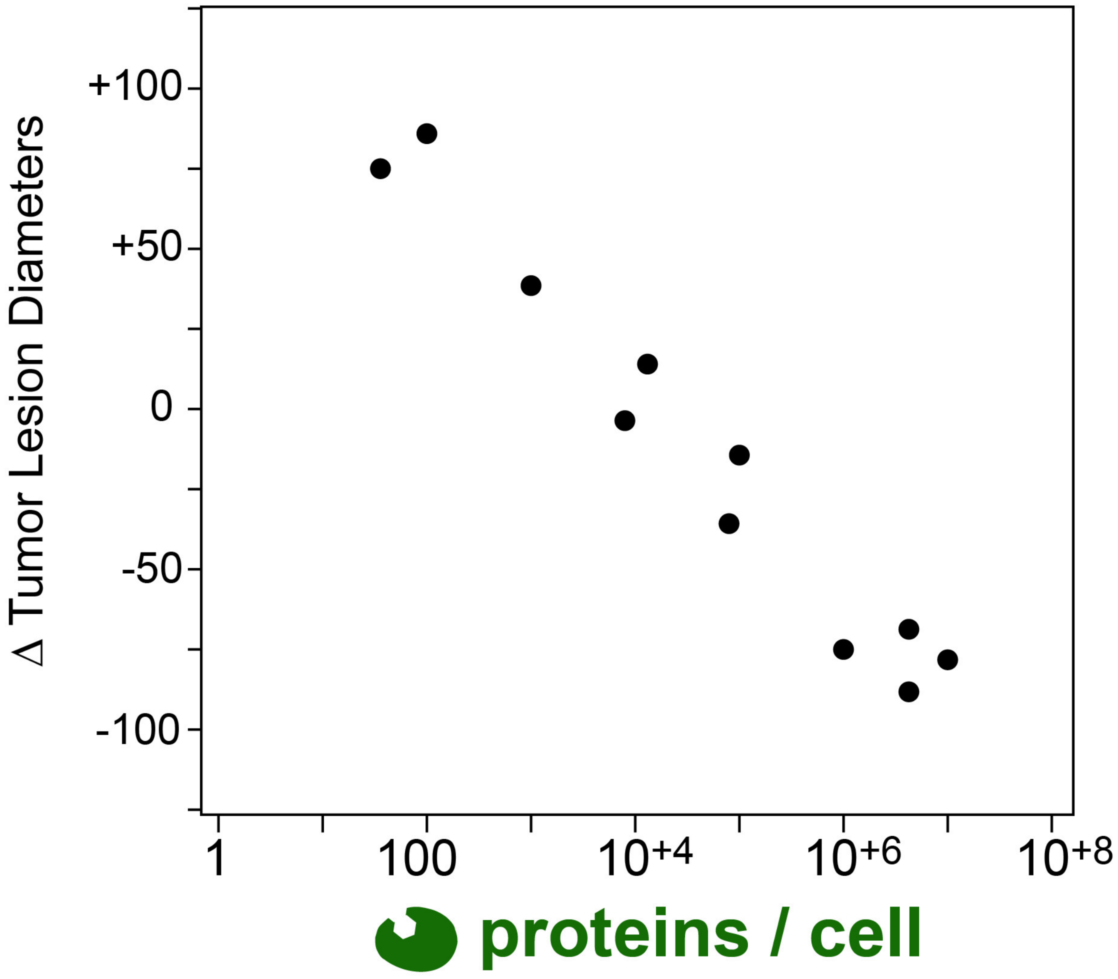




Cancer Res Treat., **2005**, 37, 290-293

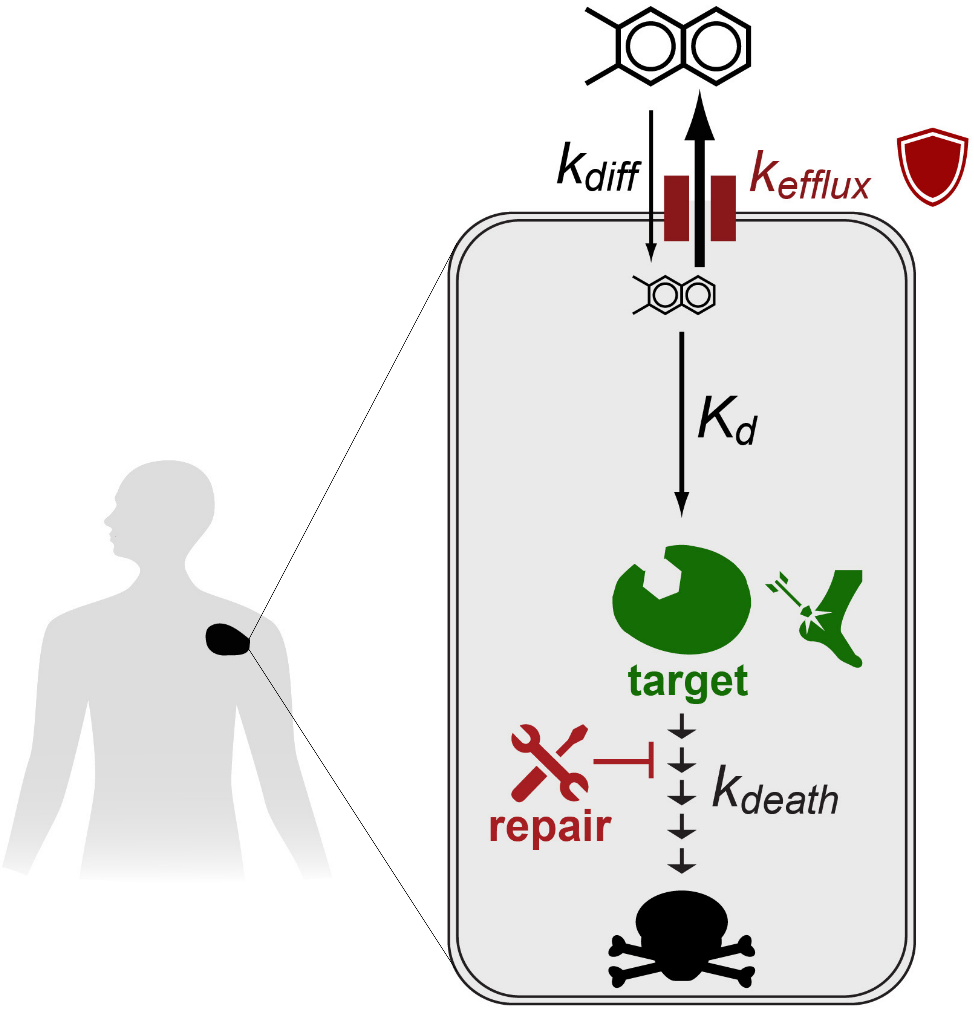
Clinical Biomarker Research: *focus on drug-target*

