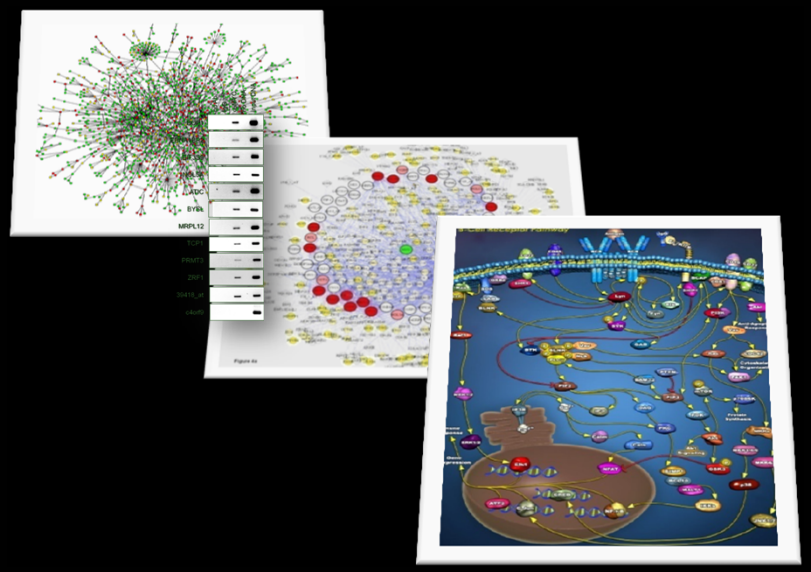


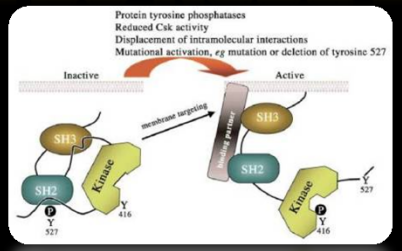
Cancer
Target
Discovery and
Development

CTD^2 Network

COLUMBIA UNIVERSITY CENTER FOR:

Systems Biology of Tumor Progression and Drug-Resistance

The Road to Drug Development



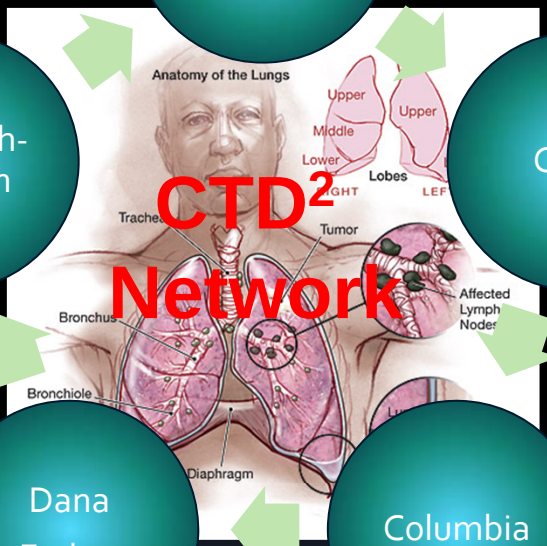
Mechanism of Action

Hit compound

Broad

UT South-western

CSHL

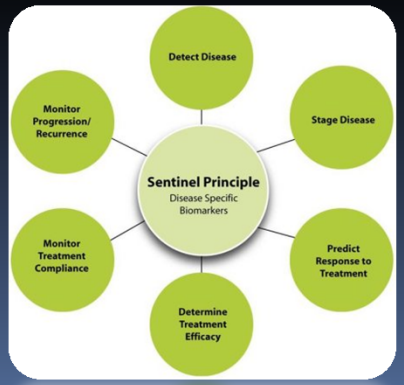


CTD² Network

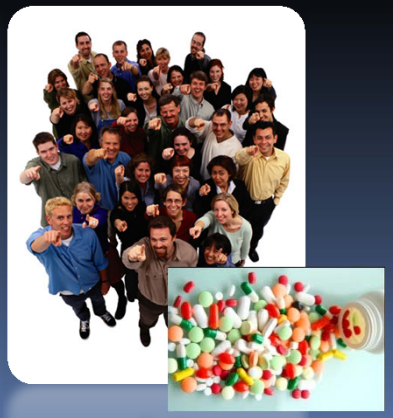
Dana Farber

Columbia

Biomarkers: Response/Efficacy

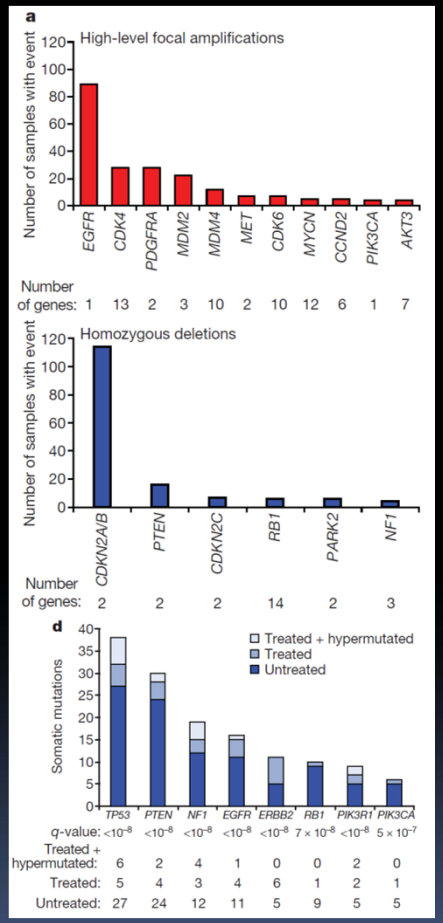


Clinical Trials



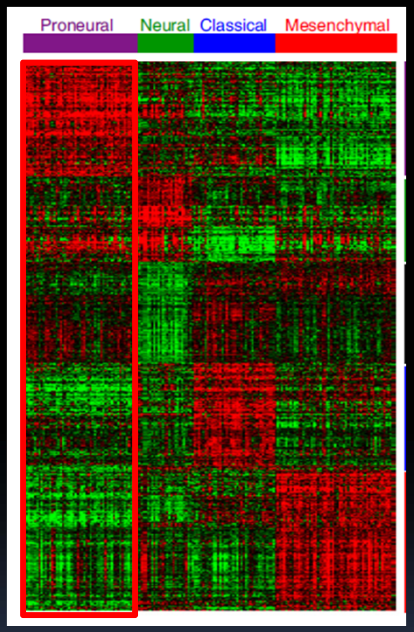
How many tumor types are there?

