



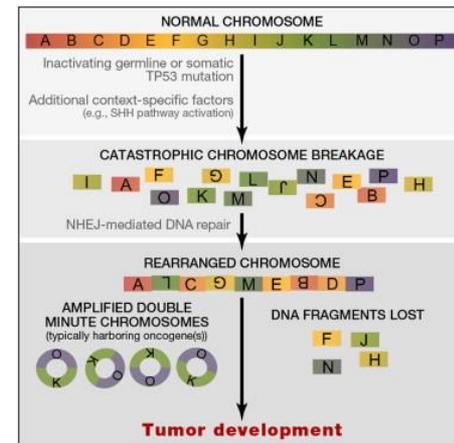
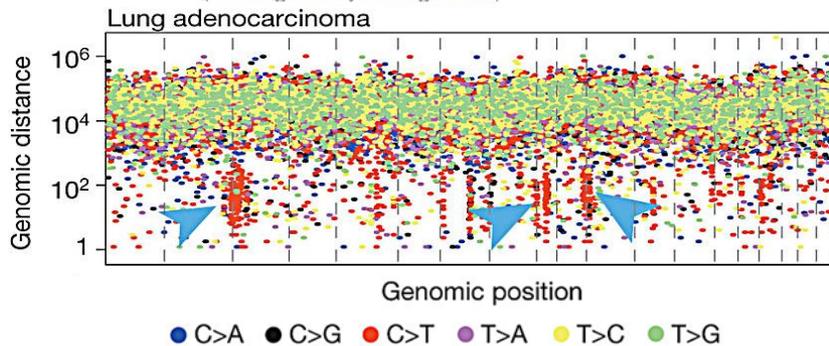
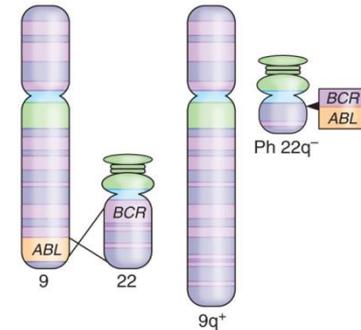
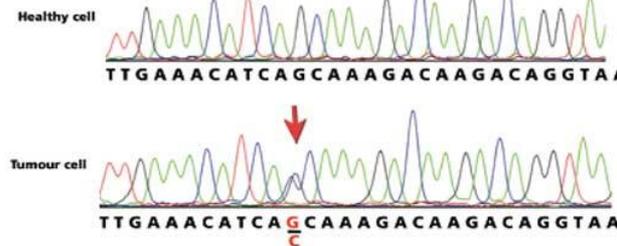
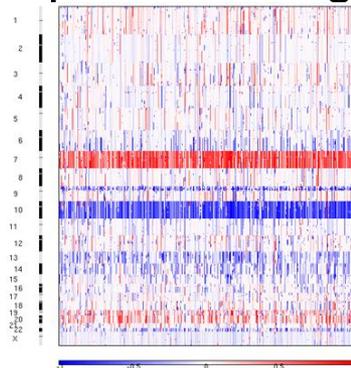
# The Cancer Target Discovery and Development (CTD<sup>2</sup>) Network RFA Concept

NCI Board of Scientific Advisers  
March 29, 2016

Daniela S. Gerhard, Ph.D.  
OCG, CCG

# Molecular Characterization is Essential but not Sufficient for Precision Oncology

- Each tumor has hundreds to thousands genomic alterations
  - Amplifications, deletions, translocations, chromothripsis, kataegis, epigenetic changes and mutations all impacting expression of genes and behavior of cells



# Molecular Characterization is Essential but not Sufficient for Precision Oncology

➤ Little is known about the cellular function of most genes, much less how the cancer-associated alterations affect it

- Distinguishing initiating vs. driver vs. contributing vs. passenger alterations in the context of intra- and inter-tumor heterogeneity
  - Drivers are genes involved in tumor maintenance;



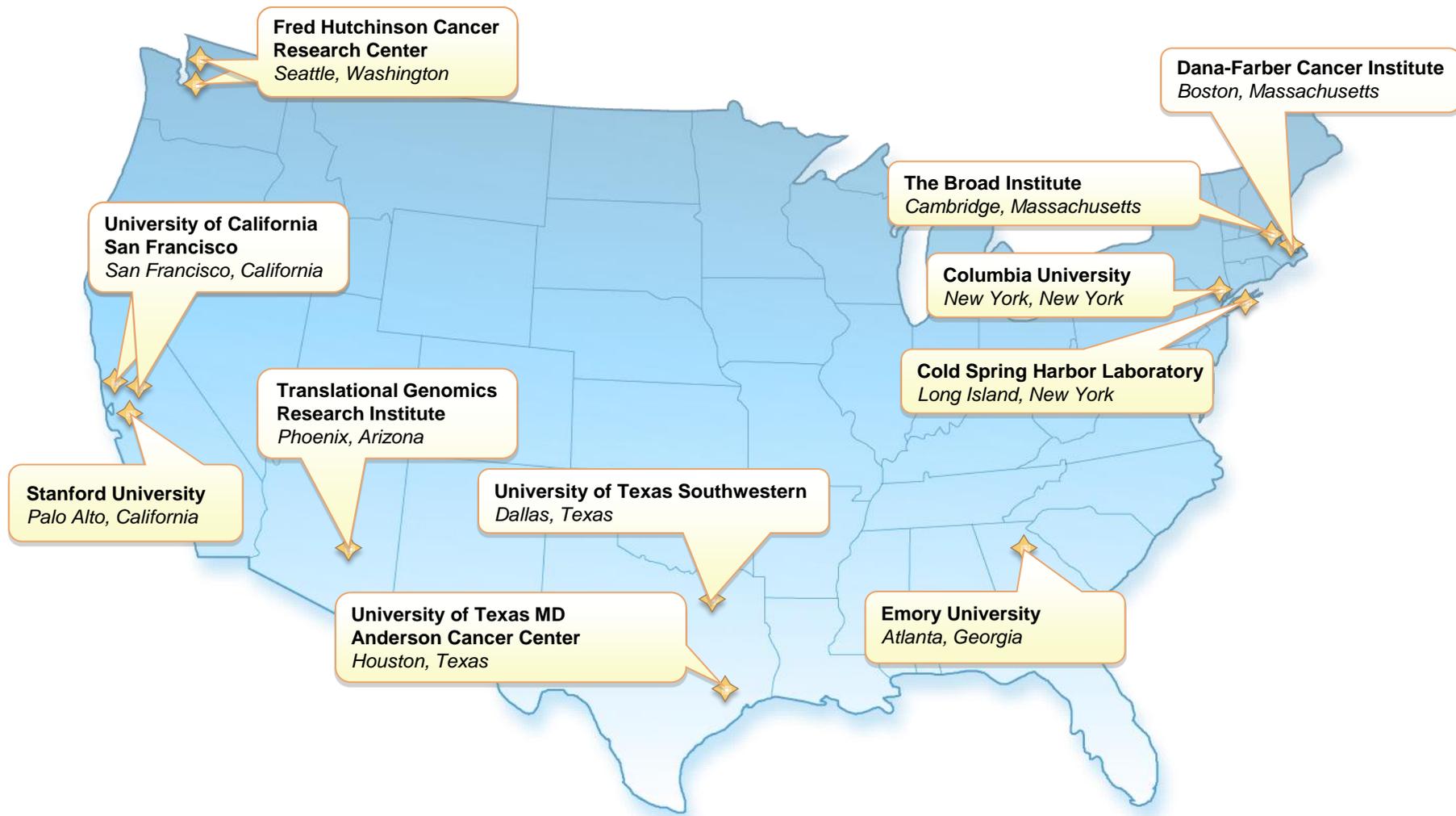
- Cancer alterations have context-specific impact
  - Context includes cell of origin, other molecular alterations in genes that may have synergistic or antagonistic impact
    - For example, NOTCH can be an oncogene or TSG
- Adaptation of cancer to environmental stimuli
  - Therapy
  - Signals from adjacent tissues