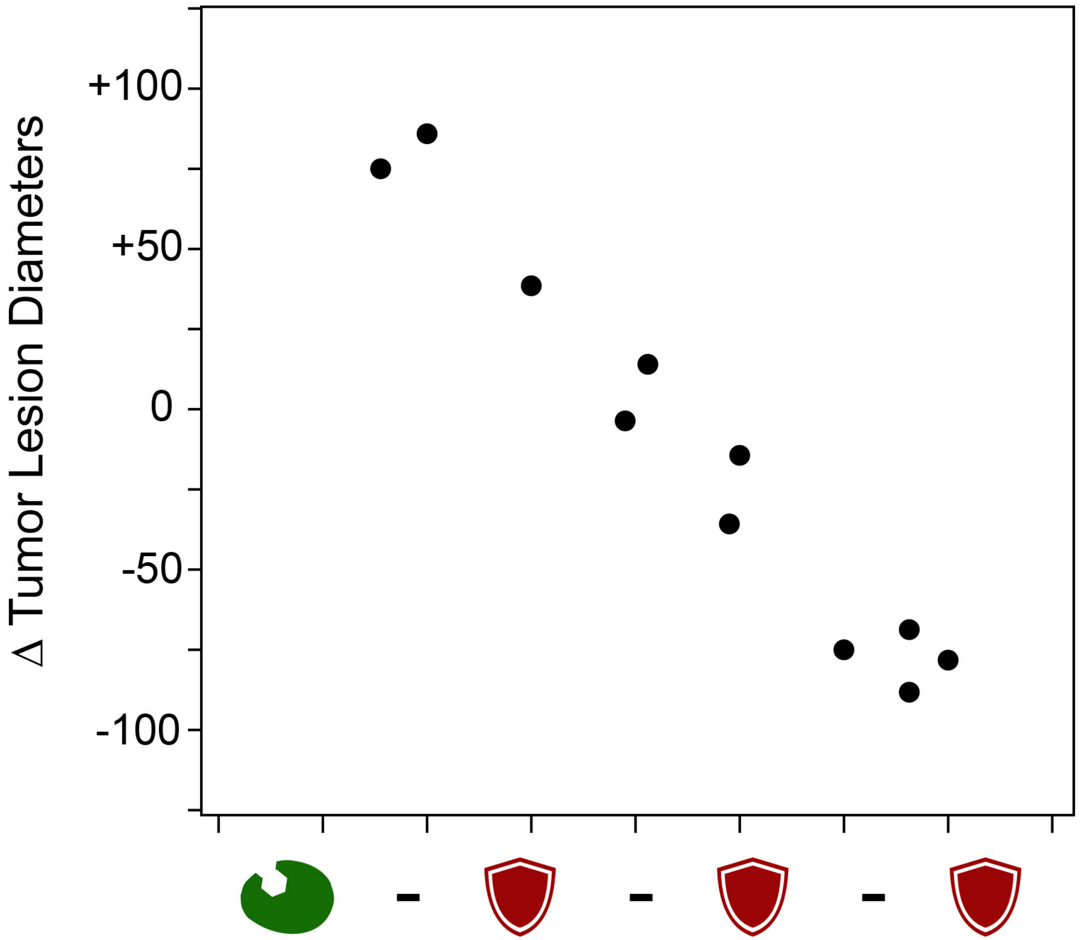




Annals of Oncology, **2016**, 27, 2004-2016

Cytotoxic chemotherapies: *1-drug / N-biomarkers*

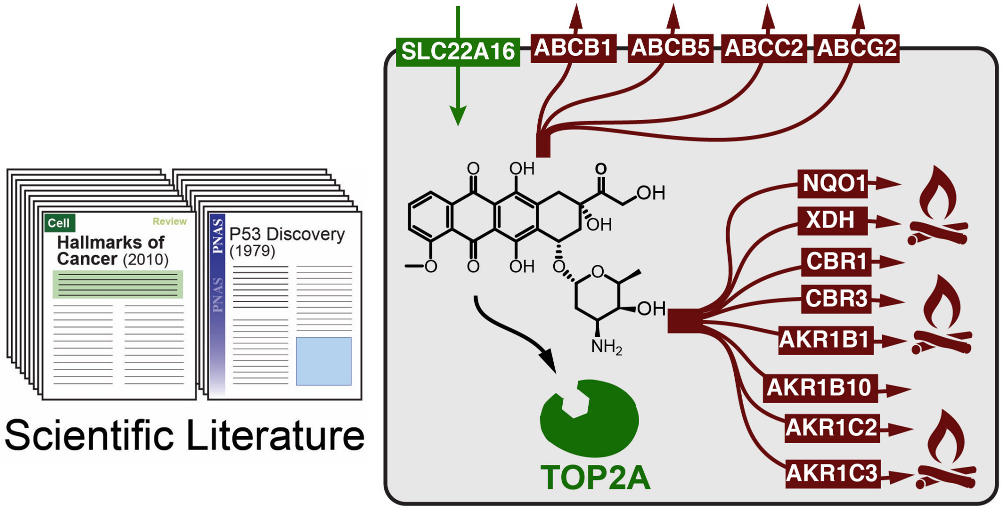


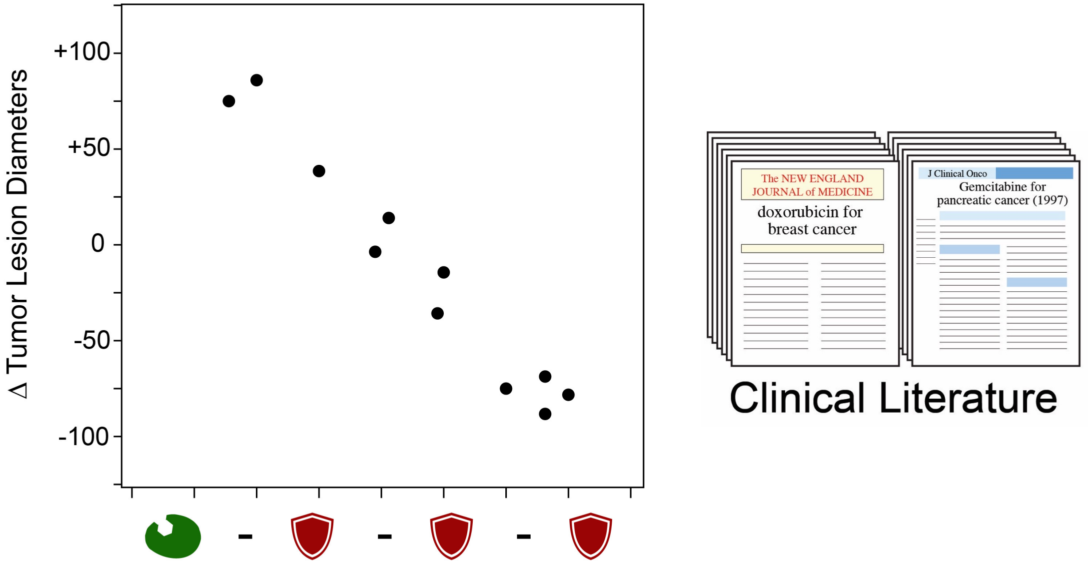


Annals of Oncology, **2016**, 27, 2004-2016

EXPERIMENTAL WORK

How do you combine N-biomarkers?



