

# Hypothesis: coordination of the junD cluster by Nrf2

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***Distant Regulatory Elements of co-regulated genes***

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## 44 regulatory elements...



utr	9 (20%)
Intergenic	20 (45%)
intron	8 (18%)
promoter	7 (16%)



[Detailed regulatory element description  
\(in tabulated textual format\)](#)

[Chromosomal distribution](#)

## Regulatory Transcription Factors...

### 10 top TFs

occurrence

30% 20%

10%

0

0.05

0.15

importance

0.25

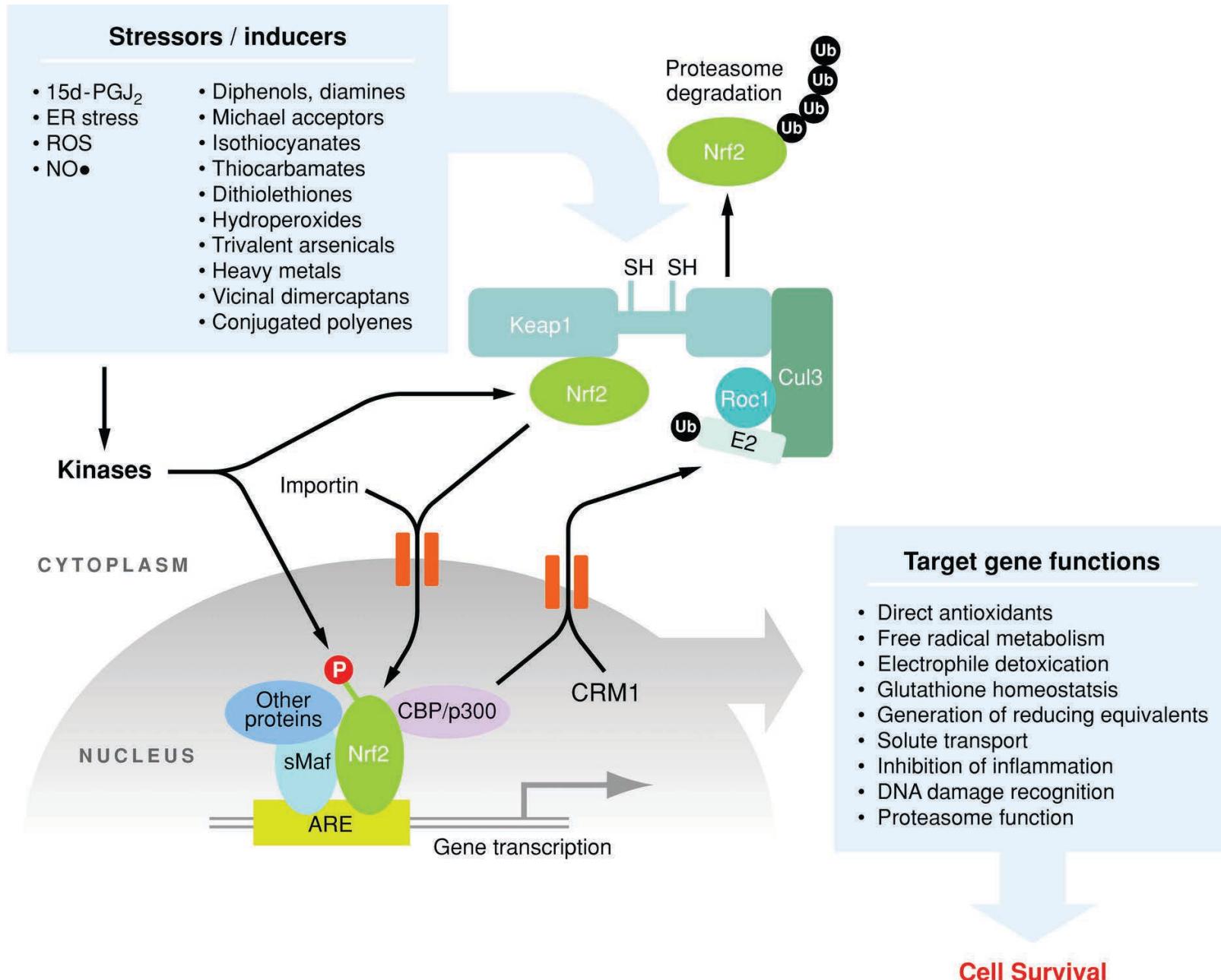
0.35

0.45

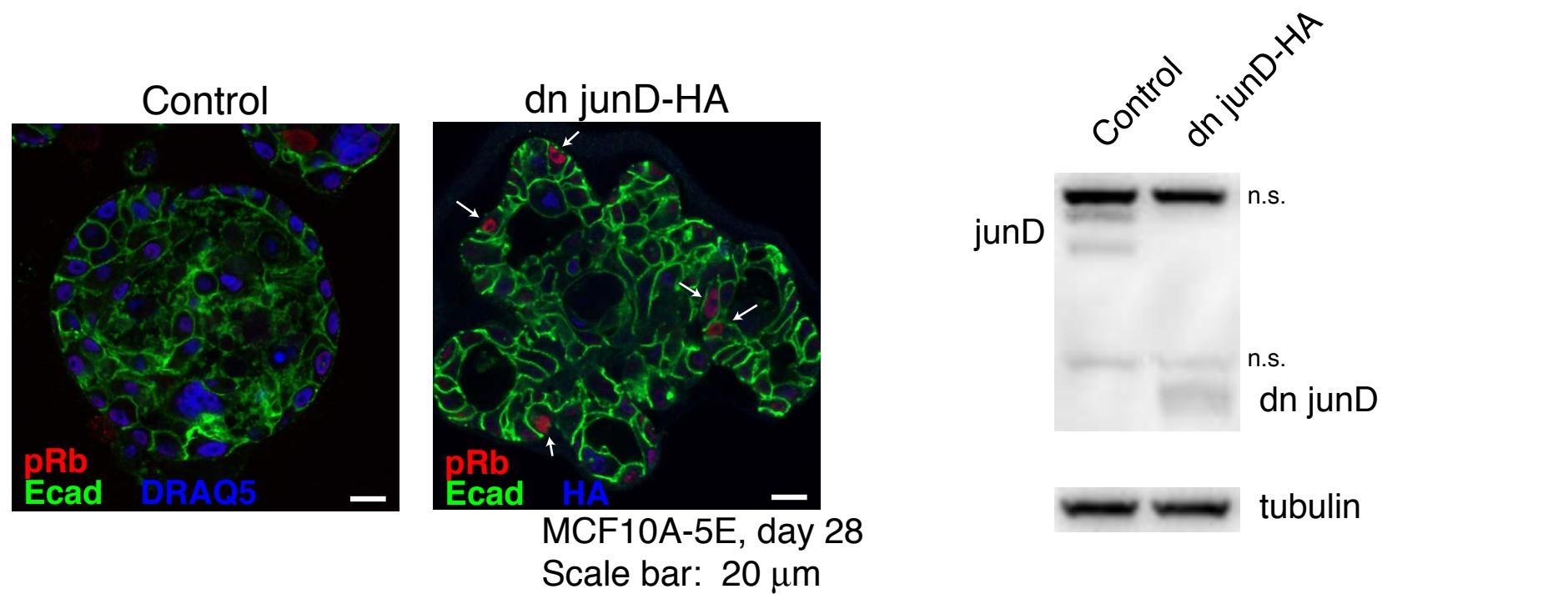
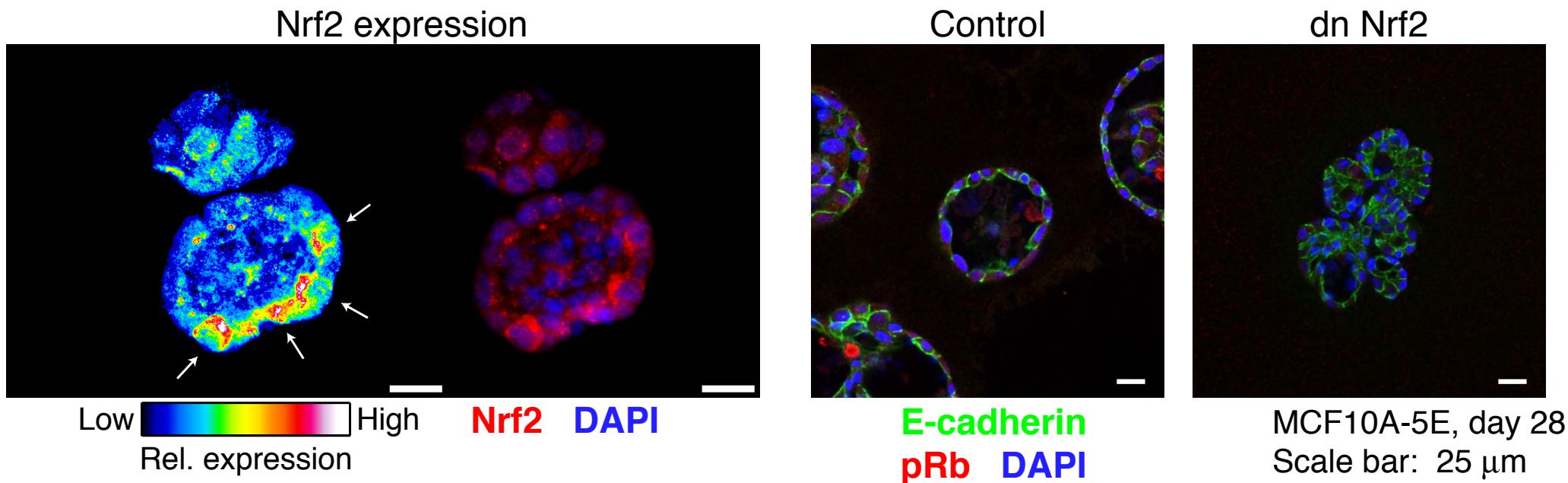
NRF2  
TAL1ALPH/  
S8  
POU6F1  
POLY  
XVENT1  
TCF11  
GATA2  
ZTA  
PPAR\_DR1

