Realizing society's expectations of the cancer community

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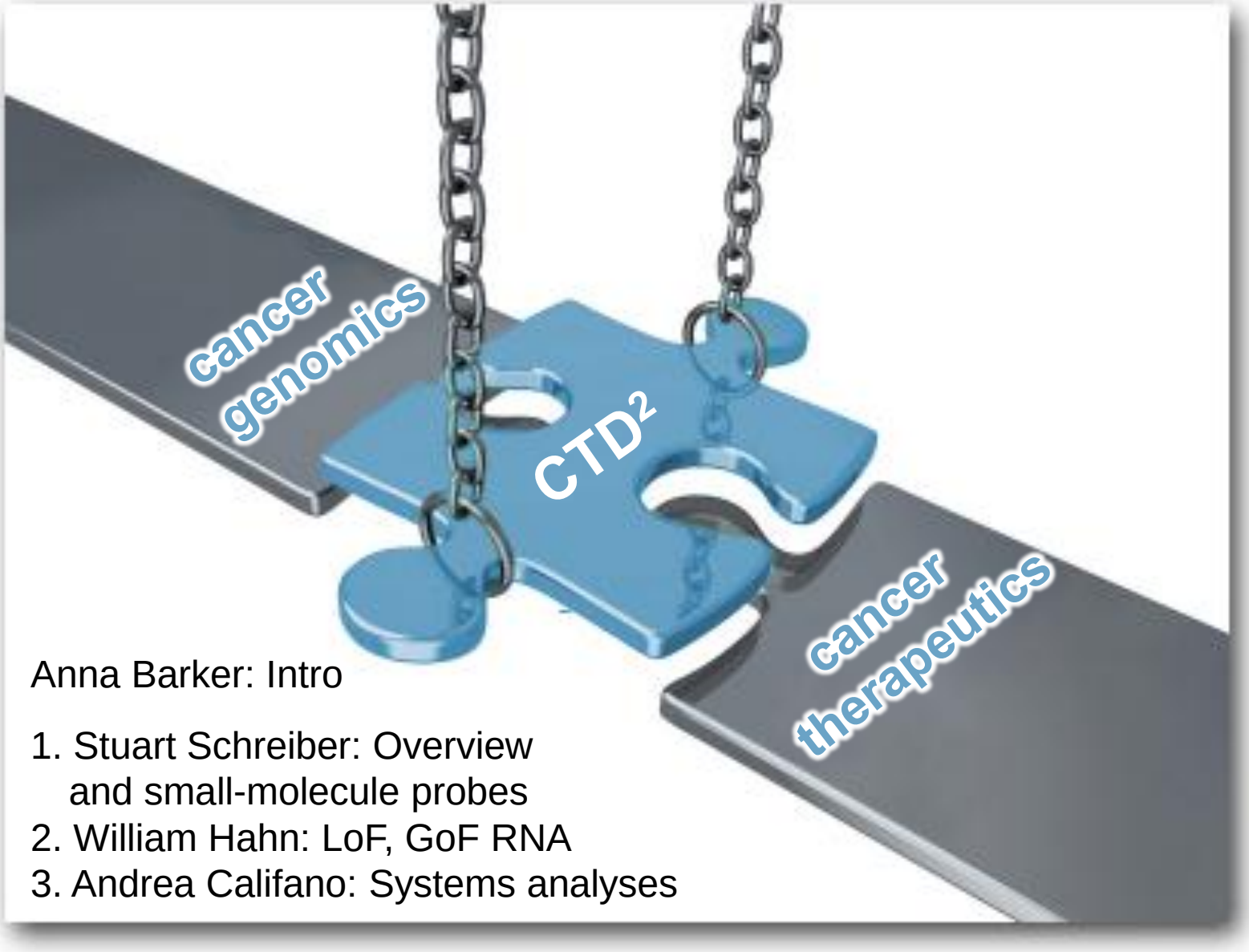


Anna Barker: Intro

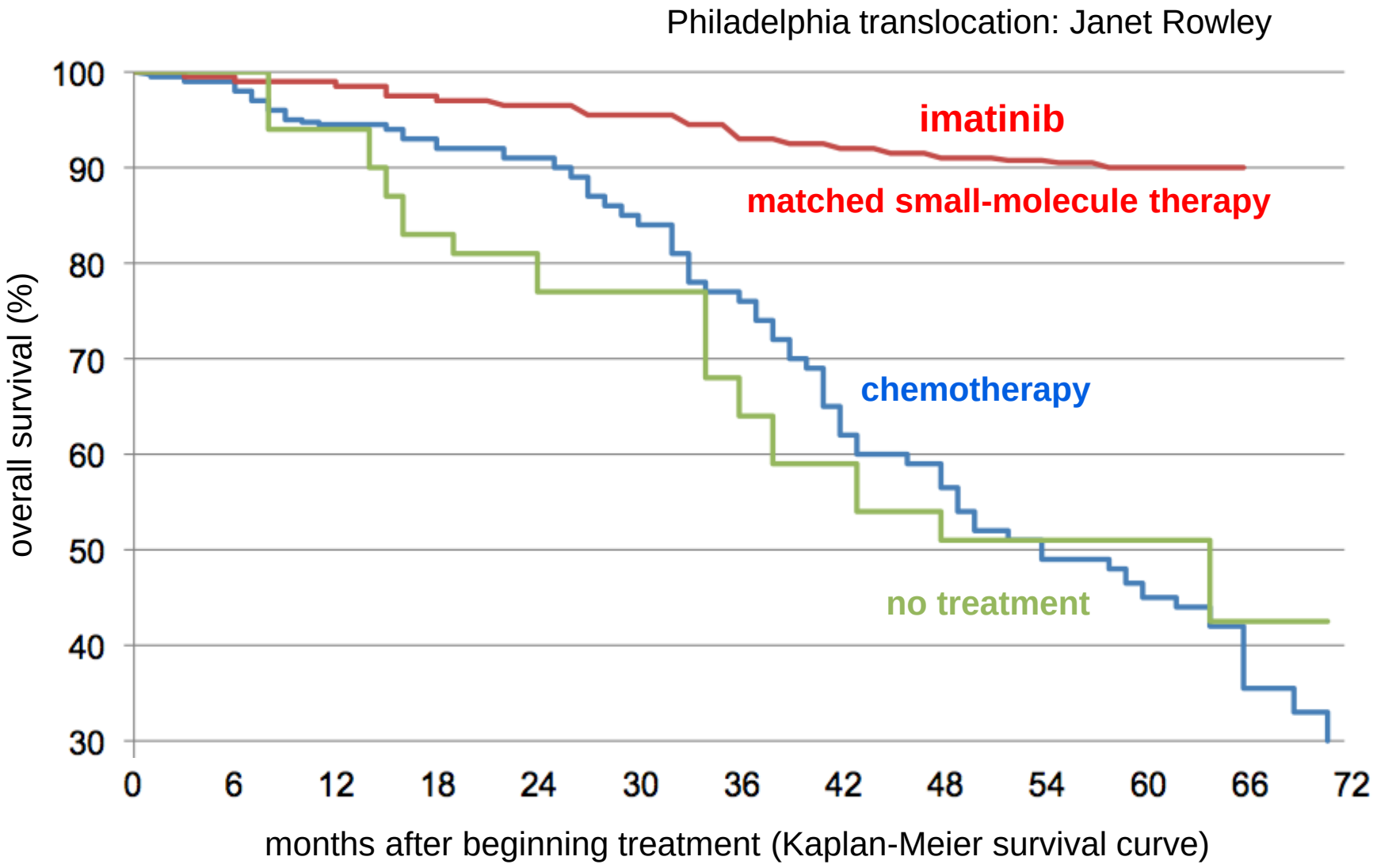
1. Stuart Schreiber: Overview and small-molecule probes
2. William Hahn: LoF, GoF RNA
3. Andrea Califano: Systems analyses

Cancer Target Discovery and Development (CTD²) Network

Office of Cancer Genomics

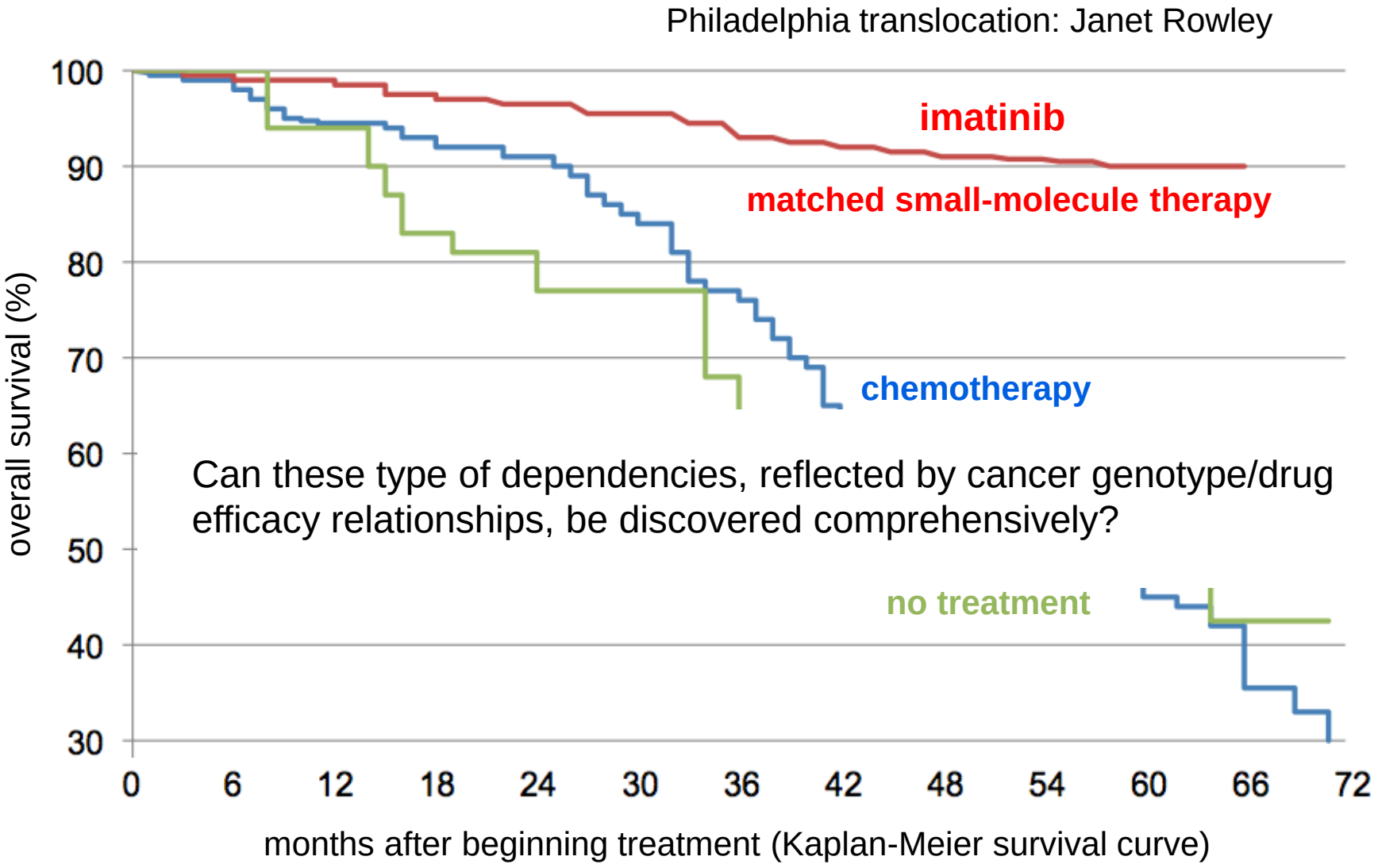
"Towards patient-based cancer therapeutics" Andrea Califano, Daniela S. Gerhard, William C. Hahn, Scott Powers, Michael Roth, Stuart L. Schreiber, in review