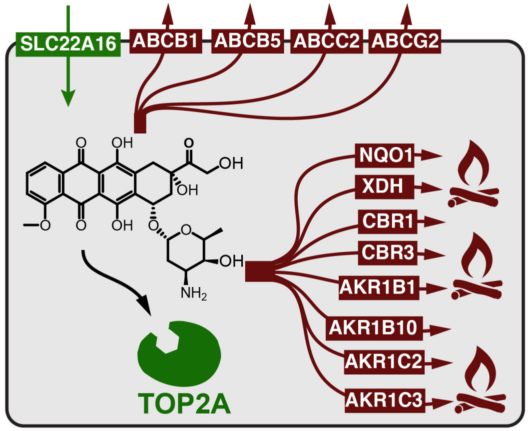


$$\Delta IC_{50} = \frac{k_{cat}/K_m}{k_{diff}}[ABCB1] + \frac{k_{cat}/K_m}{k_{diff}}[ABCG2] \ldots$$

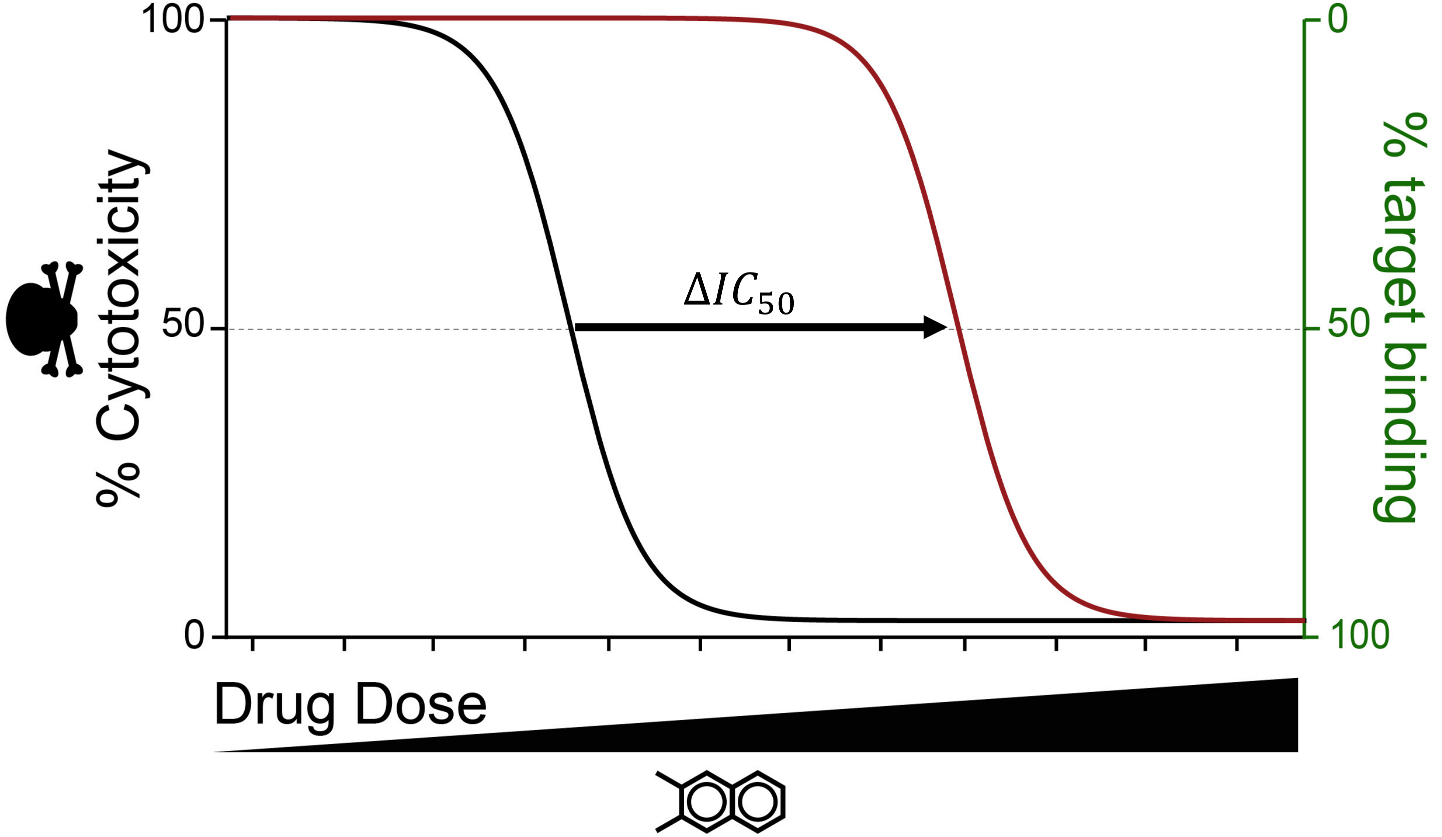
$$\Delta IC_{50} = \frac{k_{resist}}{k_{diff}} = \sum_{i=1}^{N} \frac{k_{cat}/K_m}{k_{diff}}[E]_t$$

$$\Delta\Delta IC_{50} = \frac{k_{cat}/K_m}{k_{diff}} \Delta[ABCB1]$$

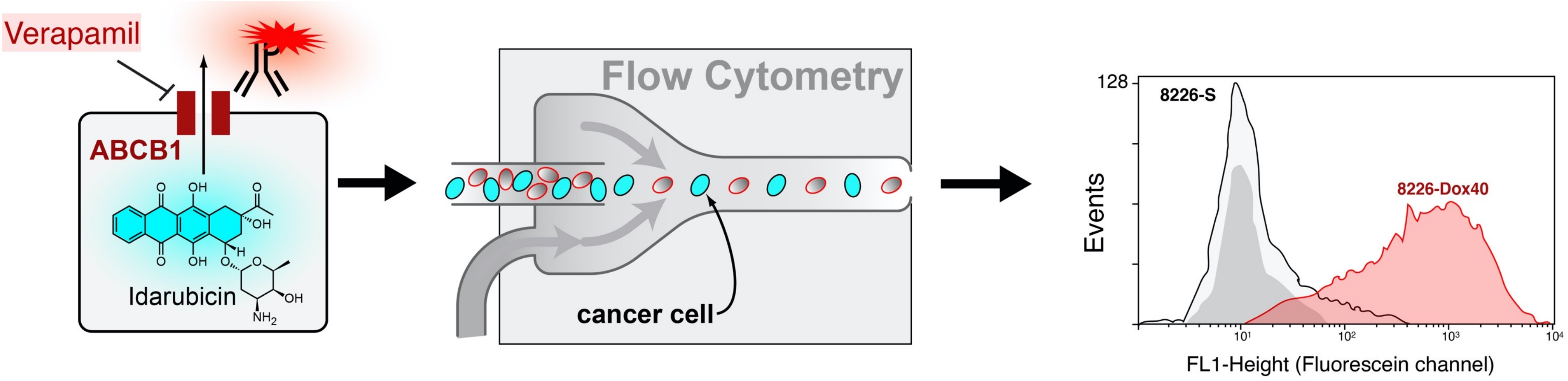
Tool to study contribution of individual biomarkers



