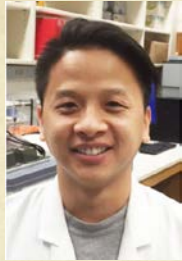


# Oncogenesis and Tumor Biology: Targeting ASCL1

**U01 CA213338-01 Developing ASCL1 and  
NEUROD1 Lineage Oncogene Targeted Therapy  
for Small Cell Lung Cancer (PI: Minna)**

John Minna  
Lab



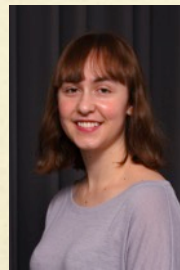
Aiden  
Nguyen

Kenneth Huffman  
Michael Peyton

Jane Johnson  
Lab



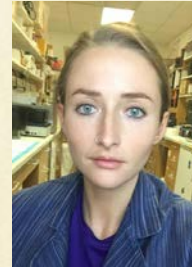
Karine  
Pozo



Demetra  
Kelenis

Rahul Kollipara  
Trisha Savage

Melanie Cobb  
Lab



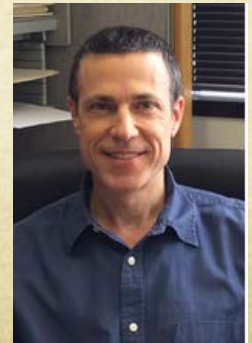
Courtney  
Powell

Svetlana Earnest  
Pearl Wichaidit

Adi Gazdar  
Lab

Victor Stastny

Luc Girard



**U01 CA213338-01**

**Developing ASCL1 and NEUROD1 Lineage  
Oncogene Targeted Therapy for Small Cell Lung  
Cancer (PI: Minna)**

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Major Goal:

To systematically classify SCLCs for their dependency on two key lineage oncogenes, ASCL1 and NeuroD1, and develop therapy targeted at these two transcription factors and their key downstream druggable targets.



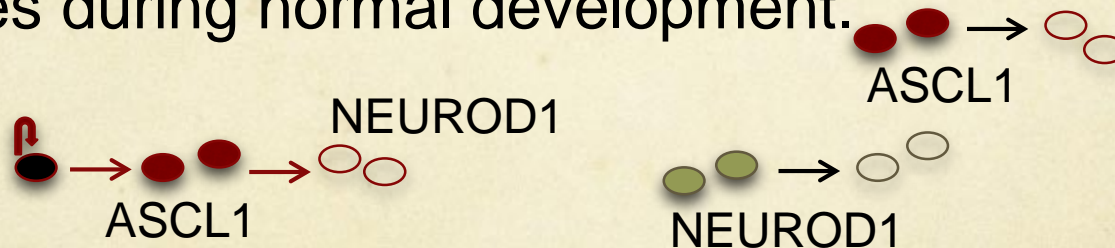
# Updating Findings on Lineage Oncogenes ASCL1 and NEUROD1 in SCLC

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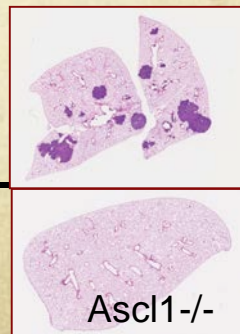
- ❖ Testing ASCL1 and NEUROD1 targets in SCLC cells and xenografts
- ❖ Identifying a group of transcription factors that cross and auto-regulate one another; testing their requirement for SCLC.
- ❖ Identifying ASCL1 interacting proteins (co-factors)
- ❖ Probing the role of ERK and the ERK-ASCL1 axis in SCLC

# ASCL1 and NEUROD1 are lineage-specific bHLH transcription factors

- They are transcriptional activators.
- They, or their transcriptional targets, may provide unique, druggable, vulnerabilities in SCLC.
- They are required in multiple neuronal and neuroendocrine lineages during normal development.