(Epi-)Genetic Alterations



Cancer Genome Atlas Research Network. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. *Nature*. 2008 Oct 23;455(7216):1061-8

Subtype Signature

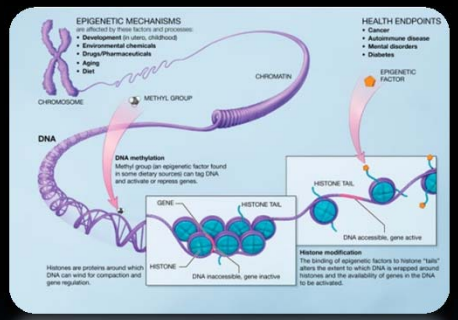


Verhaak RG et al.; The Cancer Genome Atlas Research Network. Integrated Genomic Analysis Identifies Clinically Relevant Subtypes of Glioblastoma Characterized by Abnormalities in PDGFRA, IDH1, EGFR, and NF1. *Cancer Cell*. 2010 Jan 19;17(1):98-110

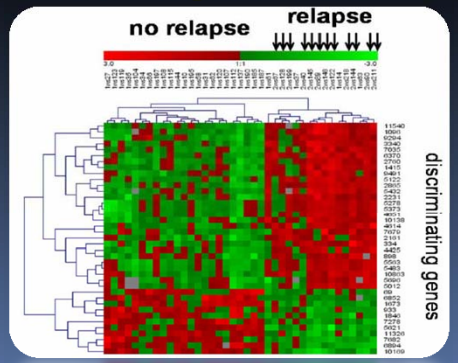
Changing the model

Genetics

Epigenetics

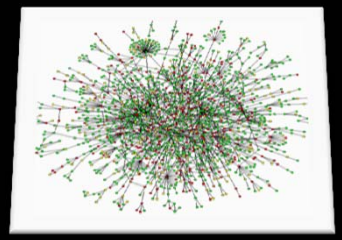


Cell Dynamics

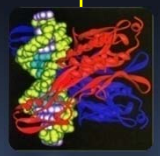


The Harsh Reality of Cancer Genetics

Cell Regulatory Logic

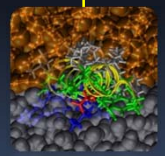


Protein DNA

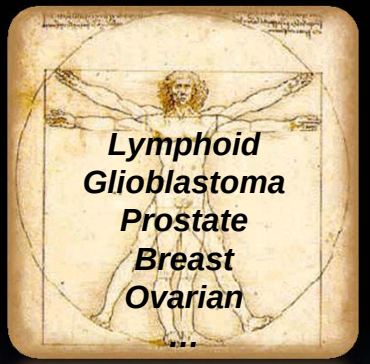


Protein Protein

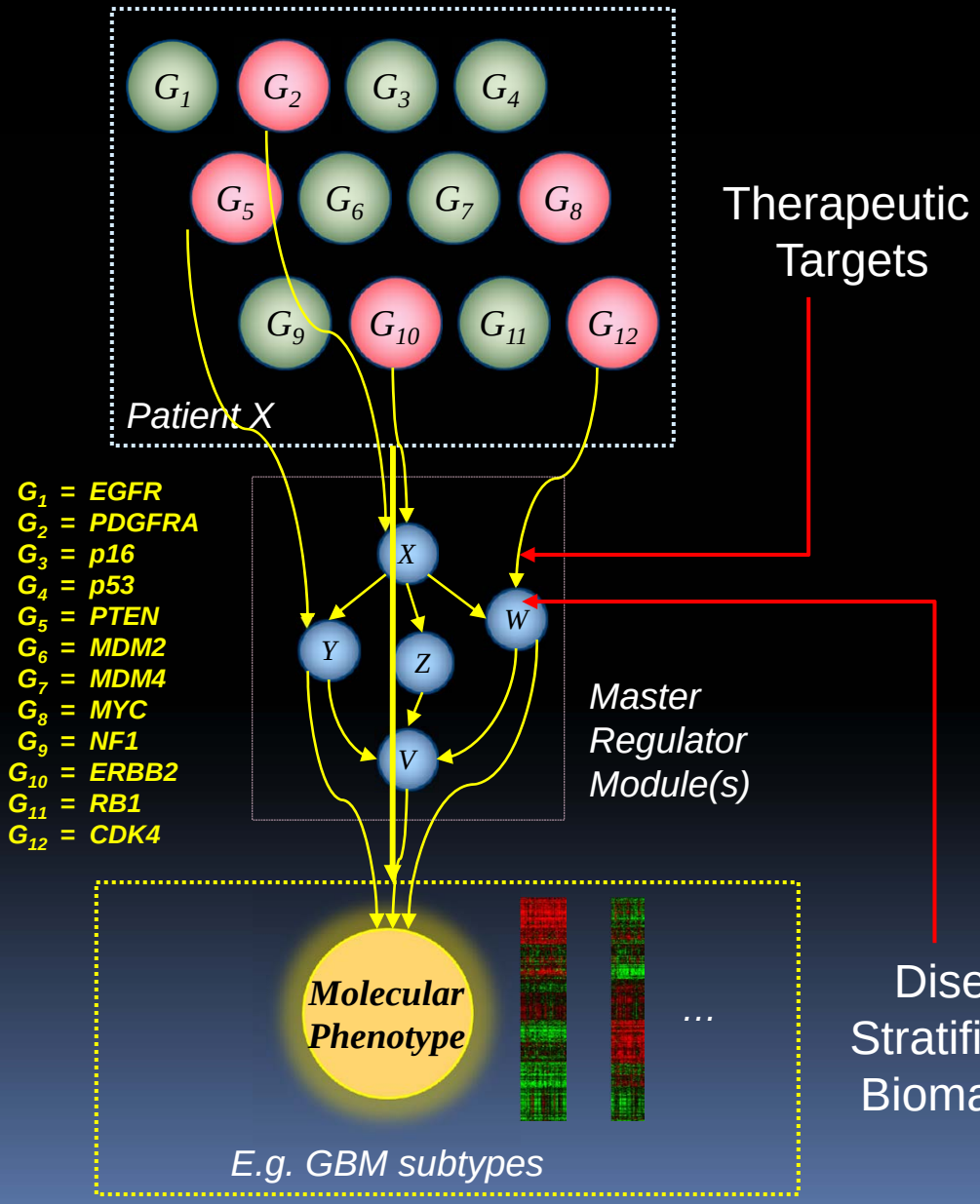
Protein Membrane



Human Cancer



GBM (Epi)Genetic Alteration Spectrum



Glioblastoma:

- Carro MS et al. *The transcriptional network for mesenchymal transformation of brain tumours*. Nature. 2010 Jan 21;463(7279):318-25.
- Master Regulators: C/EBP + Stat3

Diffuse Large B Cell Lymphoma:

- Compagno M et al. *Mutations of multiple genes cause deregulation of NF-kappaB in diffuse large B-cell lymphoma.* Nature. 2009 Jun 4;459(7247):717-21
- Master Regulator: Nf-kB pathway

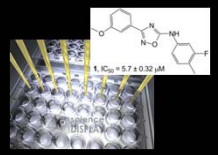
GC-Resistance in T-ALL:

- Real PJ et al. *Gamma-secretase inhibitors reverse glucocorticoid resistance in T cell acute lymphoblastic leukemia.* Nat Med. 2009 Jan;15(1):50-8.
- Master Regulator: NOTCH1 pathway