$$\frac{\Delta IC_{50}}{\Delta[ABCB1]} = \frac{k_{cat}/K_m}{k_{diff}}$$



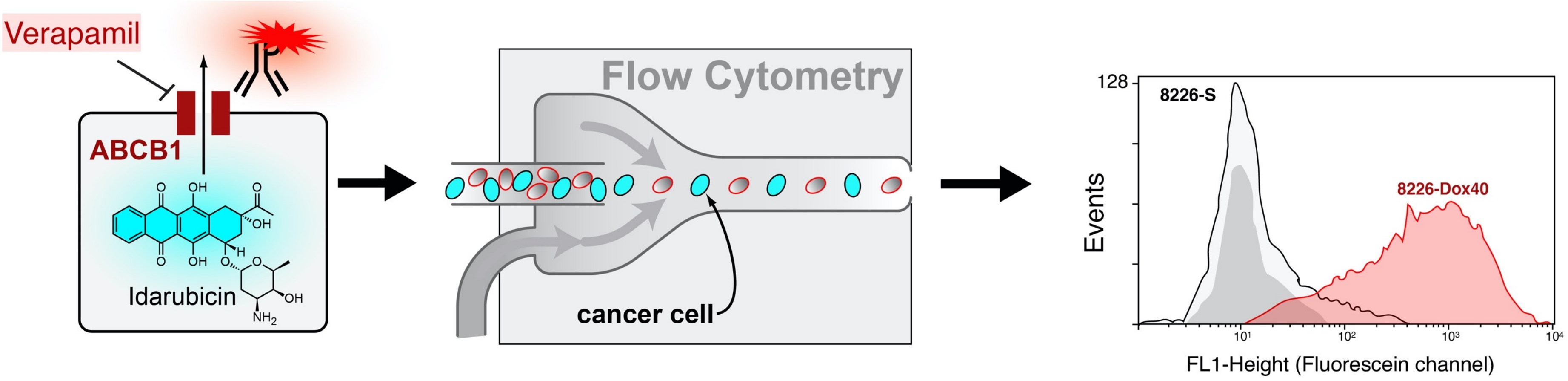
Measure Biomarker Expression: *Flow cytometry*

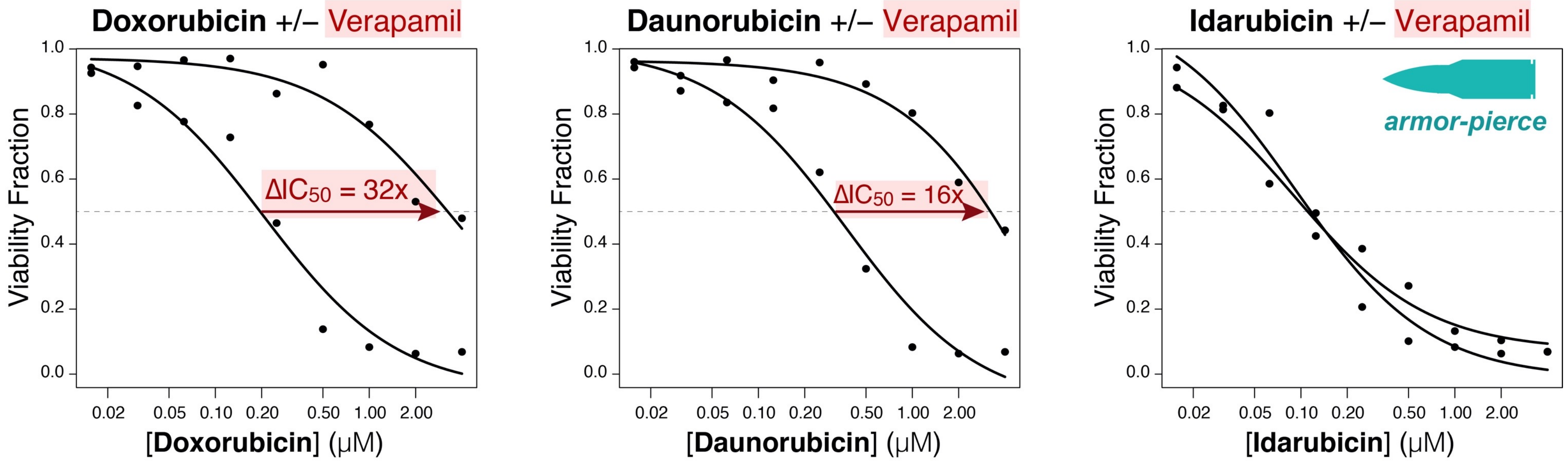


$$\frac{\Delta IC_{50}}{\Delta[ABCB1]} = \frac{k_{cat}/K_m}{k_{diff}}$$

Leukemia Research, **1999**, 23, 539-548

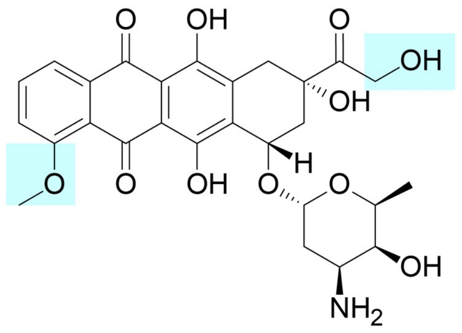
Measure Biomarker Expression: *Flow cytometry*

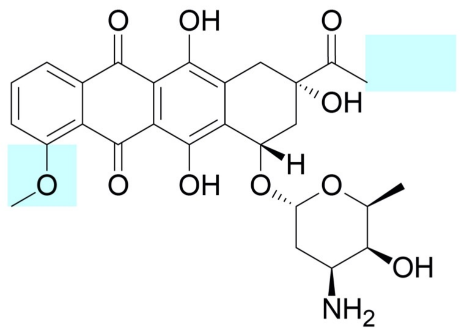


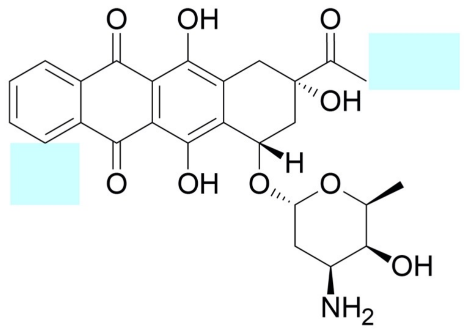


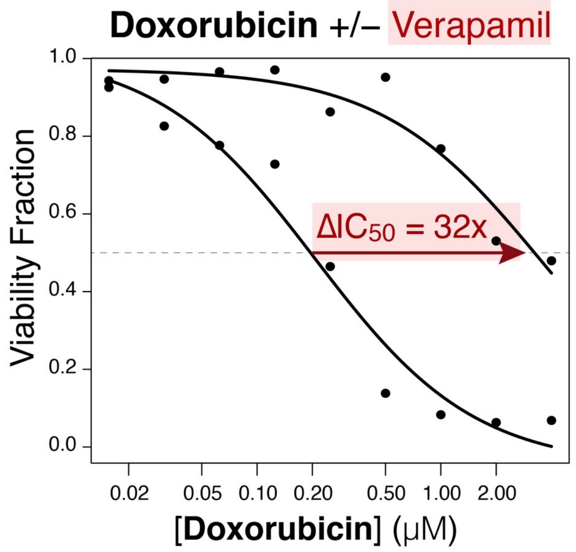
Leukemia Research, **1999**, 23, 539-548