Relating a genetic feature of a cancer to the efficacy of a drug



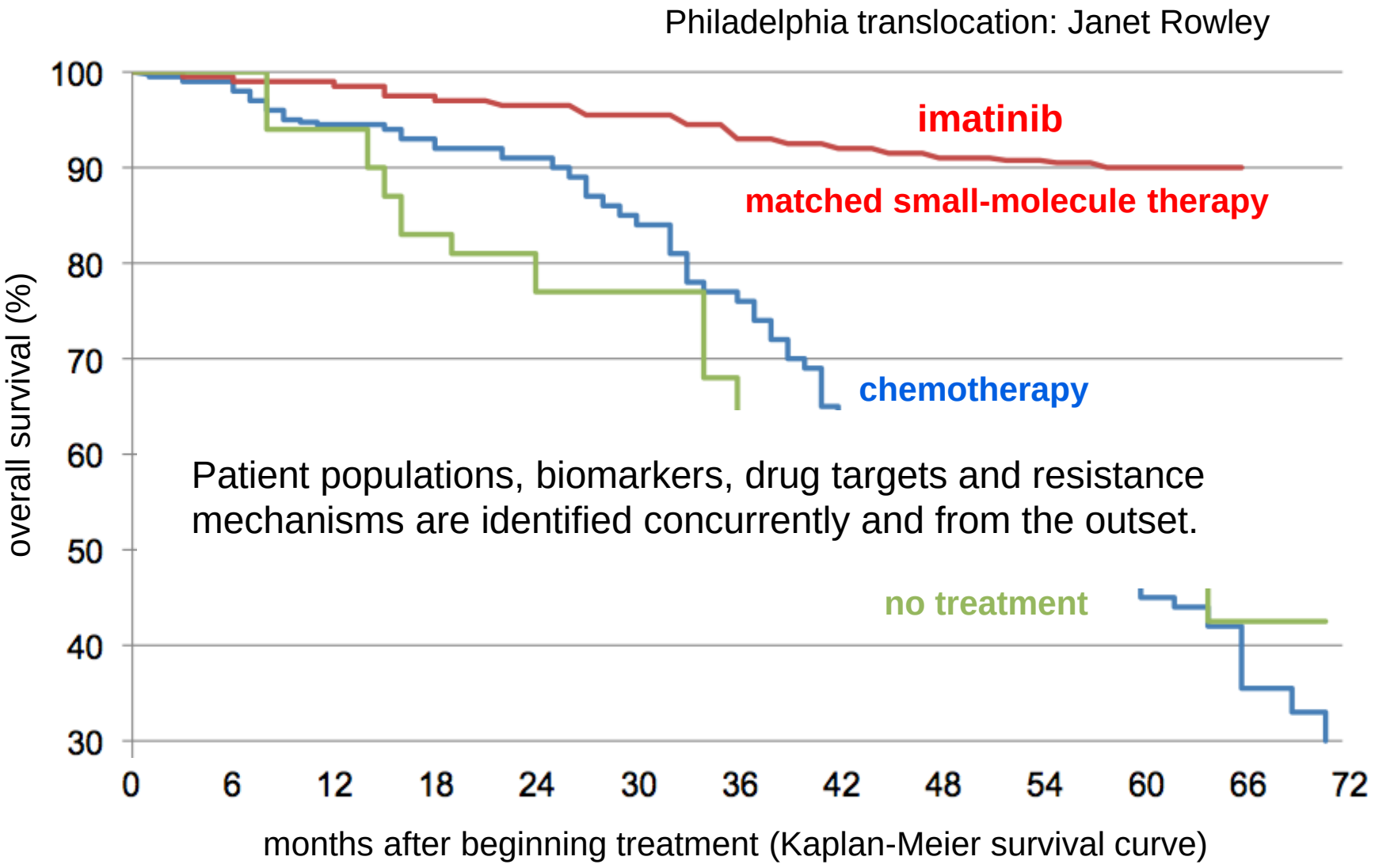
Brian J Druker, **Nature Medicine** *15*, 1149-1152 (2009)

Relate cancer genetic features to drug efficacy *comprehensively*



Brian J Druker, **Nature Medicine** *15*, 1149-1152 (2009)

Facilitate efficient paths for clinical development *prospectively*



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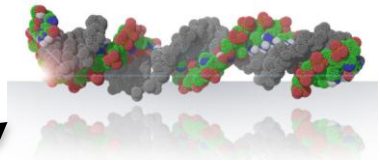

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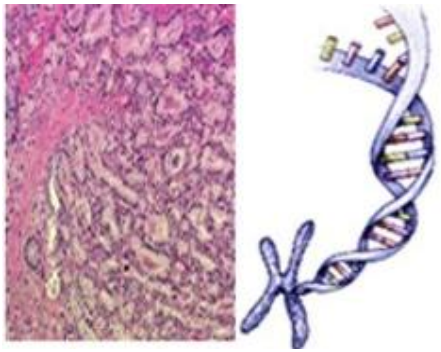
cancer genomics



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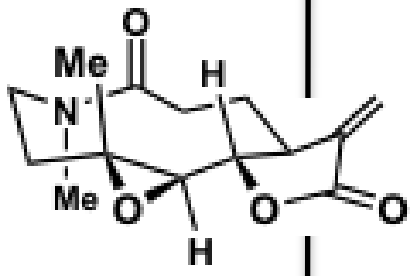
(*small-molecule probe set*)

small-molecule probes



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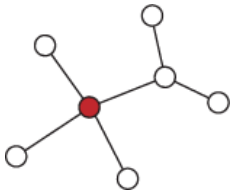

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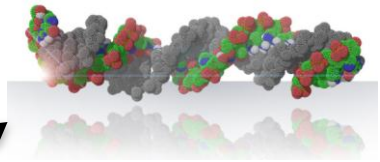

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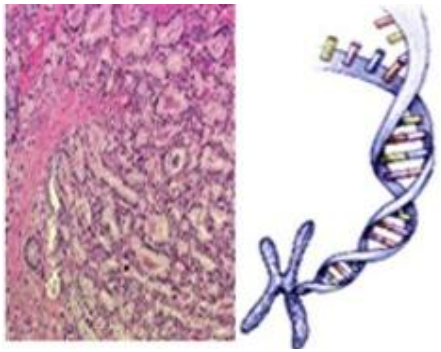

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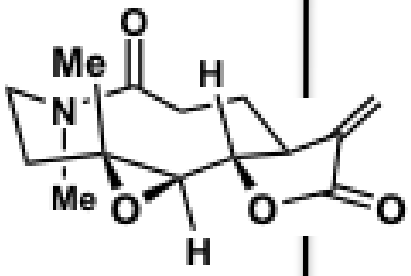

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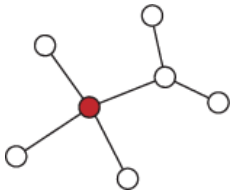

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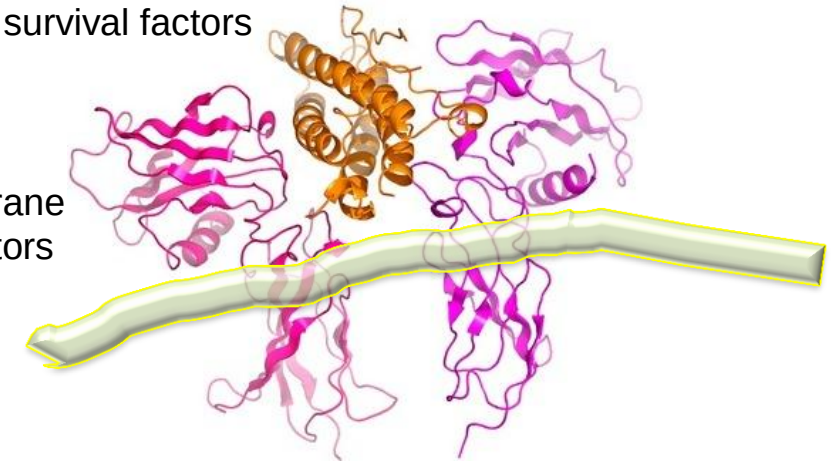
Small-molecule cancer probes against challenging targets

growth, differentiation, survival factors

Sonic Hedgehog, HB-EGF

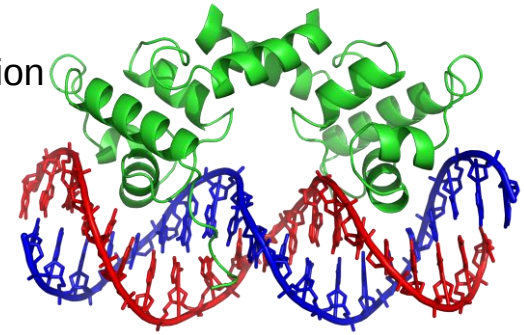


membrane receptors

DDR1

(targets of small molecules whose functions have been modulated in cells)

GPCRs, kinases, etc.



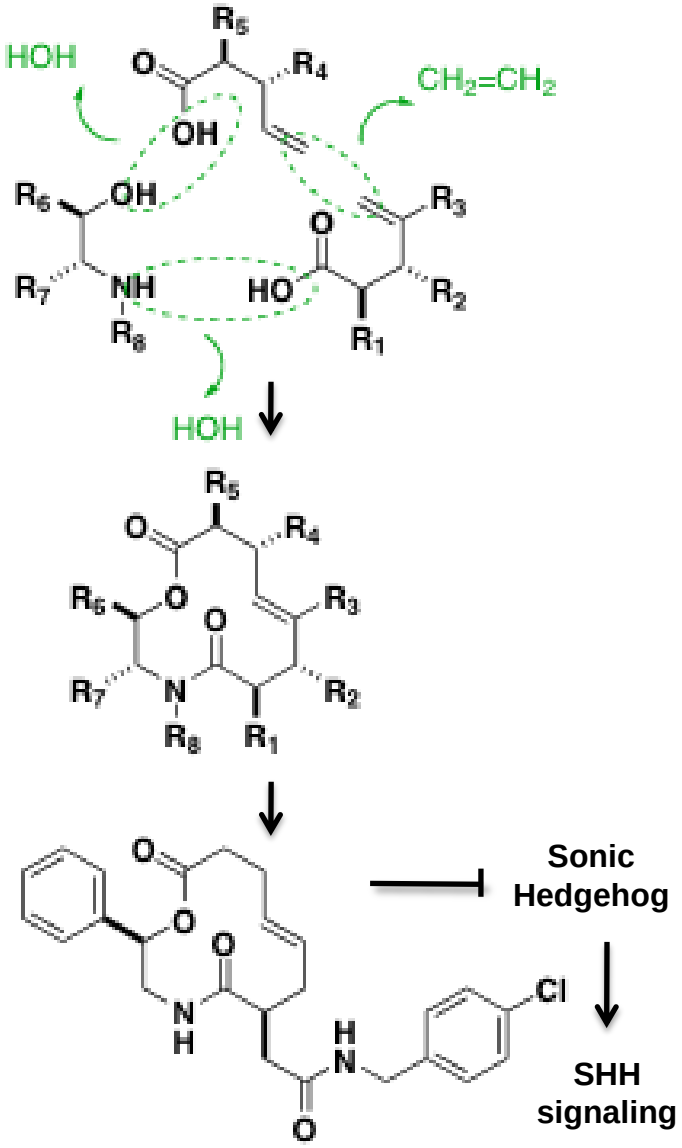
transcription factors

NFkB, GATA1, Myc, C/EBPa, HOXA13; HDAC6, JMJD2C

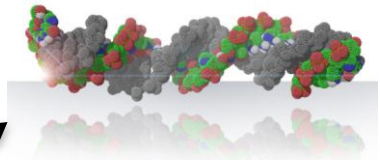
From opportunistic to disciplined: modulating challenging targets

Advances exploited by CTD^2 and enabling a disciplined approach to cancer drug discovery:

- innovations in **next-generation synthetic chemistry** that reach **'undruggable'** targets or processes.
- innovations in cell culturing and screening in physiologically relevant conditions (**tumor microenvironment**)
- innovations in determining the targets and **mechanisms** of small-molecule probes and drugs.



Cancer Target Discovery and Development (CTD^2) Network



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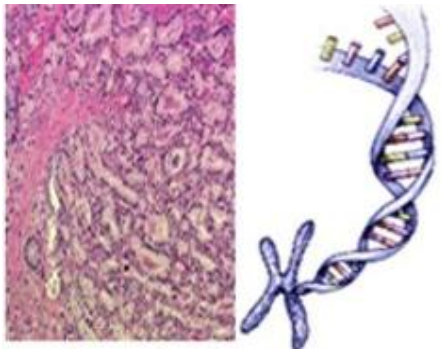

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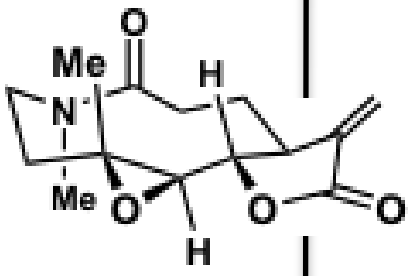

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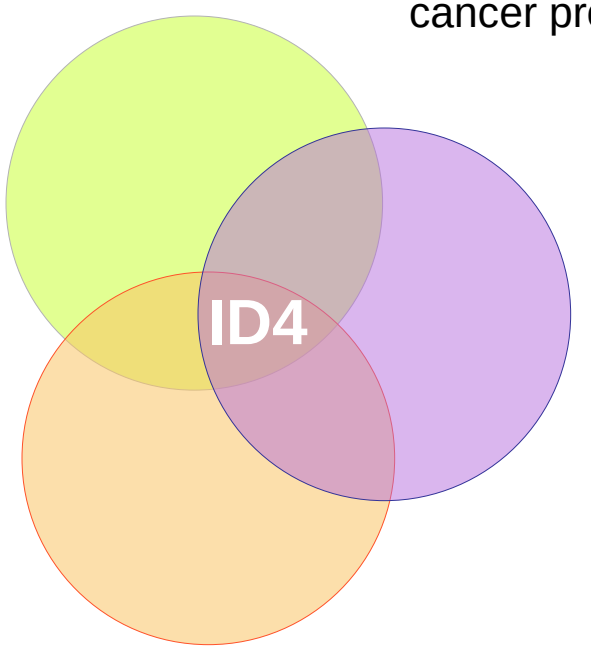

Cancer Genome Annotation

Cross reference with genes in amplified regions in OvCa (TCGA)

Gain-of-Function Genes that induce ovarian tumor formation

Bill Hahn et al.