# Response to the RFA: CTD<sup>2</sup> Multi-disciplinary Teams Were Established

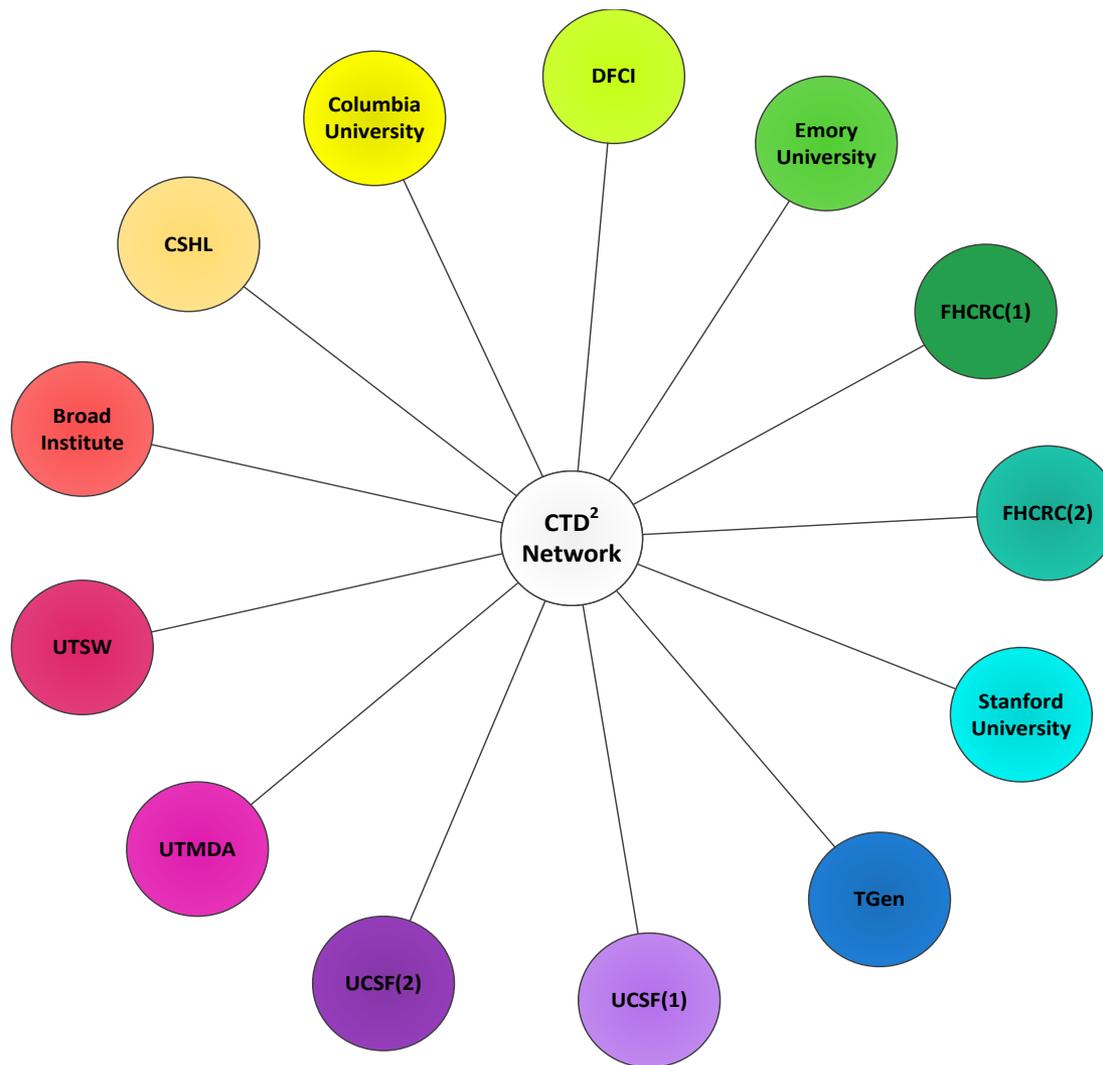
To use genome-scale experimental approaches to address these challenges and identify cancer drivers, therapeutic targets, predictive biomarkers, perturbagens (e.g. small molecules, RNAi, etc.)