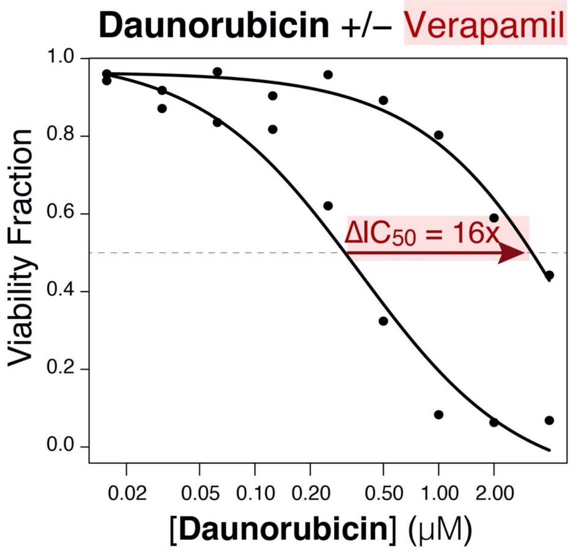
Design "Armor Piercing Chemo": *Anthracyclines*

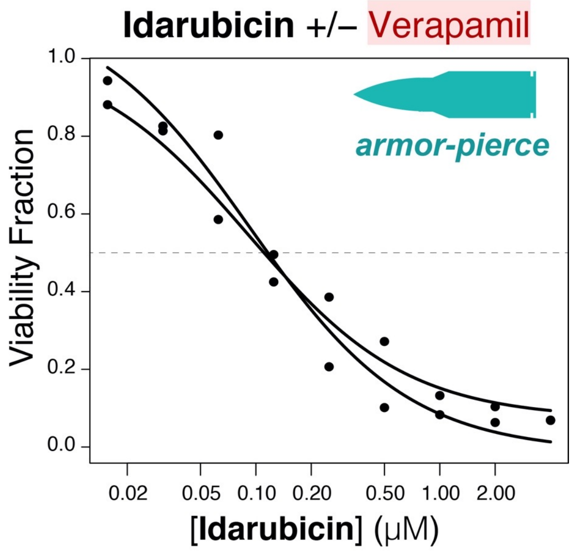










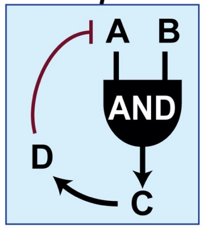


Leukemia Research, **1999**, 23, 539-548
Ann. Hematol, **1997**, 74, 57-64

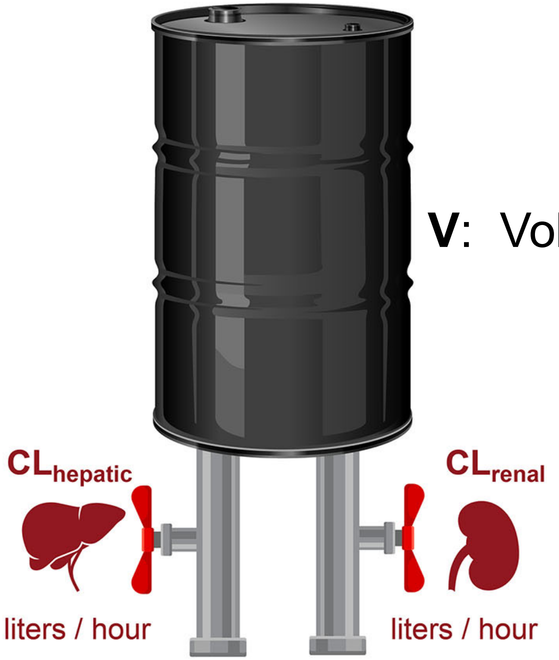
Doctoral Student Educational Approach:
experimental scientists

Pharmacist and Scientists: *improving data-numeracy*

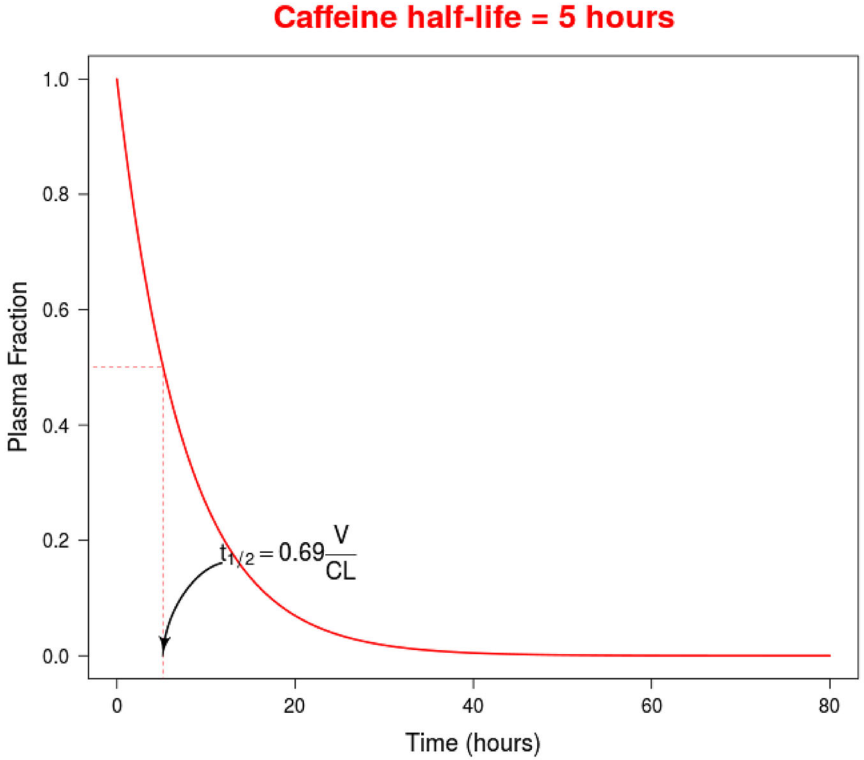
"blueprint"



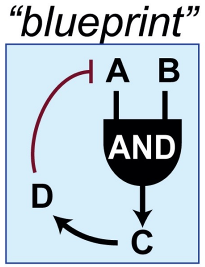
$$Plasma\ Fraction = e^{time \cdot CL/V}$$

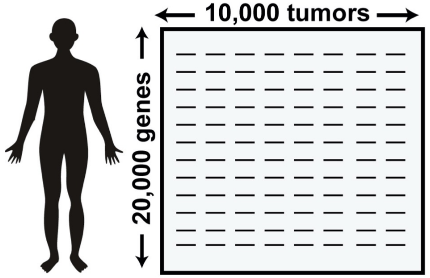


V: Volume of Distribution (liters)