[Full TF list](#)

# The Keap1–Nrf2–ARE signaling pathway

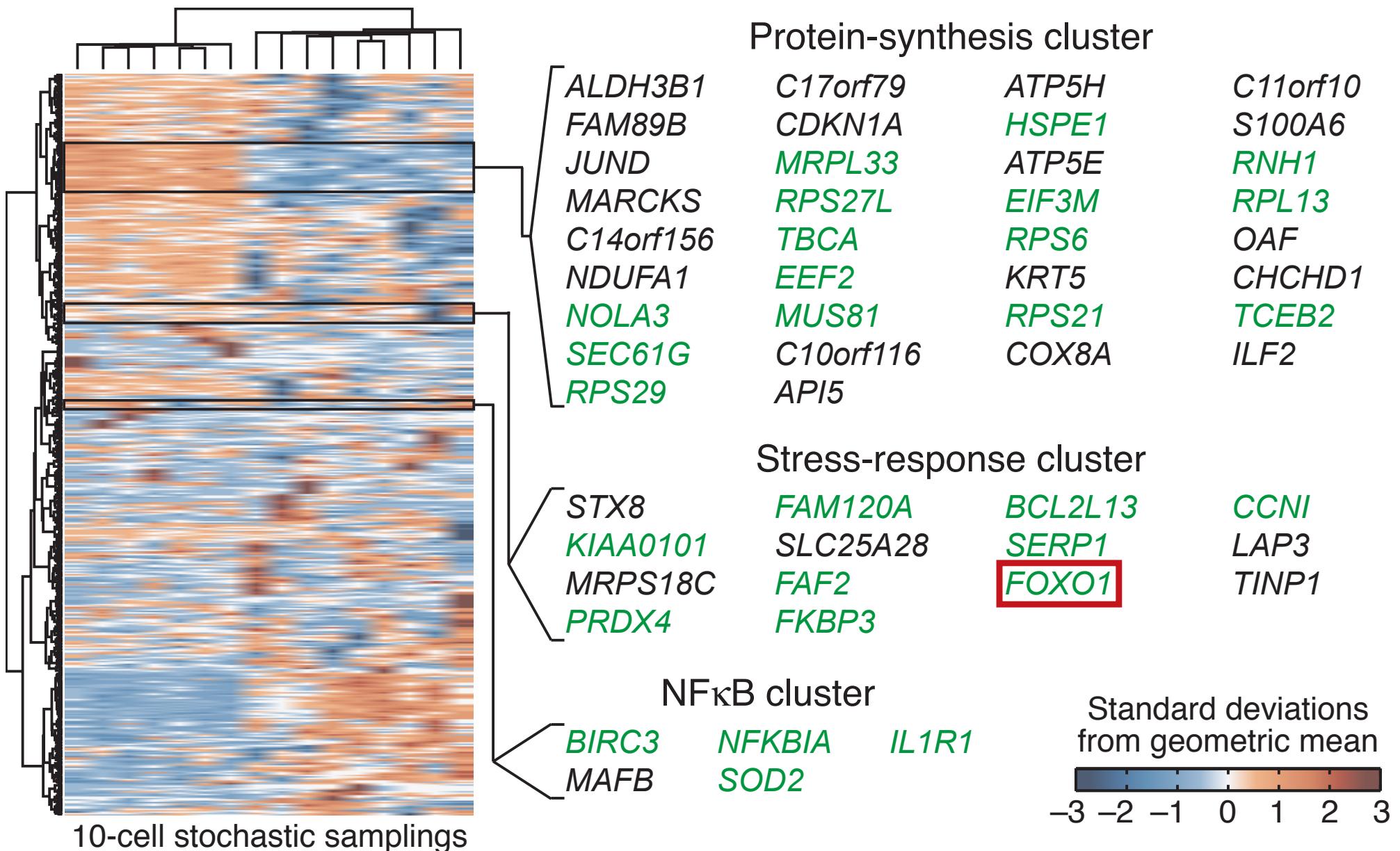


# Nrf2 expression is heterogeneous and its inhibition phenocopies junD inhibition

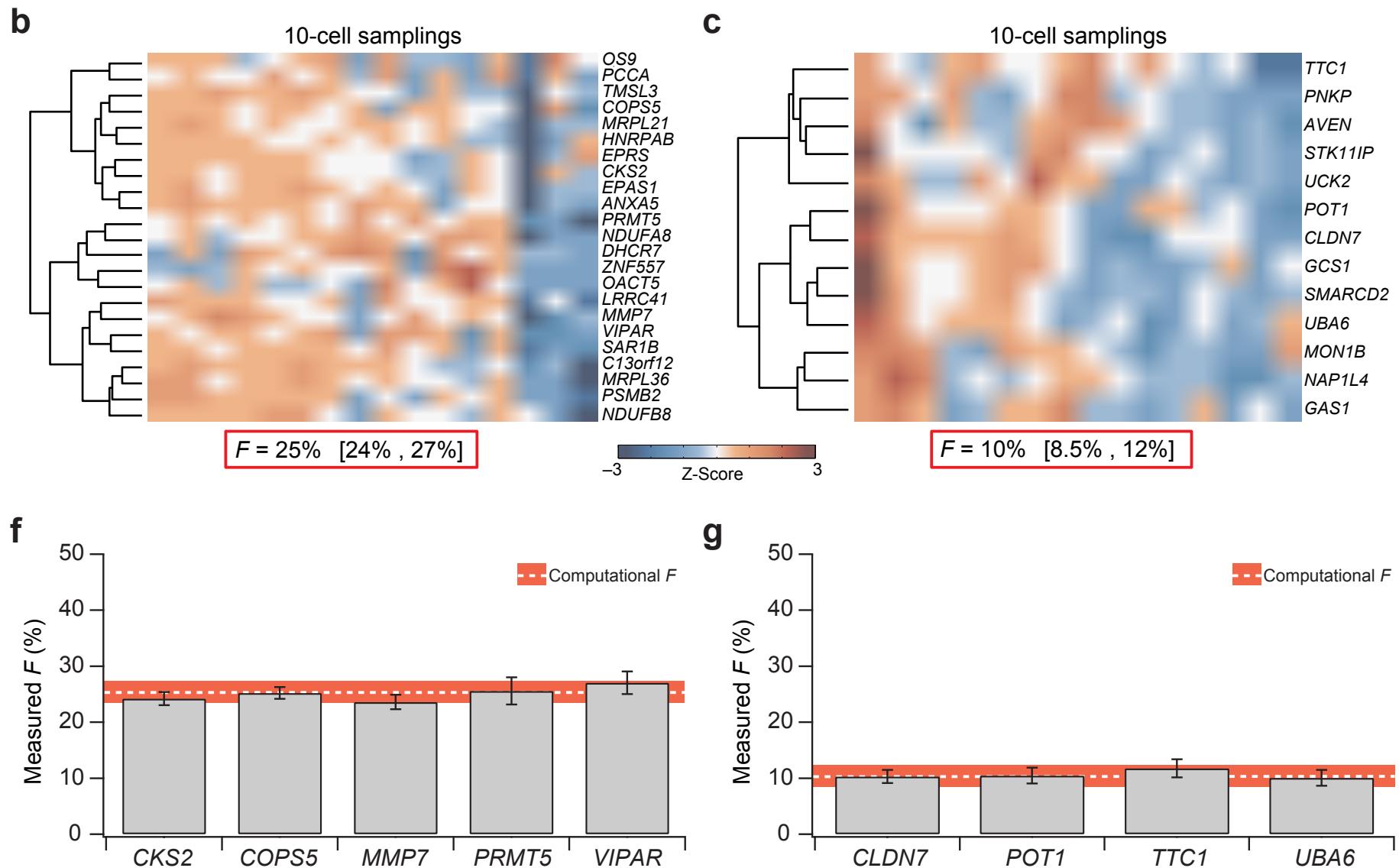




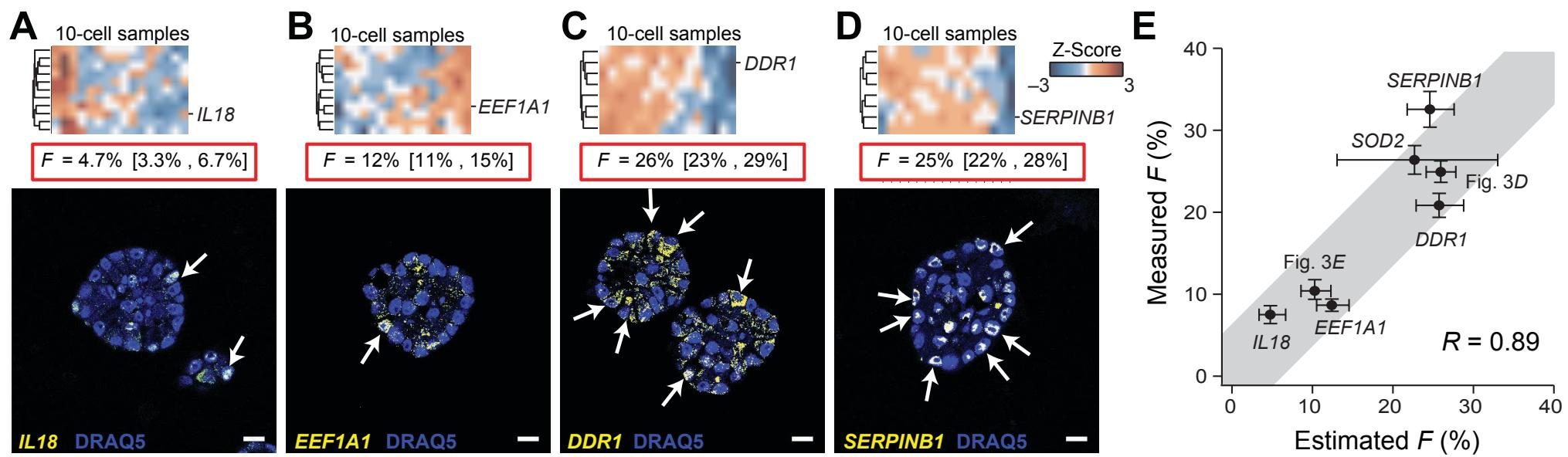
# Single-cell coregulatory programs identified by stochastic sampling