- Computation across comprehensive data sets
  - Single organ cancer type
  - Across multiple cancers
- High-throughput, high-content screening
  - Small molecules
  - RNAi
  - Protein-protein interactions
  - Combination of small molecules
- Integrate results and iterate to improve predictions
- Collaborate intra-Network
- Share all outcomes through easily accessible web pages and reagents through distributors

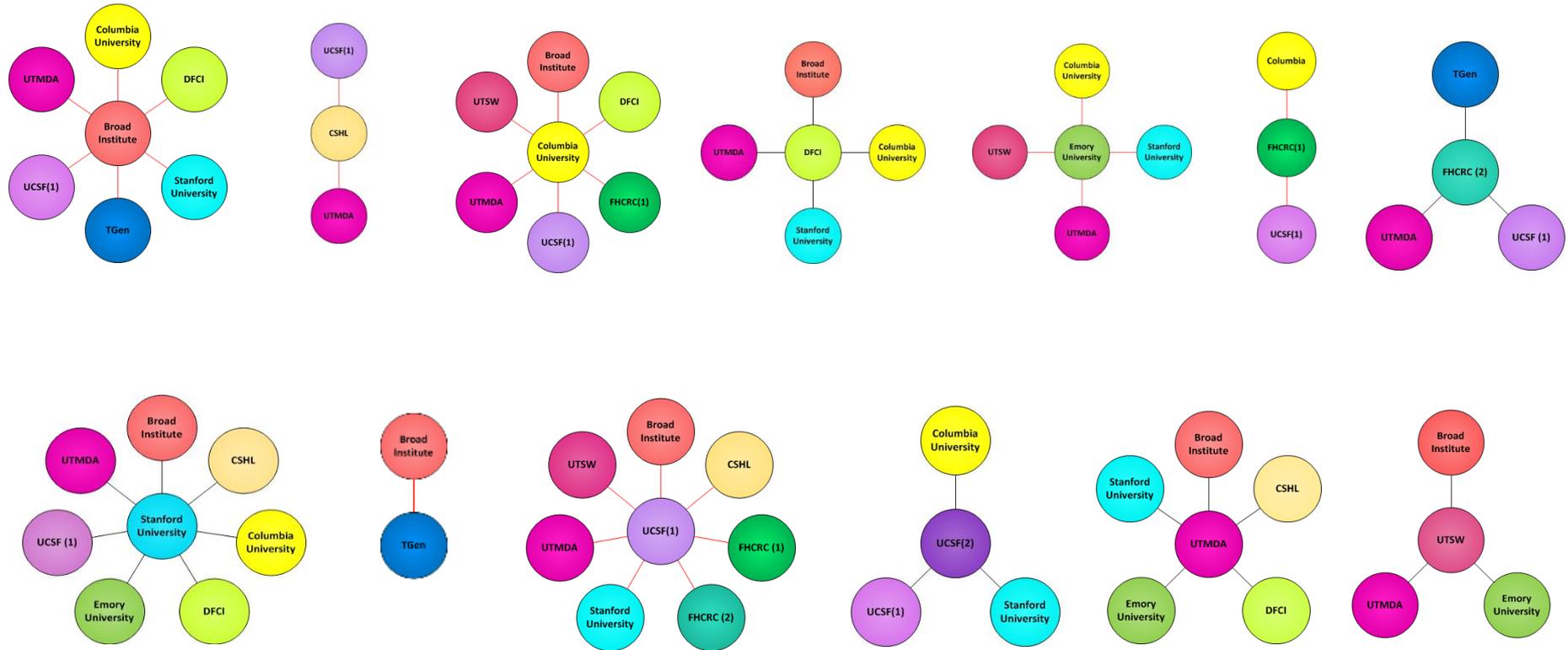
# CTD<sup>2</sup> Network: 13 Centers



# CTD<sup>2</sup> Network Centers



# CTD<sup>2</sup> Centers Collaborate: RFA Requirement



2015

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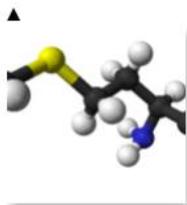
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### VIEW CTD<sup>2</sup> DATA PORTAL



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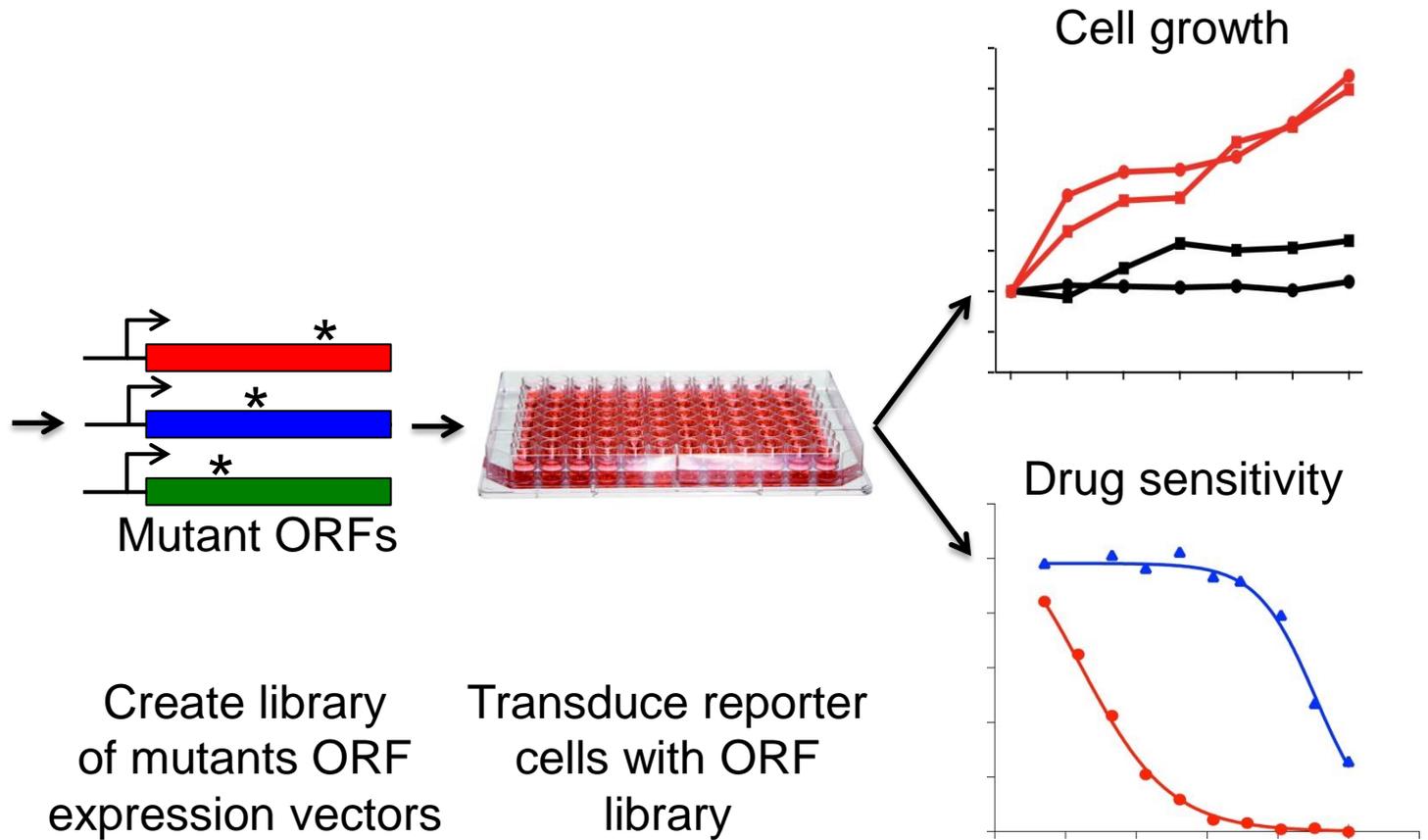
### CTD<sup>2</sup> RESOURCES