Pharmacist and Scientists: *improving data-numeracy*





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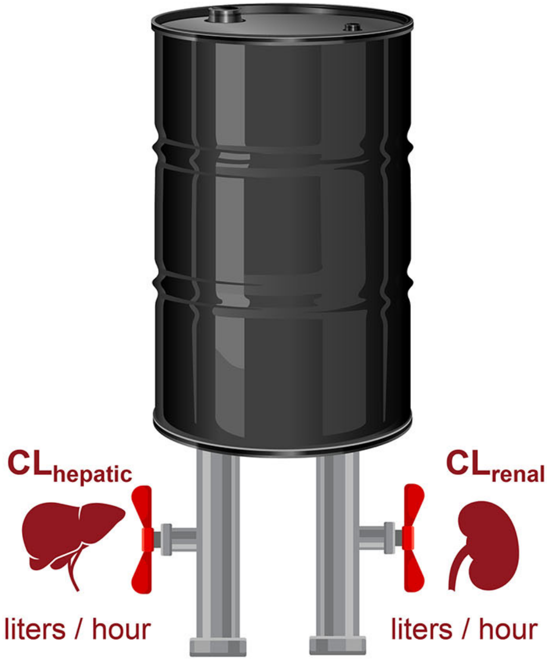
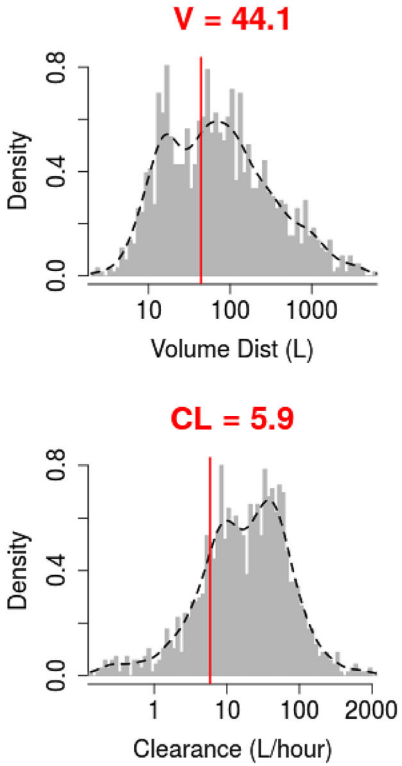
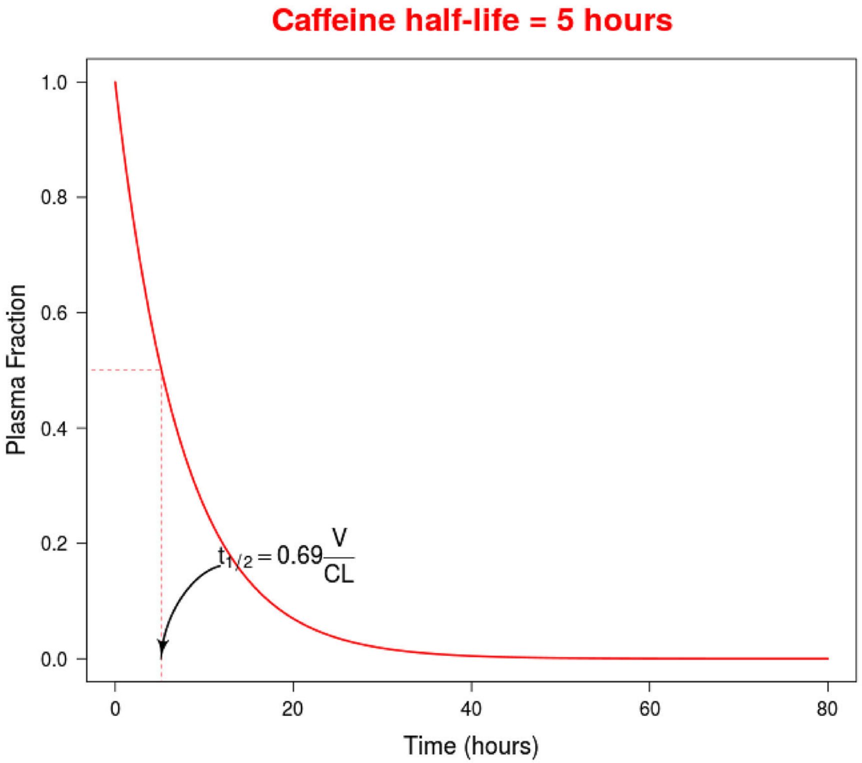
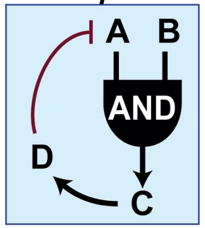


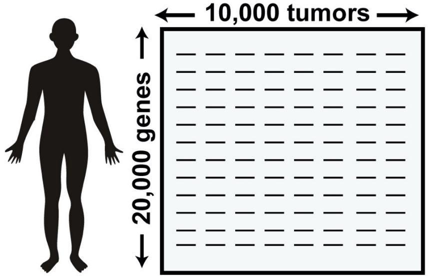




Pharmacist and Scientists: *improving data-numeracy*

"blueprint"





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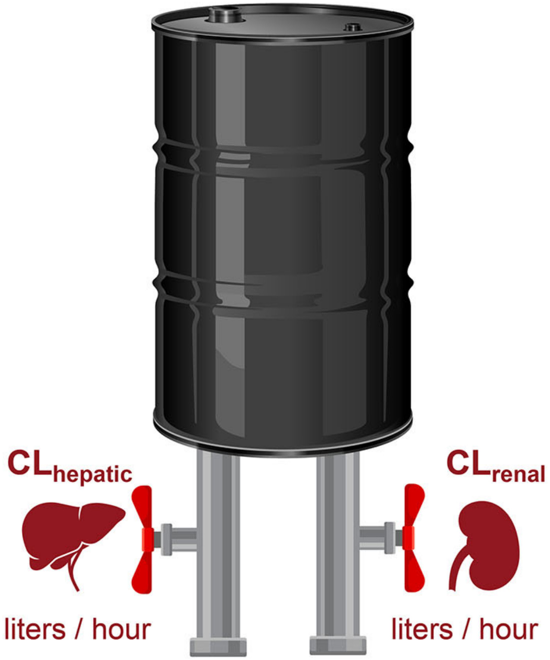
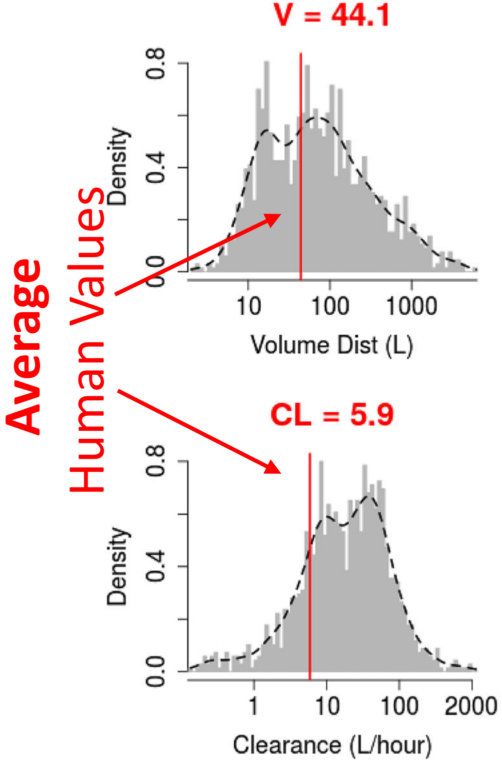
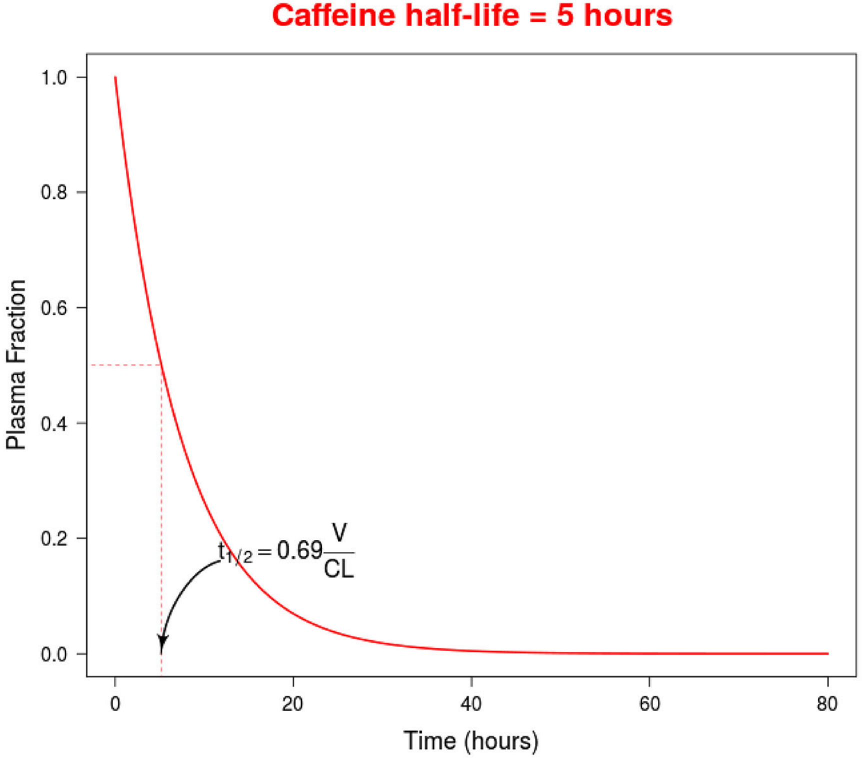
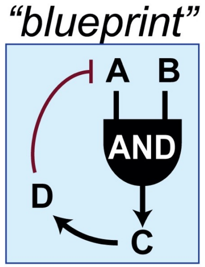
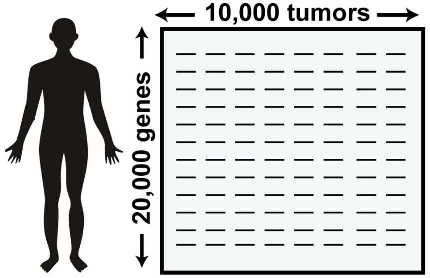






