National University Cancer Institute, Singapore

NUHS National University Health System

Functional Oncogenomics: A Tool for Identification and Validation of Targeted Therapies in Multiple Myeloma

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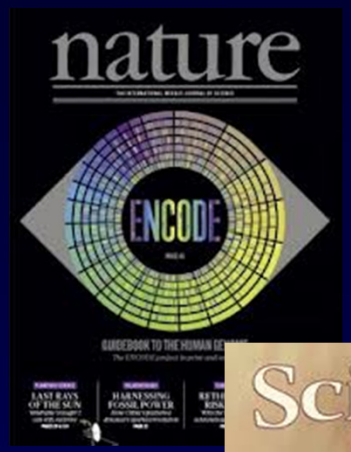
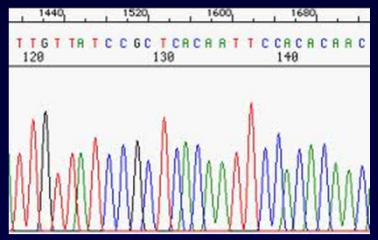
prIME oncology

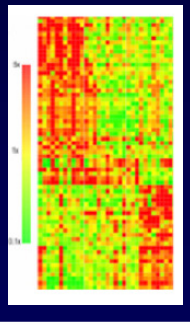
Molecular Abnormalities in Cancer



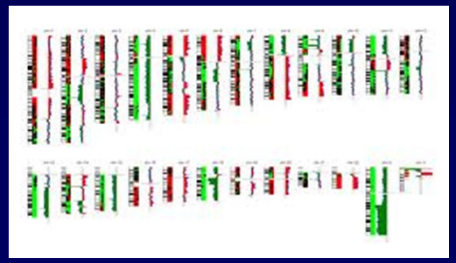
Sequencing



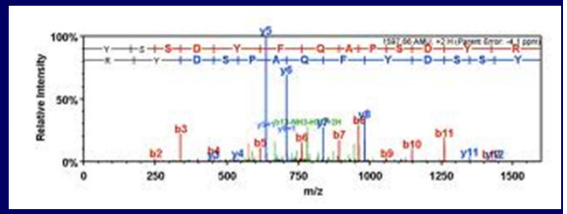
Microarray



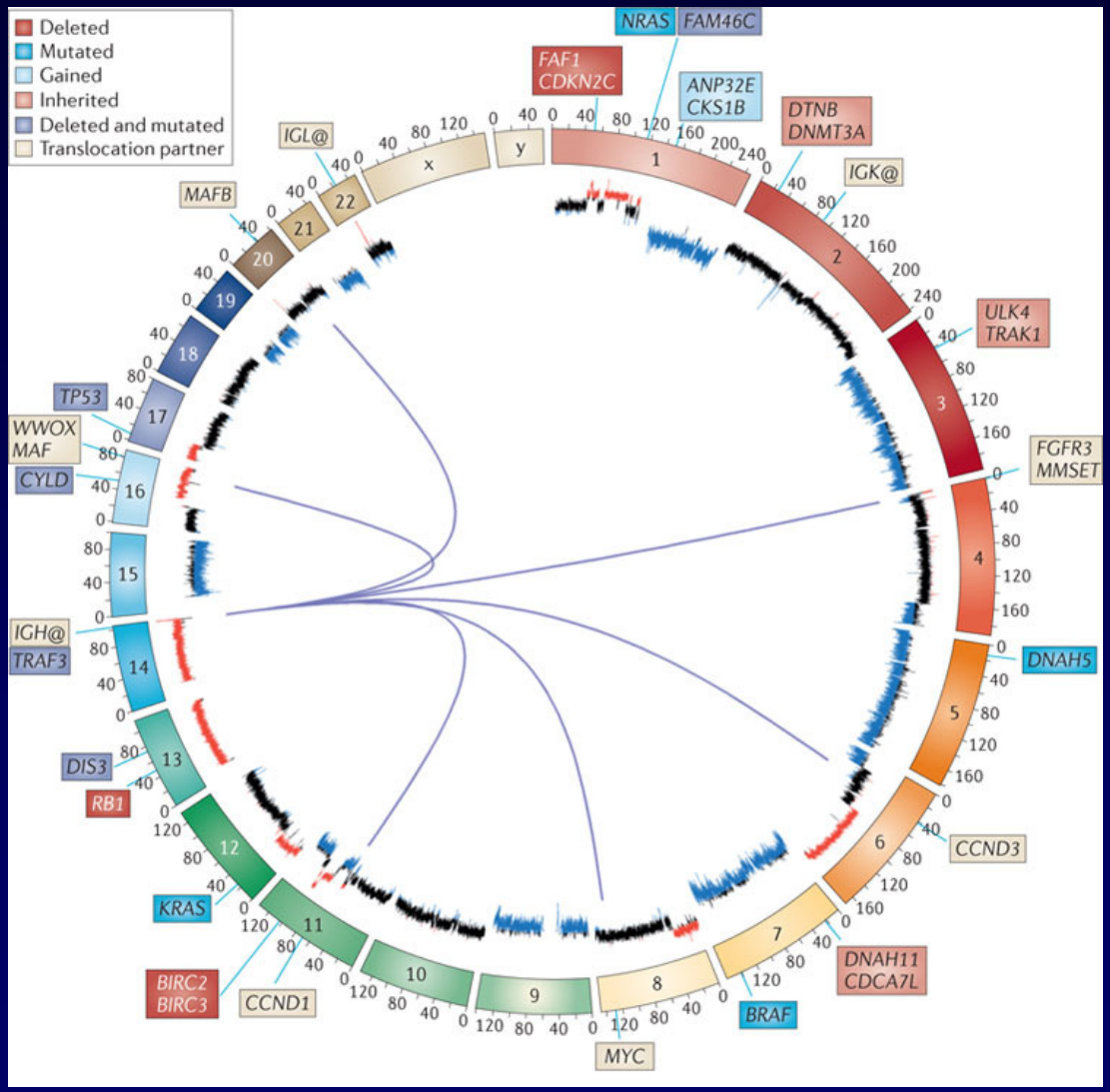
mRNA
miRNA
Methylation
Protein



Proteomics



Genomic Landscape in Multiple Myeloma (MM)