Oncogene(s) Addiction

- Identify and validate tumor-acquired **Gene and Pathway Dependencies** (Oncogene/Oncopathway addiction)

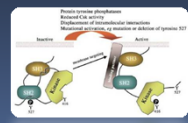
- Identify their **Small-Molecule Modulators**



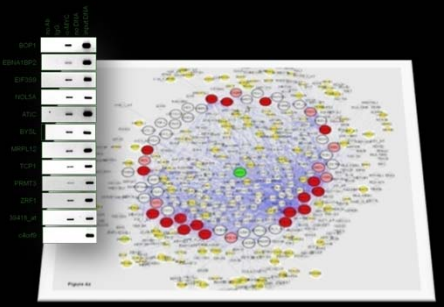
- Characterize their associated **Biomarkers of Response**

- Characterize their associated **Biomarkers of Treatment Efficacy**

- Characterize the **Mechanism of Action** of their small-molecule modulators

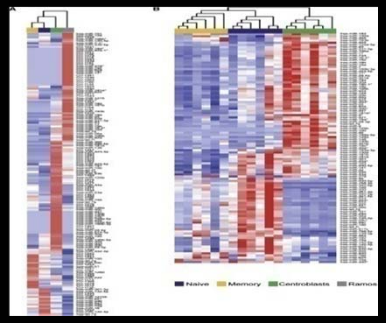


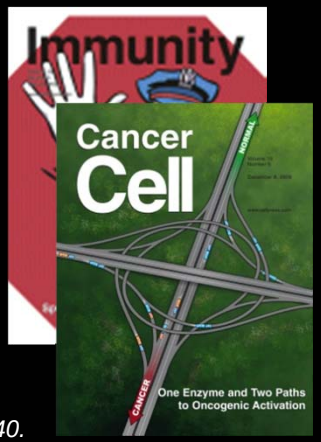
TRANSCRIPTIONAL INTERACTIONS



Zhao X et al. (2009) Dev Cell. 17(2):210-21.
Mani KM et al. (2008) Mol Syst Biol. 4:169
Palomero T et al., Proc Natl Acad Sci U S A 103, 18261 (Nov 28, 2006).
Margolin AA et al., Nature Protocols; 1(2): 662-671 (2006)
Margolin AA et al., BMC Bioinformatics 7 Suppl 1, S7 (2006).
Basso K et al. (2005), Nat Genet.;37(4):382-90. (Apr. 2005)

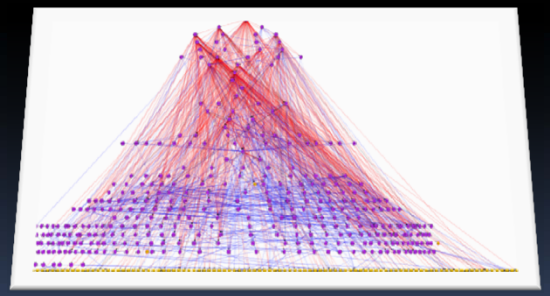
POST-TRANSCRIPTIONAL INTERACTIONS





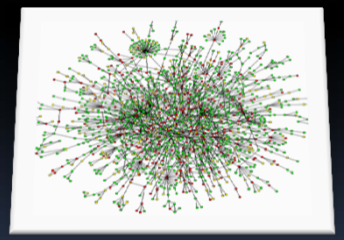
Basso et al. Immunity. 2009 May;30(5):744-52
Klein et al, Cancer Cell, 2010 Jan 19;17(1):28-40.

POST-TRANSLATIONAL INTERACTIONS



Wang K, Saito M, et al. (2009) Nat Biotechnol. 27(9):829-39
Zhao X et al. (2009) Dev Cell. 17(2):210-21.
Wang K et al. (2009) Pac Symp Biocomput. 2009:264-75.
Mani KM et al. (2008) Mol Syst Biol. 4:169
Wang K et al. (2006) RECOMB

MASTER REGULATORS AND MECHANISM OF ACTION

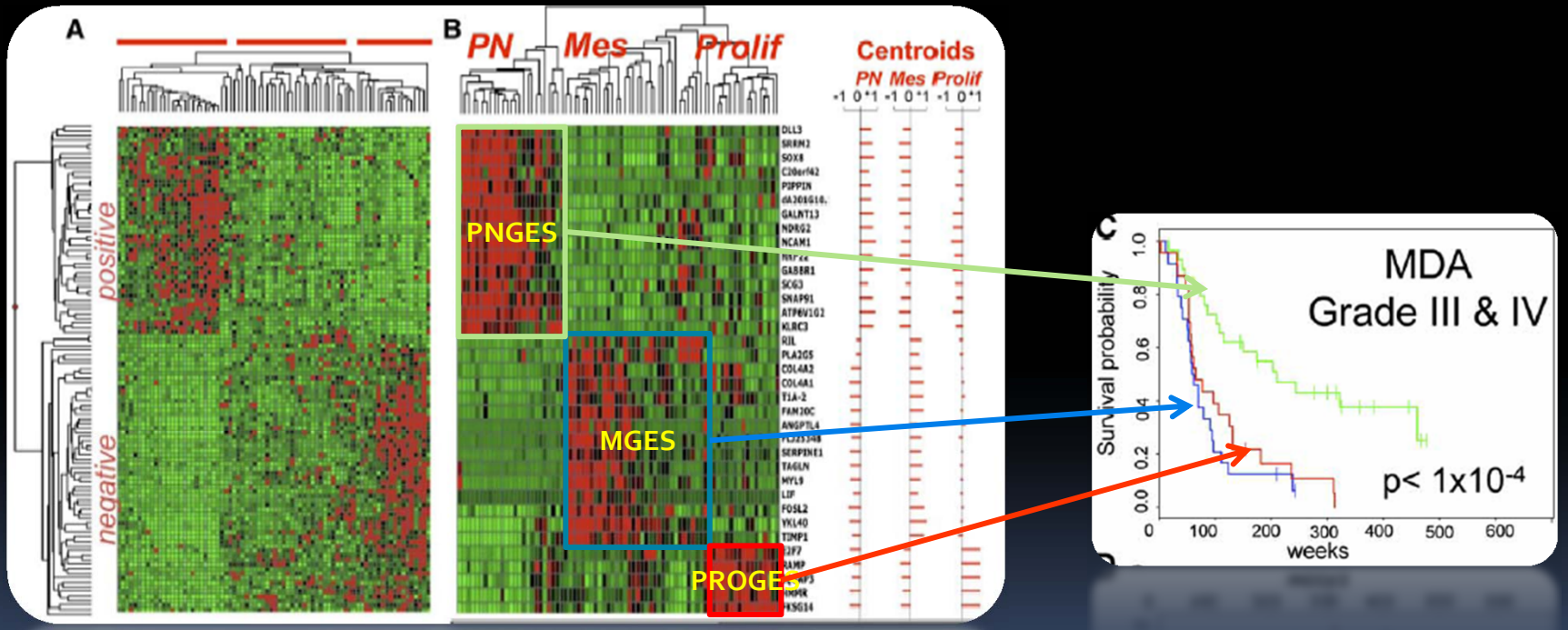


Lefebvre C. et al (2010), Mol Syst. Biol, in press
Carro MS et al. (2010) Nature 2010 Jan 21;463(7279):318-25
Mani K et al, (2008) Molecular Systems Biology, 4:169