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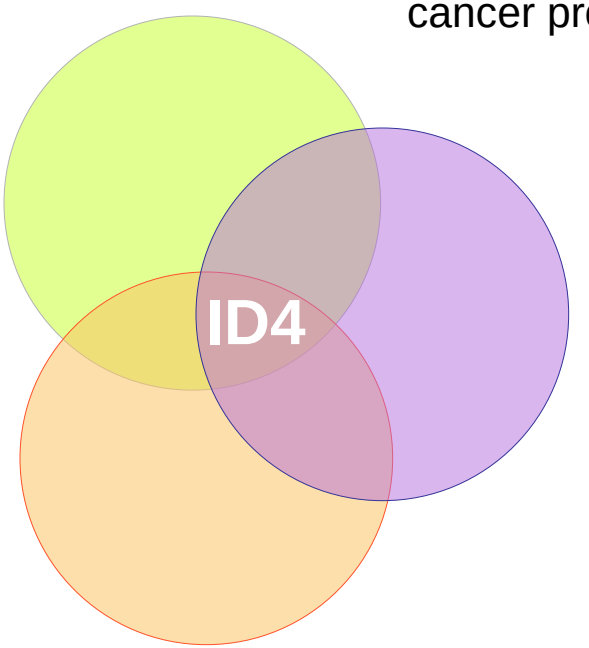

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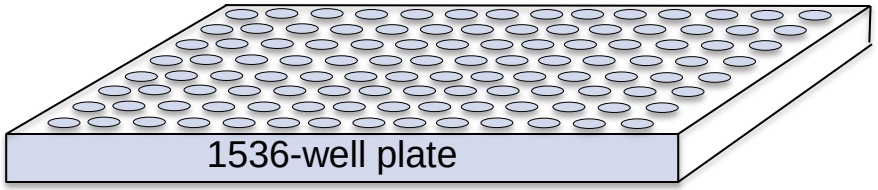
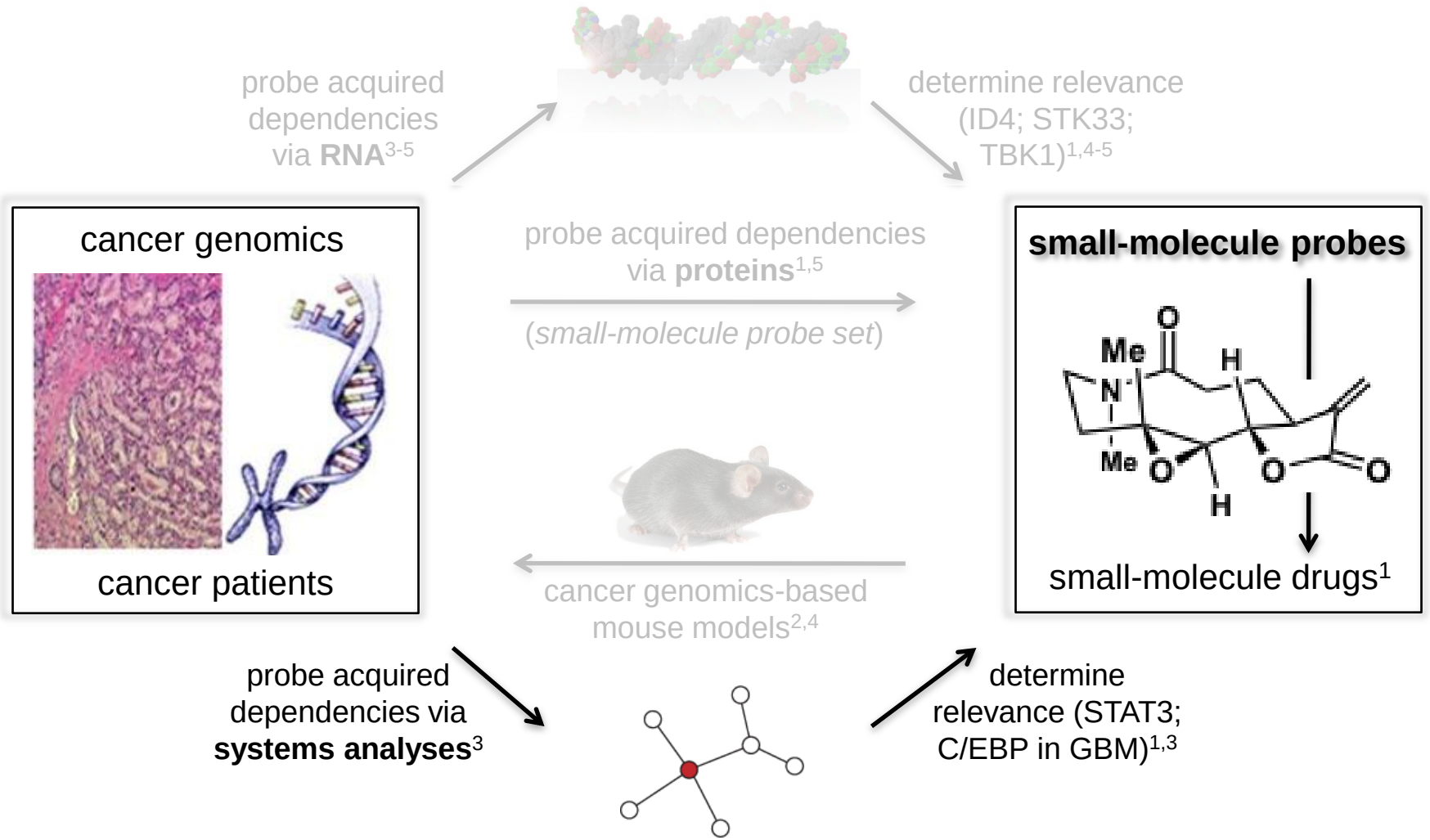


Bill Hahn et al.

Cancer Target Discovery and Development (CTD^2) Network



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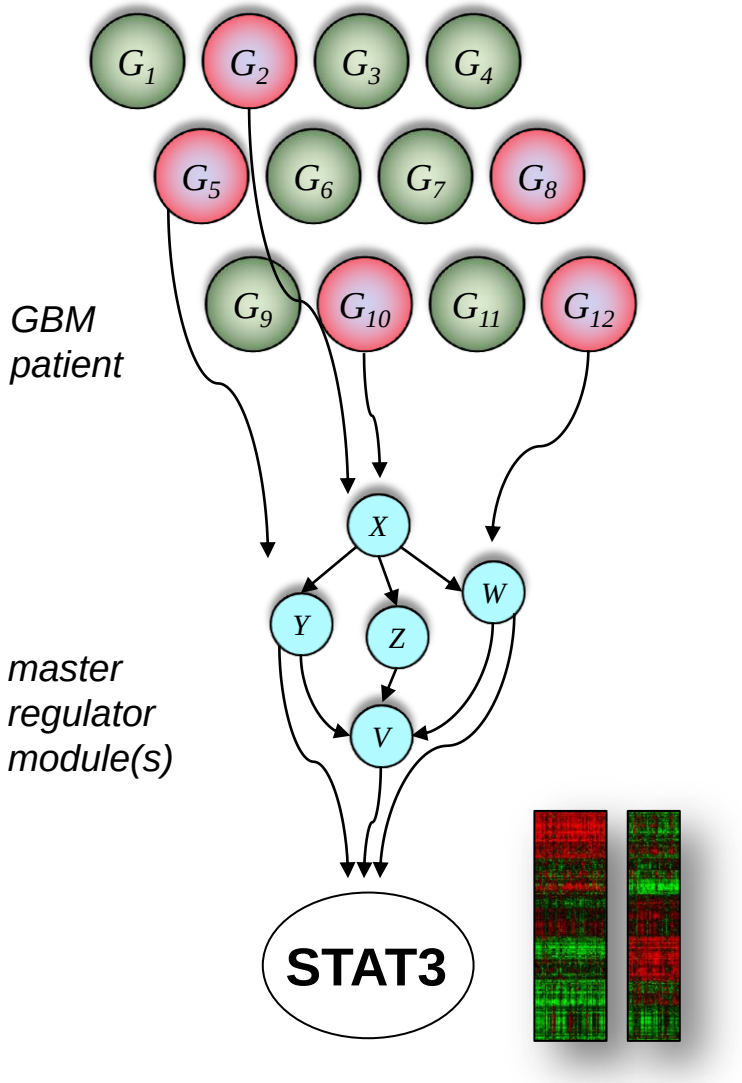

Andrea Califano et al.

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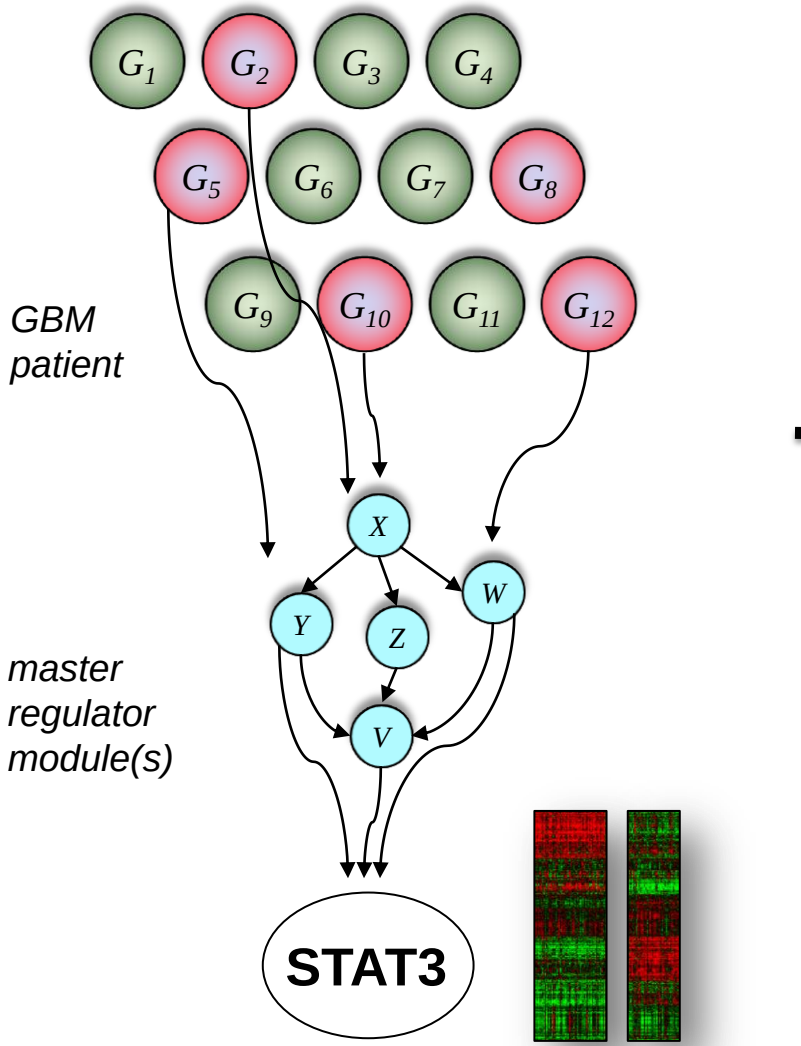

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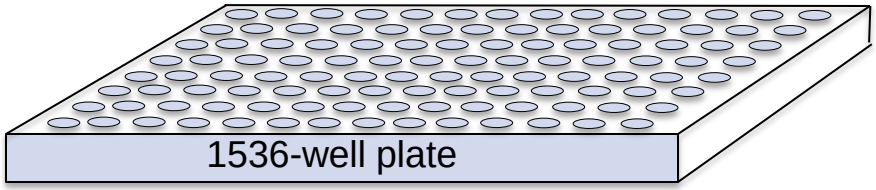
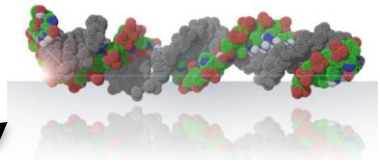


Andrea Califano et al.