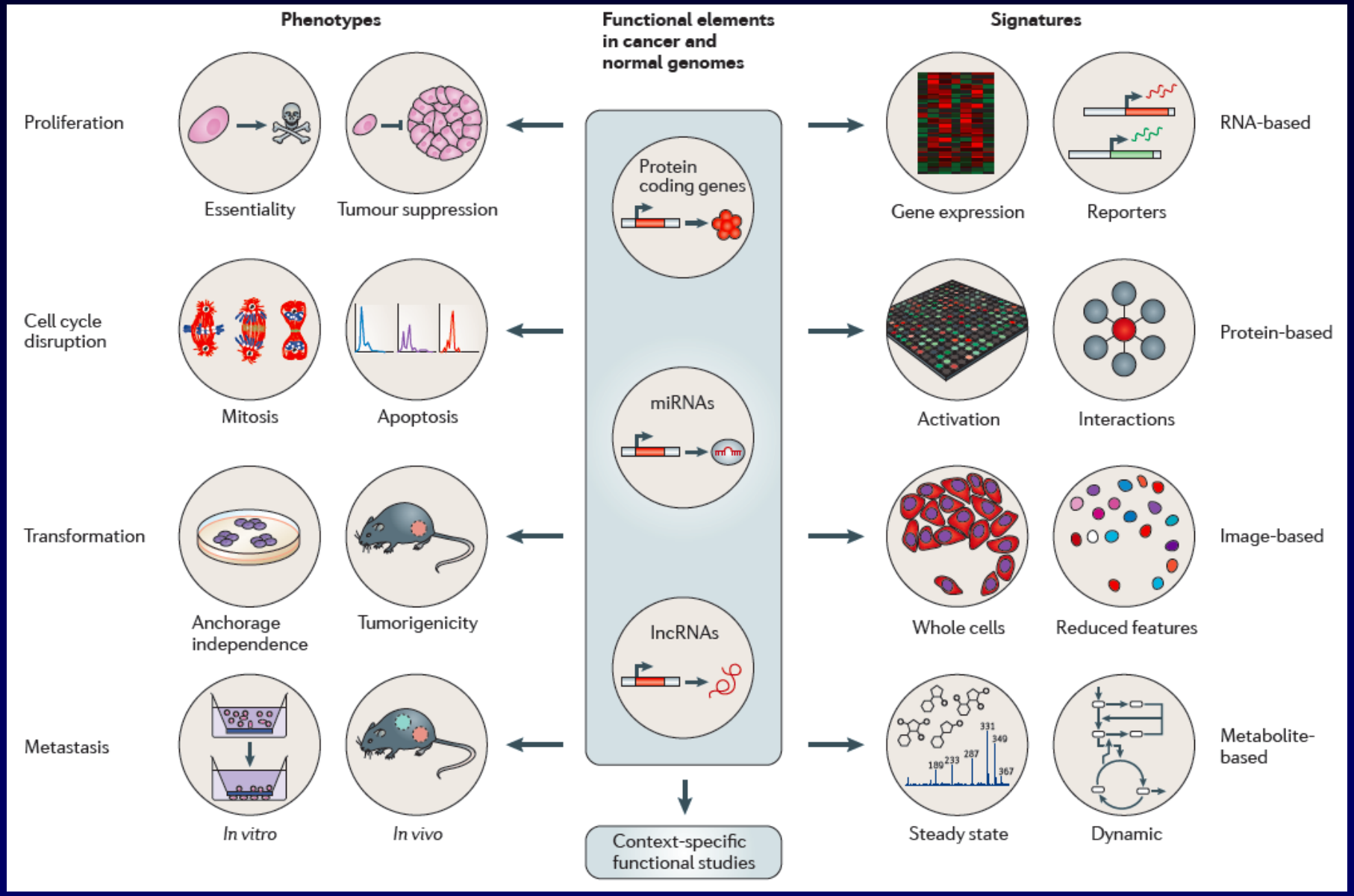


Morgan GJ, et al. *Nat Rev Cancer*. 2012;12(5):335-348.

Functional Genomics

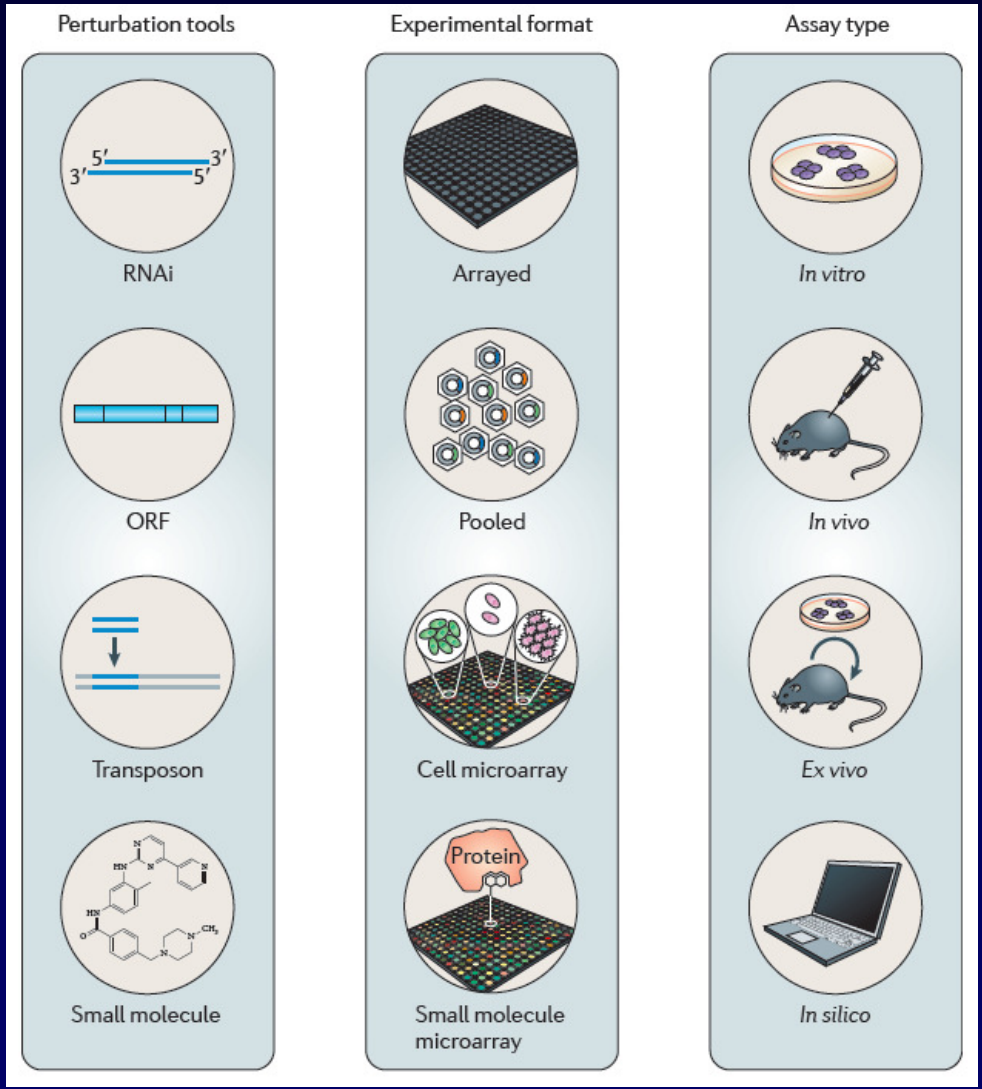
- The large-scale manipulation of gene expression or function using high-throughput approaches
- Basic tenet: Perturbation of gene function and assessment of phenotypic effects can provide insights into its biological function
- Allow establishment of causal relationship between genotype and phenotype

Overview of Cancer Functional Genomics



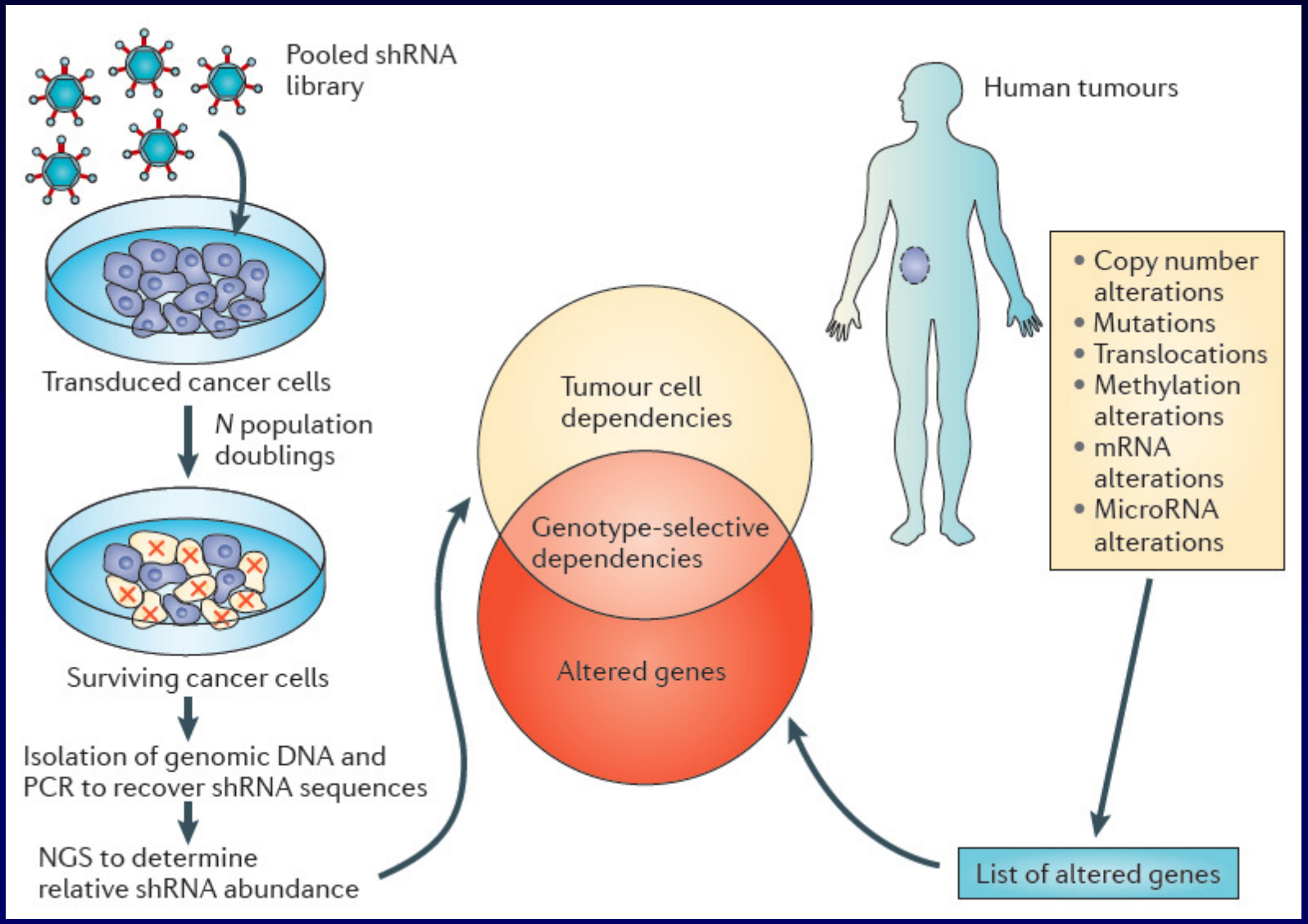
Boehm JS, et al. *Nat Rev Genet.* 2011;12(7):487-498.