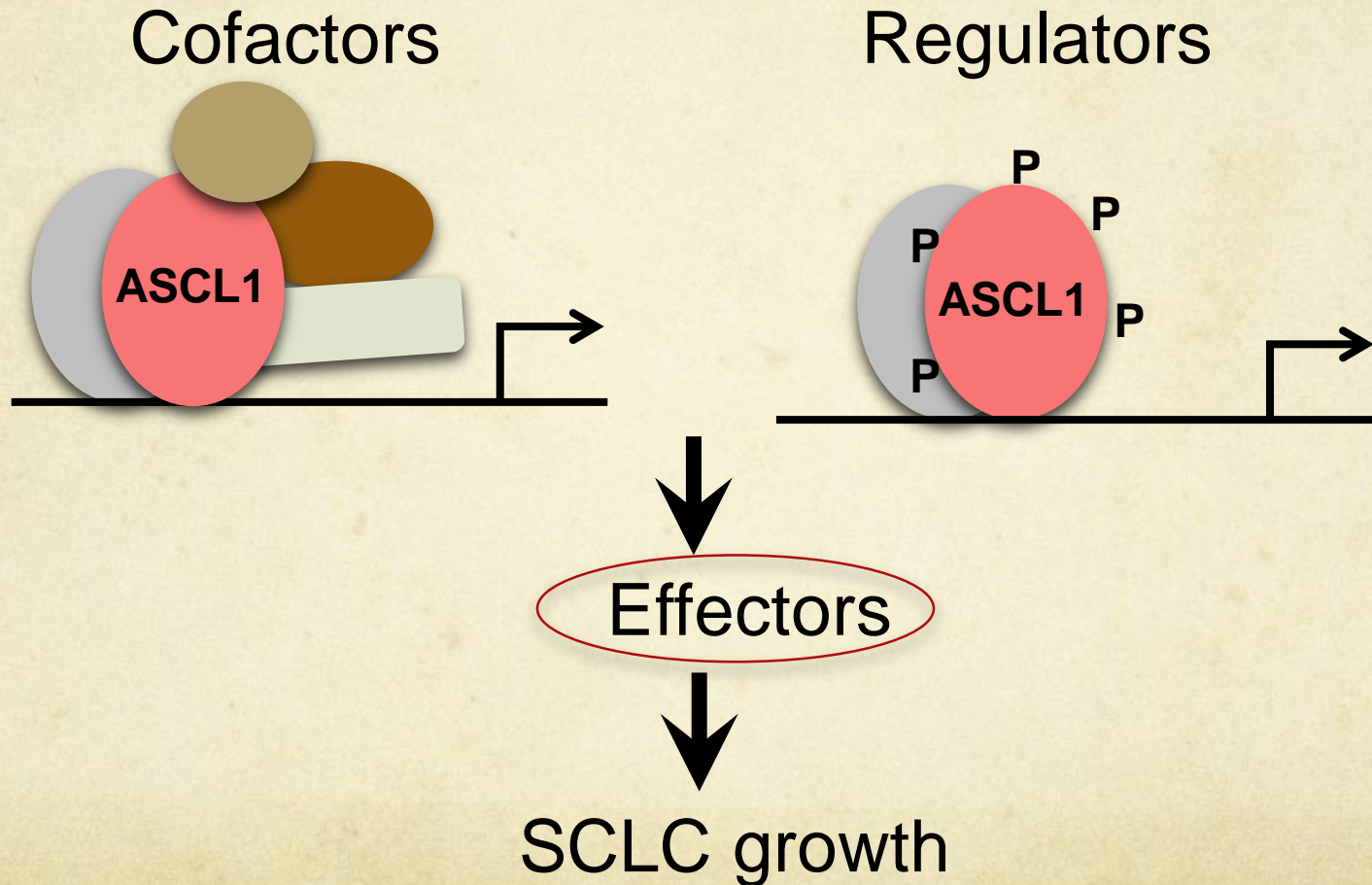


- They are not mutated in SCLC but represent lineage-specific TFs required for tumor cell survival.





# Understanding ASCL1 function in SCLC: New Biomarkers and New Targets



# Identifying downstream transcriptional targets of ASCL1 and NEUROD1 in SCLC

ASCL1 or NEUROD1

ChIP-Seq

Association

Differentially expressed genes in ASCL1<sup>Hi</sup> and NEUROD1<sup>Hi</sup> SCLC models