[The Cancer Genome Atlas \(TCGA\) Data Portal](#)  
[TARGET Data Matrix](#)  
[Online Bioinformatics Tutorials](#)  
[National Cancer Institute](#)  
[What is Cancer?](#)

# CTD<sup>2</sup> Initiative

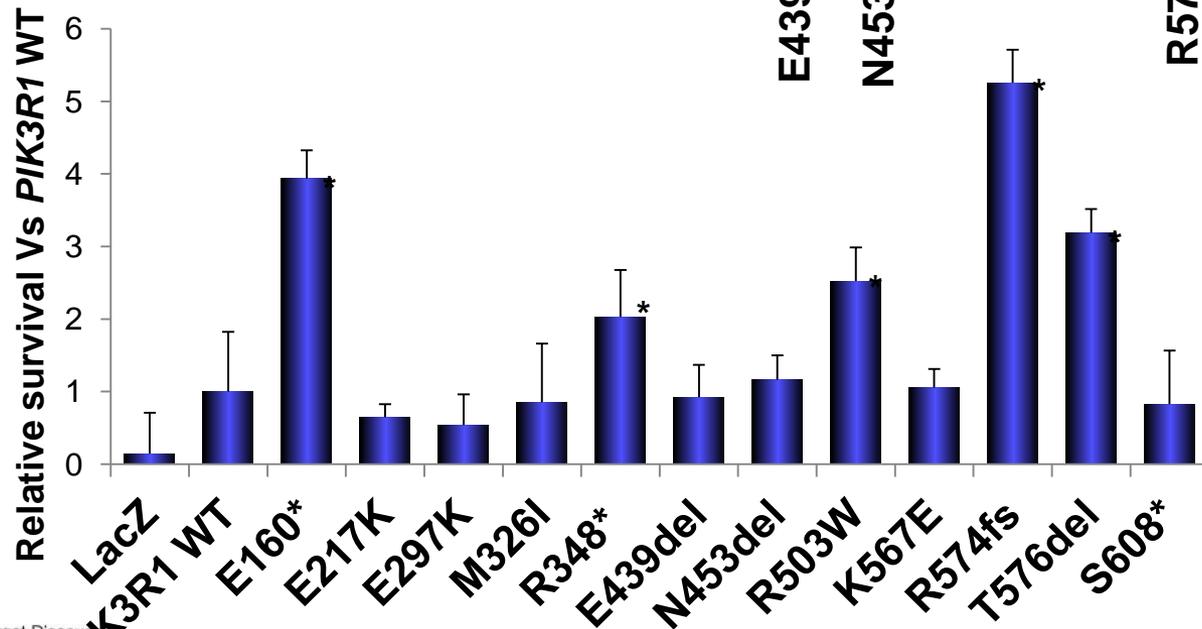
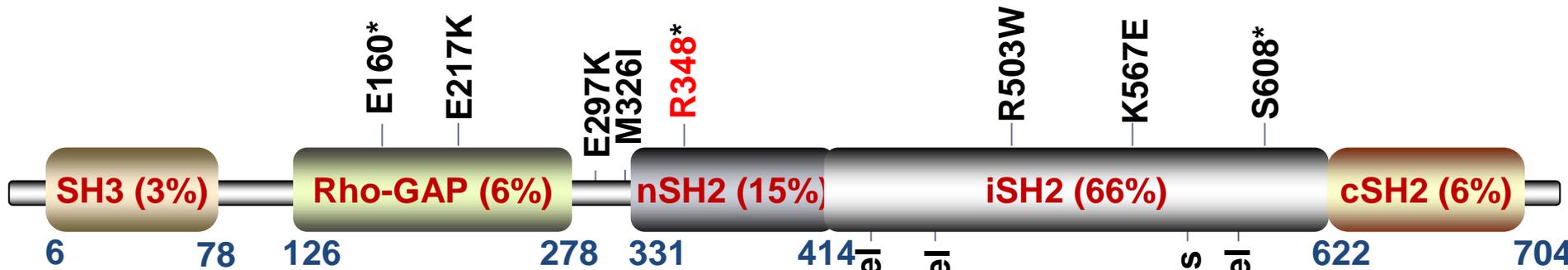
- A highly functional network that effectively addresses a major scientific challenge in cancer research
  - Efficient transition from patient-based large multi-dimensional genomic data → target validation → small molecule modulators → therapy
- Continuously improves and innovates approaches
- Forms rapid, pre-competitive collaborations
- 132 publications and counting (20 cited >40 times)
- Shifts current research paradigms in translation of patient-derived multidimensional genetic data to the clinic and utilize novel concepts, approaches and methodologies
  - Neomorphic functions are the norm, MDACC
  - New generation of CRISPRs tools, UCSF-1