Tools and Formats for Cancer Functional Genomics

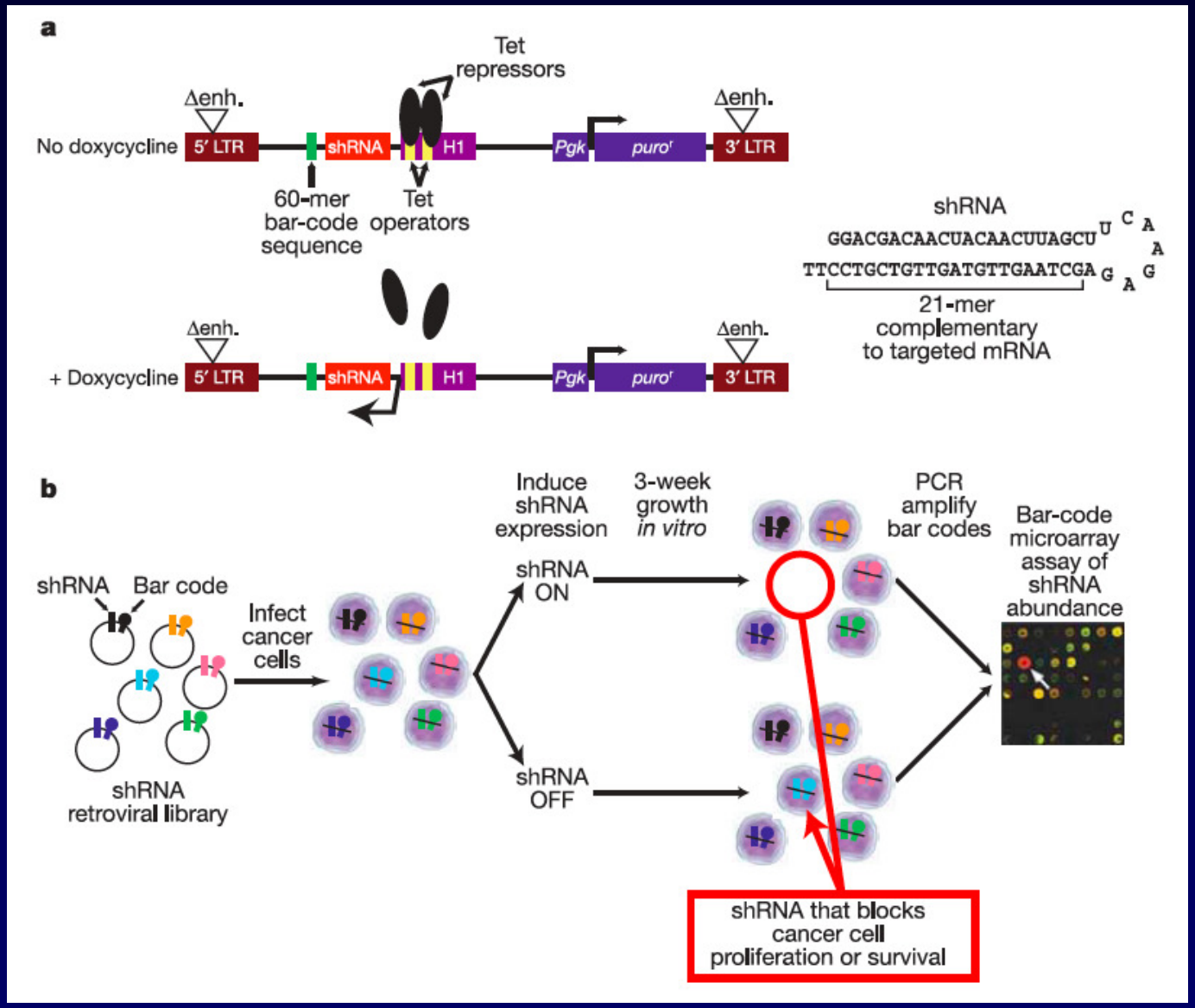


Boehm JS, et al. *Nat Rev Genet*. 2011;12(7):487-498.

RNAi Screen

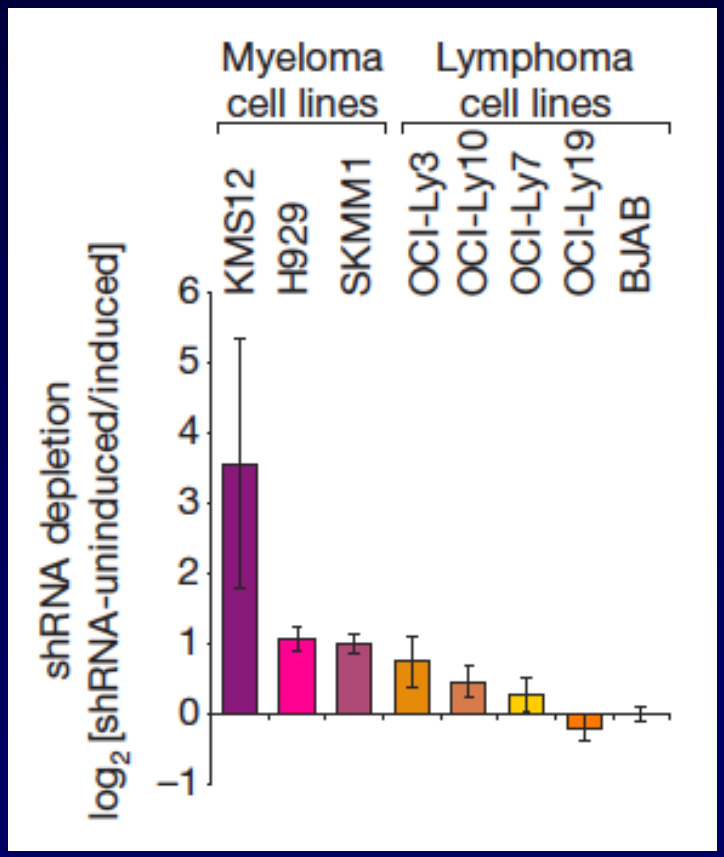


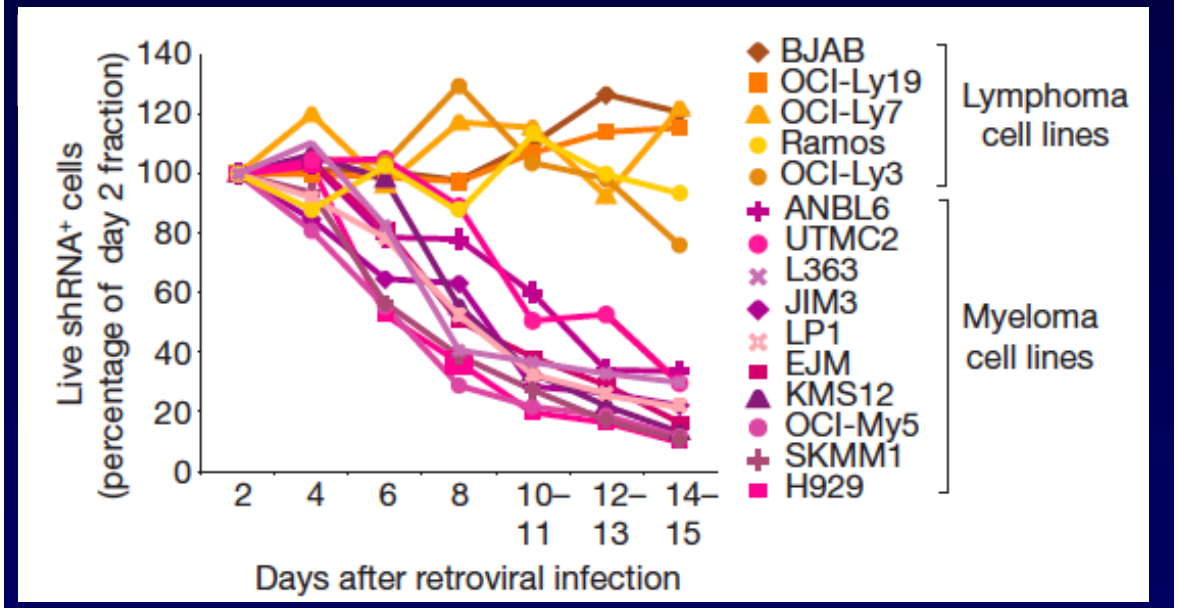
Eifert C, et al. *Nat Rev Cancer*. 2012;12(8):572-578.