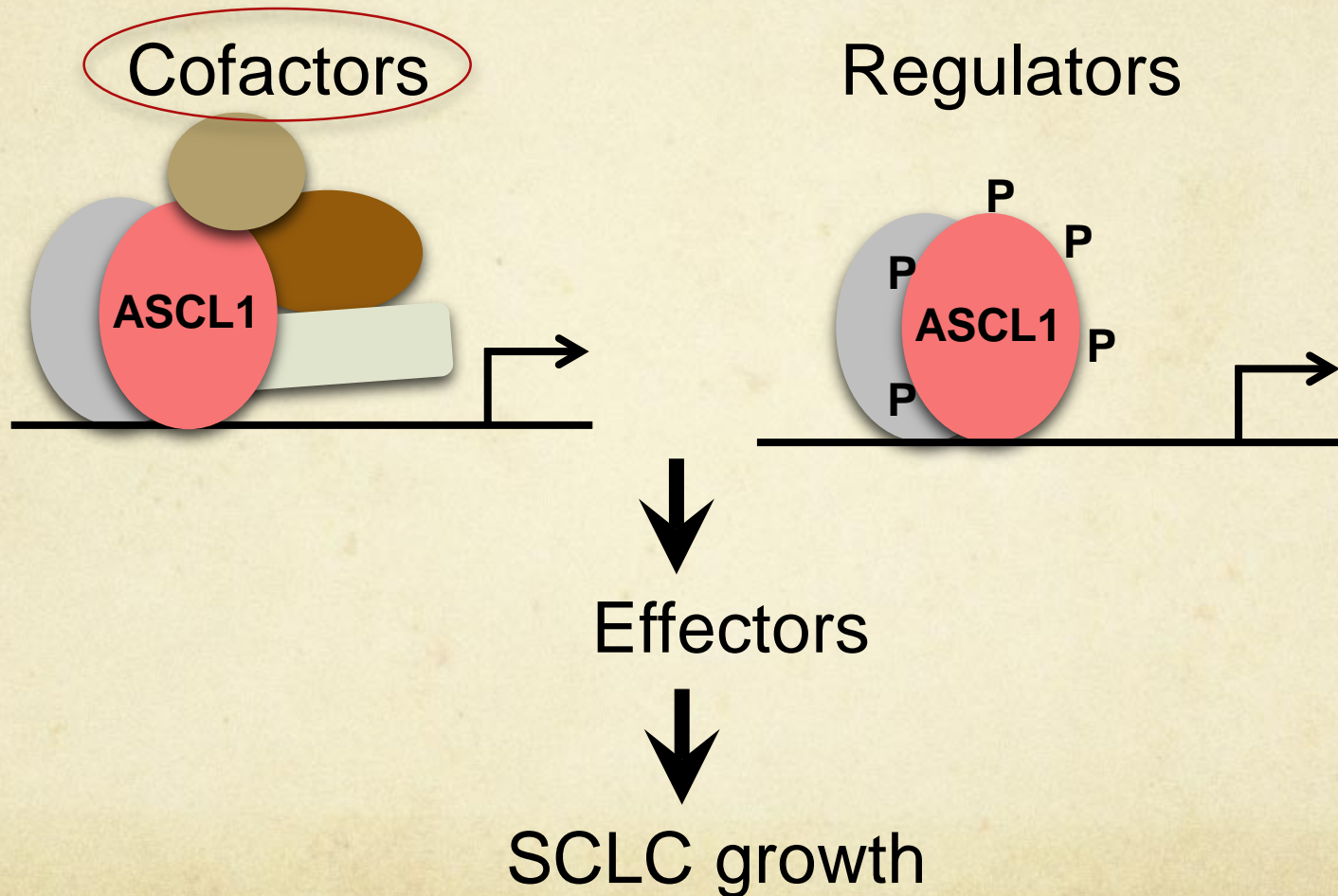
In Progress:

Drop out screen in SCLC cell lines and in xenografts using an shRNA library with a subset of these targets.

- **Some shared, most distinct**

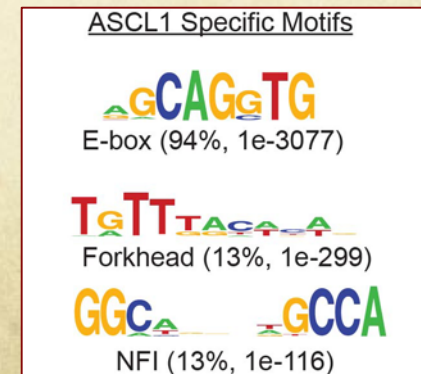
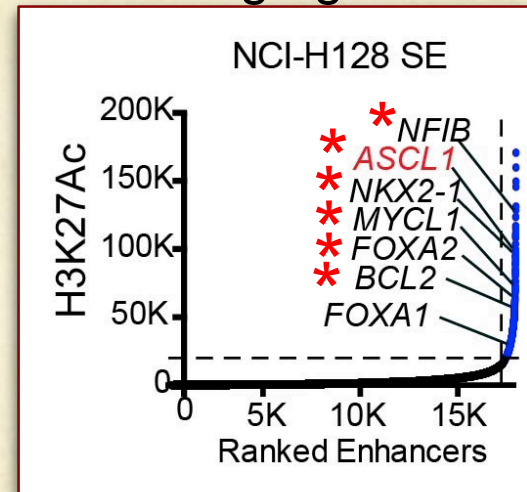
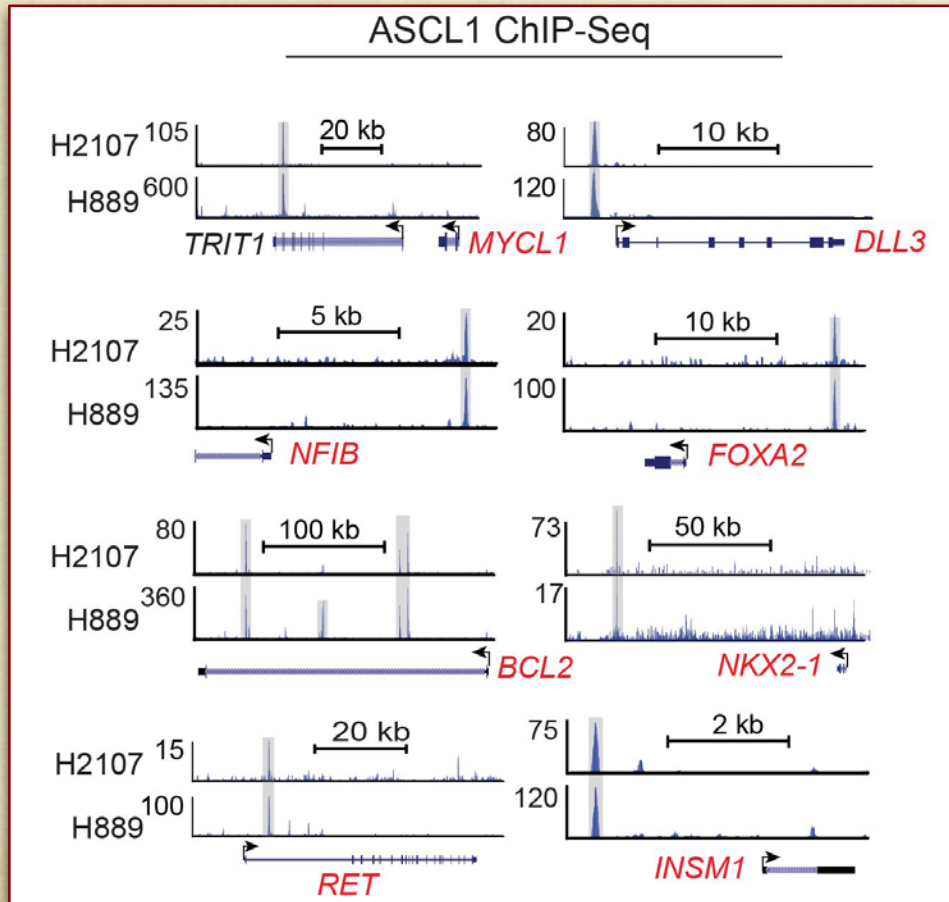