Pharmacist and Scientists: *improving data-numeracy*





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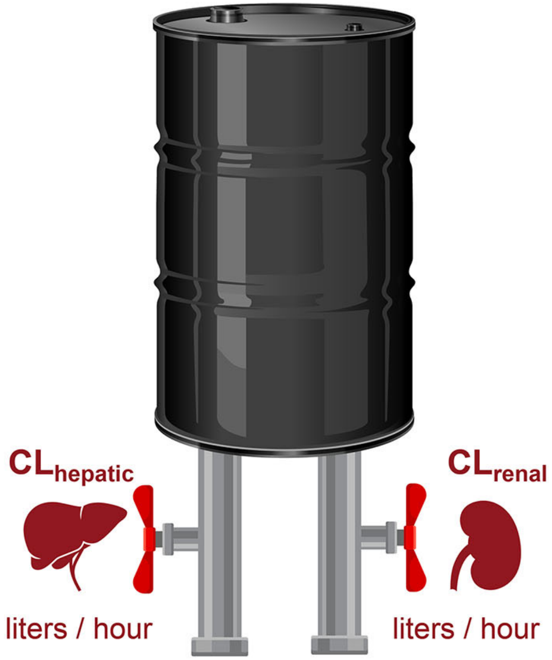
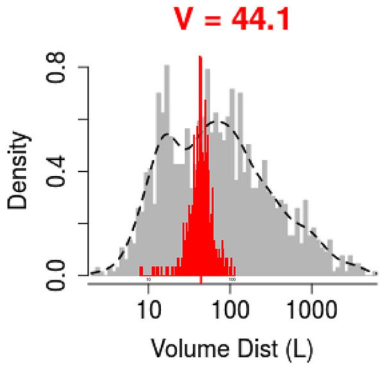
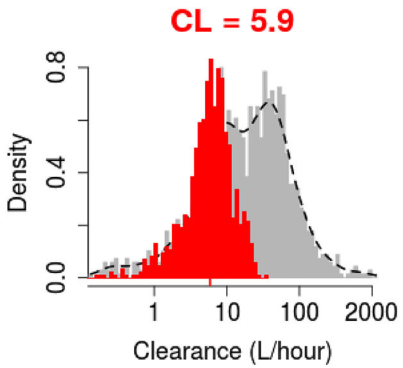
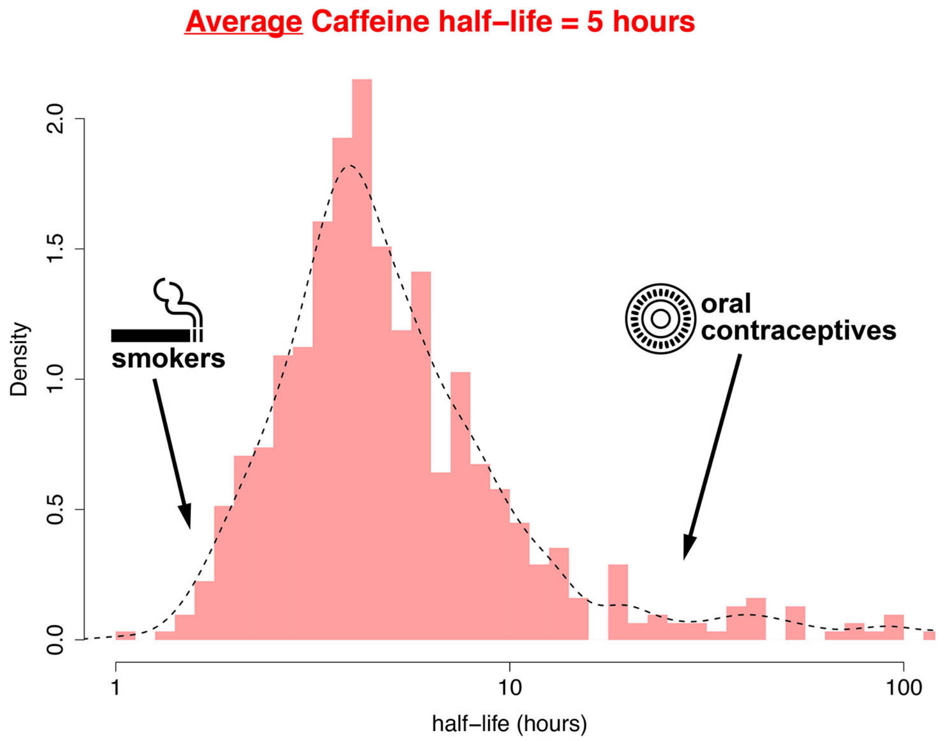