CTD^2 Network: challenging probe development projects

	Assay Project Name	Collaborator
CTD^2 Network Collaborations	Stat3 - SMM	Columbia-CTD^2
	CEBPβ/δ - SMM	Columbia-CTD^2
	ID4	DFCI-CTD^2
	tumor cell dependency	CSHL-CTD^2
	TBK1	DFCI-CTD^2
CTD^2 Broad Collaborations	Myc	Koehler / Ebert
	IDH1 mutants	Liu / Shamji
	Hb-EGF - SMM	Mandinova / Lee
	ROS dissipation	Wagner / Mandinova
	p53 mutant activation - SMM	Mandinova
	p53 mutant activation - cell based	Mandinova
	NFkB	Koehler
	ETS-TF	Garraway
	JMJD2C	Kubicek
	LSD 1	Kubicek
	EZH2	Paulk / Schreiber
	NSD family	Adams / Schreiber
	DOT1	Paulk / Schreiber
CTD^2 proposed outreach ideas	Mitochondria Glutaminase	
	JARID1A	
	Glut1	
	Deubiquitinase	

Cancer Target Discovery and Development (CTD^2) Network



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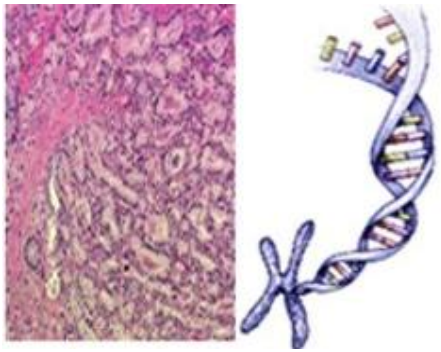

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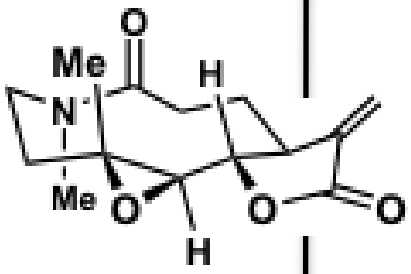

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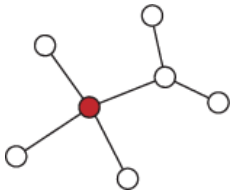

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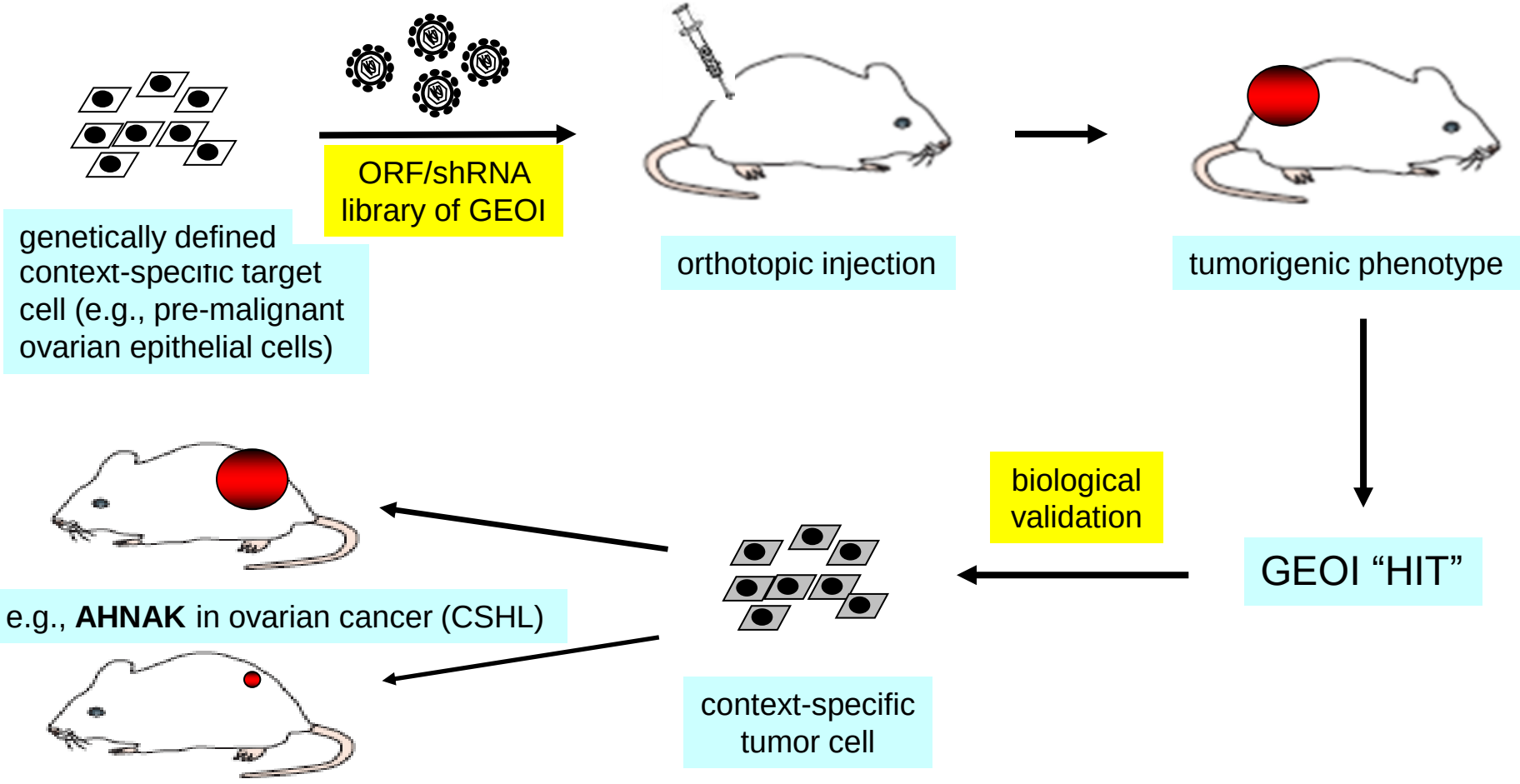
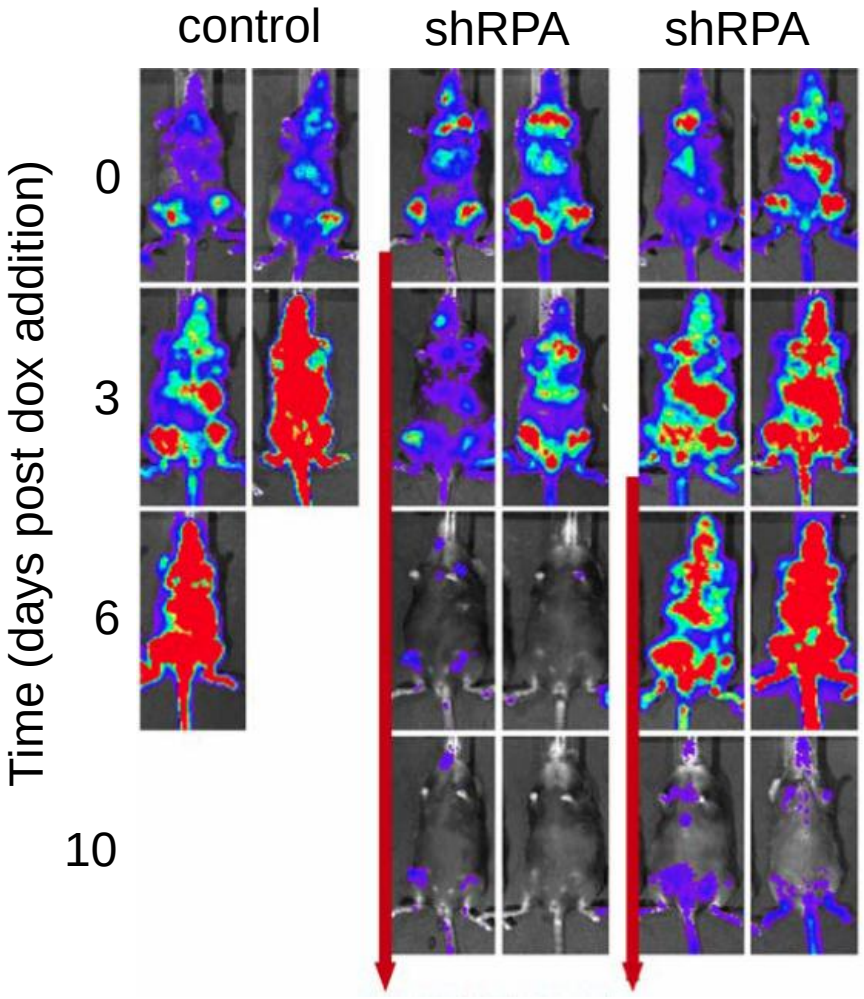
Modeling human cancers: cancer genetic features in mice



A context-specific functional genetic screening platform: **promoting cancers**

Scott Lowe, **Scott Powers**, et al.; and Ron DePinho, Linda Chin, Bill Hahn

Modeling drug target inhibition: inducible RNA *in vivo*

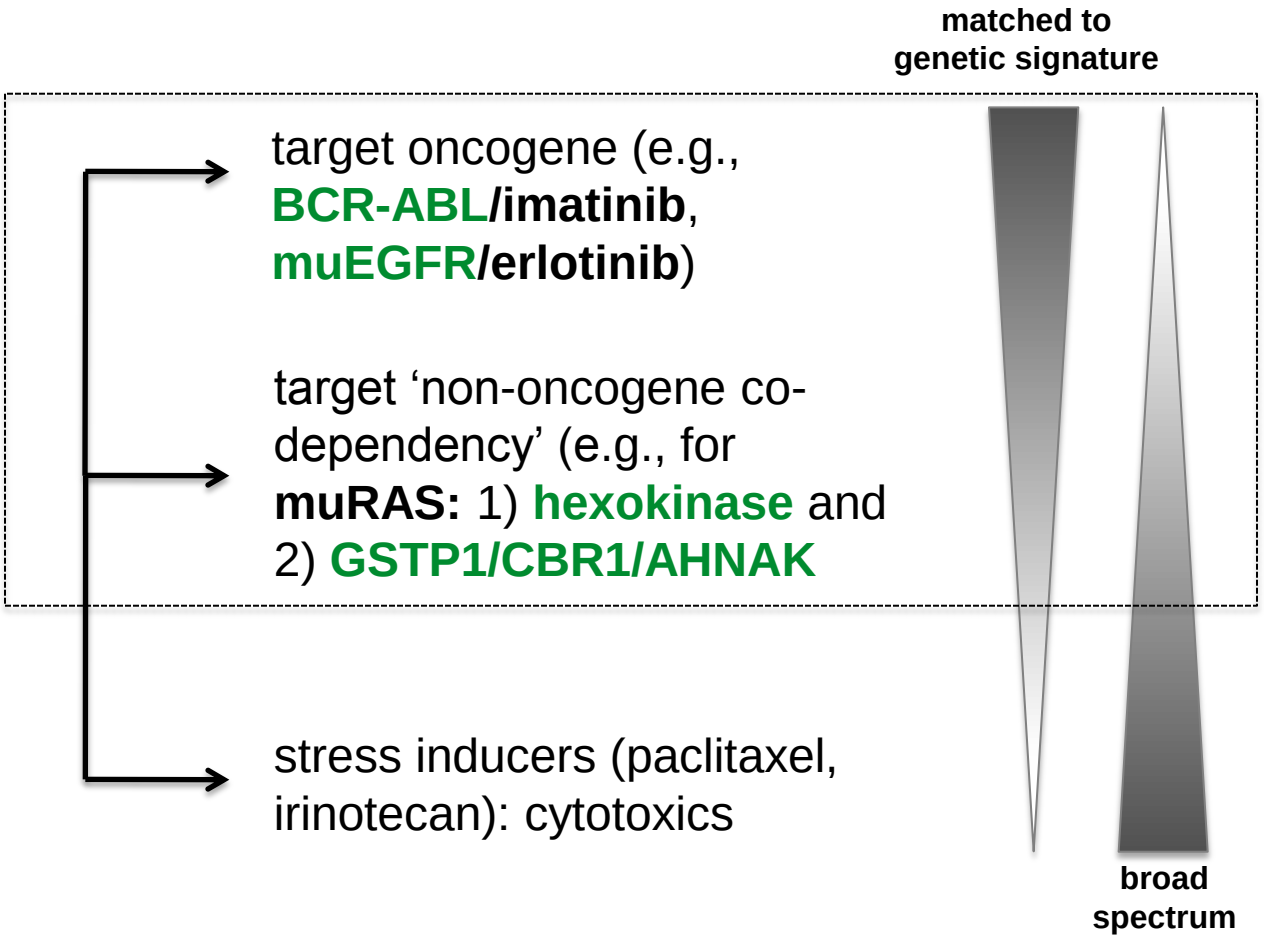


- Transplantable cancer models for target identification (screens) and validation
- Germ-line transgenic mice for functional studies and assessment of potential drug toxicities

A context-specific functional genetic screening platform: **eliminating cancers**

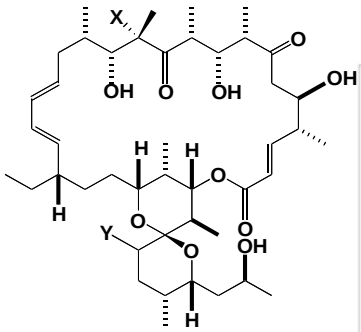
Scott Lowe, Scott Powers, et al.