# Understanding ASCL1 function in SCLC: New Biomarkers and New Targets



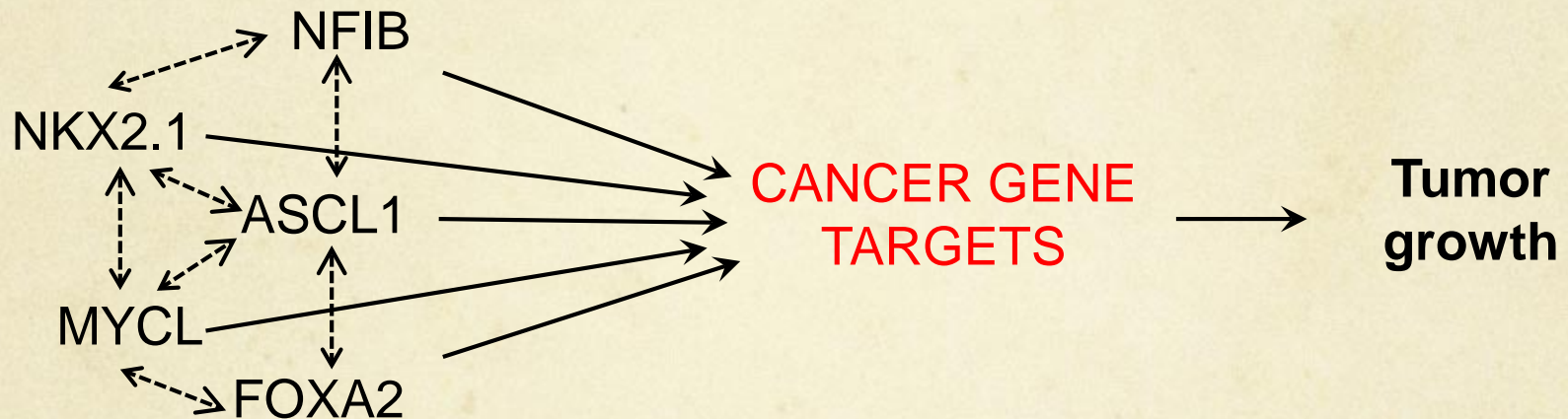
# A core TF network may co-regulate genes important for tumor biology