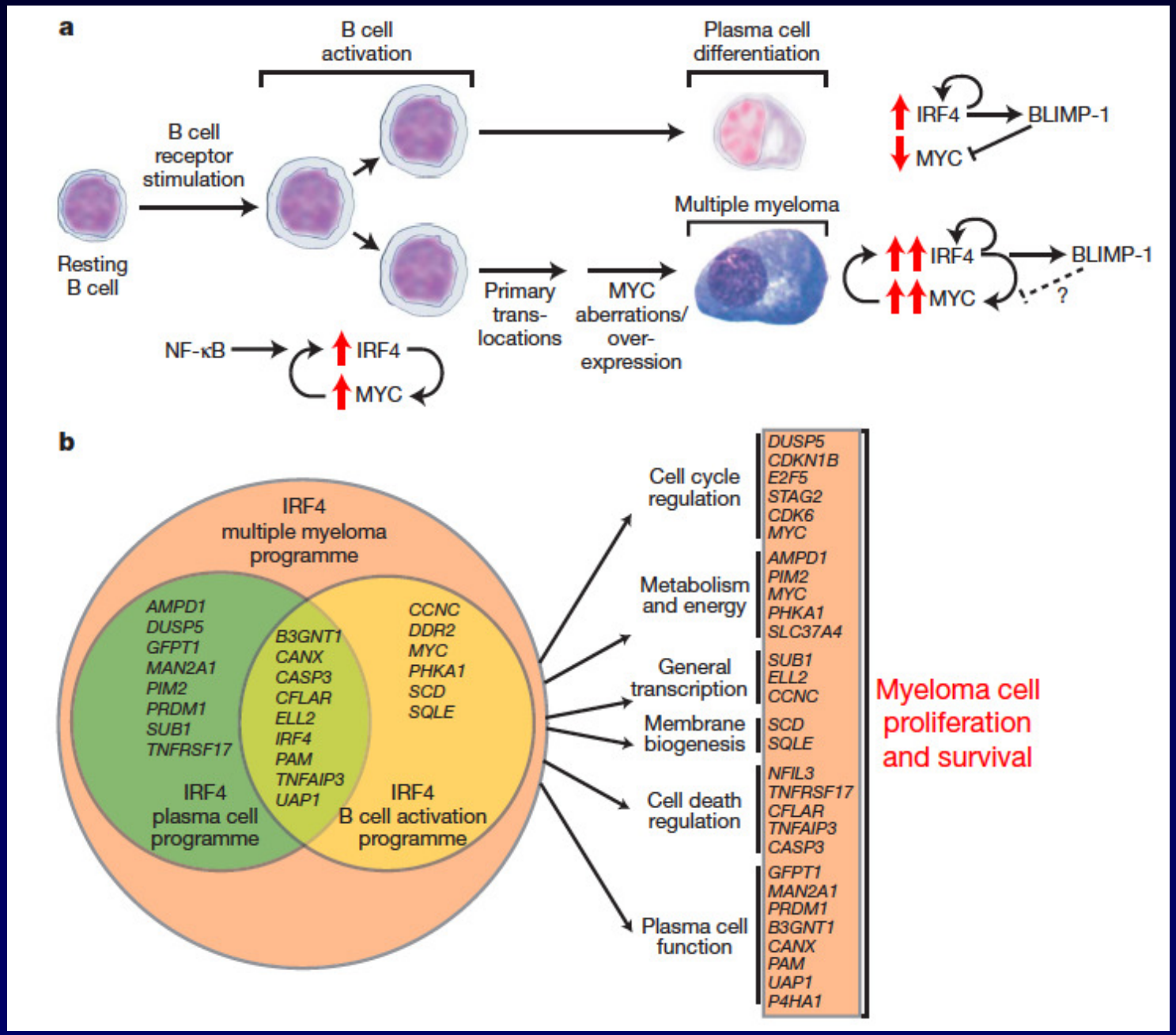
Ngo VN, et al. *Nature*. 2006;441(7089):106-110.

IRF4 Addiction in MM



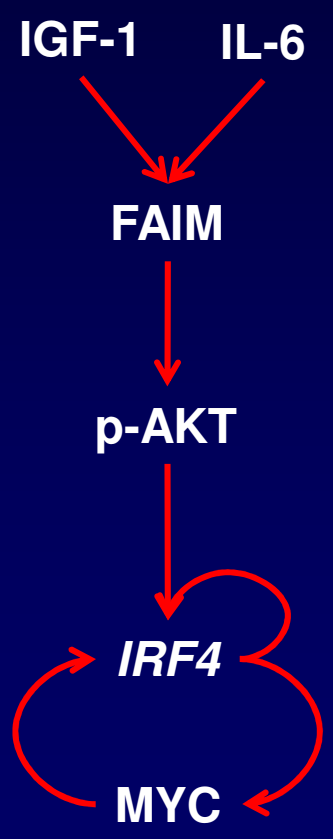


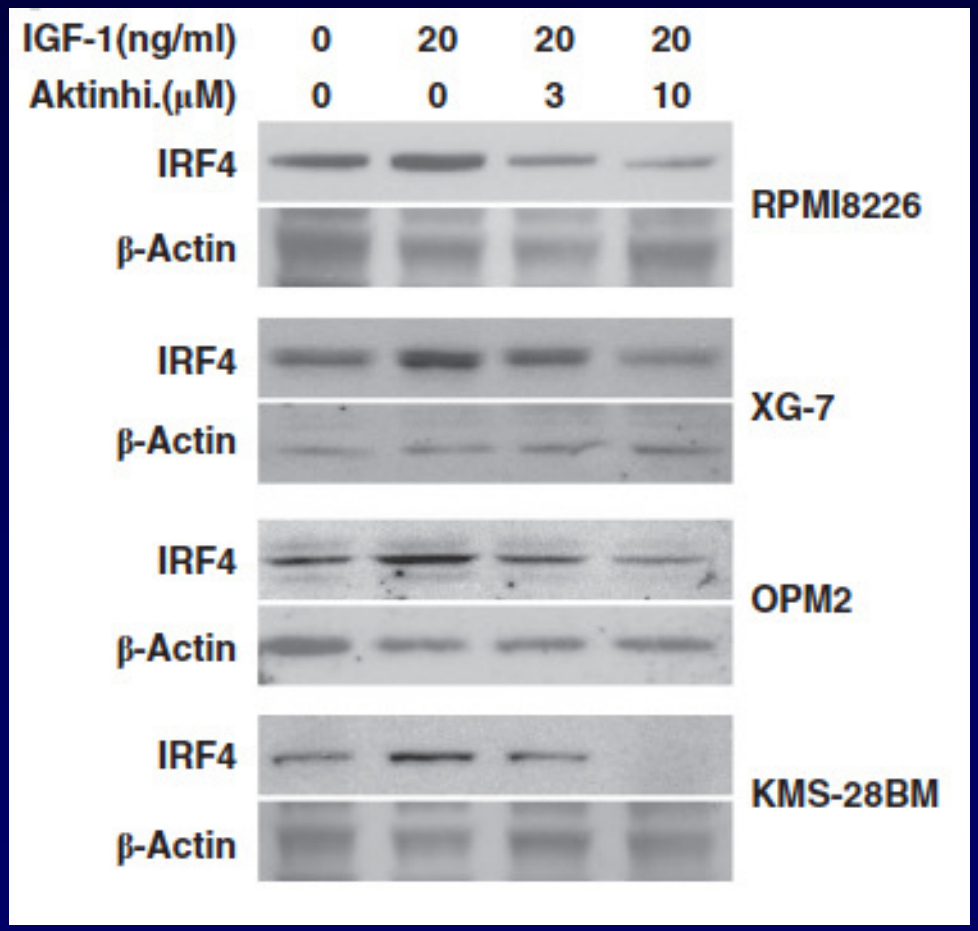
Shaffer AL, et al. *Nature*. 2008;454(7201):226-231.