# Functional Validation of Cancer Variants



# PIK3R1 Functional Mutations:

*p85 binding partner of p110 catalytic domain of PIK3CA*



\*  $P < 0.05$  compared with PIK3R1 WT

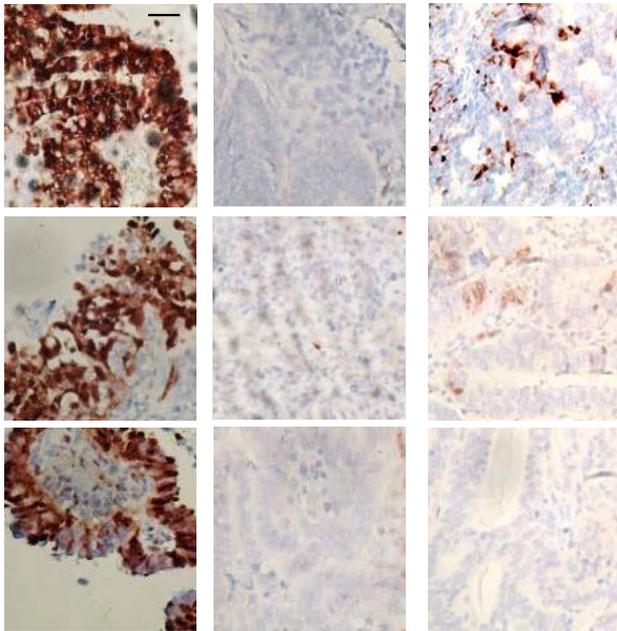
Wai Ting Cheung  
Han Liang  
Gordon Mills

# PIK3R1 R348\* is a Neomorphic Mutation Causes Addiction to MEK-ERK Signaling

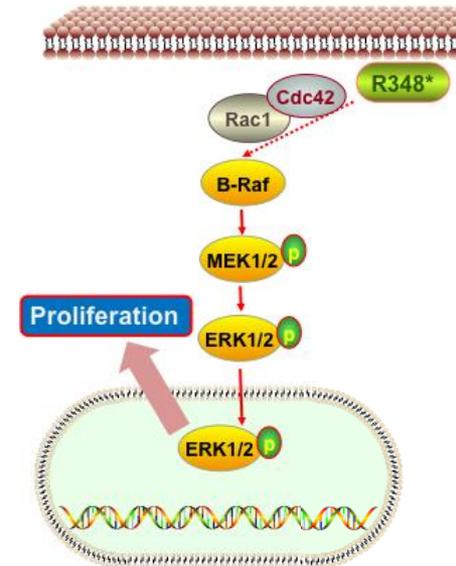
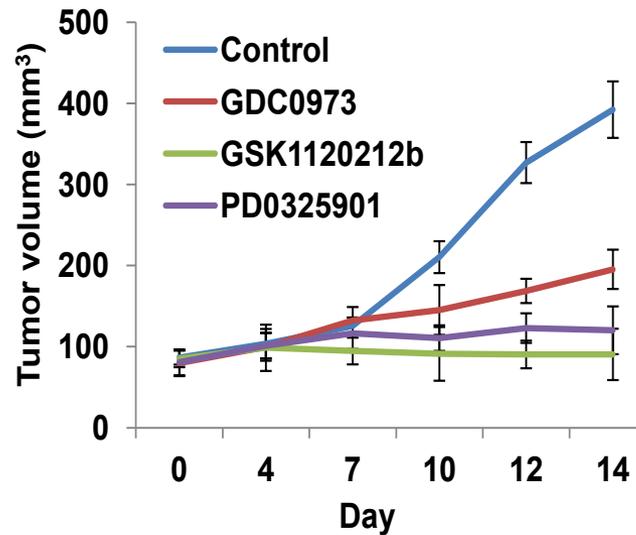
p-ERK

*PIK3R1*<sup>R348\*</sup>

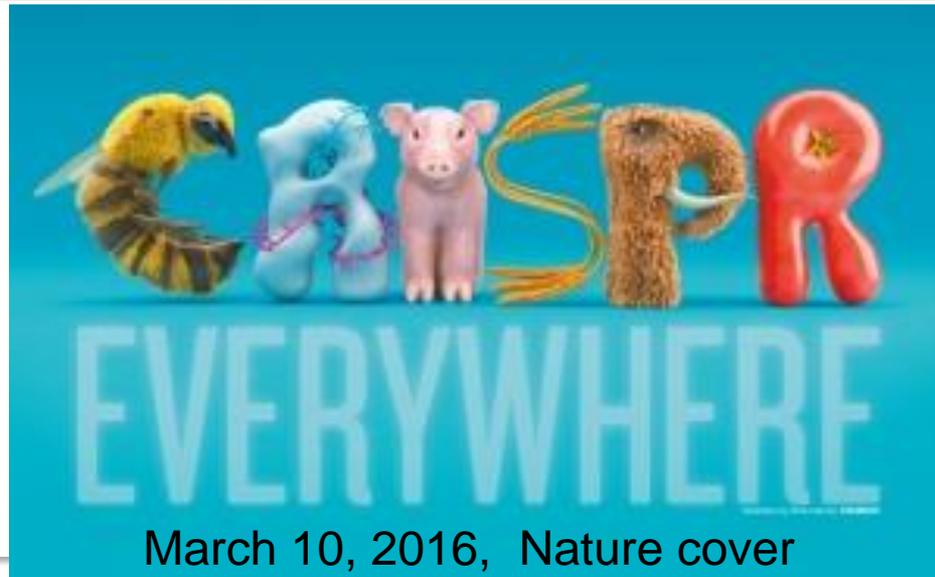
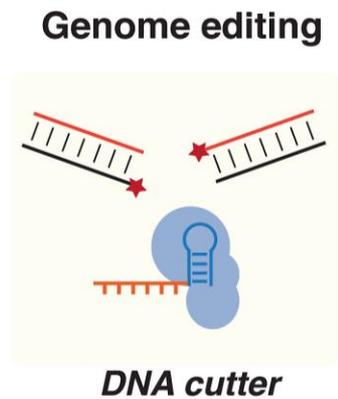
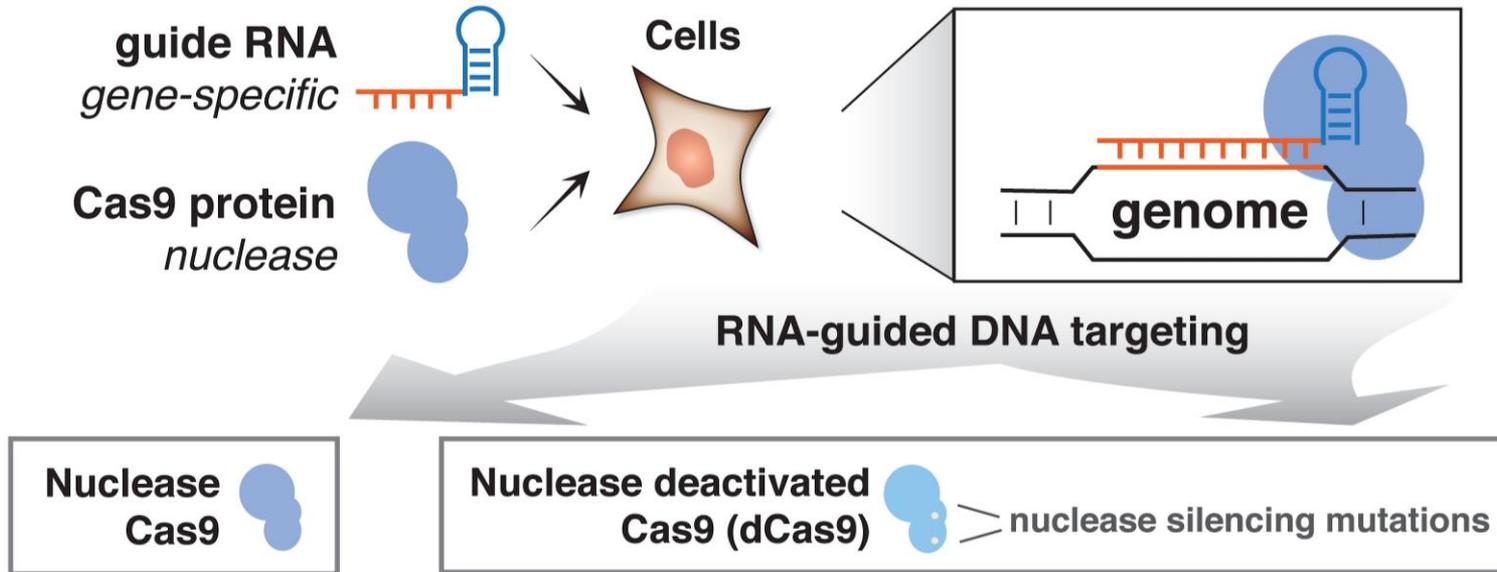
*PIK3R1* WT