Super-enhancers are associated with key cell lineage genes





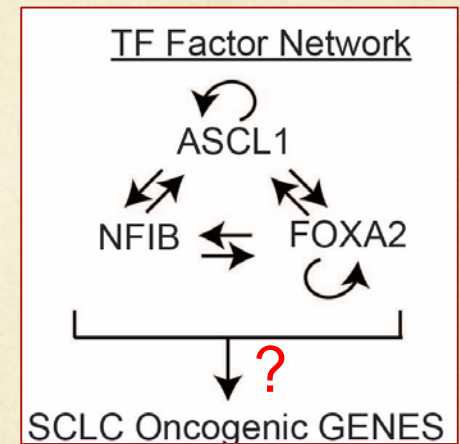
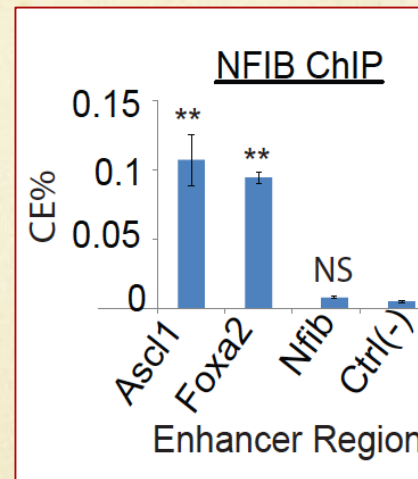
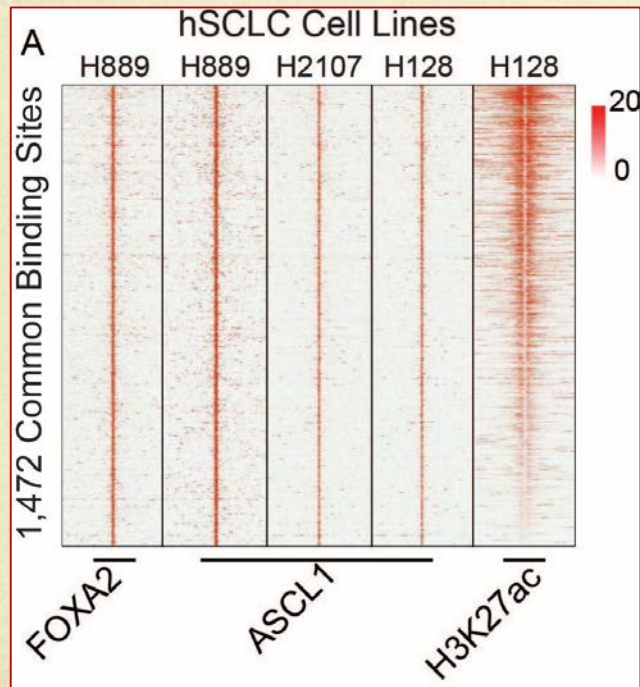
# A core TF network may co-regulate genes important for tumor biology



*Is the function of each transcription factor interdependent and necessary for tumorigenesis?*

# ASCL1 and FOXA2 bind many of the same sites in a SCLC cell line

## ASCL1/FOXA2 bound sites

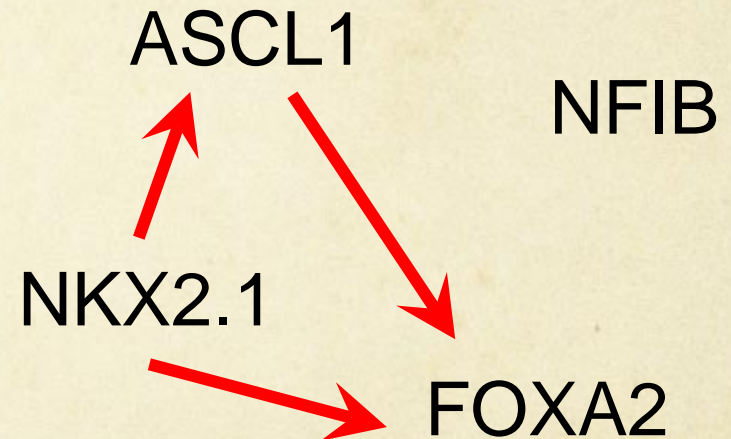
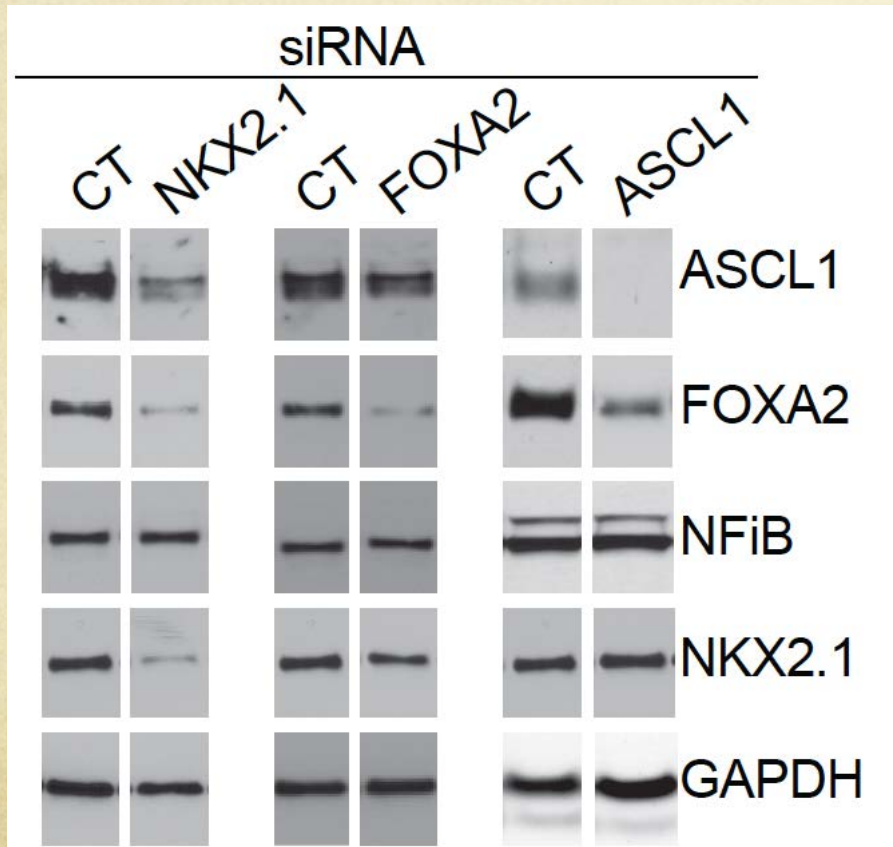