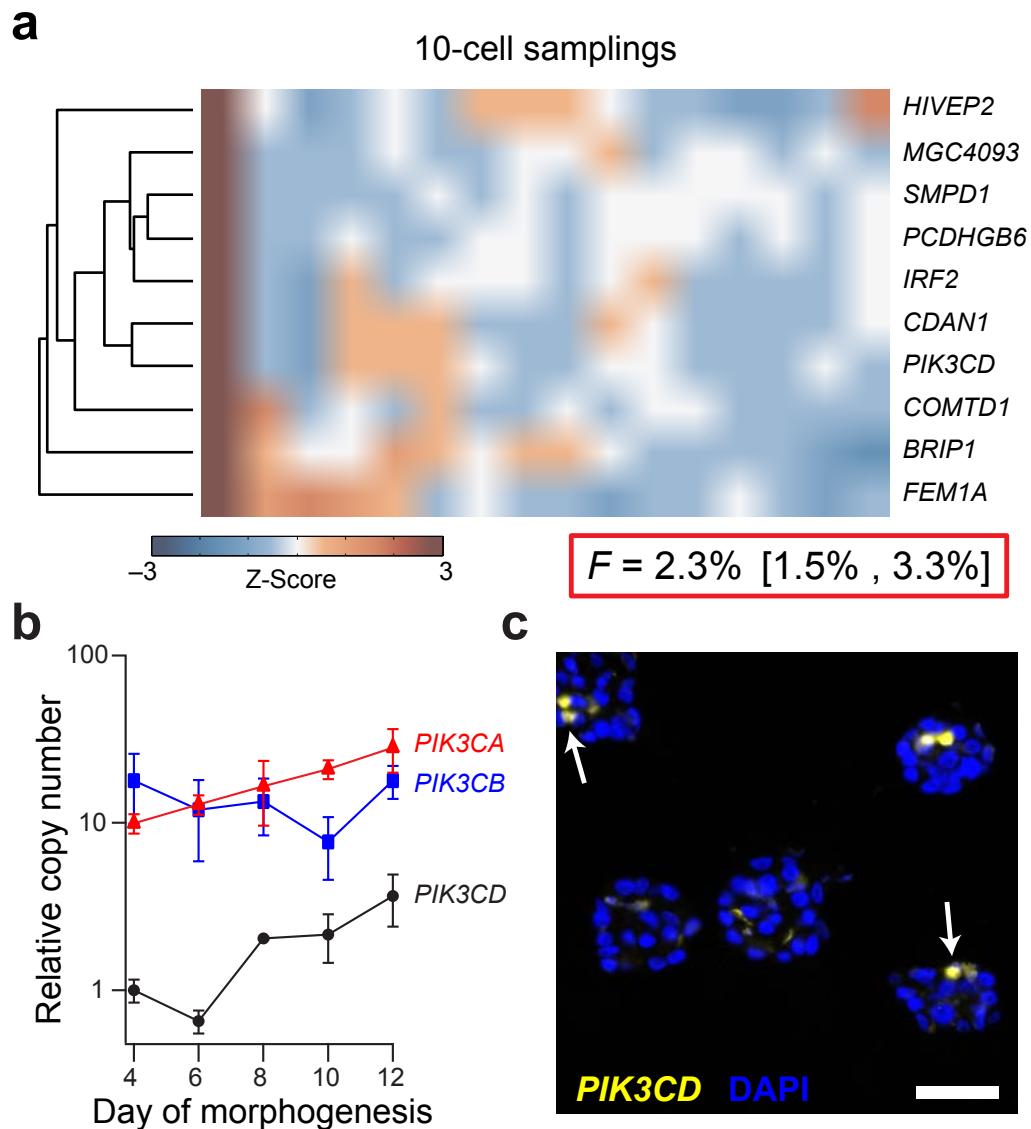
# Extension of maximum-likelihood inference to coregulated transcriptional clusters



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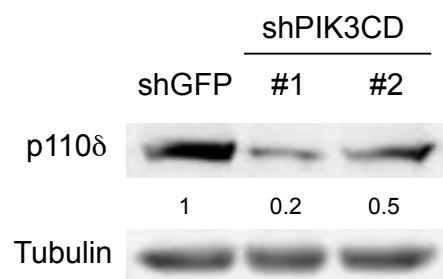


# Application of maximum-likelihood inference to a unique transcriptional regulatory state

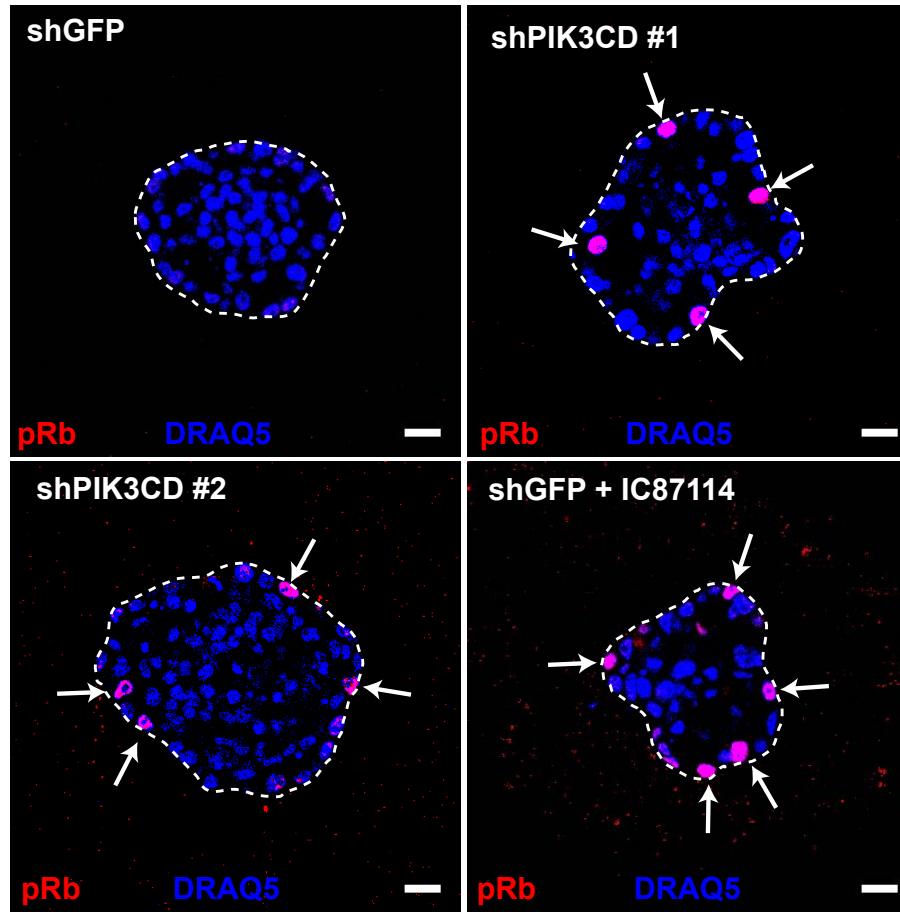


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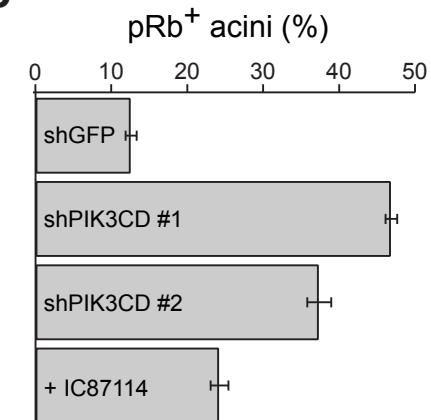
d



f



e





## ARTICLES

# Stochastic spineless expression creates the retinal mosaic for colour vision

Mathias F. Wernet<sup>1\*</sup>†, Esteban O. Mazzoni<sup>1\*</sup>, Arzu Çelik<sup>1\*</sup>, Dianne M. Duncan<sup>2</sup>, Ian Duncan<sup>2</sup> & Claude Desplan<sup>1</sup>

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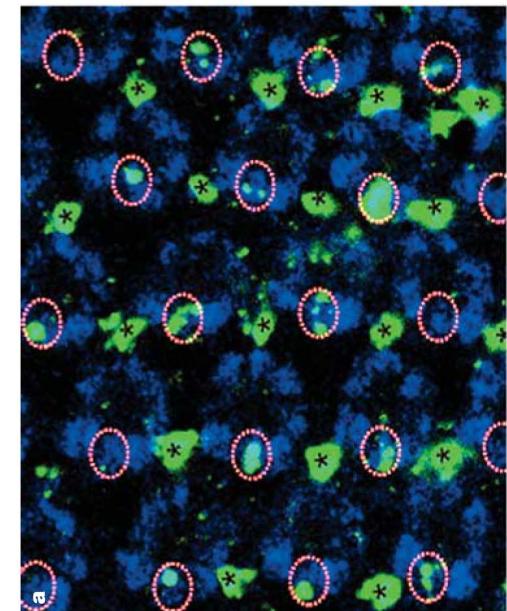
# Variability in gene expression underlies incomplete penetrance