Shaffer AL, et al. *Nature*. 2008;454(7201):226-231.

Fas Apoptosis Inhibitory Molecule Is Upregulated by IGF-1 Signaling and Modulates Akt Activation and *IRF4* Expression in MM





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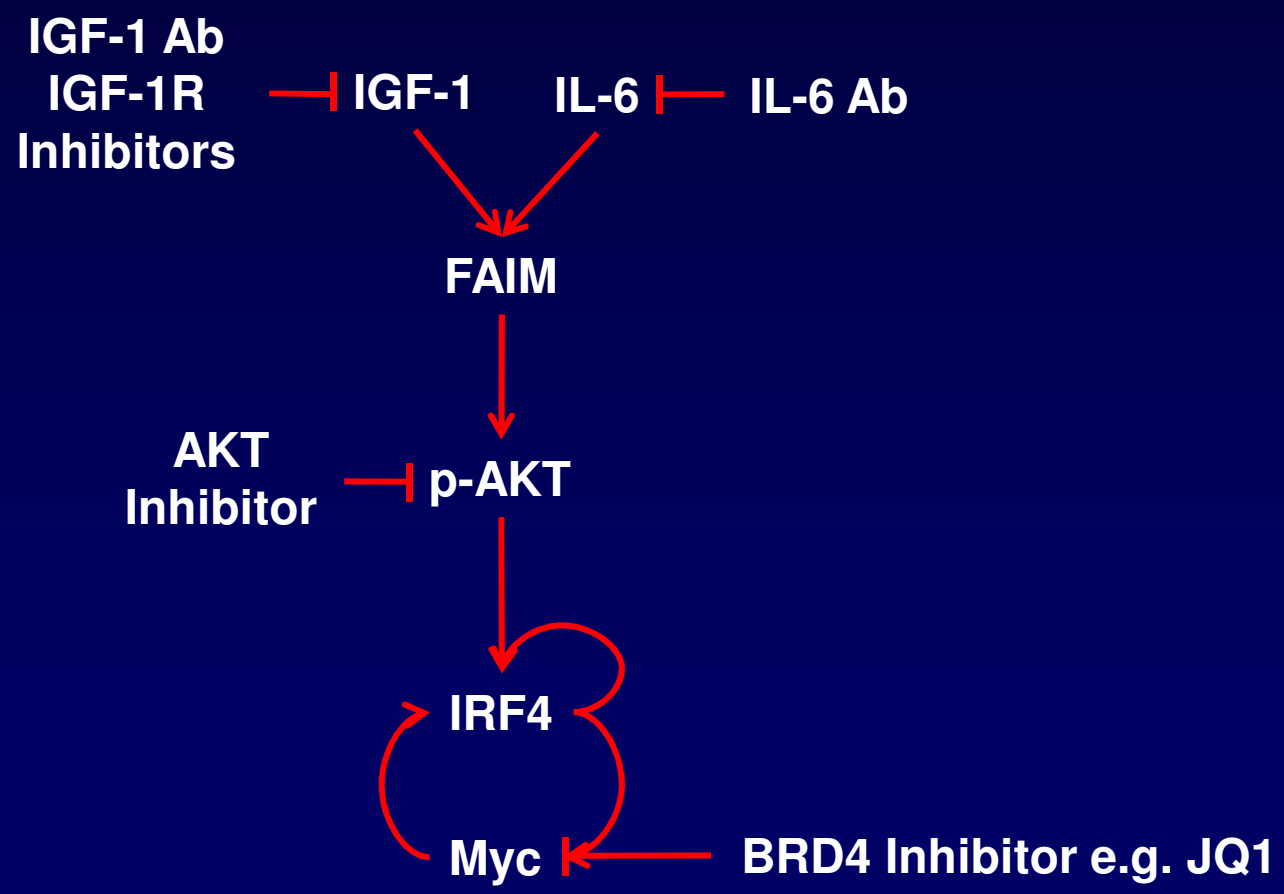
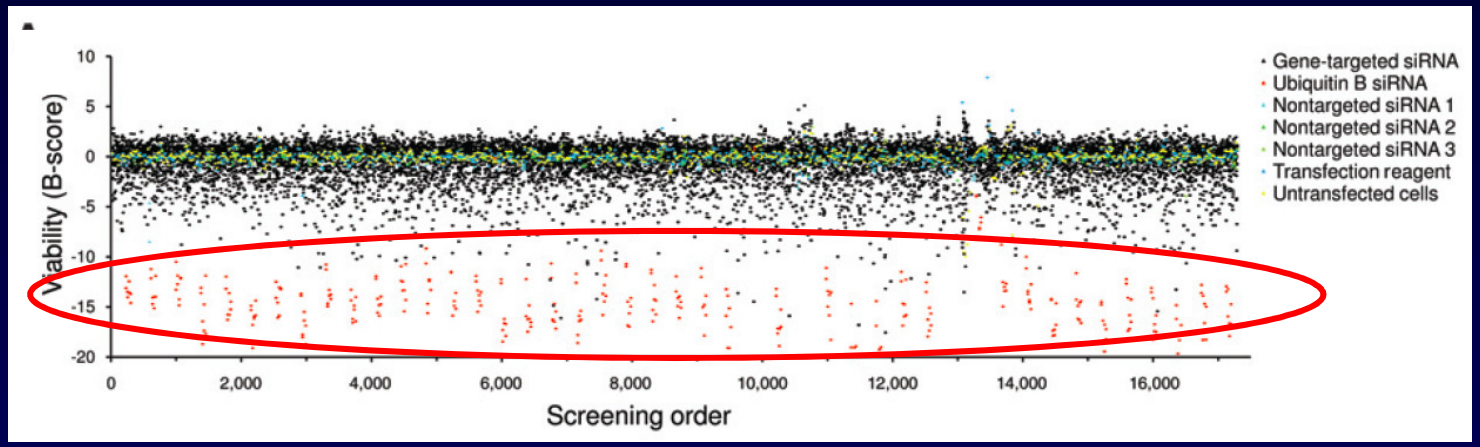
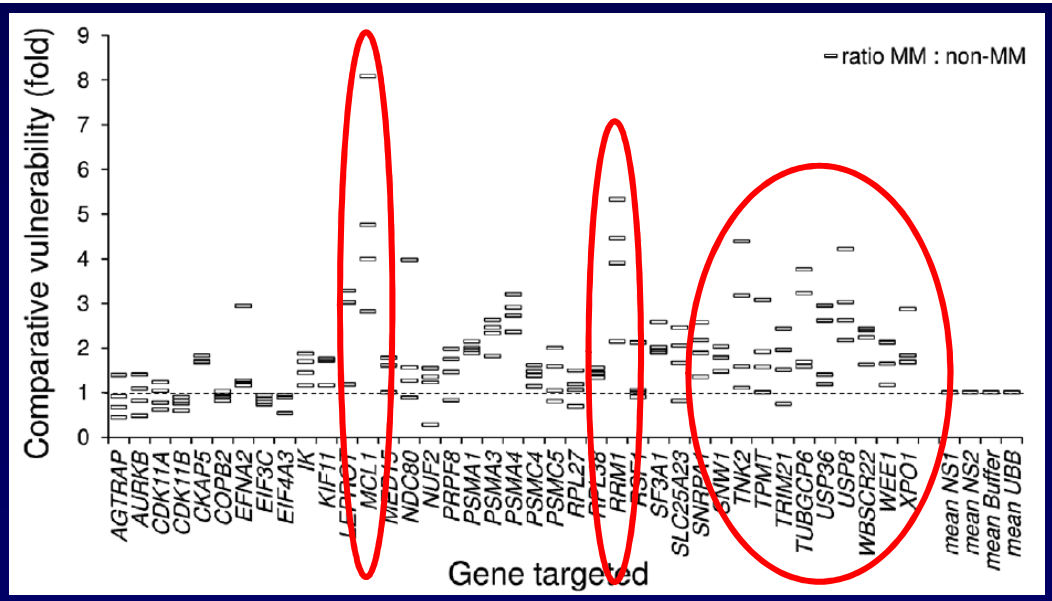
Potential Strategies to Target IRF4