*Is each transcription factor interdependent and necessary for tumorigenesis?*



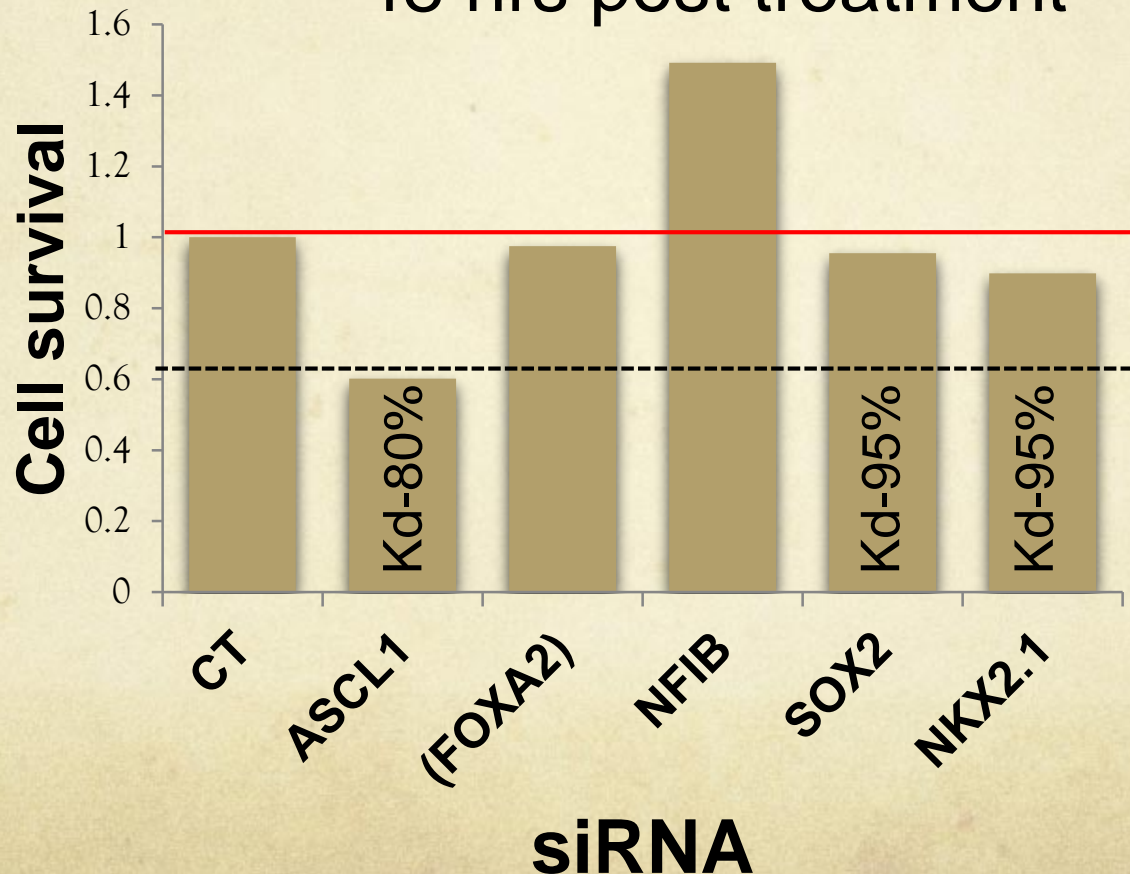
# Regulatory interactions between a subset of the core TF network