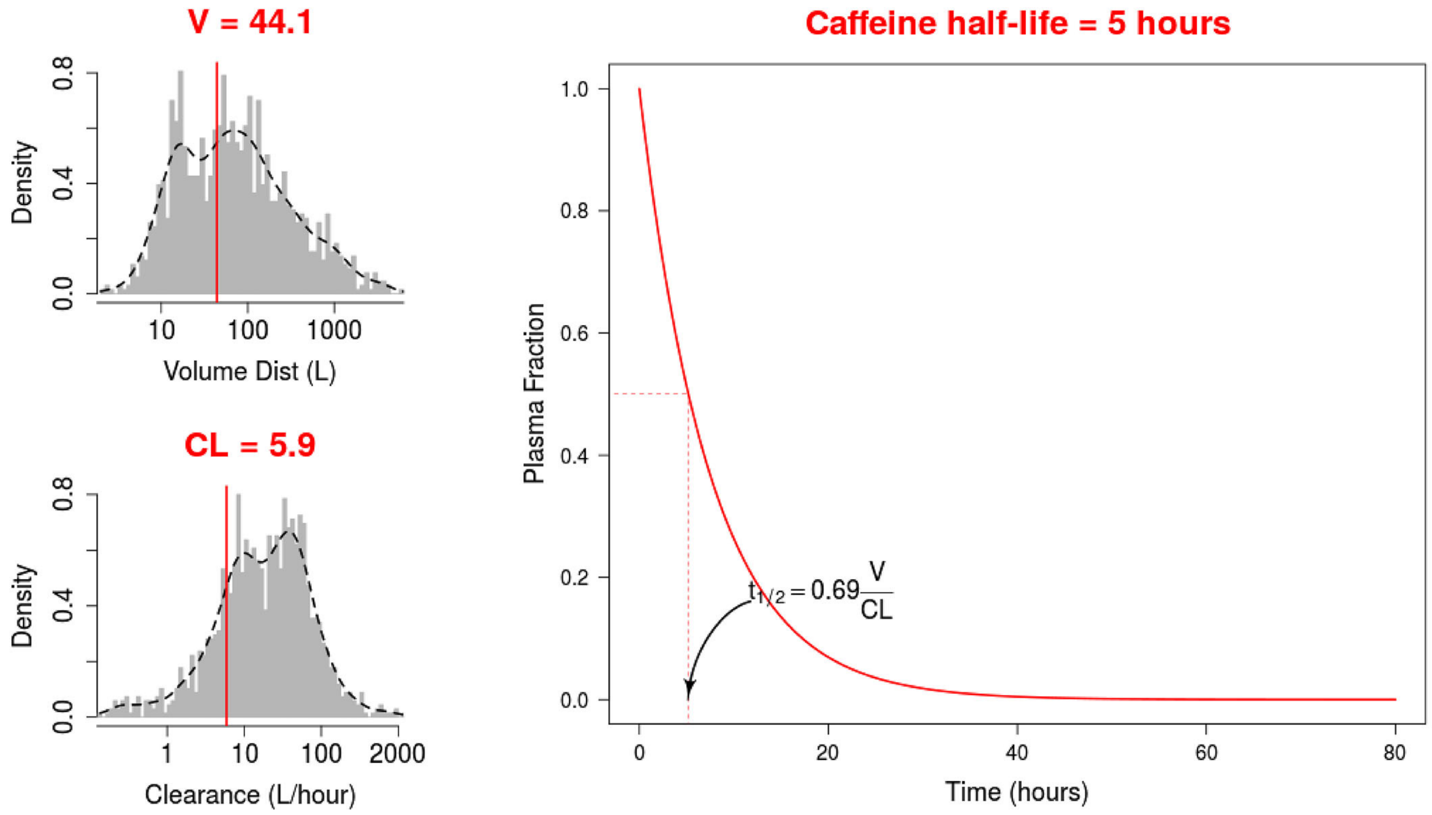
Webtool: *https://douglasslab.com/pk-db-iv/*

PK DATABASE:

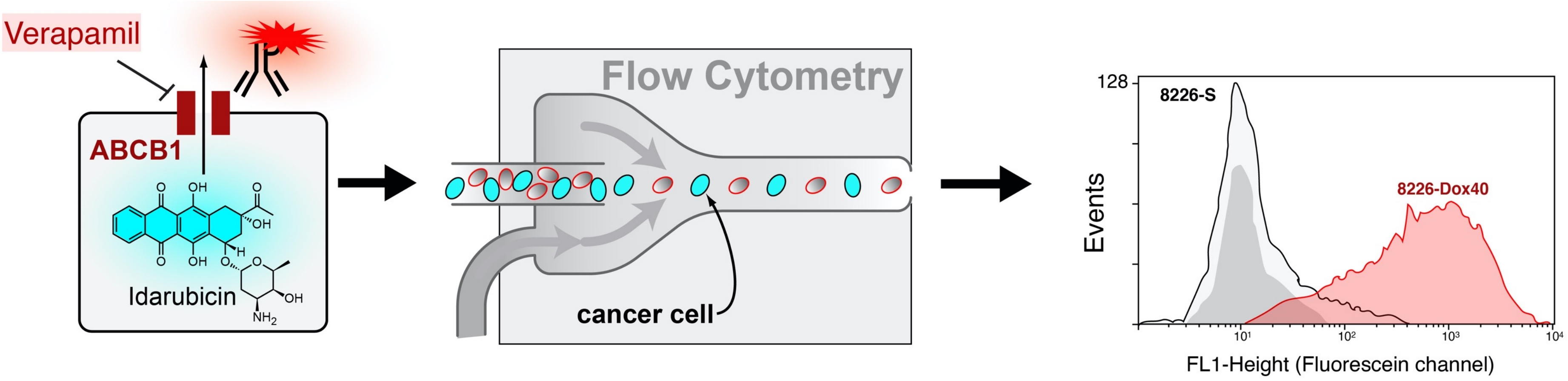
The plot below illustrates the IV-kinetics of ~1000 drugs whose pharmacokinetic parameters from a were taken from a database published in 2018 (Drug Metab Dispos 2018, 46, 1466)

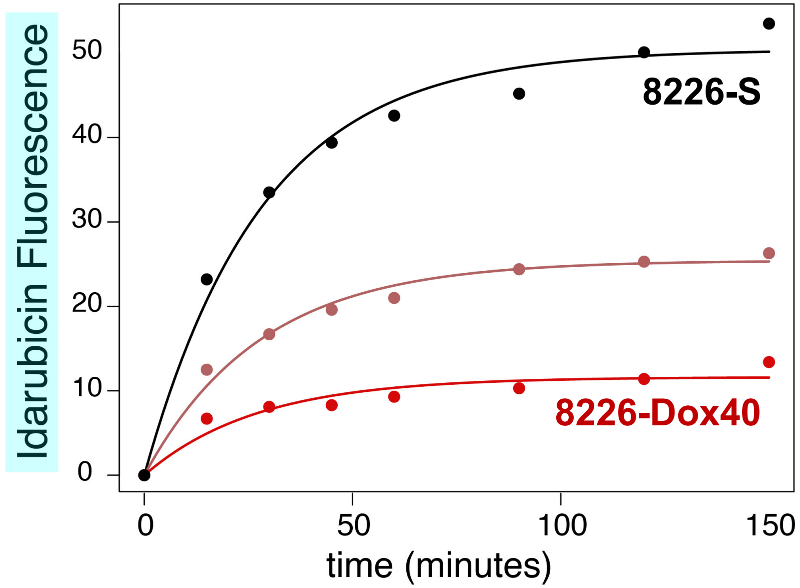
Type Drug Name below

Caffeine



Deconvolute diffusion & enzyme flux





$$[IDA]_{intra} = [IDA]_{extra} \frac{k_{diff} \cdot K_m}{k_{cat} \cdot [ABCB1]}$$

$$t_{1/2} = \frac{1}{k_{diff} + [ABCB1] \quad k_{cat}/K_m}$$

Leukemia Research, **1999**, 23, 539-548
Ann. Hematol, **1997**, 74, 57-64