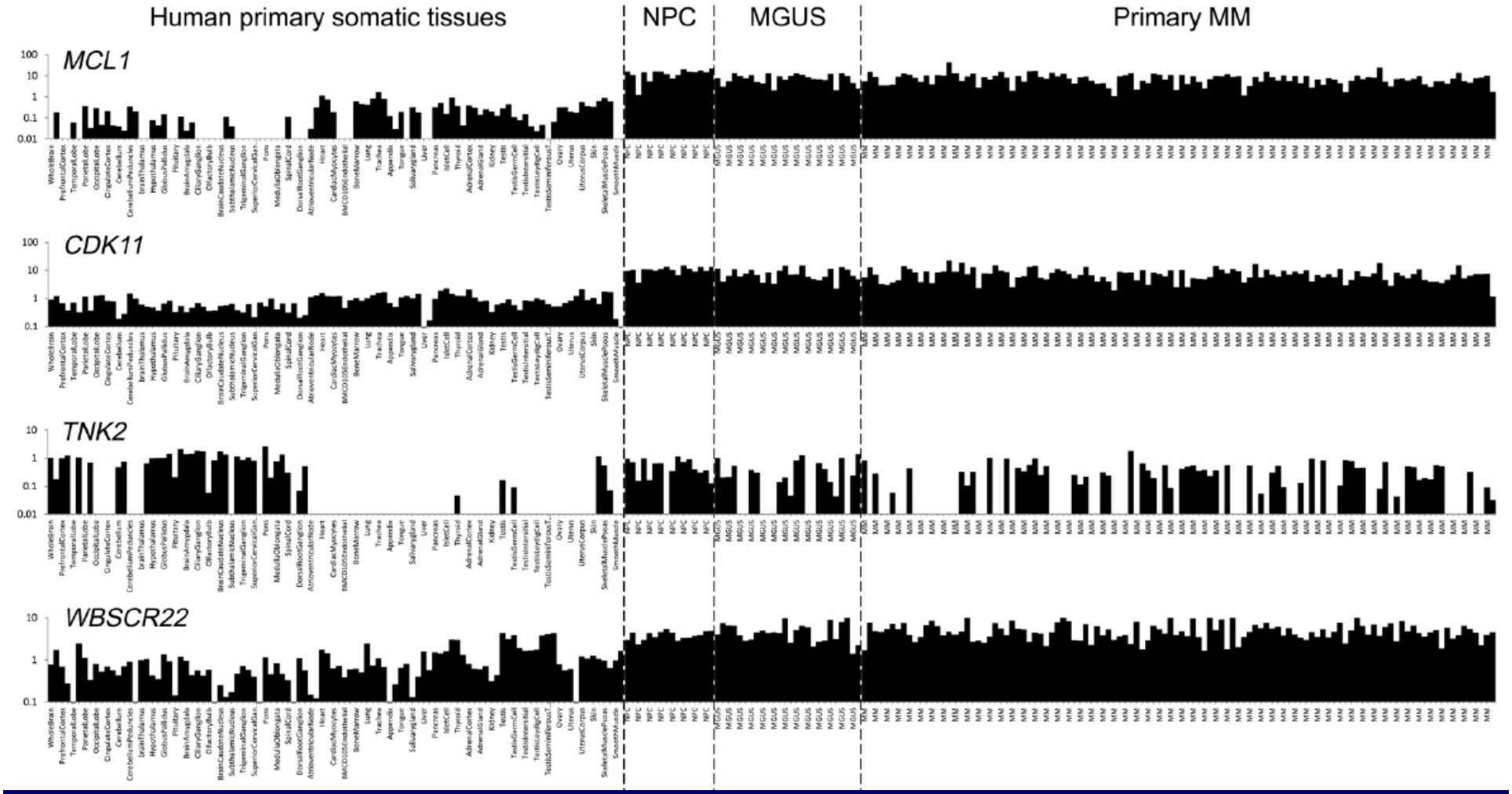
Delmore JE, et al. *Cell*. 2011;146(6):904-917.

Identification of Molecular Vulnerabilities in Human MM Cells by RNA Interference Lethality Screening of the Druggable Genome



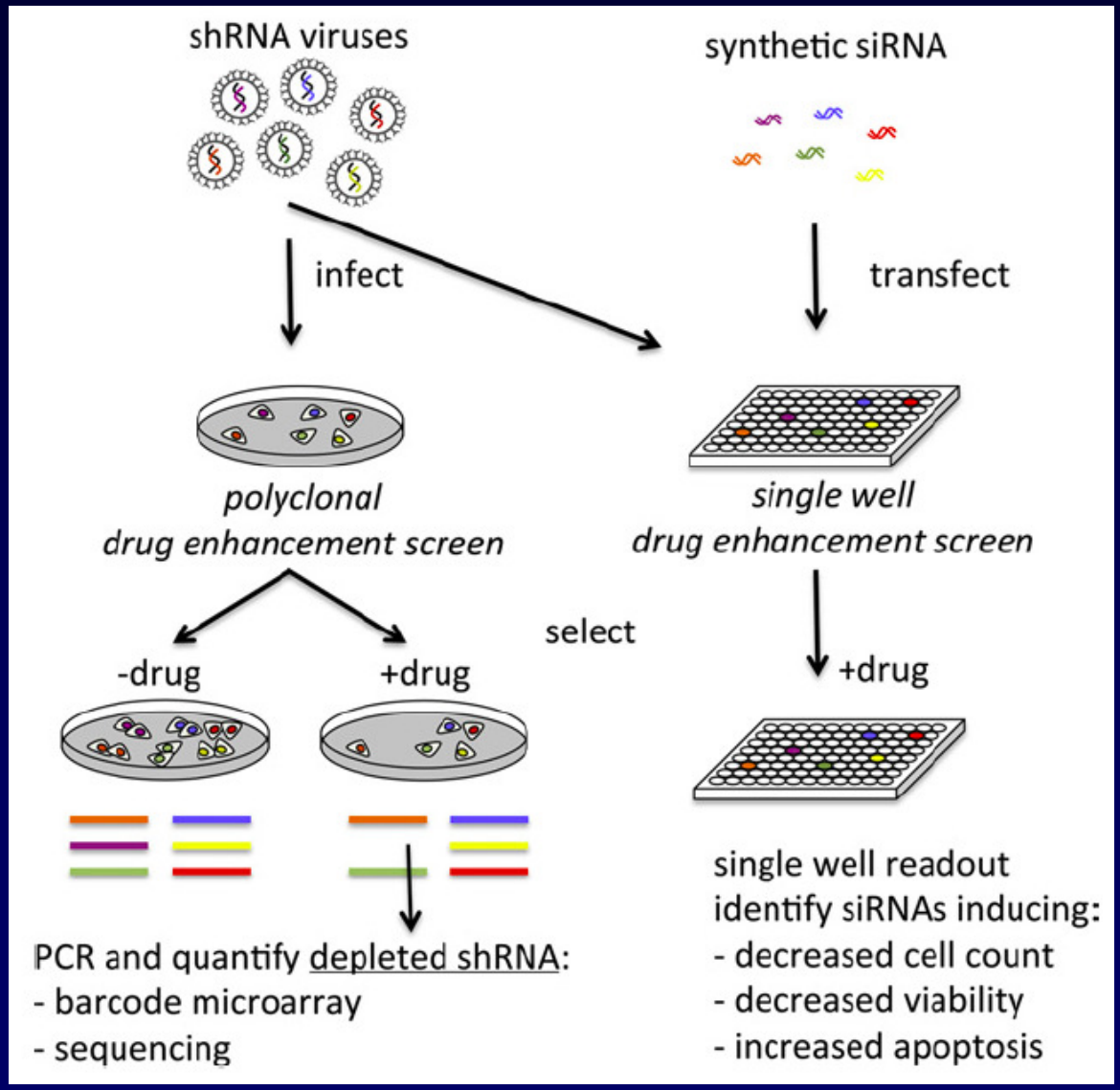


Tiedemann RE, et al. *Cancer Res.* 2012;72(3):757-768.