Mesenchymal Subtype of High-Grade Gliomas

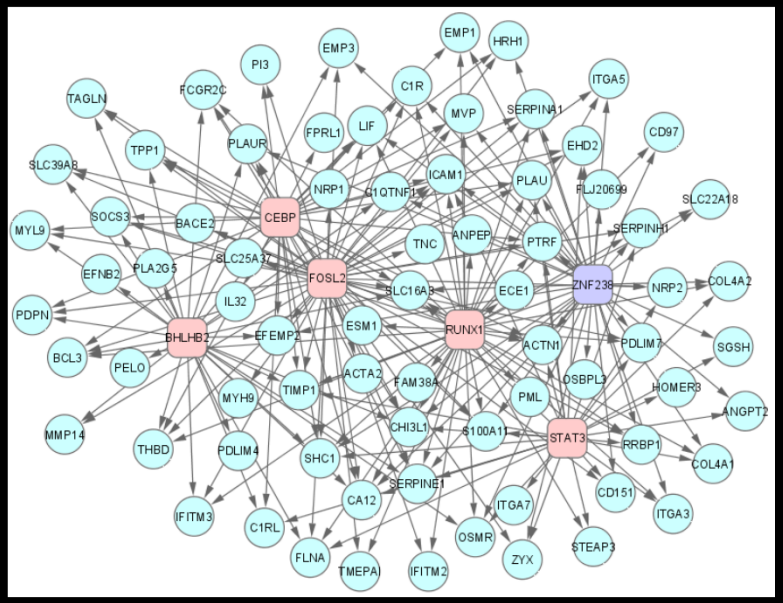
Unsupervised clustering of 76 high grade tumors by expression of 108 genes that are positively or negatively associated with survival reveals 3 tumors classes (Proneural (PN), Mesenchymal (Mes) and Proliferative (Prolif).

Phillips *et al*., *Cancer Cell,* 2006



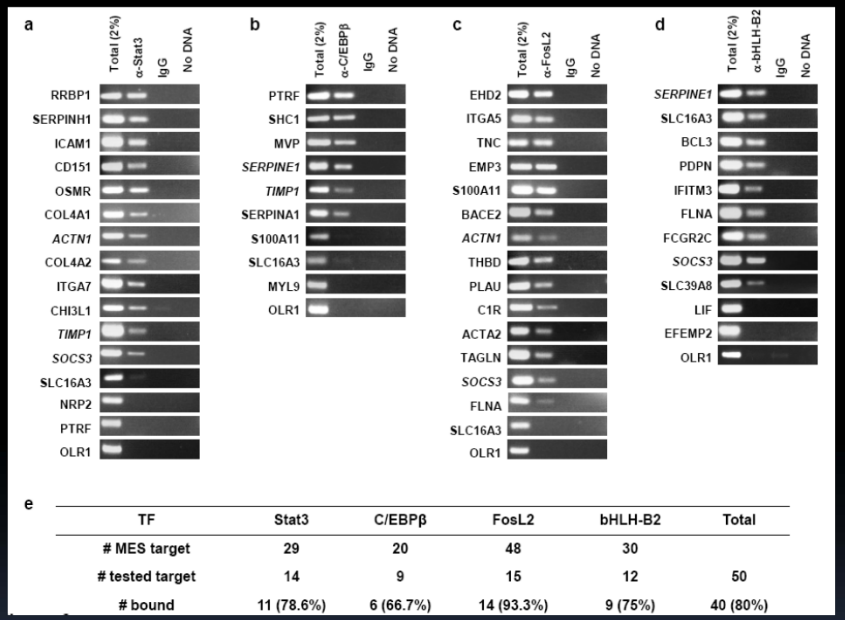
Malignant gliomas belonging to the mesenchymal sub-class express genes linked to the most aggressive properties of glioblastoma (migration, invasion and angiogenesis).

Identification of a mesenchymal regulatory module



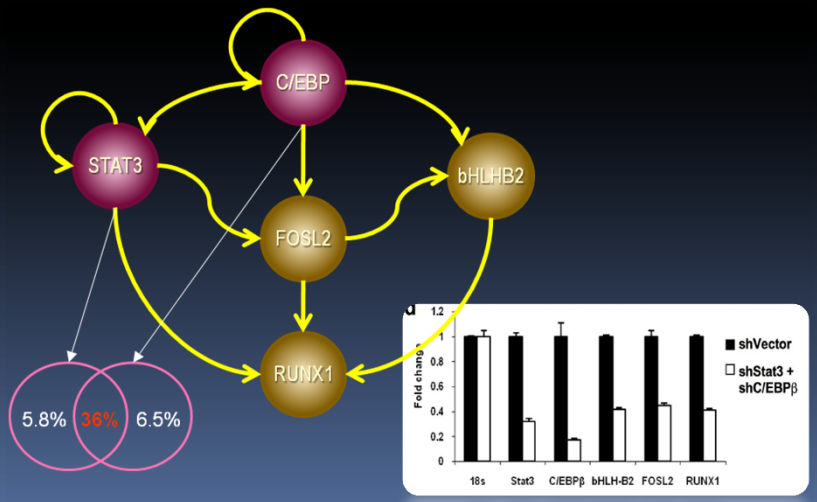
Mes signature genes
Activator
Repressor

Master Regulators control >75% of the Mesenchymal Signature of High-Grade Glioma



TF	Stat3	C/EBPβ	FosL2	bHLH-B2	Total
# MES target	29	20	48	30	
# tested target	14	9	15	12	50
# bound	11 (78.6%)	6 (66.7%)	14 (93.3%)	9 (75%)	40 (80%)