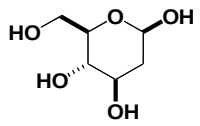
Targeting non-oncogene co-dependencies (synthetic lethality)

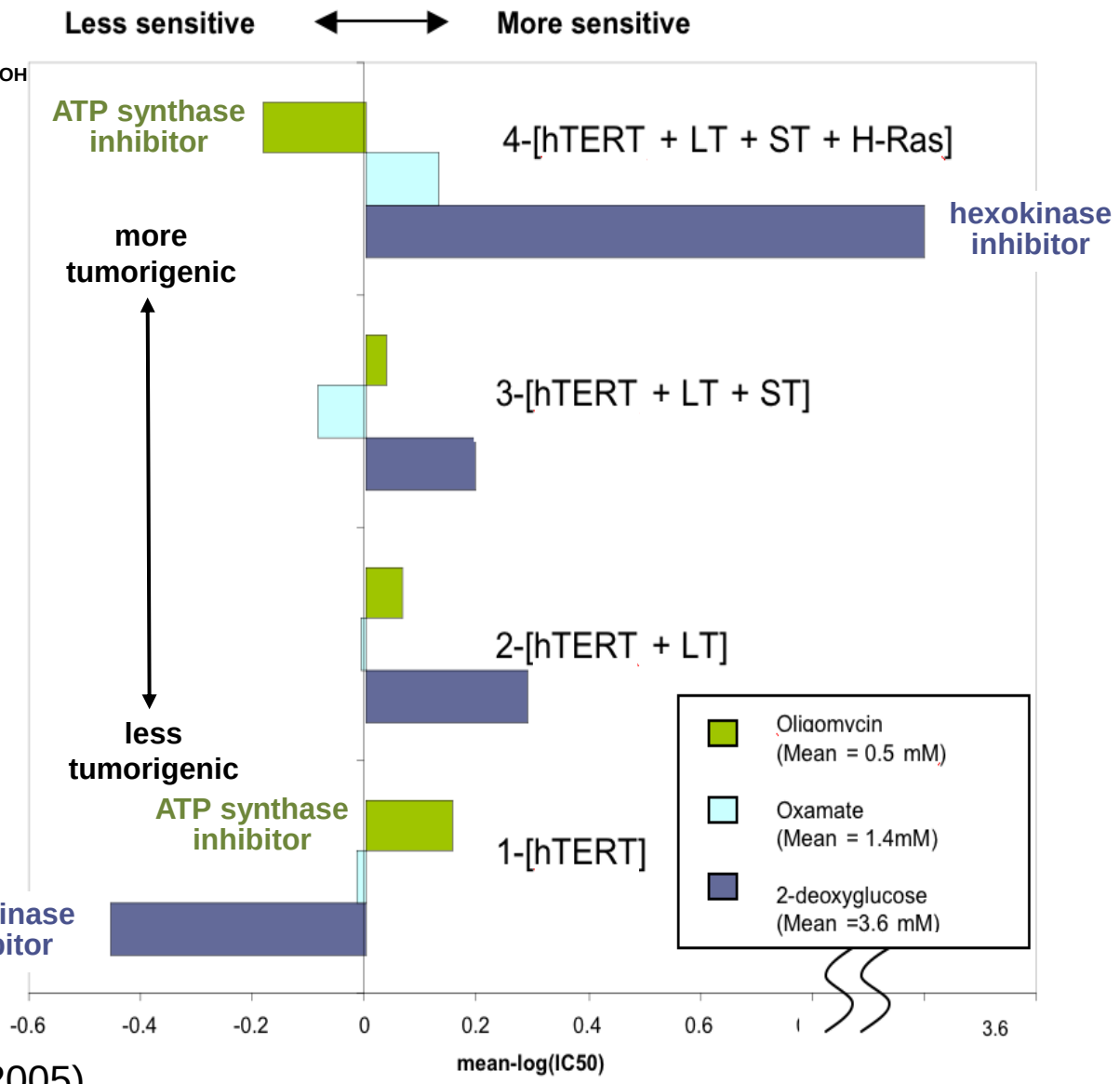


Stockwell, Haggarty, SLS, *Chem & Biol*, **6**, 71-83 (1999);
see also: Luo, Solimini, Elledge, *Cell*, **136**, 823-37 (2009)

RAS changes cancer metabolism and small-molecule sensitivity

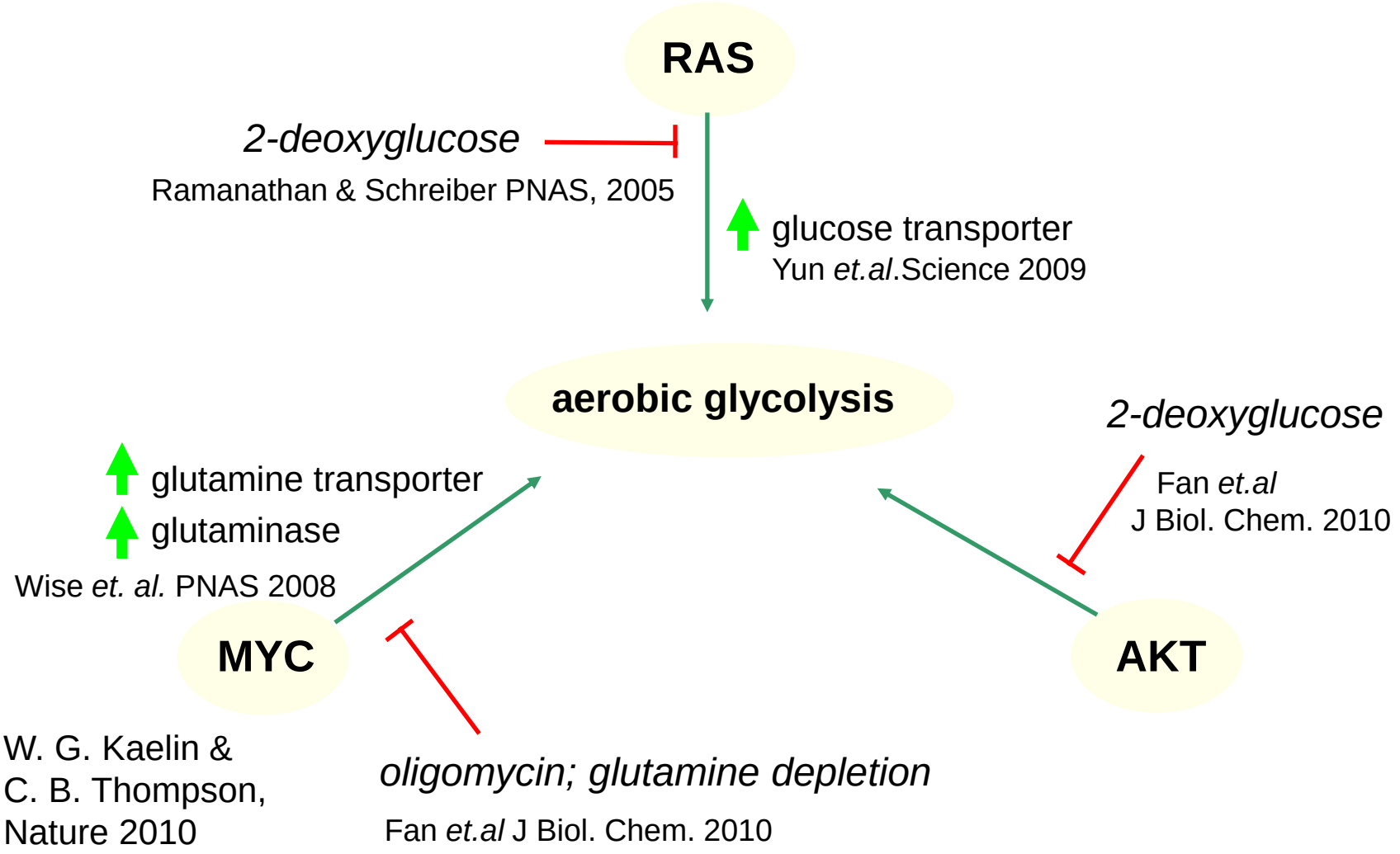




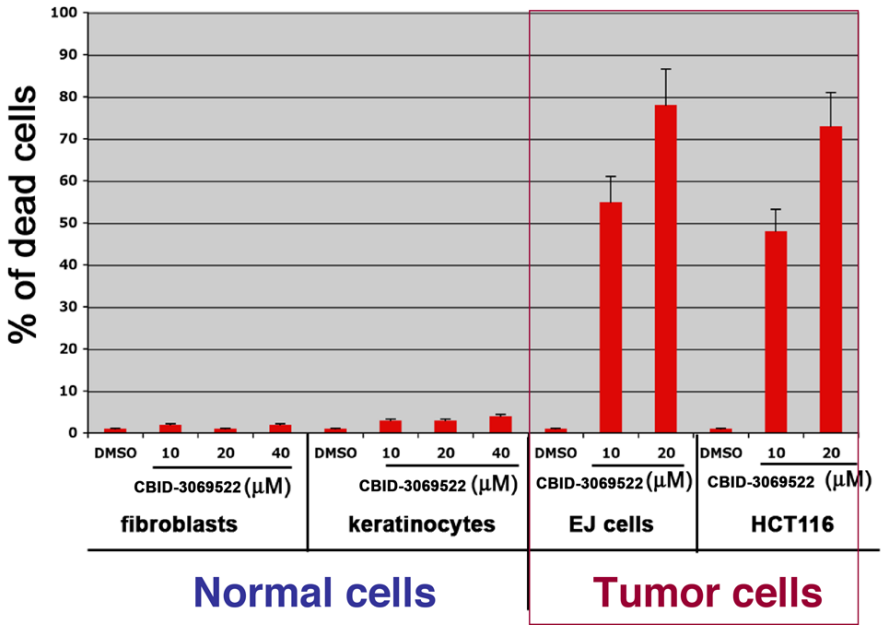


Arvind Ramanathan, SLS (2005)

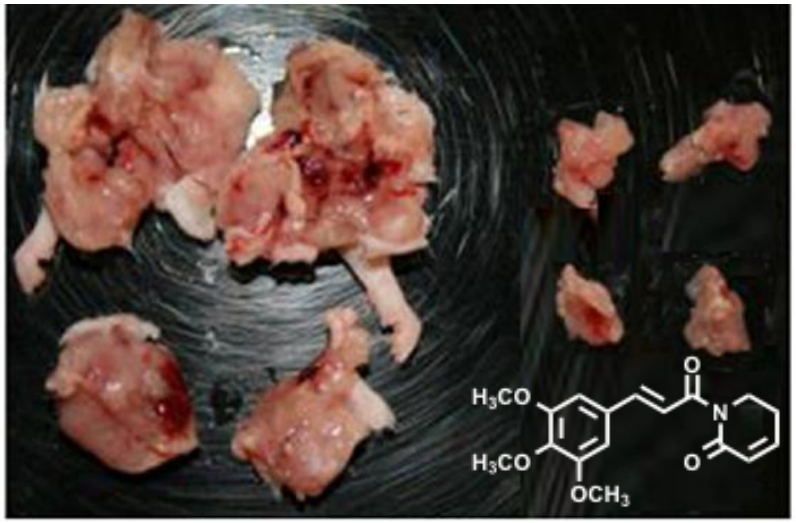
Drugs matched to genetic features, **not** cancer metabolism



RAS changes ROS biology and small-molecule sensitivity



MMTV-PyVT transgenic mouse breast cancer model

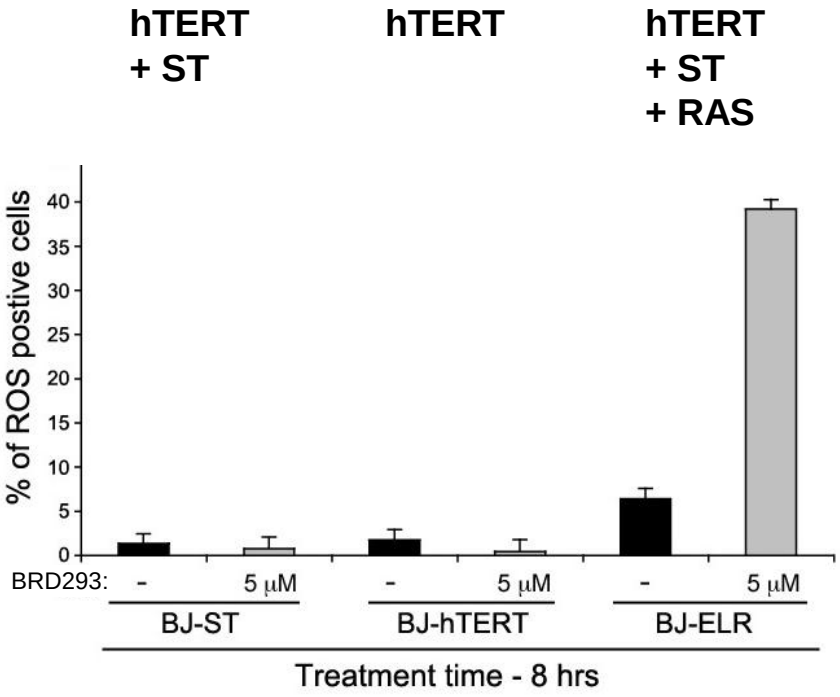


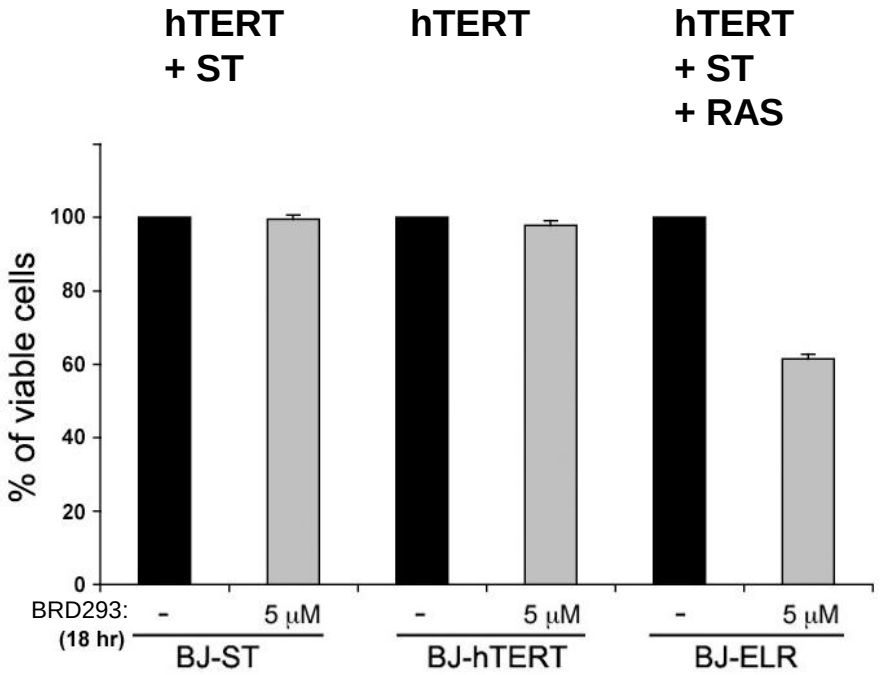
control **BRD2293**

- Discovered in an **NCI ICG** probe project
- Induces cell death/apoptosis in transformed but not in normal cells
- Prevents tumor growth *in vivo* (xenograft and spontaneous cancer models) in low doses safely
- Quantitative proteomics reveals a target: **GSTP1/CBR1/AHNAK** complex, and mechanism-of-action studies reveal a process: **dissipation of ROS**