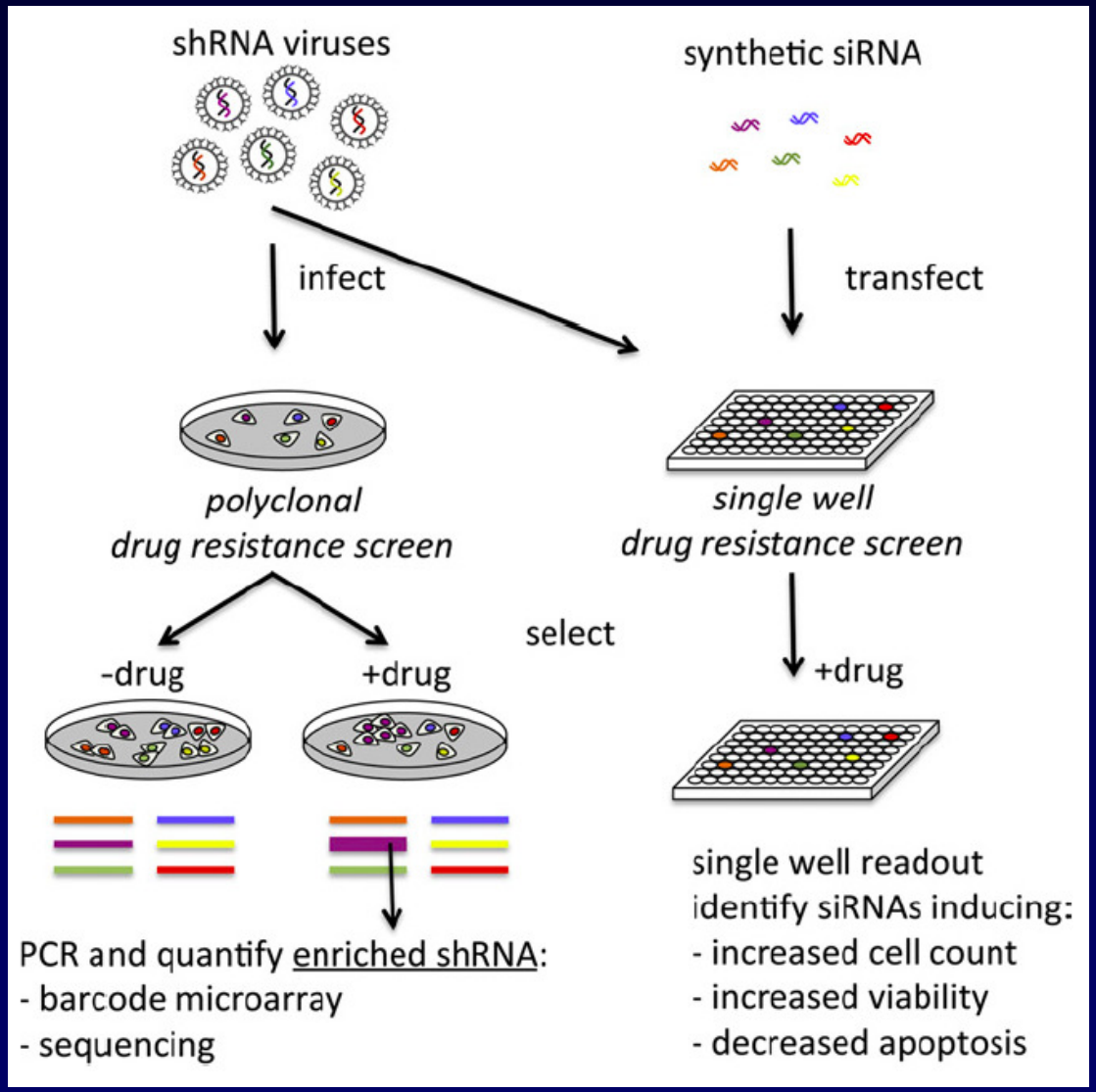
Tiedemann RE, et al. *Cancer Res*. 2012;72(3):757-768.

RNAi Screen for Drug Enhancer



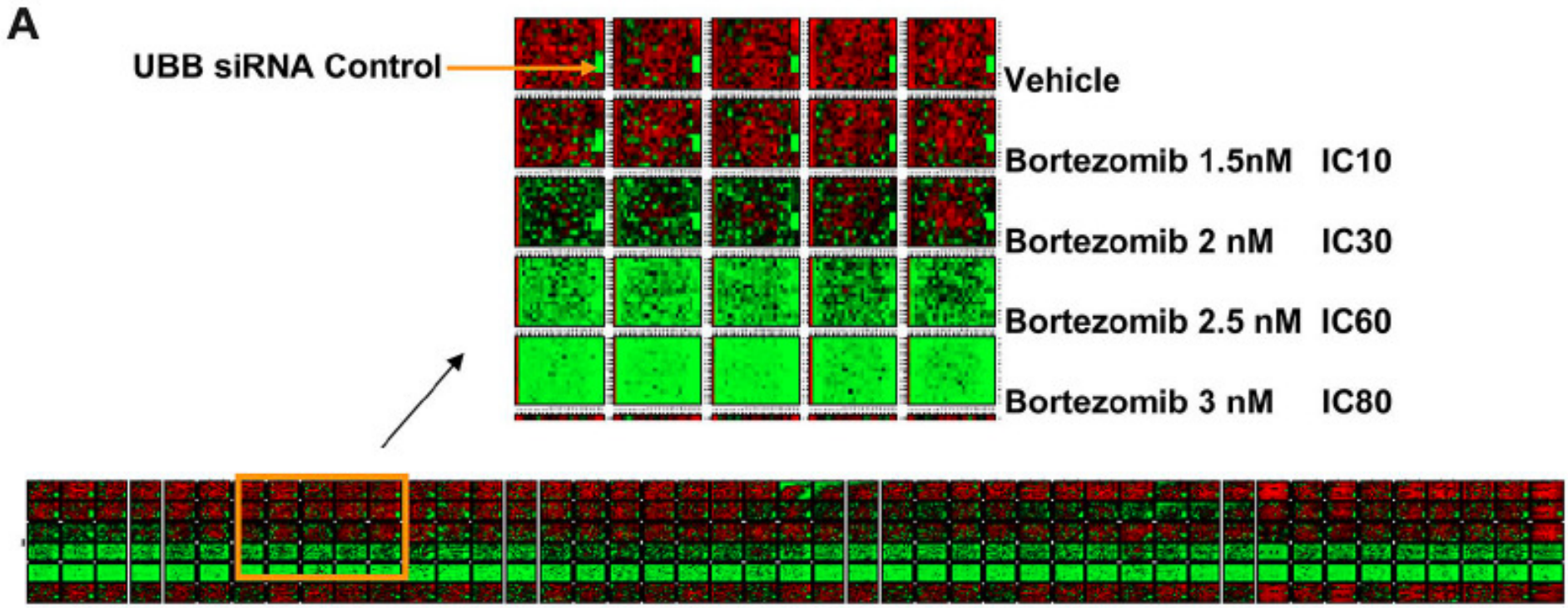
Berns K, et al. *Drug Resist Updat.* 2012;15(5-6):268-275.

RNAi Screen for Drug Resistance



Berns K, et al. *Drug Resist Updat.* 2012;15(5-6):268-275.

Rnai Screen of the Druggable Genome Identifies Modulators of Proteasome Inhibitor Sensitivity in Myeloma Including *CDK5*



Zhu YX, et al. *Blood.* 2011;117(14):3847-3857.

Primary Screen

Bortezomib sensitizers identified in KMS11

Gene ID	No. of sIRNA	GEP	Gene ID	No. of sIRNA	GEP
BAZ1B	2	P	*PSMB7*	3	P
CCNK	2	ND	*RAB 8B*	3	P
CDC42SE2	3	P	*RB1CC1*	2	P
CDK5	2	P	*STK6*	2	P
CEBPA	2	P	*TFAP4*	2	P
CHD4	2	P	*TFE3*	2	P
CRKL	3	P	*TNFAIP3*	4	P
CTNNB1	2	P	*TNK1*	2	P
DCAMKL1	2	ND	*TOP1*	2	P
ENC1	2	P	*USP8*	2	P
MAST2	2	P	*VAMP2*	3	P
MDM4	2	P	*VBP1*	2	P
MIF	2	P	*VDAC3*	2	P
NCOR1	2	P	*WTAP*	3	P
NM37	2	P	*XOC*	2	P
OGT	2	P	*XRCC5*	2	P
PSMA5	3	P	*YY1*	3	P
PSMB2	4	P	*ZNF197*	2	P
PSMB3	4	P			

Zhu YX, et al. *Blood.* 2011;117(14):3847-3857.