Response to MEK inhibitors

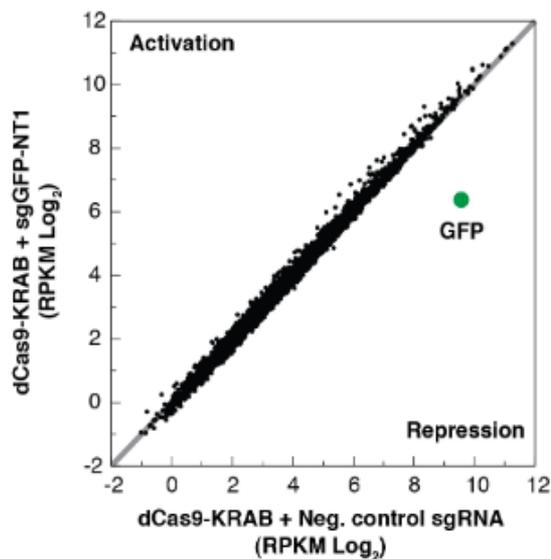
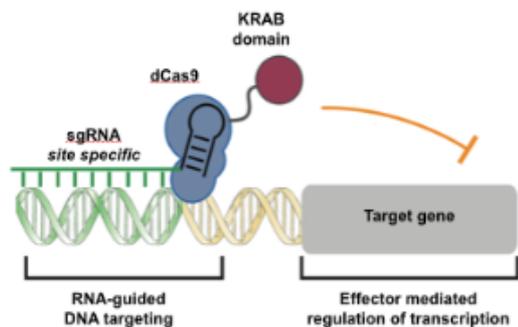


# CRISPRs: Gene Regulation by Excision



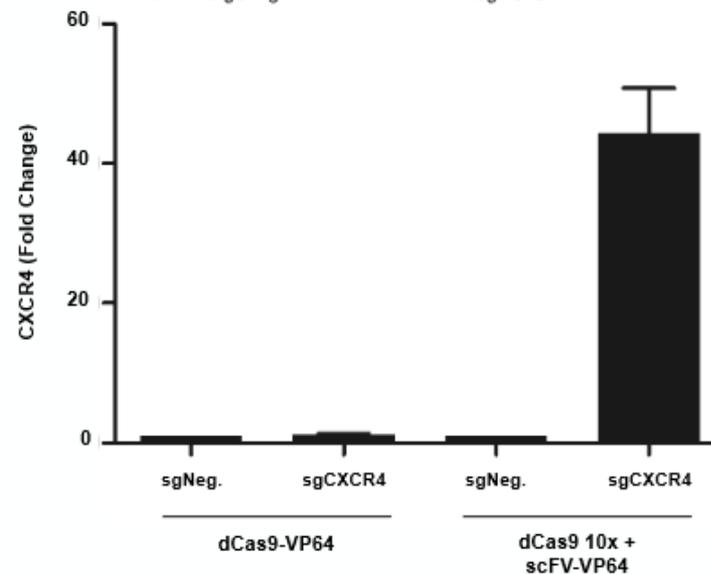
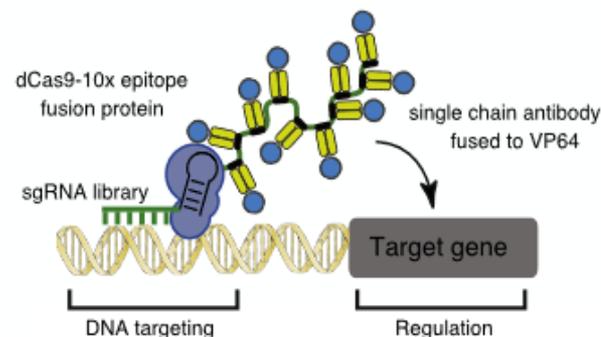
# Retooling CRISPRs: Turn Genes On or Off