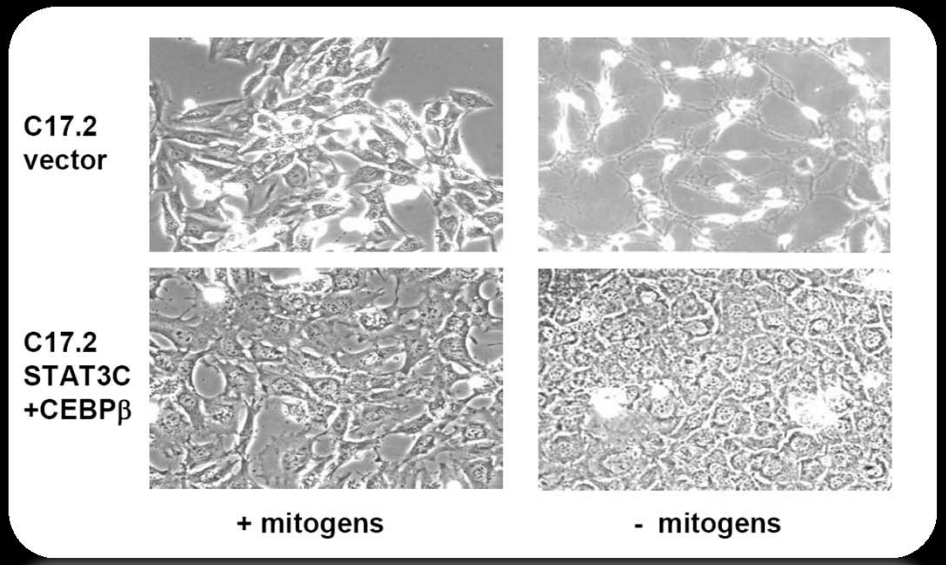
Hierarchical Regulatory Module

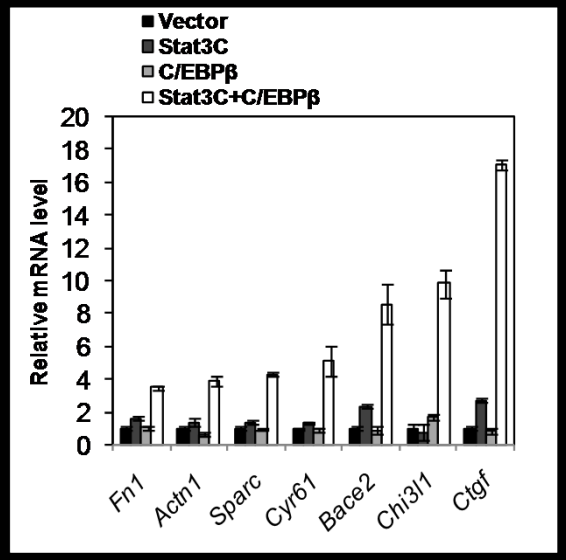


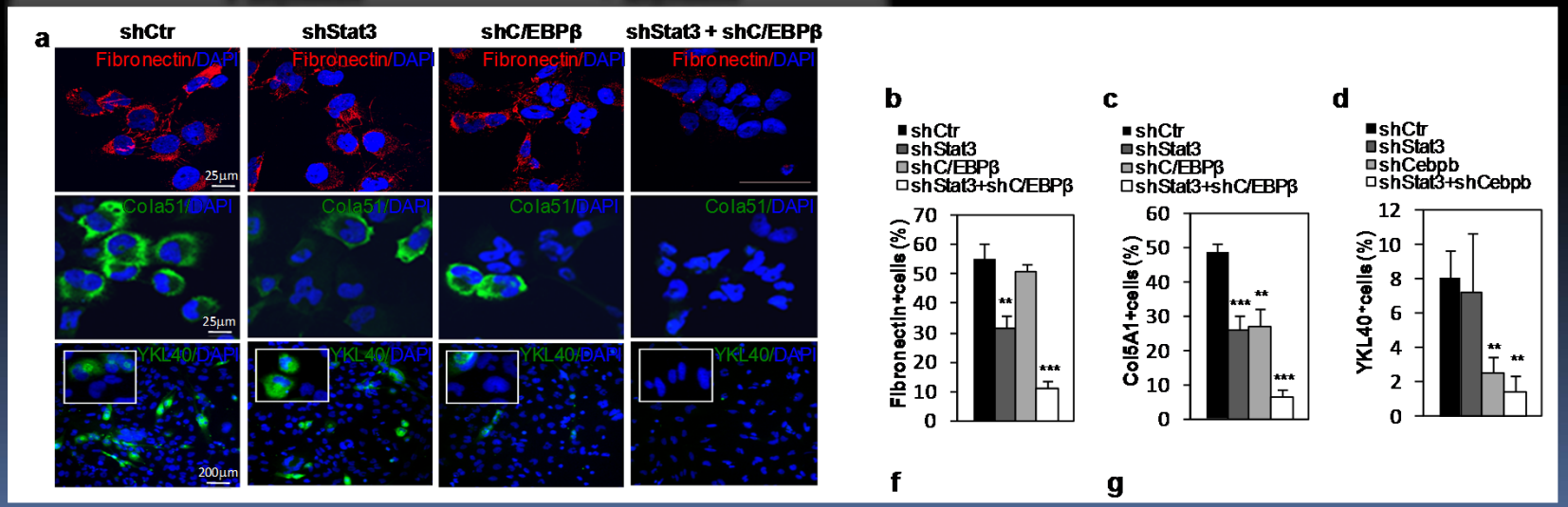
Biochemical Validation of ARACNe Inferred Targets of Stat3, C/EBPb, FosL2, and bHLH-B2

	C/EBPβ		Stat3		FosL2		bHLH-B2		Runx1	
	nES	p value	nES	p value	nES	p value	nES	p value	nES	p value
MGES Enrich.	3.23	0.0001	3.59	0.0001	3.92	< 1E-4	4.36	< 1E-4	3.82	< 1E-4

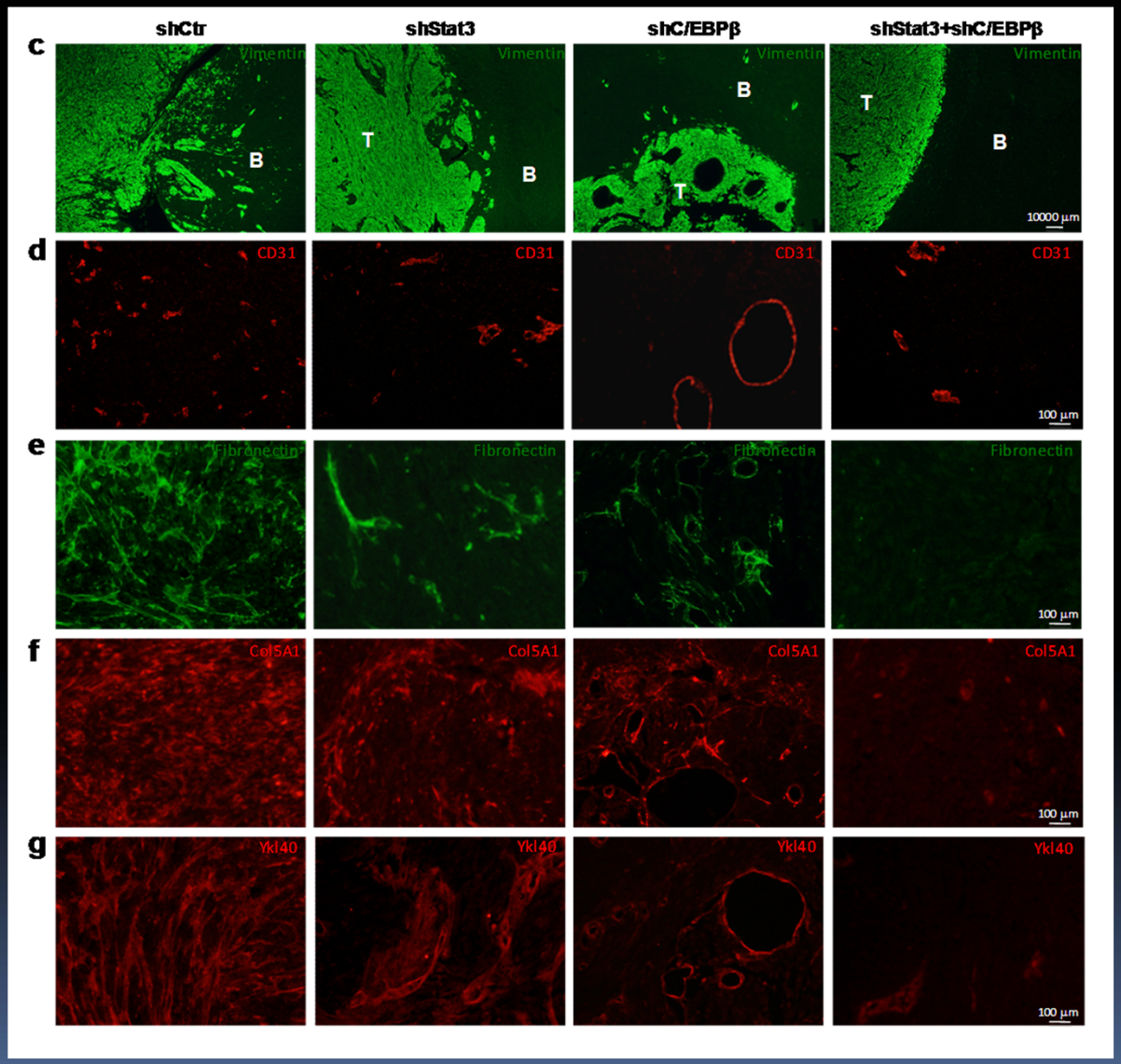
C/EBPβ and Stat3 modulate mesenchymal lineage in mouse neural stem cells and human glioma cells