Arjun Raj<sup>1,2\*</sup>†, Scott A. Rifkin<sup>1,2\*</sup>†, Erik Andersen<sup>2,3</sup> & Alexander van Oudenaarden<sup>1,2</sup>

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*spineless* *ELAV*

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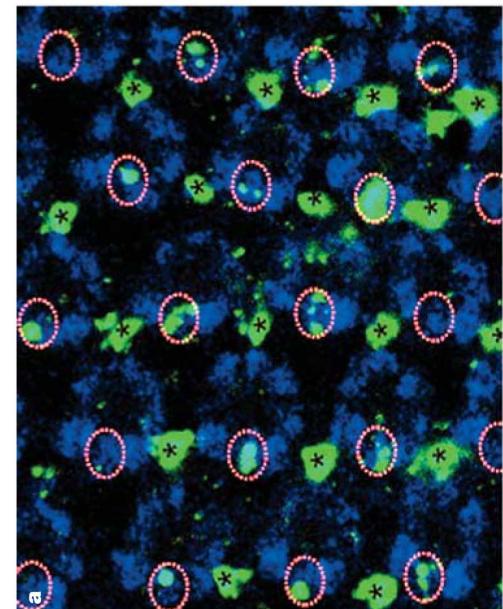
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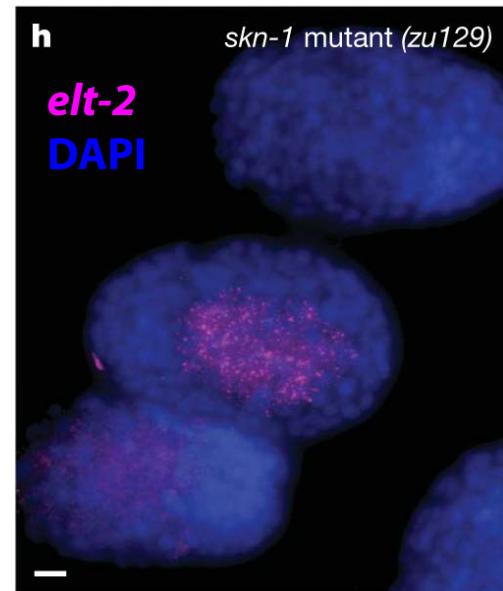


*spineless* ELAV

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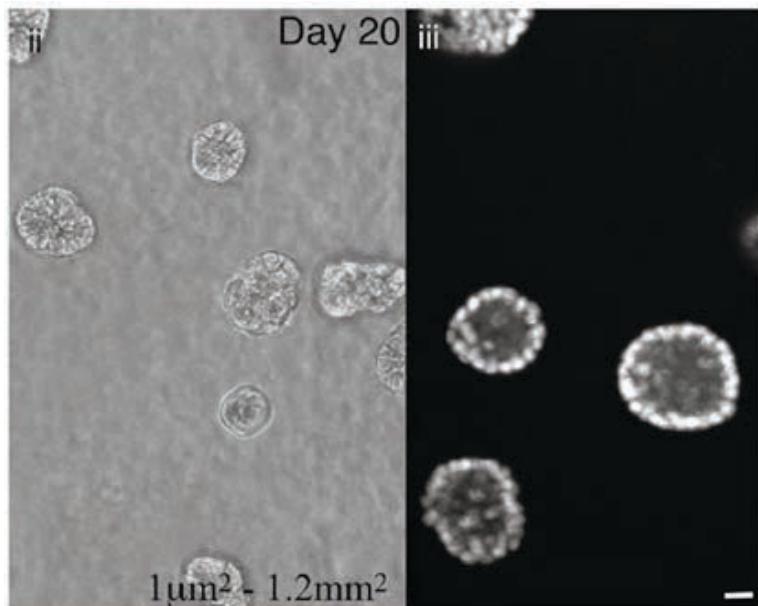
h

*skn-1* mutant (*zu129*)

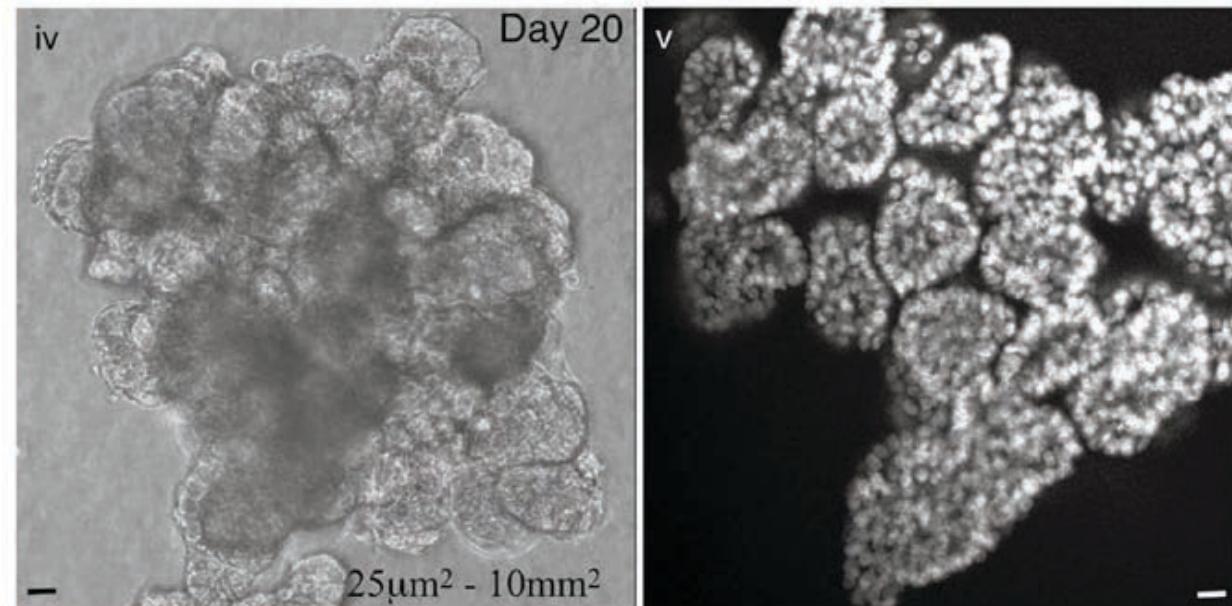
*elt-2*  
DAPI

# Heterogeneous multiacinar formation upon inducible activation of ErbB2–ErbB2 homodimers

No dimerizer

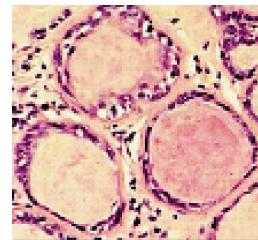


With dimerizer

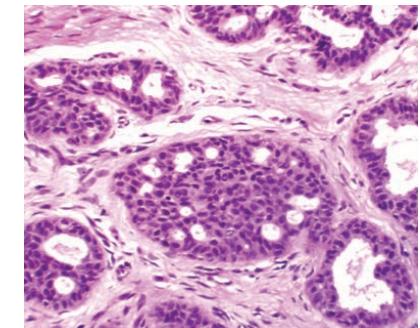


Muthuswamy et al., *Nat Cell Biol* 3:785 (2001)

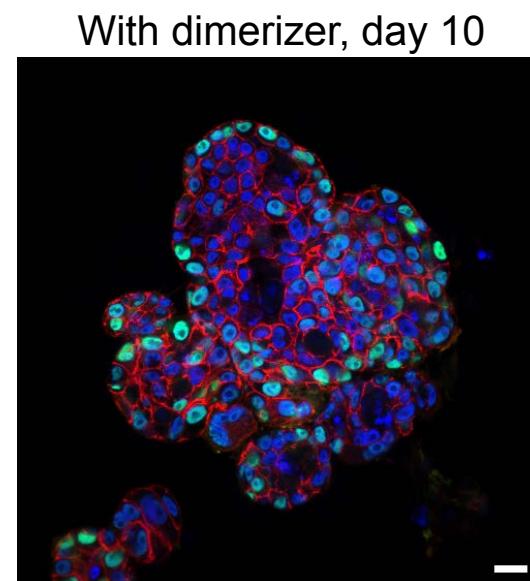
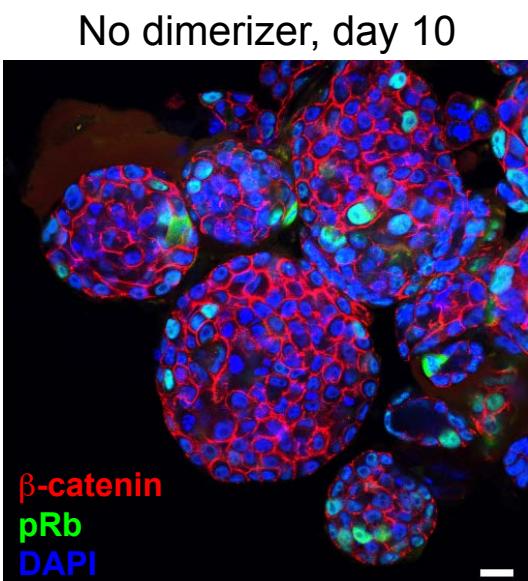
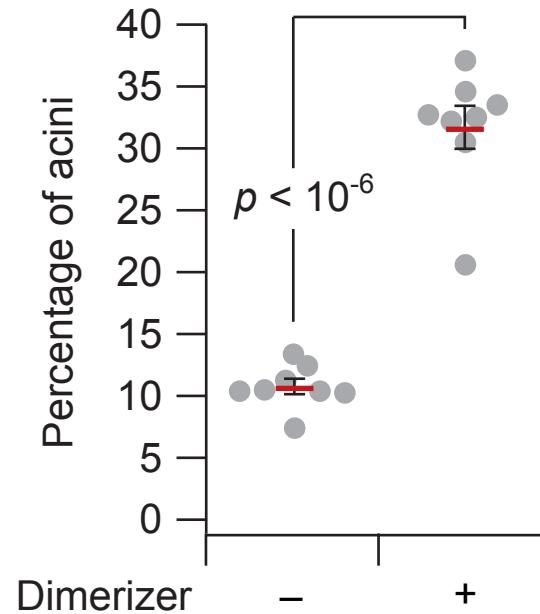
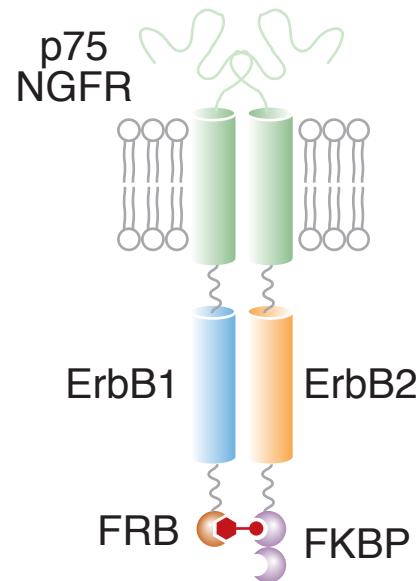
Normal acini:



Ductal carcinoma in situ:

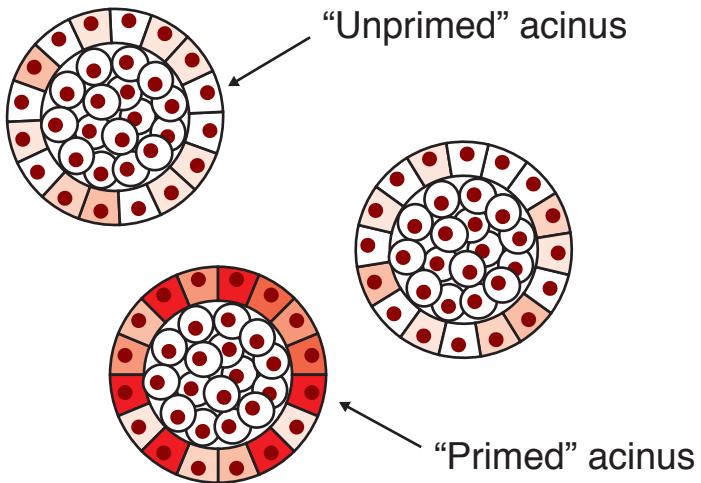


# Clonal activation of ErbB1-ErbB2 causes a multiacinar phenotype that is incompletely penetrant

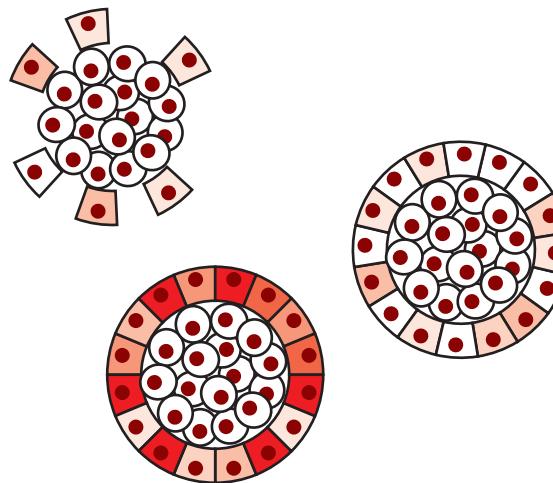


# Identifying heterogeneously regulated transcriptional programs in ErbB1-ErbB2 acini

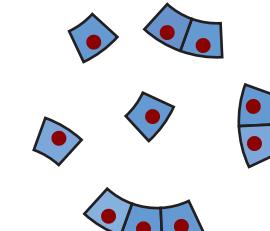
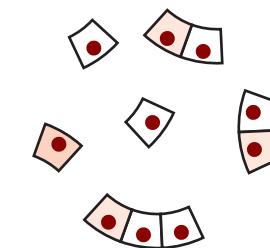
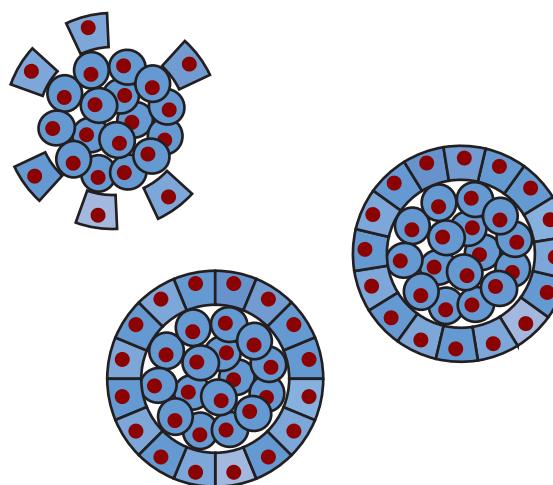
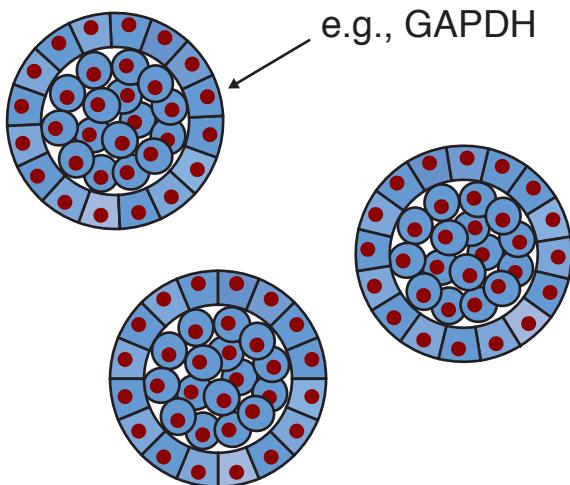
Sectioning