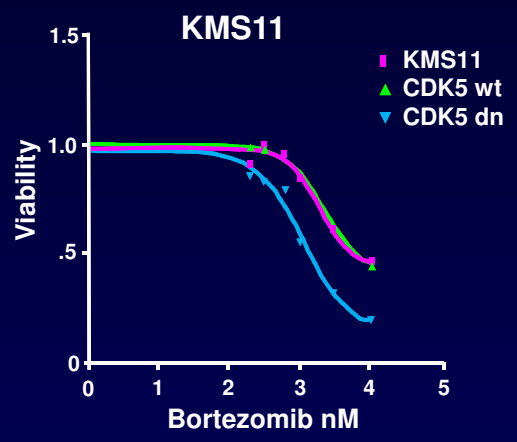
Validation

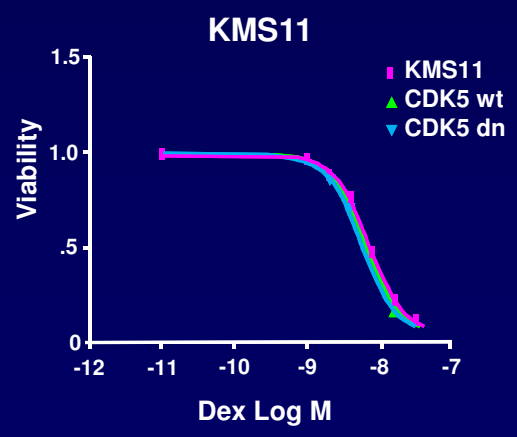
Top ranking sensitizers from KMS11 HTS

Sample ID	No. of sIRNA	Mean EC50
BAZ1B	2	1.4
CDC42SE2	3	1.5
CDK5	2	0.8
MDM4	2	1.2
NME7	2	1.3
PSMA5	3	0.8
PSMB2	4	1.1
PSMB3	4	0.9
PSMB7	3	1.2
RAB8B	2	1.4
TFE3	2	1.6
TNFAIP3	2	1.5
TNK1	2	1.5
TOP1	2	1.6
VAMP2	3	1.7
YY1	2	1.5

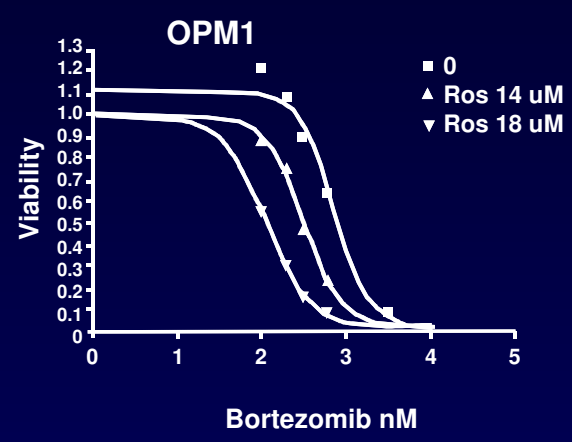
Control EC50 = 2.2

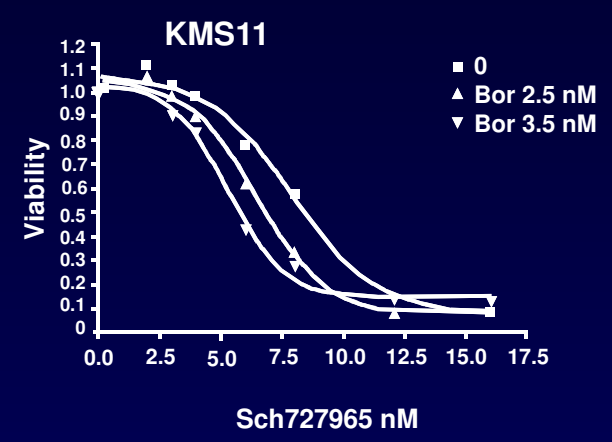
Sensitizing effect is specific to Bortezomib





Synergism Between Bortezomib and CDK Inhibitors





	Bortezomib 2.5 nM		Bortezomib 3.5 nM	
	OPM1	KMS11	OPM1	KMS11
SCH 727965 4 nM	-0.05	-0.14	-0.11	-0.24
SCH 727965 6 nM	-0.14	-0.32	-0.46	-0.88
SCH 727965 8 nM	-0.29	-0.80	-1.03	-1.06
SCH 727965 12 nM	-0.53	-0.77	-1.05	-0.23
SCH 727965 16 nM	-0.39	-0.04	-0.08	-0.60

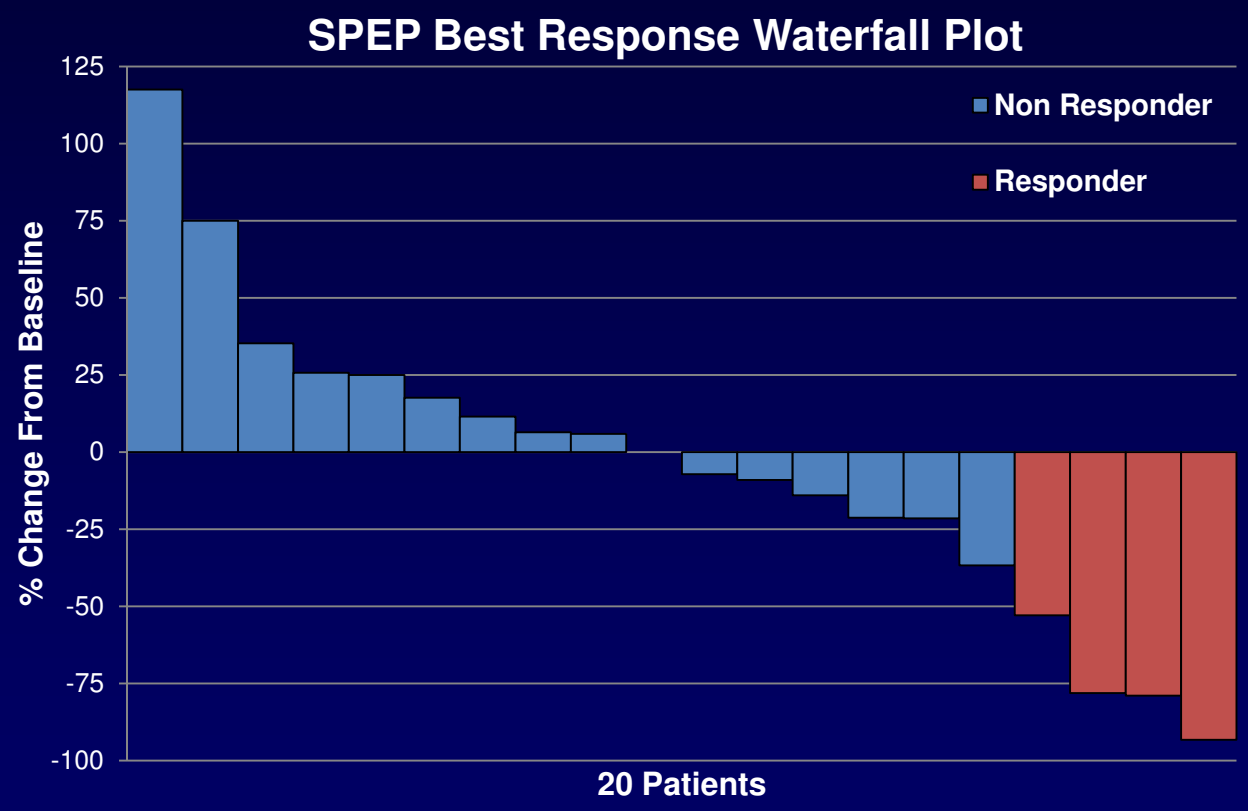
Zhu YX, et al. *Blood.* 2011;117(14):3847-3857.

Phase 1/2 Trial of a Novel CDK Inhibitor Dinaciclib (SCH727965) in Patients With Relapsed Multiple Myeloma Demonstrates Encouraging Single Agent Activity

Shaji Kumar, Betsy LaPlant, Wee Joo Chng, Jeffrey Zonder, Natalie Callander, Vivek Roy, Briant Fruth, Charles Erlichman, A. Keith Stewart

Phase 2 Consortium (P2C)

Serum M-Protein Responses



Kumar SK, et al. *Blood.* 2012;120: Abstract 76.

Conclusions

- Functional genomics approaches complement current structural genomics efforts and can greatly help identify critical genes in different context
- In the coming years, the results of these studies will greatly increase our understanding of biology and identify therapeutic targets in myeloma
- Some of the results have already identified actionable targets that are currently being tested in clinical trials

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Kong Peng Lam

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NRF RCE Grant
NMRC Center Grant
MOE AcRF

Thank You