H2107 ASCL1<sup>high</sup> SCLC cells  
48 hrs post treatment



# ASCL1 loss is detrimental to SCLC survival

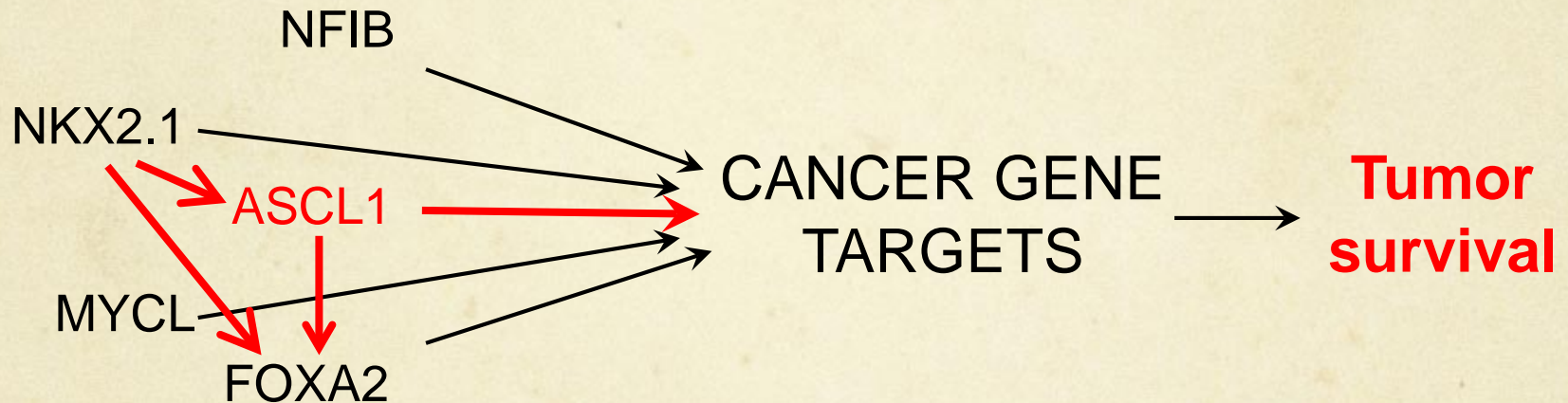
H2107 ASCL1<sup>high</sup> SCLC cells  
48 hrs post treatment





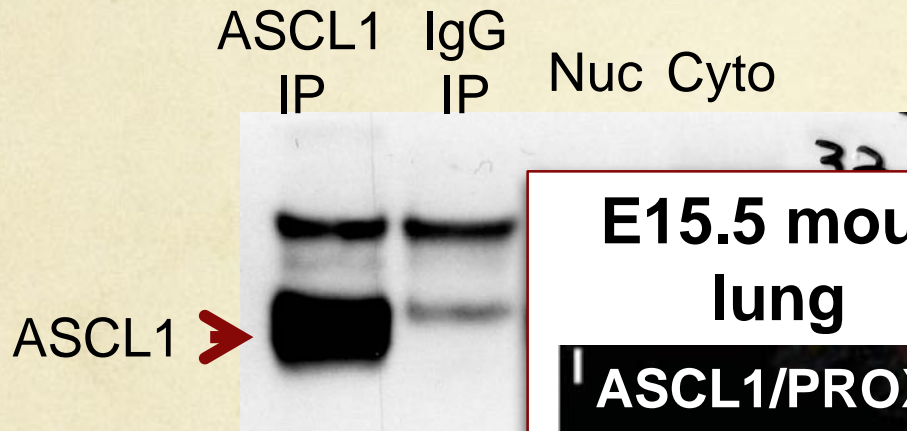
# A core TF network may co-regulate genes important for tumor biology

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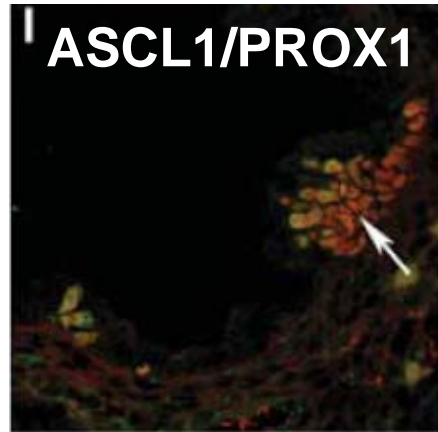
# Identifying ASCL1-cofactors in SCLC

Co-IP Mass Spec from SCLC (H2107)