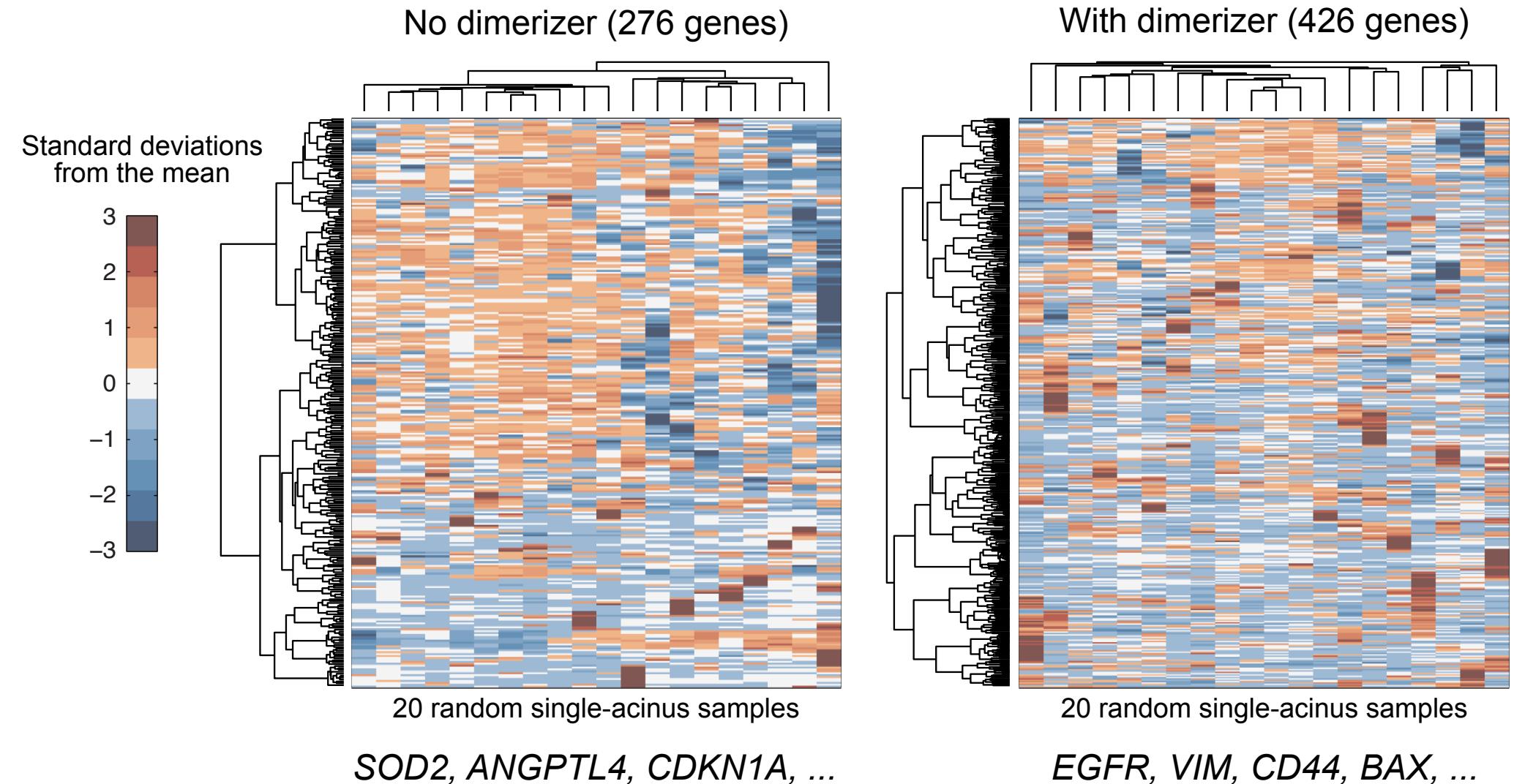
Microdissection



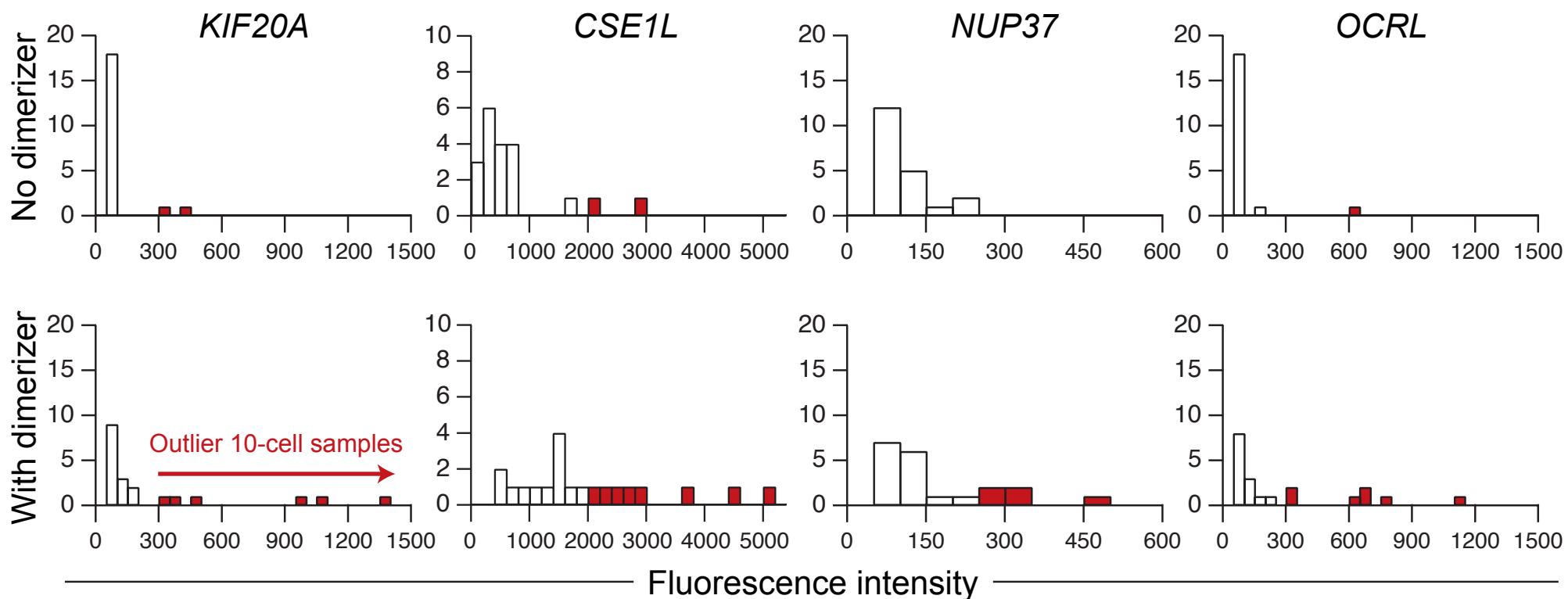
Amplification



# Heterogeneously regulated transcripts in ErbB1-ErbB2 cells cultured as 3D spheroids

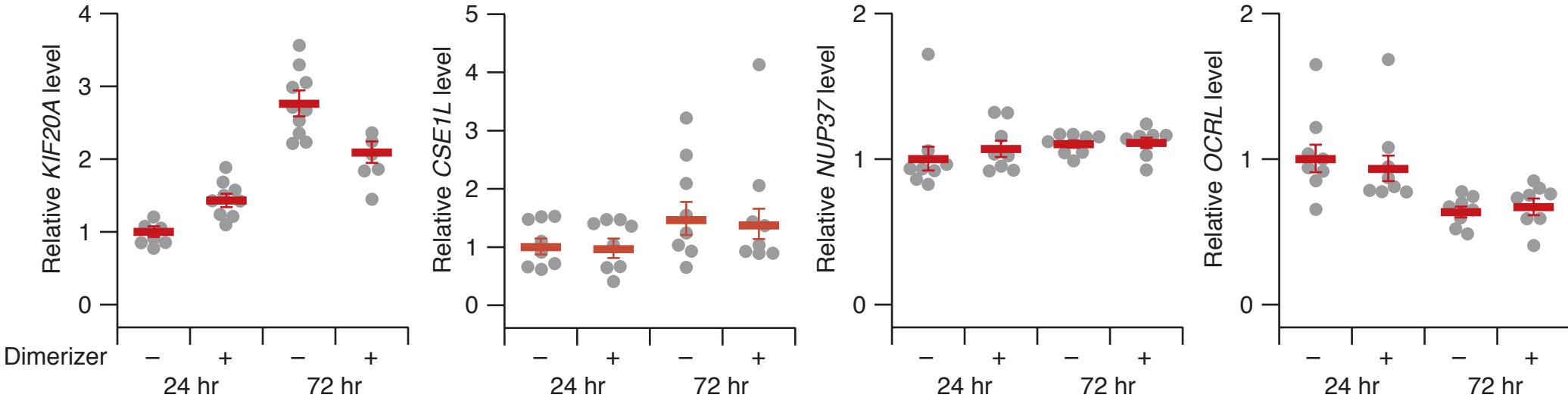


# Regulatory heterogeneities that emerge upon ErbB1-ErbB2 dimerization

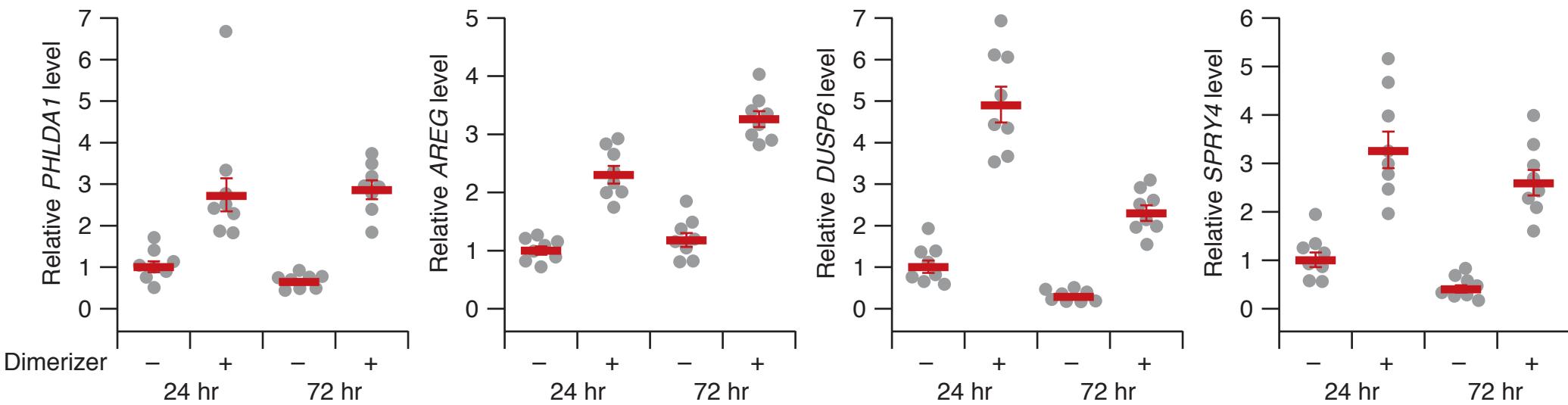


# Stochastic profiling identifies genes missed by conventional approaches

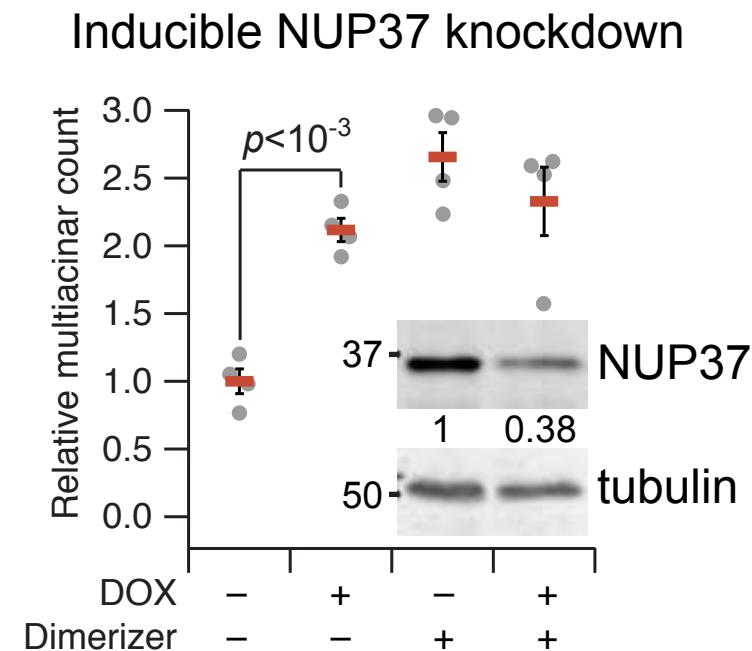