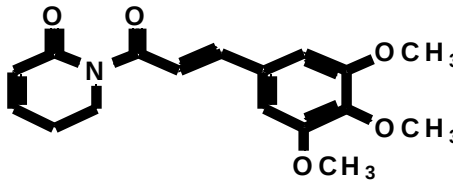
"Sensing the cancer genotype by targeting stress response to ROS results in selective killing of cancer cells by a small molecule", **submitted**

Sensitivity to BRD293 is conferred by mutant RAS





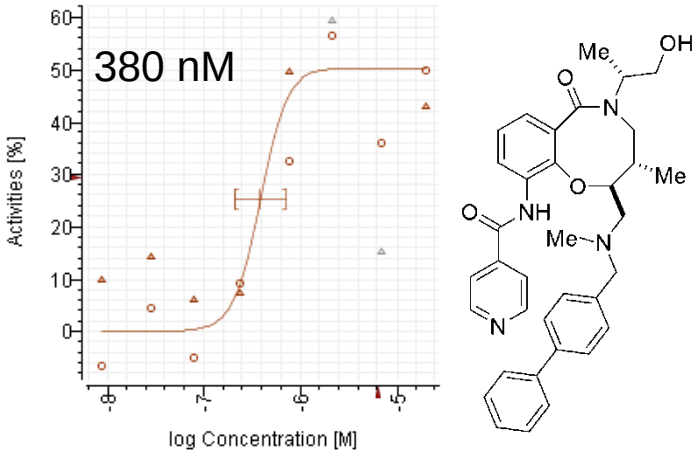
human primary BJ fibroblasts with serial transfections + BRD2293 =

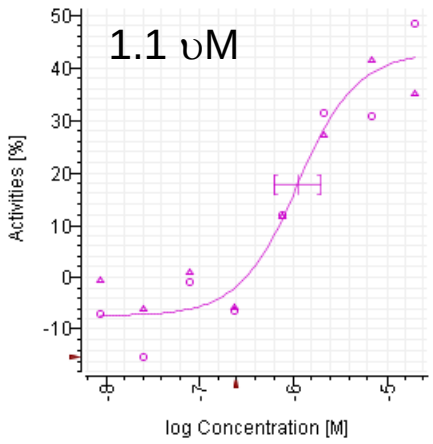


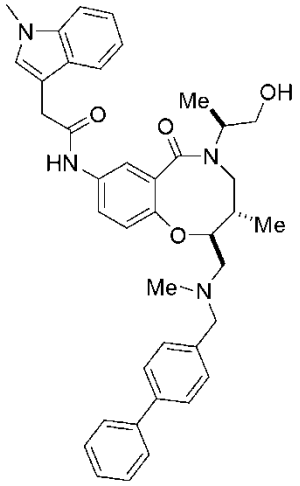
Anna Mandinova, Sam Lee

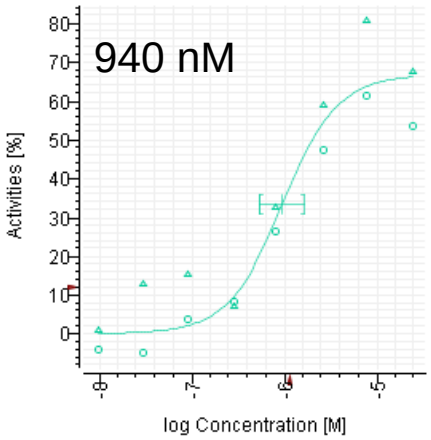
Mutant **RAS** increases levels of **ROS** in cells: Lee et al., *J. Biol. Chem*. **274**, 7936-7940 (1999)

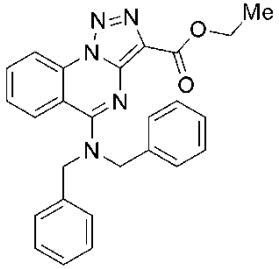
CTD^2 **probe development** for additional targets in ROS biology

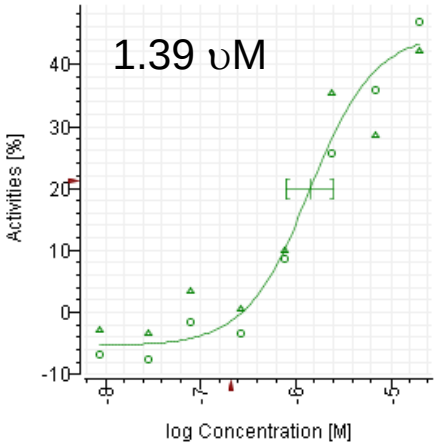


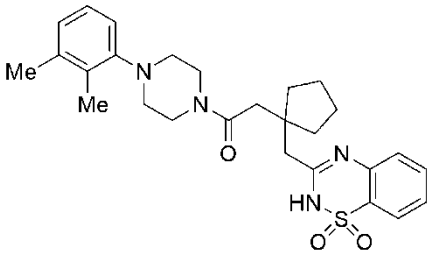






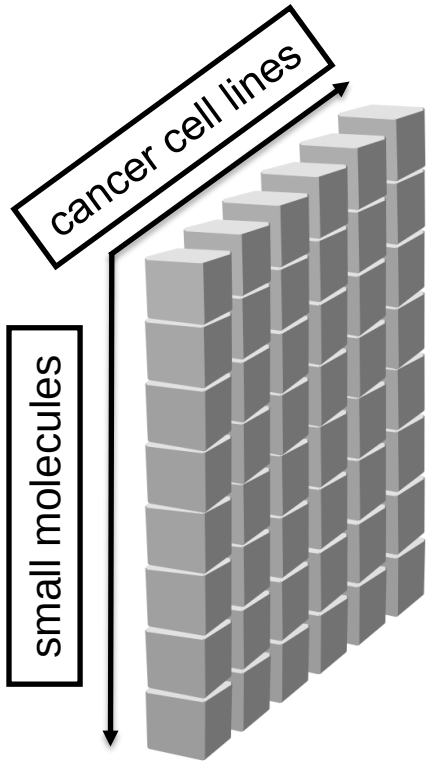




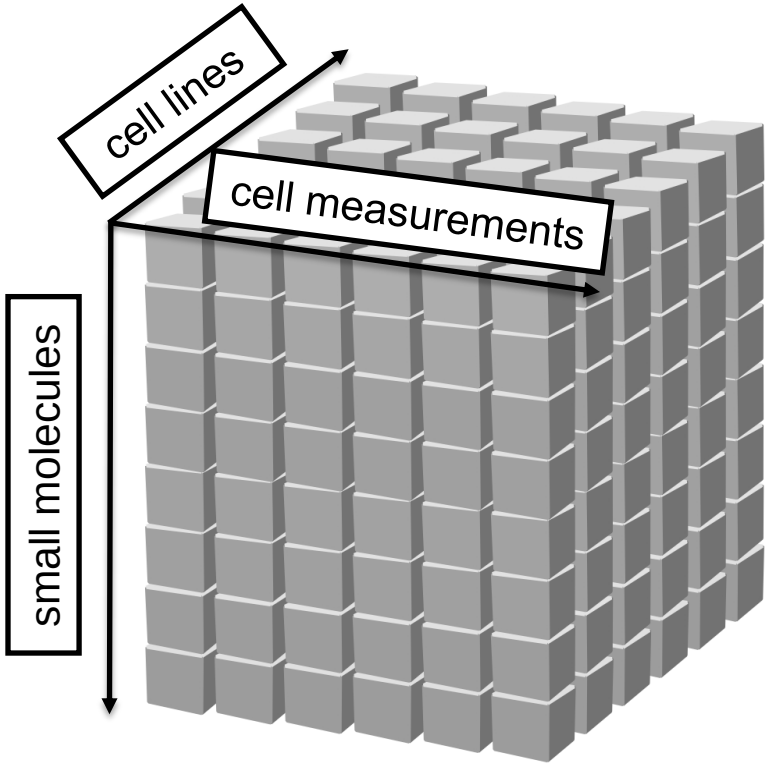


Cancer drugs matched to genetic features, **not** ‘ROS metabolism’

Cell-line models of cancer: from NCI-60 to ChemBank

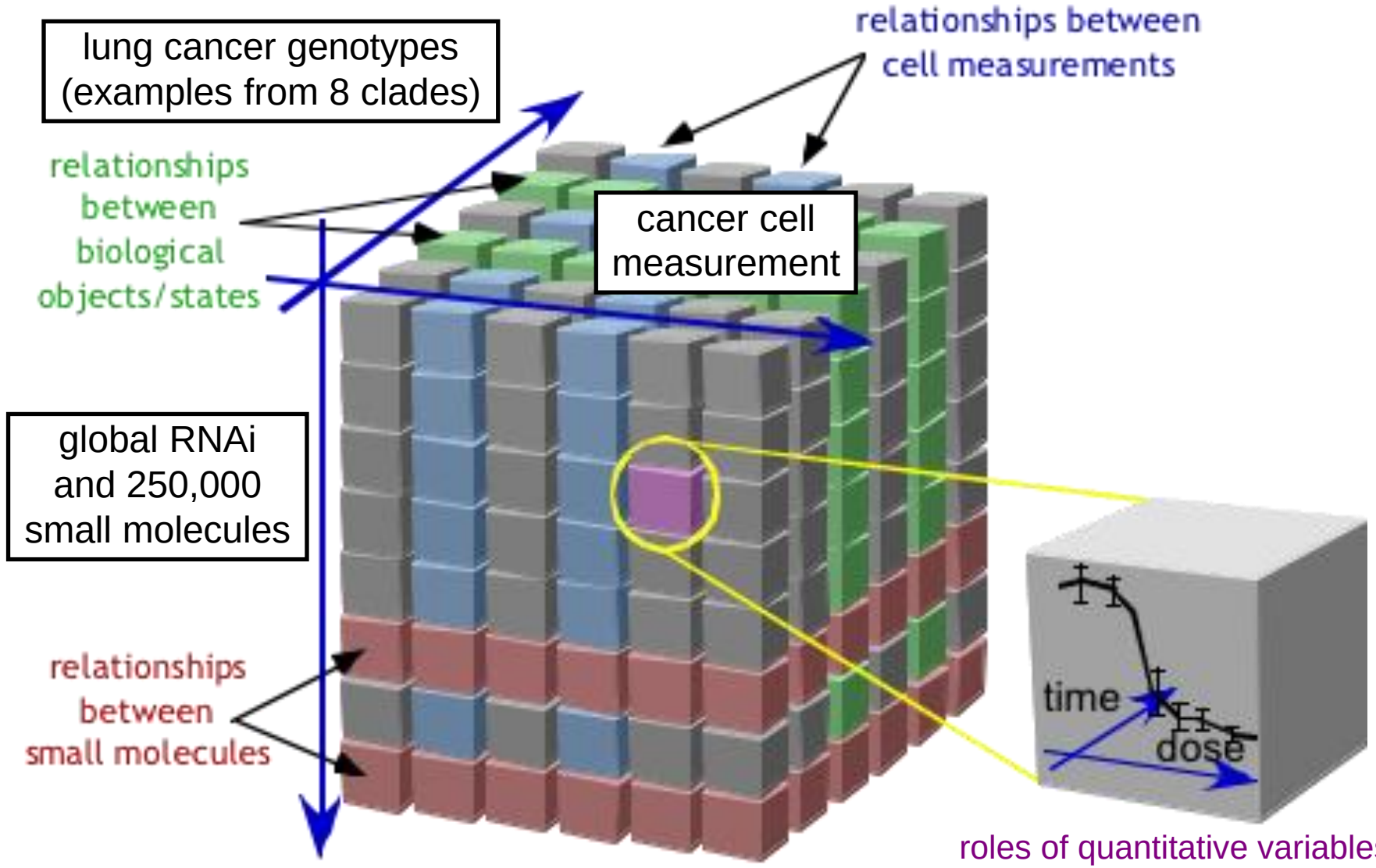


NCI-60: Cancer cell line/small molecule sensitivity relationships (GI_{50} measurements)