**E15.5 mouse lung**

**ASCL1/PROX1**

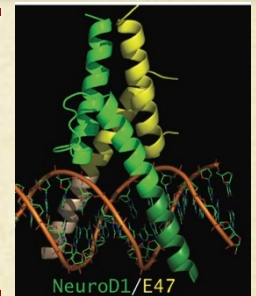


McGovern et al., 2010

**247 interactors**

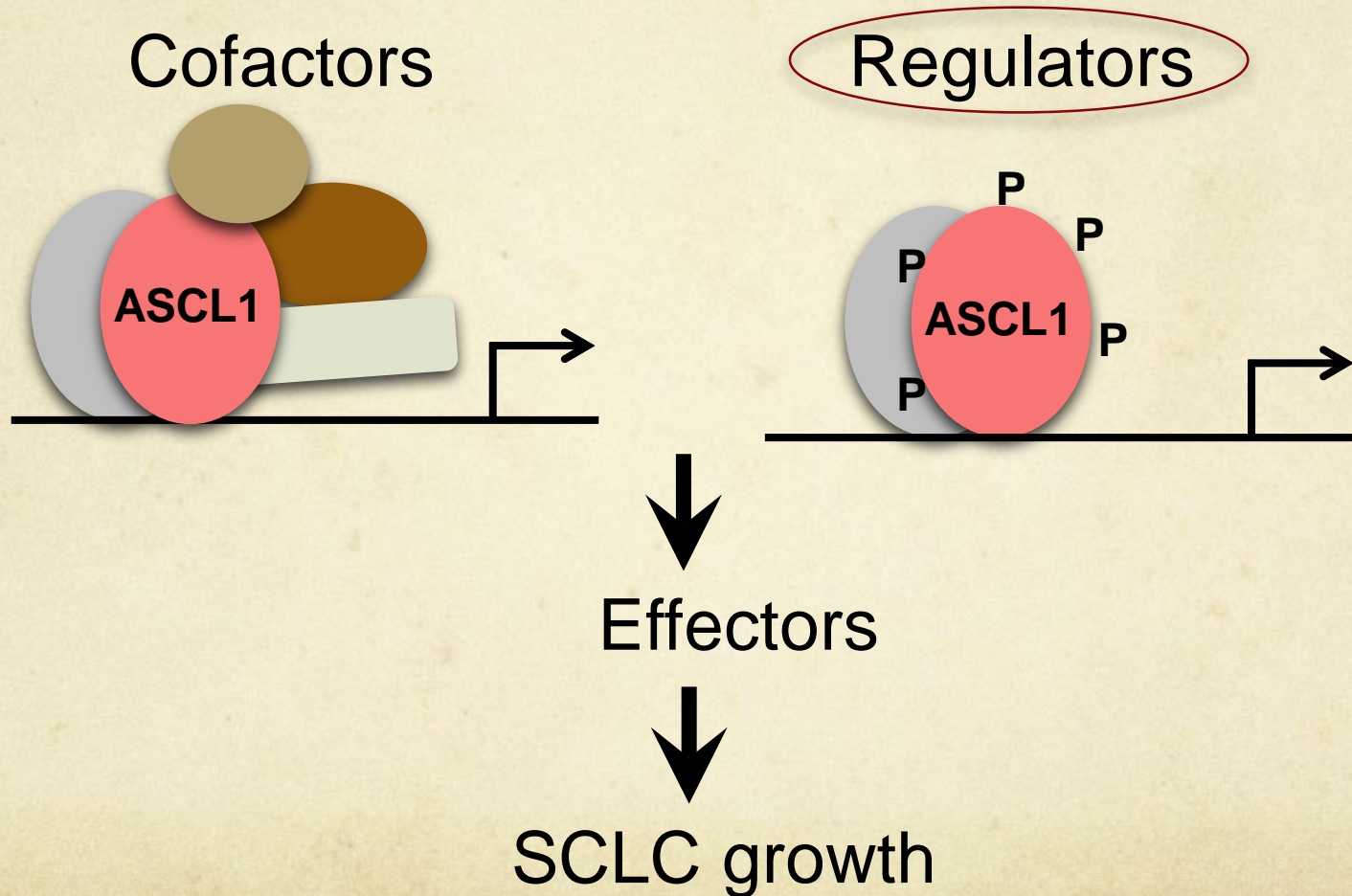
E12/E47  
HEB  
E2.2

NKX2.1  
PROX1  
TRIM28  
CDK2





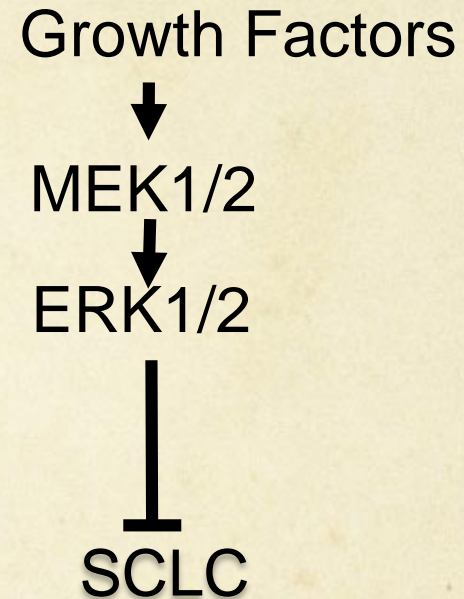
# Understanding ASCL1 function in SCLC: New Biomarkers and Targets



# ERK in SCLC and an ERK:ASCL1 Axis

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- SCLC express relatively low levels of phosphoERK
- SCLC cells (ie H82 and H889) are insensitive to MEK inhibitors







# Ongoing studies on Lineage Oncogenes ASCL1 and NEUROD1 in SCLC

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- ❖ Testing ASCL1 and NEUROD1 targets in SCLC cells and xenografts
- ❖ Identified a TF network; testing requirements for SCLC.
- ❖ Identified ASCL1 interacting proteins; testing how they modulate ASCL1 activity
- ❖ Probing the role of ERK and the ERK-ASCL1 axis in SCLC



# Acknowledgements

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## **Johnson Lab**

Trisha Savage  
Mark Borromeo  
Rahul Kollipara  
Karine Pozo  
Demetra Kelenis

## **Melanie Cobb**

Svetlana Earnest  
Pearl Wichaidit

## **John Minna**

Kenneth Huffman  
Michael Peyton  
Longshan Li  
Alex Augustyn  
Aiden Nguyen

## **Adi Gazdar**

Victor Stastny

## **Luc Girard**

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