## CRISPRi



Gilbert et al., *Cell* 2013

## CRISPRa



Tanenbaum et al., *Cell* 2014



# CTD<sup>2</sup> Intra-Network Data Portal

- Makes collaborations easier
- Allows rapid graduation of data to Public Data Portal

**CTD<sup>2</sup> INTRA-NETWORK DATA PORTAL**

*Last Updated: March 10, 2016*  
For target annotated CTD<sup>2</sup> Informer Set and other resources please see [HERE](#)

Project Title	Experimental Approaches	Data	Principal Investigator	Contact Name
<b>Cold Spring Harbor Laboratory (CSHL) : Computational and Functional Approaches to Validate Cancer Genome Targets</b>				
ORF and shRNA Screening for Driver Genes and Tumor Cell Dependencies	<ul style="list-style-type: none"> <li>ORF and shRNA screening</li> <li>mouse model technology</li> </ul>	Raw/Analyzed Data (DCC)	Scott Powers, Ph.D.	Jinyu Li
<b>Columbia University : Systems Biology of Tumor Progression and Drug Resistance</b>				
Master Regulator Genes of the FL Transformation to DLBCL	<ul style="list-style-type: none"> <li>transcriptional-level signal transduction network reverse engineering (ARACNe)</li> <li>master regulator analysis (MARINA)</li> </ul>	coming soon	Andrea Califano, Ph.D.	Kenneth Smith
Analysis of Regulatory Networks Determining the Mesenchymal Subtype of Glioblastoma (GBM)	<ul style="list-style-type: none"> <li>master regulator analysis (MARINA)</li> <li>functional copy number variation analysis</li> <li>modulator (MINDy) analysis</li> </ul>	coming soon		
Master Regulators of Ovarian Cancer	<ul style="list-style-type: none"> <li>master regulator analysis (MARINA)</li> </ul>	coming soon		
Master Regulators of Neuroblastoma Subtypes	<ul style="list-style-type: none"> <li>master regulator analysis (MARINA)</li> </ul>	coming soon		
<b>Emory University : High-Throughput Protein-Protein Interaction Interrogation in Cancer</b>				
High-Throughput Protein-Protein Interaction Dataset for Lung Cancer-Associated Genes	<ul style="list-style-type: none"> <li>high-throughput orthogonal protein-protein interaction screening</li> </ul>	Raw/Analyzed Data (DCC)  Dashboard Submission(s)	Haian Fu, Ph.D.	Andrei Ivanov
mRNA-seq Analysis of FFPE Prostate Cancer Tissues	<ul style="list-style-type: none"> <li>expression profiling by mRNA-seq</li> </ul>	Raw/Analyzed Data (GEO,SRA)		
Long, Xu et al. (Cancer Res)				

# Goals of Proposed Renewal

- New genomic data will be integrated into the bioinformatic component, which currently includes TCGA, TARGET, CGCI, such as NCI supported clinical trials and studies (Alchemist, Match (adult and pediatric), Exceptional Responders, etc.)
  - Nimble, flexible and open to new opportunities
- Accelerate the translation of patient genomic data into clinical application
  - Innovate the integration of computational mining large scale genomic data analyses and N of 1 application
  - Identify and confirm novel therapeutic target candidates
  - Identify and confirm novel modulators within specific cancer context (cellular or mutational) in vitro (cell lines) or in vivo (novel cancer models, e.g. organoids or conditionally reprogramed cells, others)
    - Pharmacogenomic screens to understand mechanism of action
    - CRISPRs, RNAi
  - Continue to share models, methods, data and resources with the scientific community through web site(s) and distributors

# Examples of Resources to be Developed & Scientific Questions to be Addressed

- Collaborative activities to maximize useful shared data
  - Use of the 320 compound “CTD<sup>2</sup> informer set” in screening campaigns, analyze and make data available through the web sites and publications
  - Develop methods to interpret results from different types of experimental read-outs
  - Modify informer set to include compounds which target cellular metabolites, enzymes



# Examples of Resources to be Developed & Scientific Questions to be Addressed

- Collaborative activities to maximize useful shared data - continued
  - Results from all CRISPR screens will be assembled in the CTD<sup>2</sup> Data Portal
  - Use of “control” screening models/cell lines to improve interpretation
  - Compare the various CAS9 enzyme constructs and the impact on interpretation of the results
- Use new cancer models for high-throughput functional studies to define biologically relevant targets, modulators or biomarkers
  - Development of methodologies for the community
  - Determine if the growth conditions impact on interpretation of results of CRISPR, small molecule, RNAi and cDNA screens
  - Share results which can serve as bases for preclinical testing or the next phase
- Define pathway and gene redundancies
  - Identify approaches to overcome them
- High-throughput combination screening of small molecules and CRISPRs
  - Identify genes which overcome resistance to precision treatments
- Other

# Questions from the BSA Sub-committee-1

- What evaluation criteria will be used to ascertain the quality of the data?  
And
- Are established metrics in place to evaluate high throughput data?
  - Development of the “Tier” concepts and publishing the document for others to use if they are so inclined
    - PI subgroup (rotating appointment) reviews Dashboard submissions
  - D-HIP group reviews submissions to ensure uniformity of metadata
    - All metadata is registered at NCI’s caDSR (dictionary with definitions)
  - Codification of QC metrics for the various high-throughput screens; each one will have their own technical issues to consider—in progress. Will be shared through the Data Portal for each project—be transparent. Examples:
    - Use of multiple RNAi(s) and cell lines in a screening campaign
      - Development of software to identify seed sequences which would lead to off-target effects
    - Replicate reproducibility and either remove failures or repeat a screen
    - Remove data with “low/high signal” depending on the assay
    - Small molecule HTS use dilution series; use of a compound with known

# Questions from the BSA Sub-committee-2

- How are current networks organized? And
- What is your vision of the types of networks that will be established?
  - Centers deposit “raw” prepublication data into intra-Network Portal
    - Use of “uniform controls” will allow cross-Center analyses
  - Centers collaborate to accelerate their research
  - Continue monthly teleconferences in which pre-publication data are discussed
  
- Going forward, how do you anticipate using TCGA data?
  - Expect that all NCI (and other) large scale genomic data will be used by the next set of Centers
  - NCI will launch Genomic Data Commons June 1, 2016 making high-content genomic data easier to access
    - Includes clinical, sample, molecular data