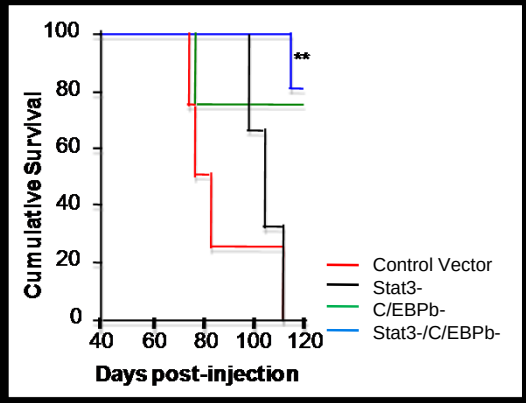




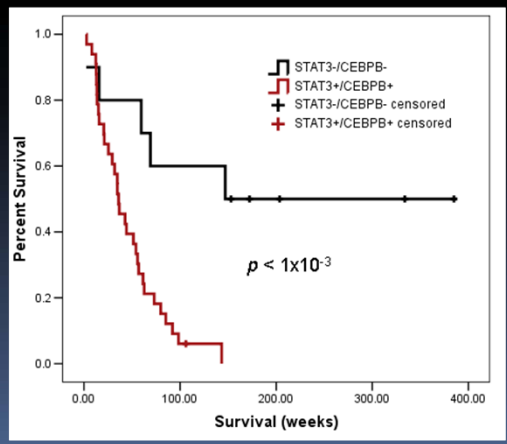
Mouse immunohistochemistry



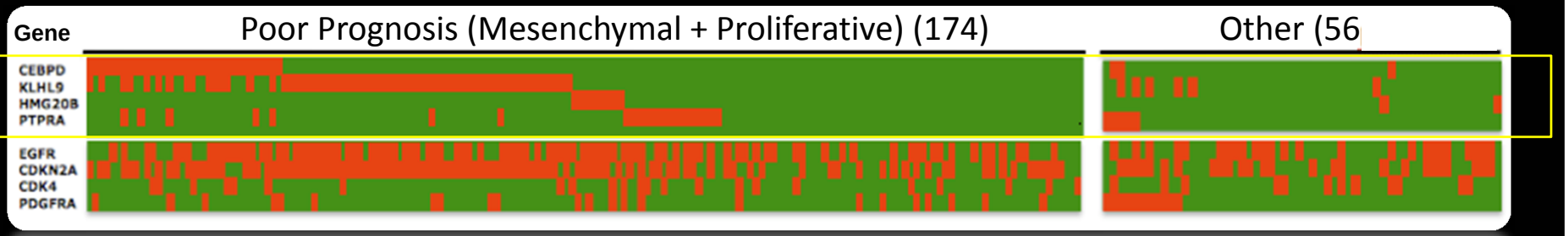
Mouse



Human



Pathway-Wide Association Study (PWAS)

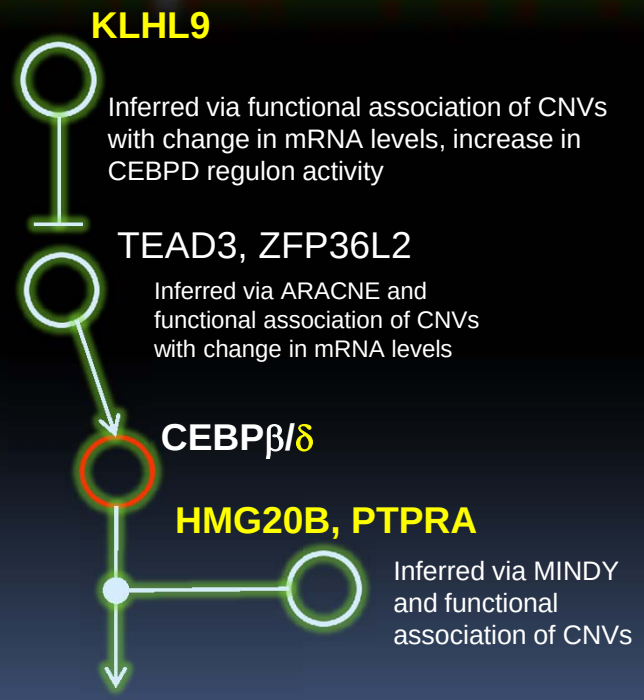


Significantly Altered

Not Altered

Mutation		CHR	OR	p-value
C/EBPδ (amp) TF	Master Regulator	8	4.61	0.004
PTPRA (amp)	MINDy Modulator of C/EBP subunits (YP)	20	4.78	0.032
HMG20B (amp)	MINDy Modulator of C/EBP subunits (TF)	19	2.83	0.042
KLHL9 (del)	Ubiquitin Conjugating Ligase. Modulates TEAD3, which is a Transcriptional Activator of C/EBP subunits	9	4.70	0.018