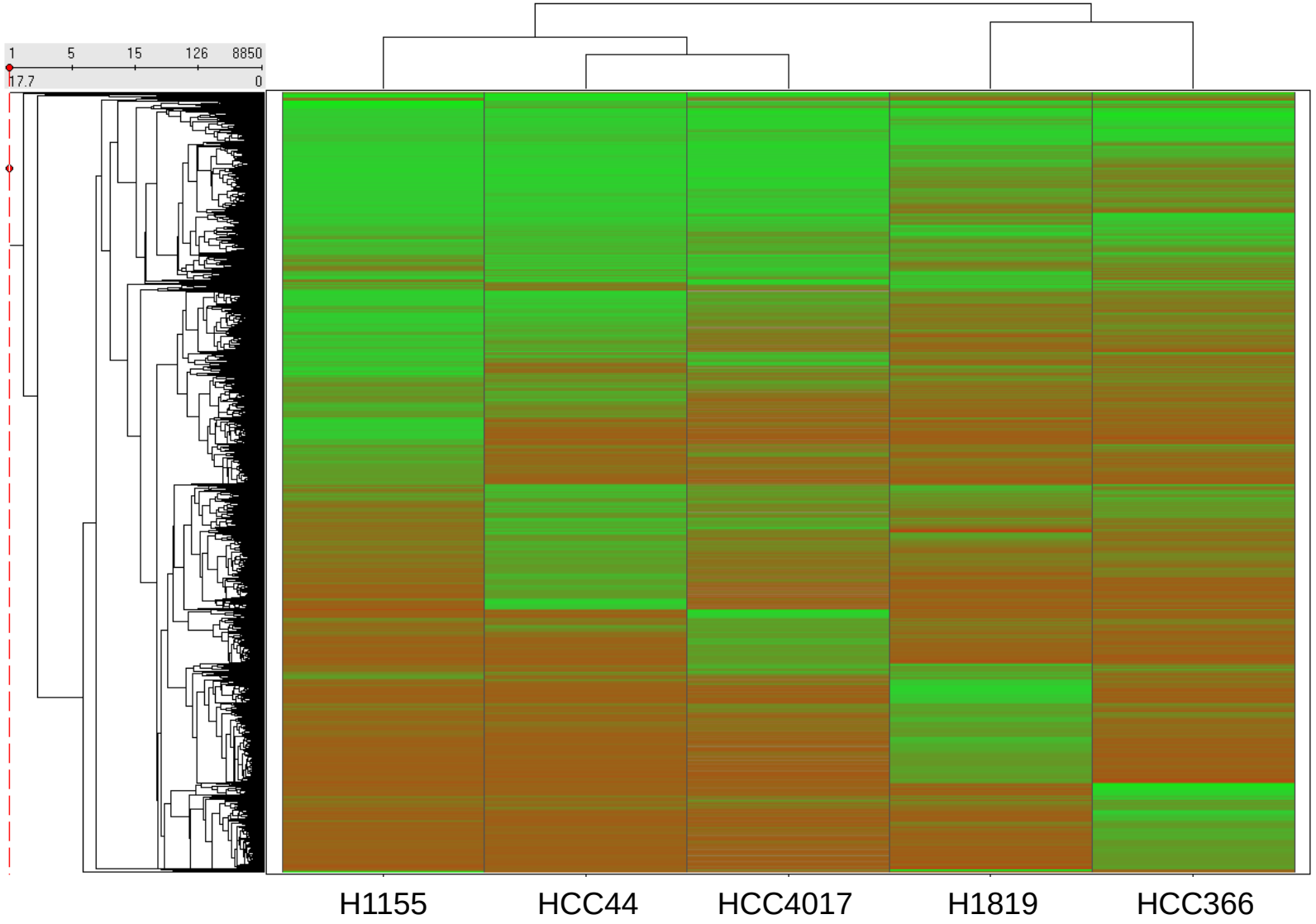
NCI-sponsored ChemBank: Cancer cell line/small molecule sensitivity/cell measurement relationships (Paul Clemons)

Next-generation cancer cell line databases: CTD^2 at UTSW



See also studies at **MGH** (Settleman, Haber & collaborators)

HTS identifies selective small-molecule vulnerabilities in NSCLC

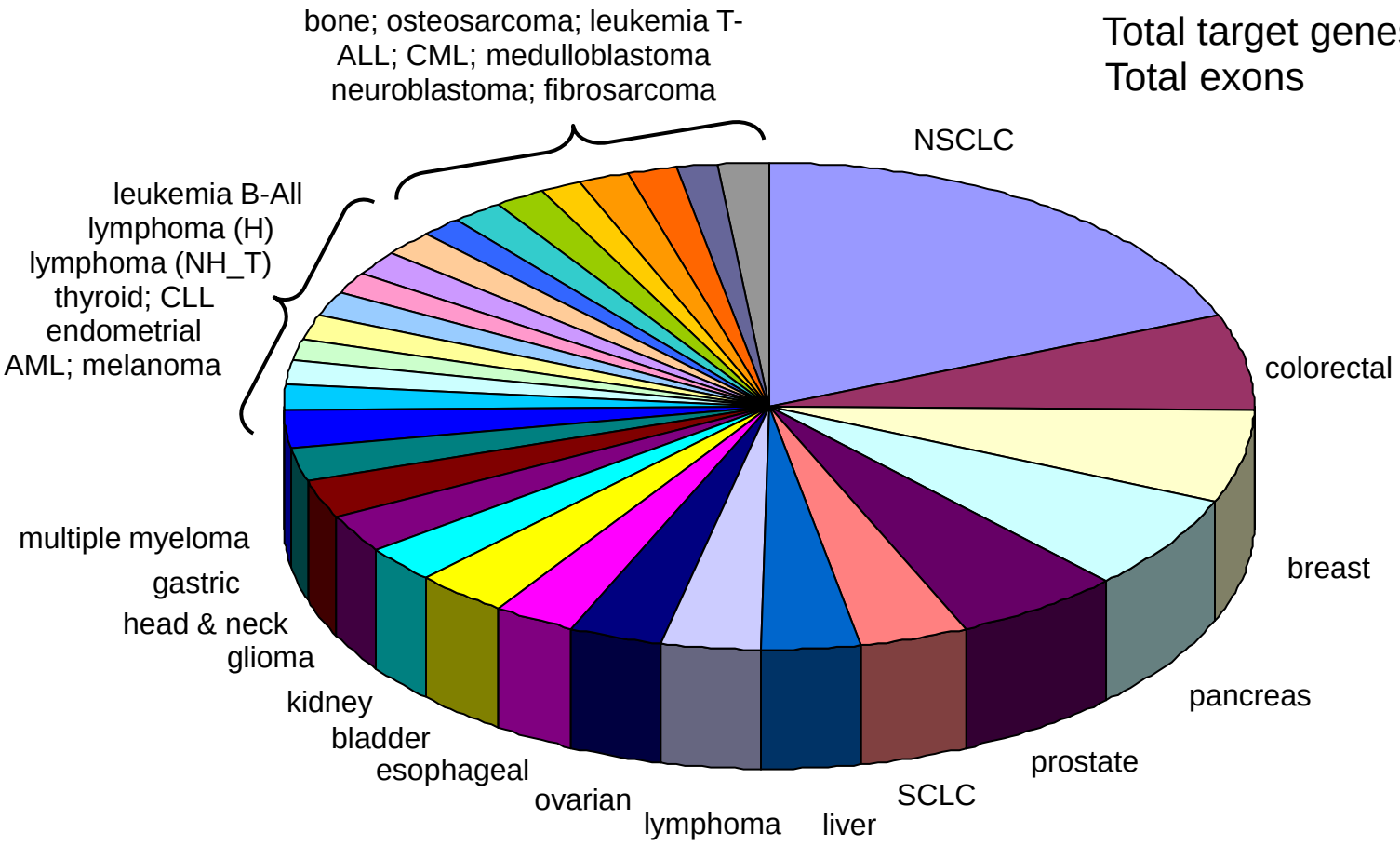


Cancer cell line encyclopedia: a promising public resource

CCLE 1,000 genomically characterized cancer cell lines:

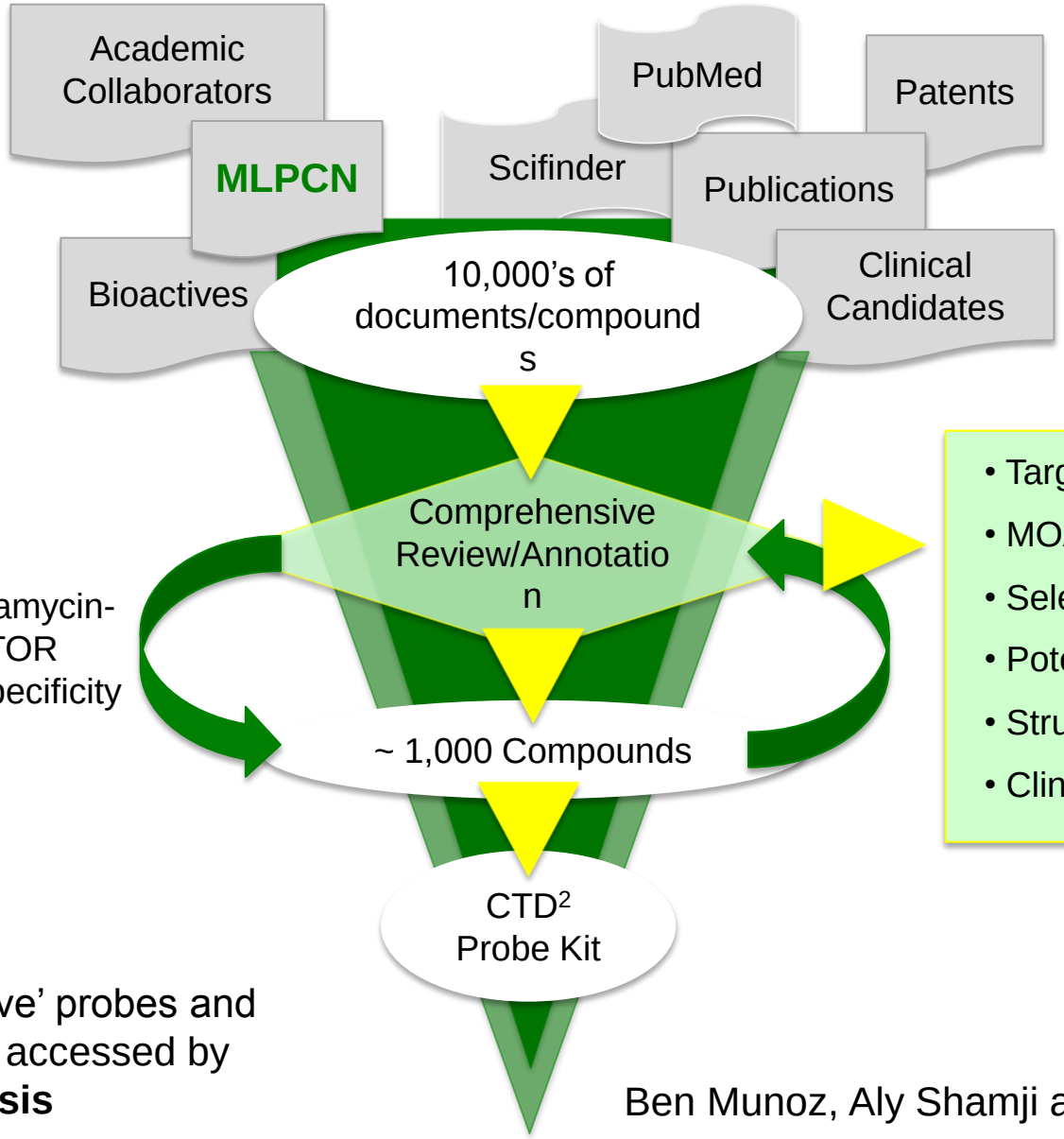
- **copy number** (Affy SNP 6.0 array)
- **gene expression** (U133 + 2 array)
- **mutation profiling** (OncoMap v3):

Total target genes	**1,645**
Total exons	**25,261**



Broad/Novartis CCLE Project: Jordi Barretina, Levi Garraway, Bill Sellers, and collaborators

CTD^2 probe kit: highly **specific** SM probes of new cancer targets



e.g., dominant rapamycin-resistant allele (mTOR S2035T) proves specificity towards mTOR

225 'narrowly active' probes and growing; **36%** are accessed by **complete synthesis**