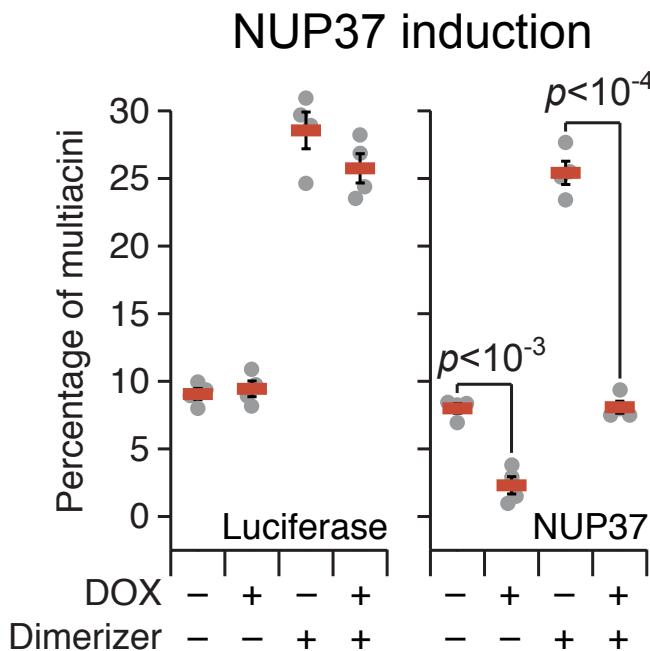
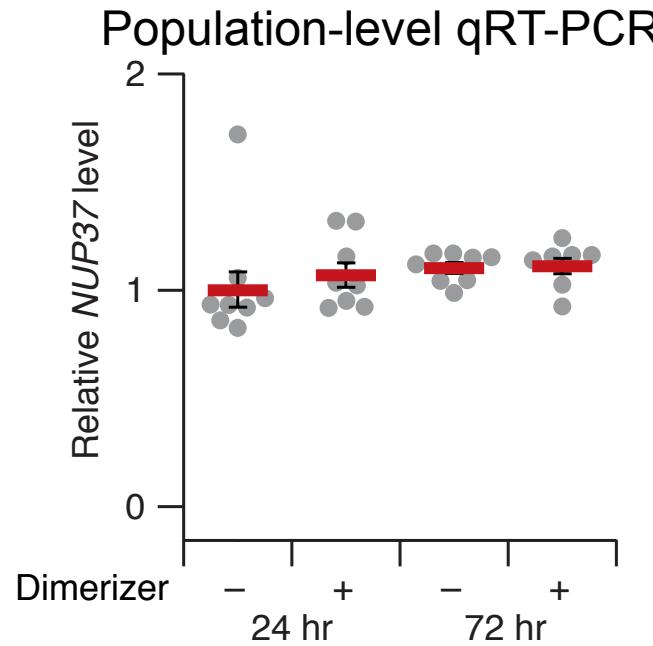
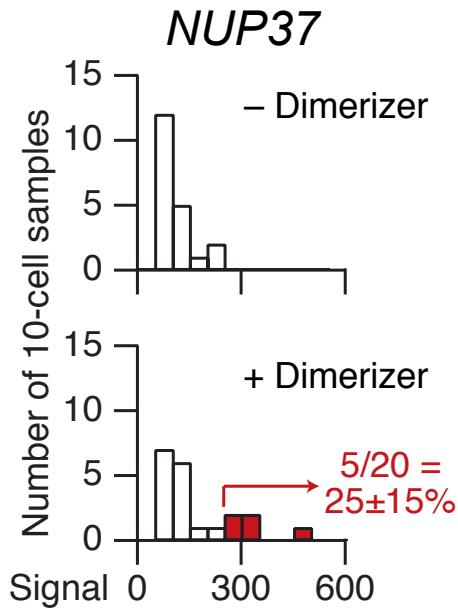
Candidate multiacinar regulators:



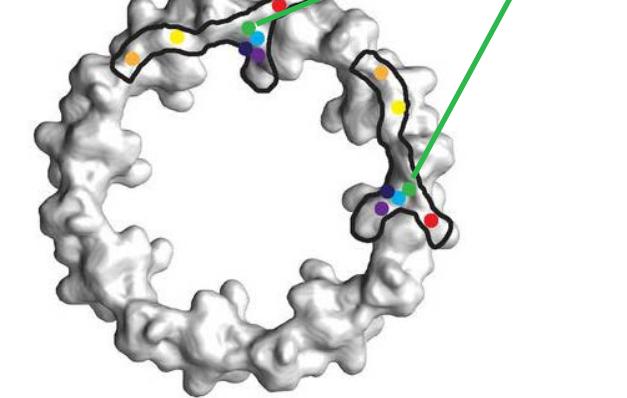
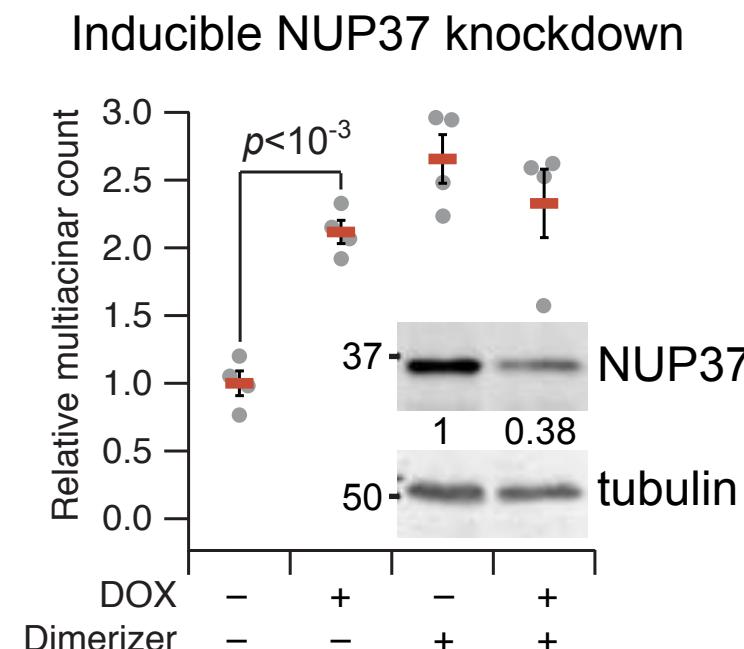
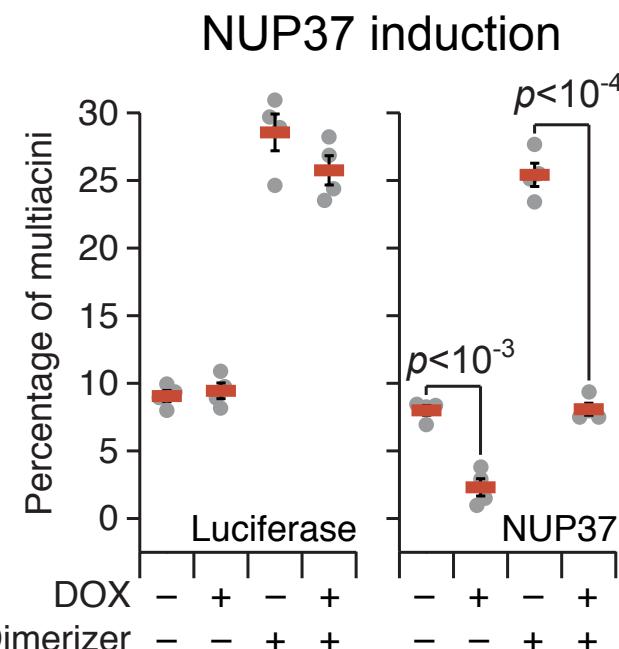
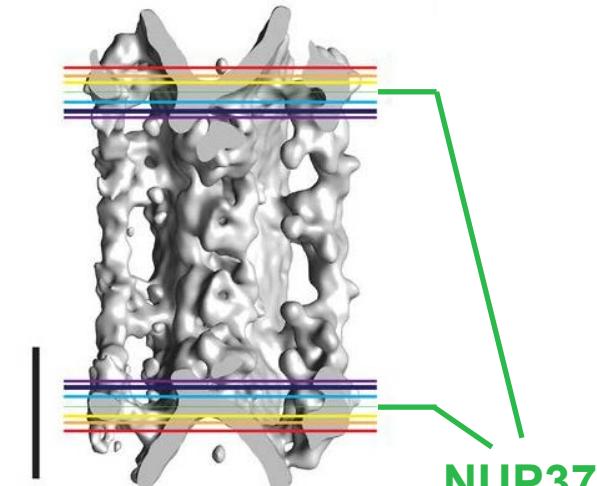
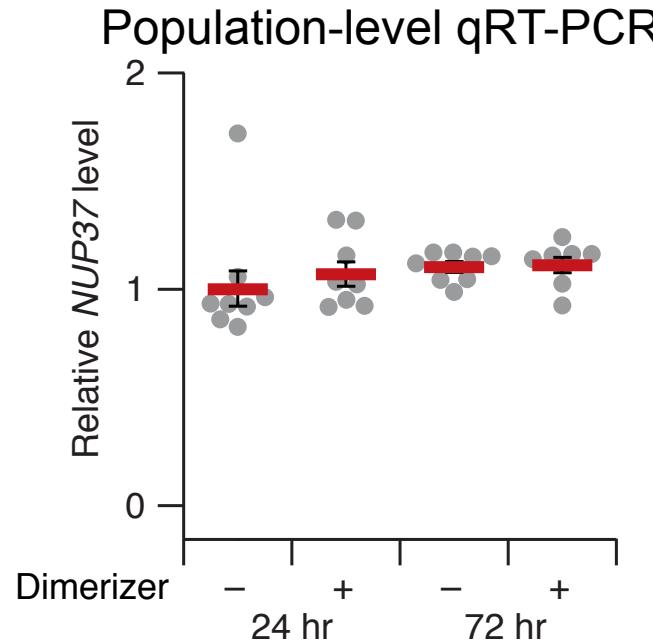
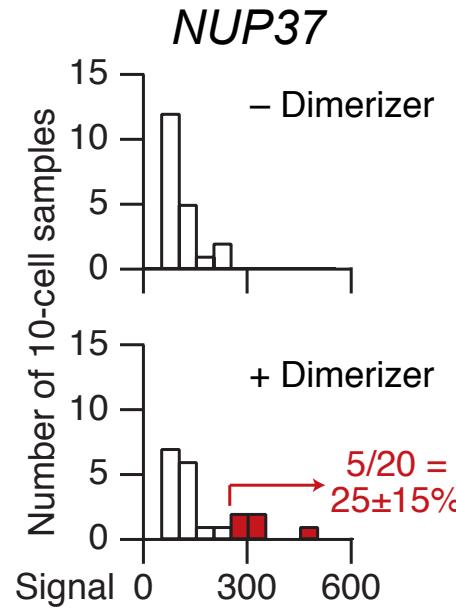
Transcripts globally induced by ErbB2 activation in 3D:



# Suppression of multiacinus formation by a subunit of the NPC

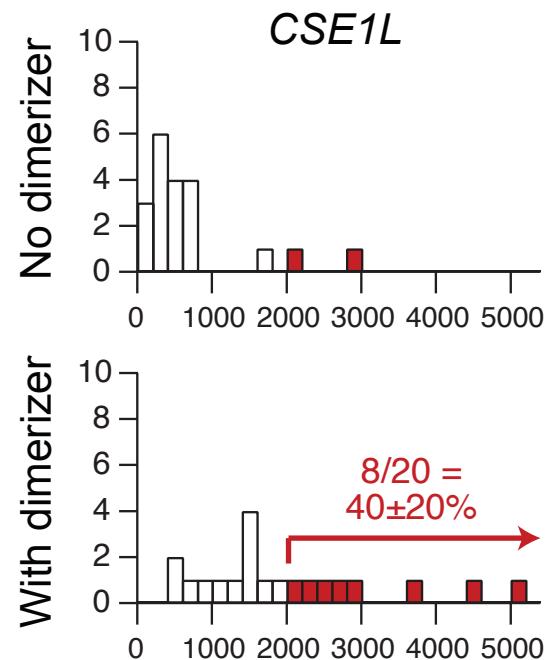


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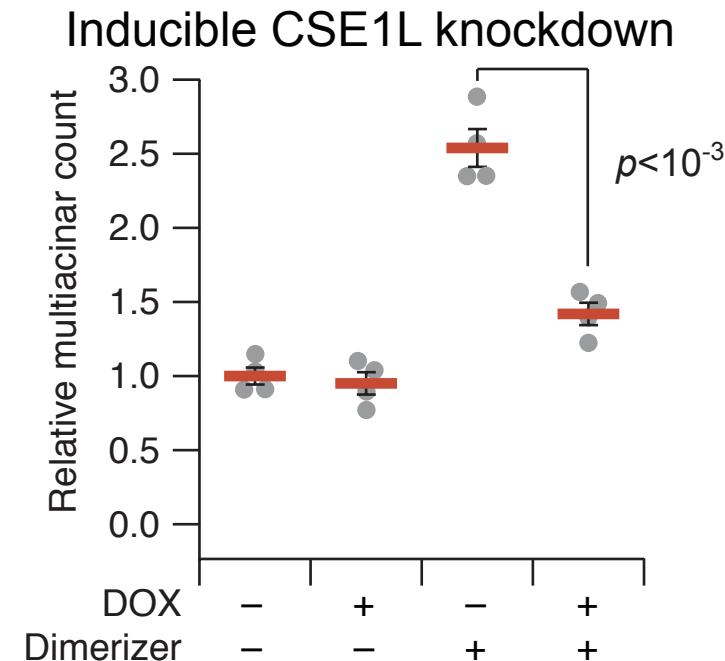
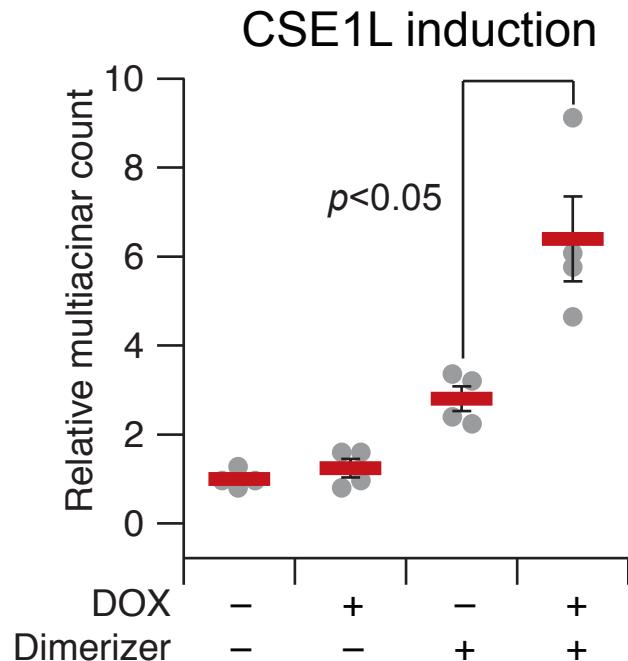
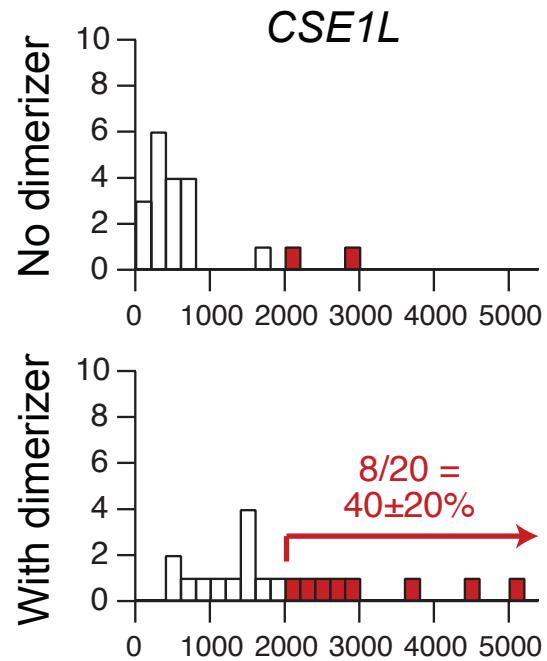


Science 341:655-8 (2013)

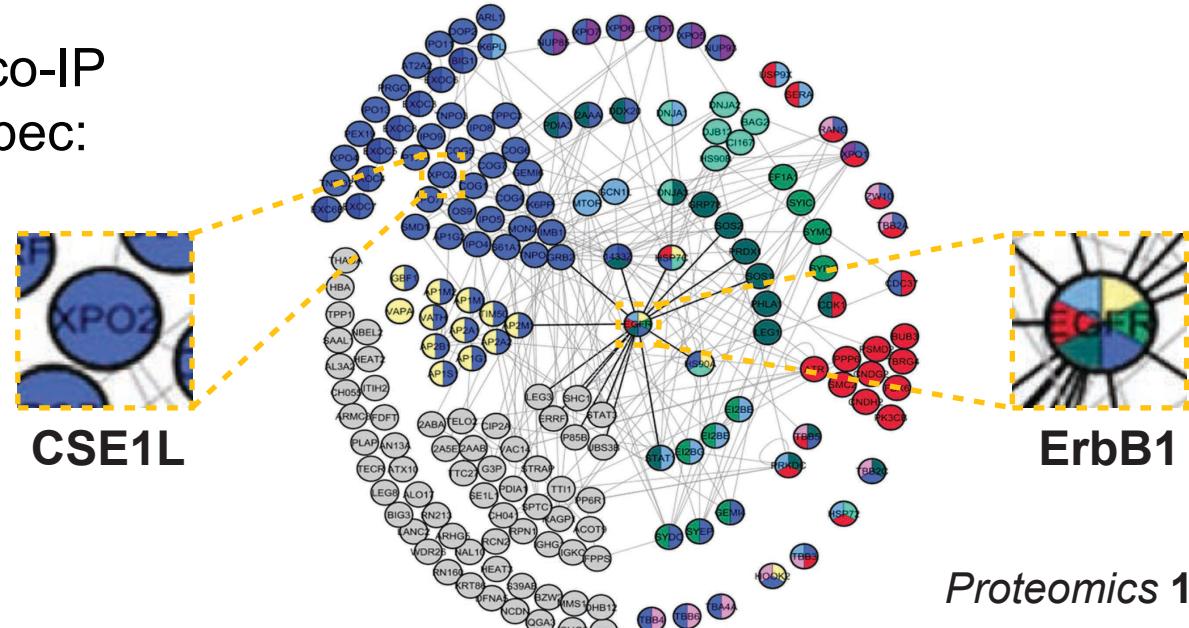
# ErbB2-induced multiacinar penetrance is enhanced by the exportin, *CSE1L* (*XPO2*)



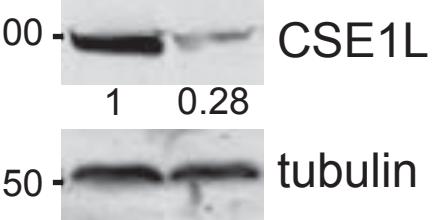
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ErbB1 co-IP mass spec:



Proteomics 13:3131–44 (2013)





# Acknowledgments

JUND–TGFBR3 circuit

Chun-Chao Wang, Leen Jamal  
Kristen Atkins (Dept. of Pathology)

ErbB2 incomplete penetrance

Lixin Wang, Sameer Bajikar,  
Christiane Fuchs, Fabian Theis  
(Helmholz Center, Munich)

<http://bme.virginia.edu/janes/>



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