Odd Ratio = 5.405, *p*-value = 1.12e-6

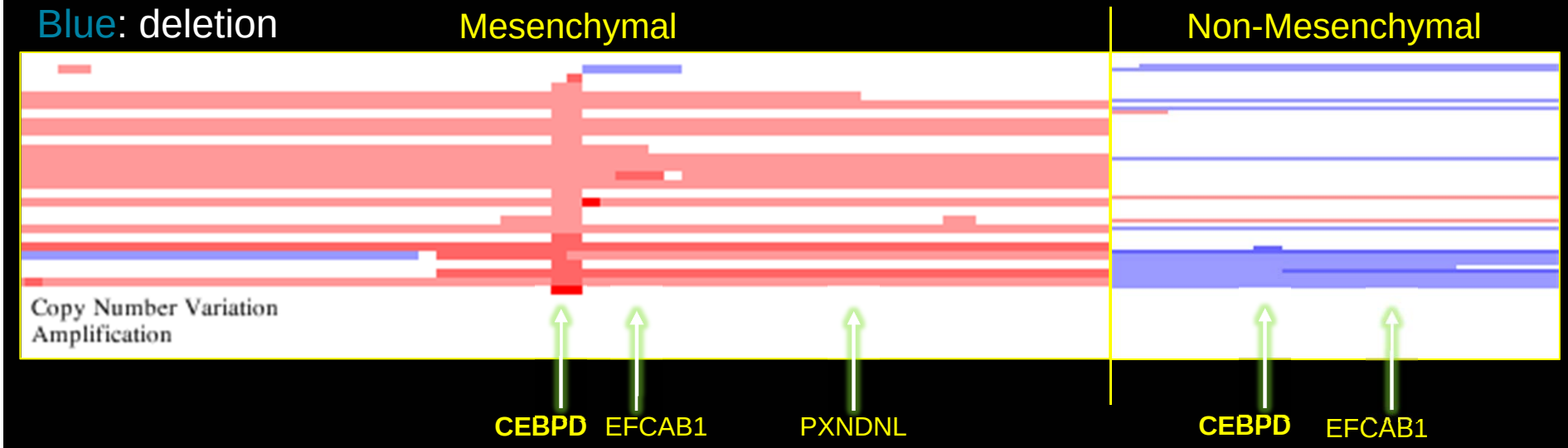


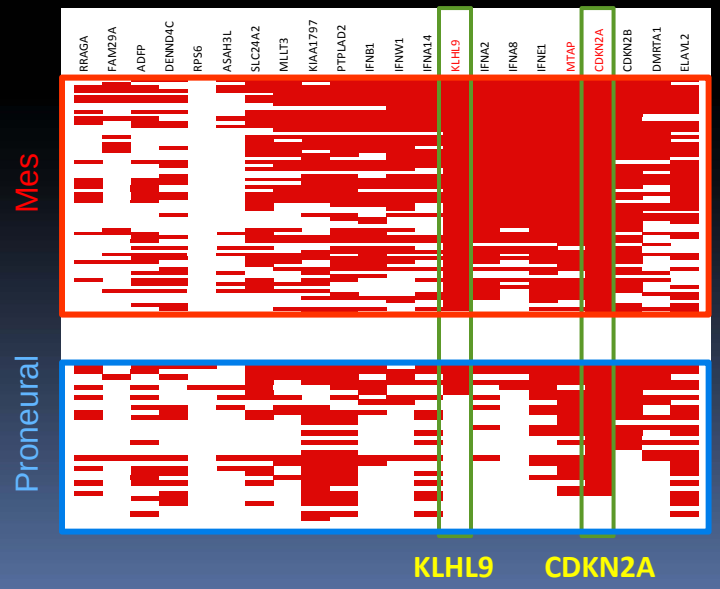
MES signature

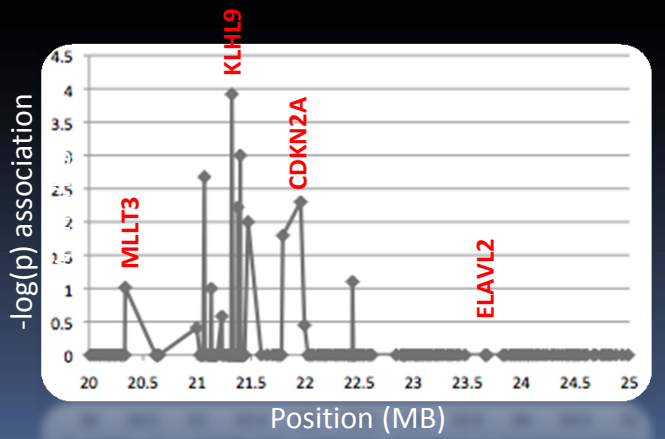
Focal Amplification of C/EBPδ locus

Red: amplification

Blue: deletion

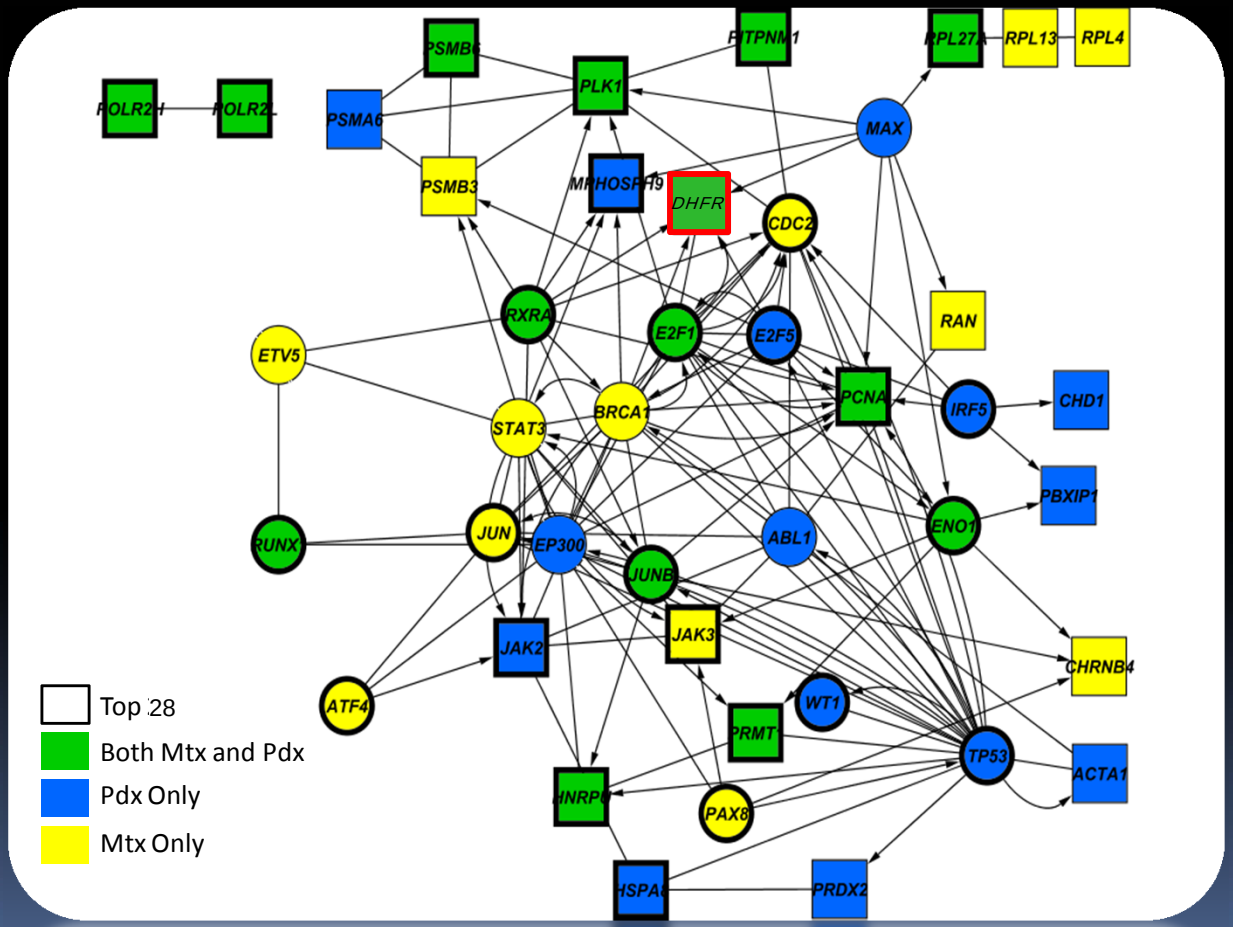






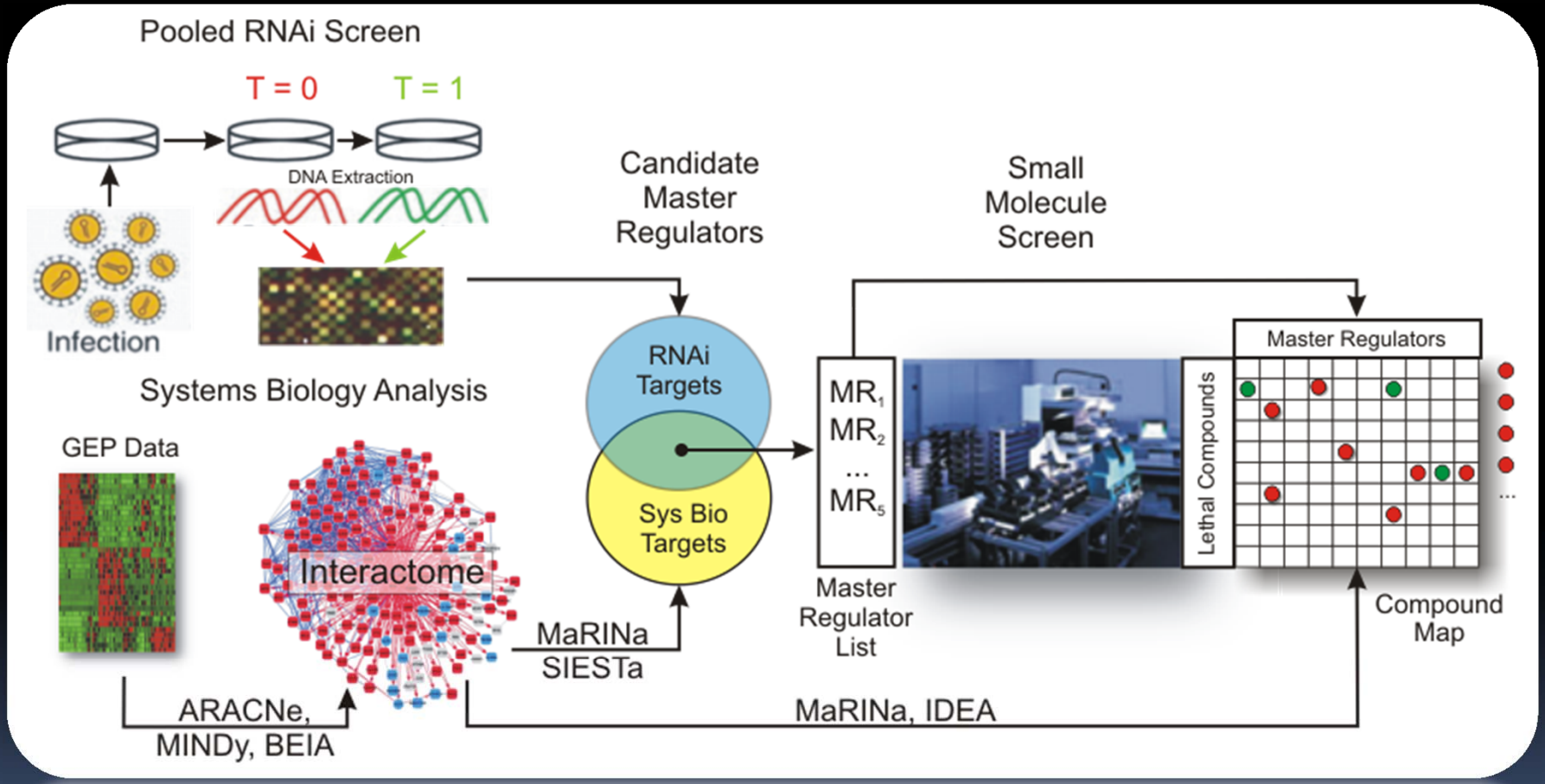
The Network Address of a compound

Network-based Activity Signature for Methotrexate and Pralatrexate (both are DHFR inhibitors): NetMoA



CTD²: Cancer Target Discovery and Development Network

Systems Pharmacology at Columbia University



A Califano (PI), R. Dalla-Favera, A. Ferrando, A. Iavarone, B. Stockwell, J. Silva

Network Collaborations

- Collaboration with the Broad Institute (S. Schreiber)
  - Identification of Small-molecule inhibitors of Stat3 and C/EBP
- Collaboration with UT Southwestern (M. White, J. Minna)
  - Validation of synergistic oncopathway dependencies in tyrosine kinase signaling networks, in Non Small Cell Lung Cancer
- Collaboration with Dana Farber (B. Hahn, L. Chin, R. DePinho) and the Broad Institute (S. Schreiber)
  - Identification and validation of oncopathway addiction in ovarian cancer
- Collaboration with CSHL (S. Powers, S. Lowe)
  - Prioritization of genetic aberrations as drivers of oncogenesis in ovarian cancer from Genome Wide Association Studies

CTD² Conclusions

Traditional Discovery		CTD² Model
Linear discovery pipeline	→	Parallel discovery pipeline ▫ Target(s) + small-molecule modulators + biomarkers + MoA
Individual Technological Platform	→	Integrated, State-of-the-Art Technological Platforms ▫ RNAi + Systems Biology + Chemistry + HT Screening + Functional Genomics
Potential for Translation	→	Direct Path to Translation
Small Individual functional datasets	→	Large-Scale functional datasets in vitro and in vivo
Partial data sharing	→	Complete, network-validated data + model + reagent sharing
Investigator Excellence	→	Investigator Network Excellence