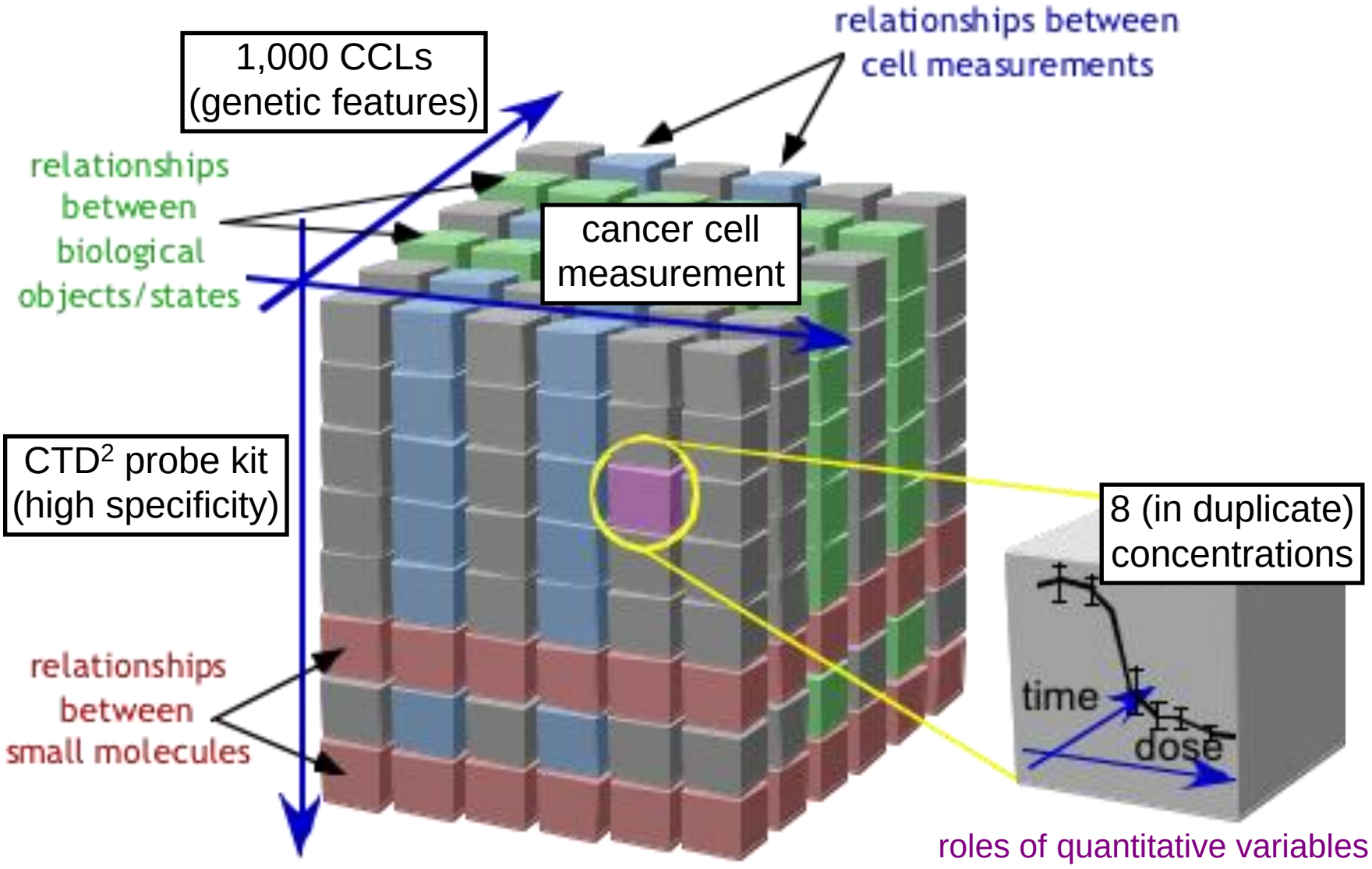
Ben Munoz, Aly Shamji and the CTD^2 team

CTD^2 probe kit representative examples; a living collection

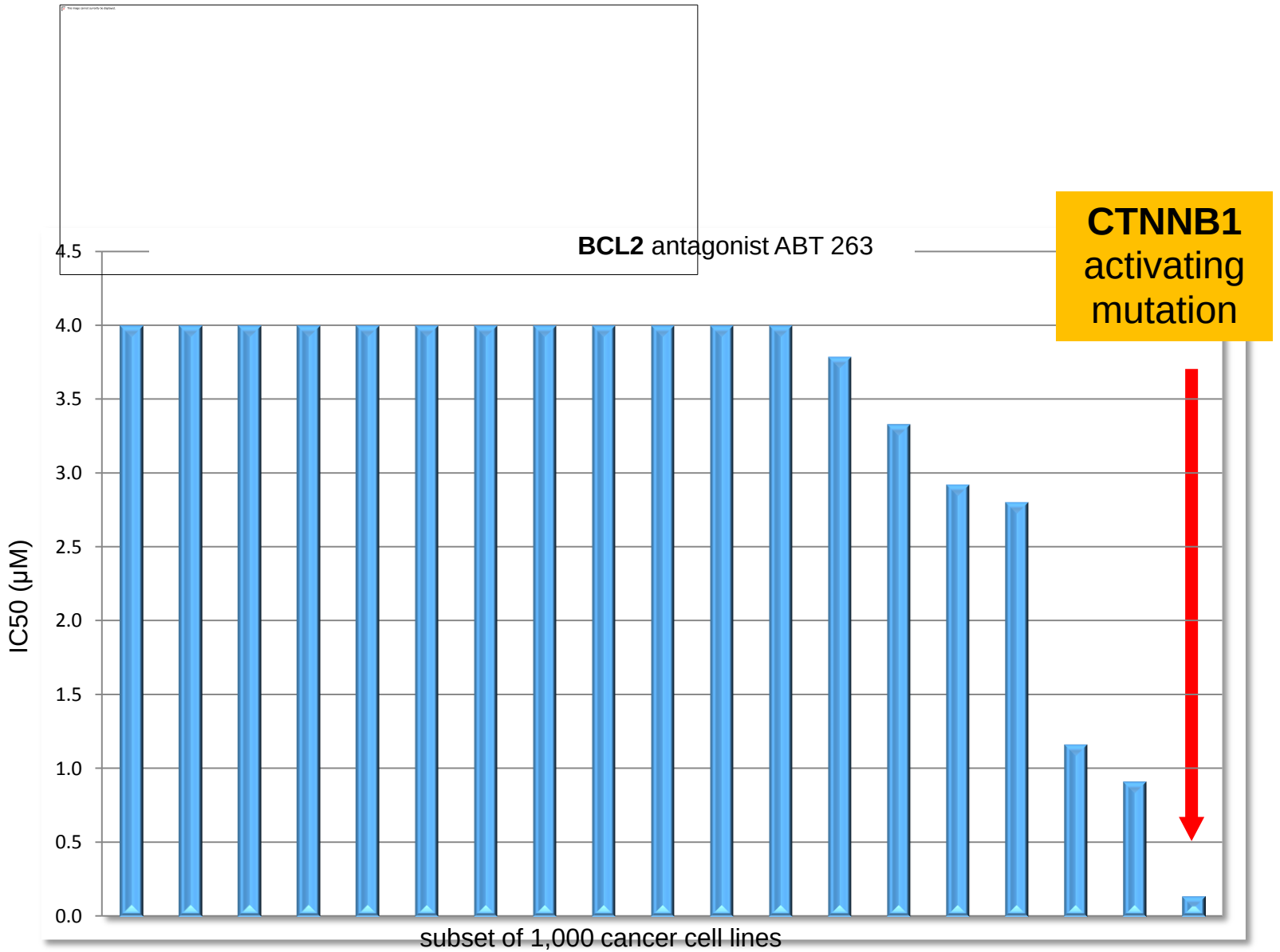
Compound	Pathways	Target/Dependencies	Potency	Selective	Efficacious	Clinical Candidate
KU-0059436	DNA damage response	PARP1/2	✔	✔	✔	✔
SNX-2112	proteotoxic stress	HSP90	✔	✔	✔	✔
JTT-705	metabolism	CEPT	✔	✔	✔	✔
MLN4924	proteotoxic stress	NAE	✔	✔	✔	✔
MK-0591	metabolism	FLAP	✔	✔	✔	✔
SRT-1720	chromatin	SRT1 activator	✔	✔	✔	
BRD-293	ROS	ROS metabolism	✔	✔	✔	
XAV-939	DNA damage response	tankyrase	✔	✔		
SJ-172550	DNA damage response	MDMX	✔	✔		
SCH529074	DNA damage response	muP53 DBD	✔	✔		

reported in past several months

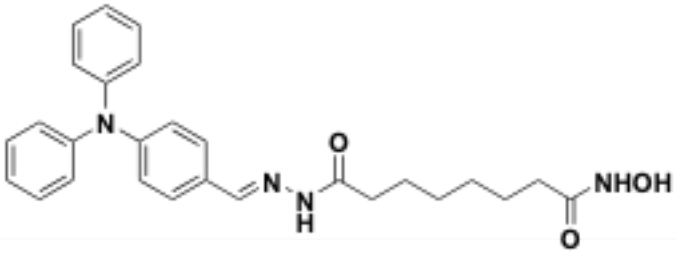
CCLE and the CTD^2 small-molecule probe kit (*in progress*)



CTD^2 pilot of the probe set suggests new clinical directions



CTD^2 pilot of the probe set suggests new therapeutics (HDAC6)



novel CTD^2 **HDAC6** inhibitor WT161

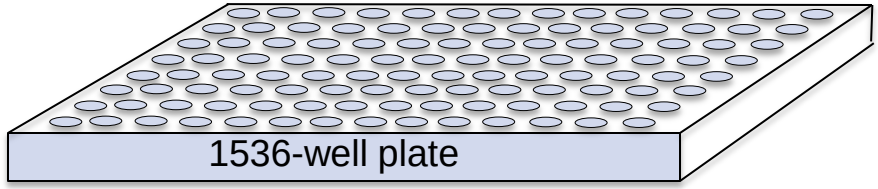
VHL loss-of-function mutation

IC50 (μM)

4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

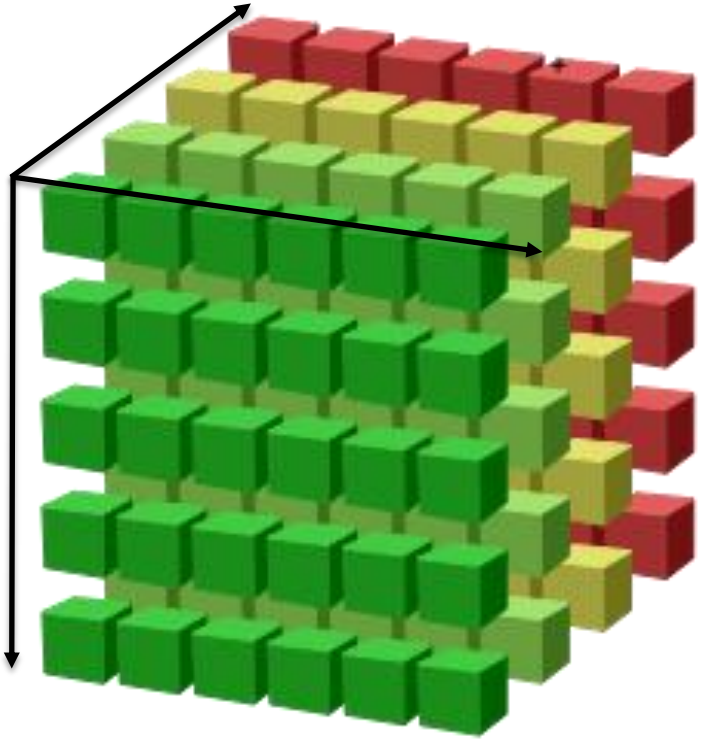
subset of 1,000 cancer cell lines

CTD^2 is discovering and using small-molecule probes of cancer



small-molecule probes

e.g., **BRD293**



RNA LoF/GoF; systems analyses

probe development projects

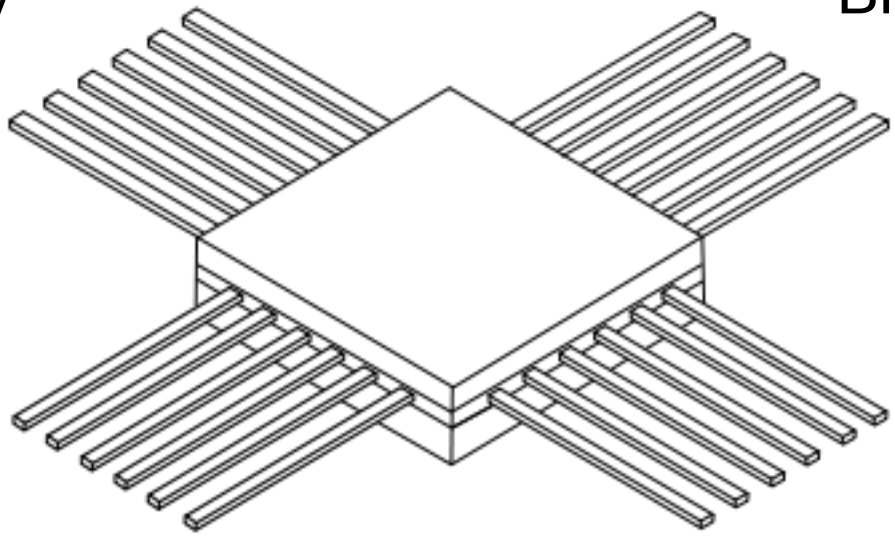
Discover small-molecule probes that target non-traditional cancer dependencies (**TFs**; **chromatin**; etc.)

Discover relationships between cancer genetic features and small-molecule efficacies

CTD^2 Network: an integrated approach to cancer therapeutics

Chemical Biology

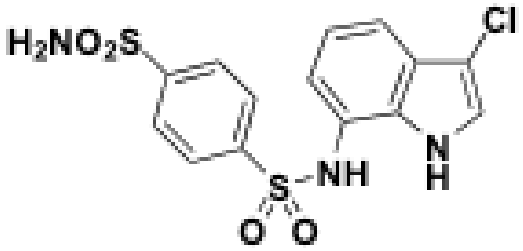
Cancer Biology



Cancer Genomics

Cancer Therapeutics

CTD^2 pilot of the probe set suggests new therapeutics



indisulam
BRD-6043