# Mechanism and Cost

- Mechanism:
  - U01 Cooperative Agreement Grants
    - Critical for pre-competitive collaborations
    - Essential for communication
    - Important for governance
  
- Open competition
  - No presumption of current Centers
  - Establish the best network possible from proposed grants
  
- Budget: \$12M for year 1
  - Fund up to 12 centers

# Program Evaluation Criteria: Examples

The program will be evaluated by a number of parameters:

- The number of publication as well as journal's H index
  - How many times the manuscripts were cited
- Are the results, methods, tools, etc. developed by scientists used in academia and industry?
  - Frequency of data portal visits and data downloads
  - How do the results impact on the number of proposals received at the NIH following up of CTD<sup>2</sup> findings
- Number of validated probes and/or targets
  - Were the results of the projects transitioned into preclinical testing?
  - Inclusion of CTD<sup>2</sup> results as a basis of an early phase clinical trial
- Other appropriate specific evaluation parameters will be determined once the composition of network is known



**NATIONAL  
CANCER  
INSTITUTE**

[www.cancer.gov](http://www.cancer.gov)

[www.cancer.gov/espanol](http://www.cancer.gov/espanol)

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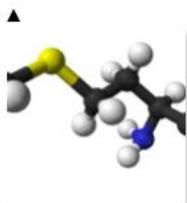
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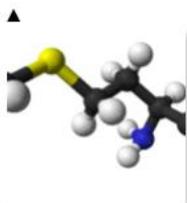
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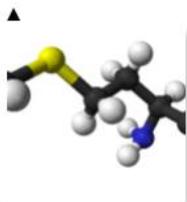
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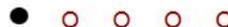
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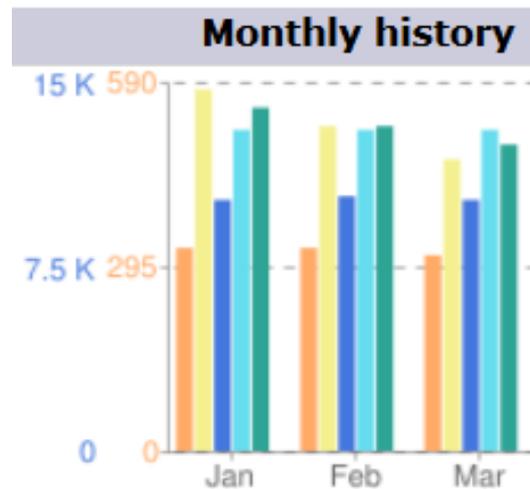
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# CTD<sup>2</sup> Network Funded Tools

Name	Function	Usages	Downloads
<b>ATARIS: Analytic Technique for Assessment of RNAi by Similarity</b>	<i>Reduces off-target effects from data in phenotypic screens using multiple RNAi reagents</i>	Avg 18 users/month	
<b>CTRP: Cancer Therapeutics Response Portal</b>	<i>Connects cellular features to small molecule sensitivities for &gt;800 cell lines</i>	Avg 600 users/month	
<b>DecoRNAi: Deconvolution Analysis of RNAi Screening data</b>	<i>Quantitates and annotates off-target effects of primary RNAi screening datasets</i>	No data available	
<b>DeMAND: Detecting Mechanism of Action based Network Dysregulation</b>	<i>Uses gene expression profiles of treated and untreated cell lines to determine mechanism of action of small molecules</i>		326
<b>DIGGIT: Driver-gene Inference by Genetical-genomics and Information Theory</b>	<i>Integrates patient-matched genomic mutation and gene expression data with corresponding gene regulatory networks to identify candidate driver mutations</i>		1190
<b>EDDY: Evaluation of Differential Dependency</b>	<i>Estimates differential dependencies for a set of genes between two conditions</i>	No data available	
<b>FuSiOn: Functional Signature Ontology</b>	<i>Searchable ontology map built from gene expression data from human kinome screens</i>	No data available	
<b>MethylMix</b>	<i>Identifies differentially and transcriptionally predictive methylated genes within a disease</i>	Avg 99 users/month	2125
<b>MINDy2/ CINDy: Modulator Inference by Network Dynamics/ Conditional Inference of Network Dynamics</b>	<i>Assess the effect of candidate proteins on a transcription factor of interest</i>		129
<b>PiHelper</b>	<i>Integrates drug target and antibody target interactions from publicly available resources to facilitate research in systems pharmacology, perturbation biology, and proteomics</i>	No data available	
<b>PARIS: Probability Analysis by Ranked Information Score</b>	<i>Uses a mutual information-based metric to rank data, such as shRNA/gene dependencies in cell lines, genomic features, and chemical sensitivities</i>	Avg 87 users/month	
<b>Project Achilles Portal</b>	<i>Uses genome-wide pooled shRNA screens to identify and catalog genetic vulnerabilities associated with genetic or epigenetic changes across hundreds of cancer cell lines</i>	2000 users/month	
<b>The Cancer Genome Atlas Clinical Explorer</b>	<i>A platform to query TCGA data to identify clinical-genomic associations</i>	Avg 500 users/month	
<b>VIPER/ MARINA: Virtual Inference of Protein-activity by Enriched Regulon analysis/Master Regulator Inference algorithm</b>	<i>MARINa uses the transcriptional targets of each transcription factor as a multiplexed reporter assay to infer the transcription factors controlling the transition between related cellular states. VIPER extends MARINa to single samples and any regulatory protein</i>		3359

# CTD<sup>2</sup> Network Data Portal: Metrics

Do we have sufficient volume of traffic, and more importantly qualified traffic that is actually using our data sets?



Orange bar and numbers on left Y axis- unique visitors  
 Yellow bar-number of visits  
 Blue bar and number on left Y axis- pages accessed  
 Cyan blue bar- number of hits  
 Green bar and numbers on right Y axis- bandwidth

Month	Unique visitors	Number of visits	Pages	Hits	Bandwidth
Jan 2016	334	589	10,909	13,999	152.31 MB
Feb 2016	332	532	11,041	14,007	142.91 MB
<b>Mar 2016</b>	321	475	10,953	13,989	135.90 MB

NCI is working on to allow tracking actual downloads—in progress