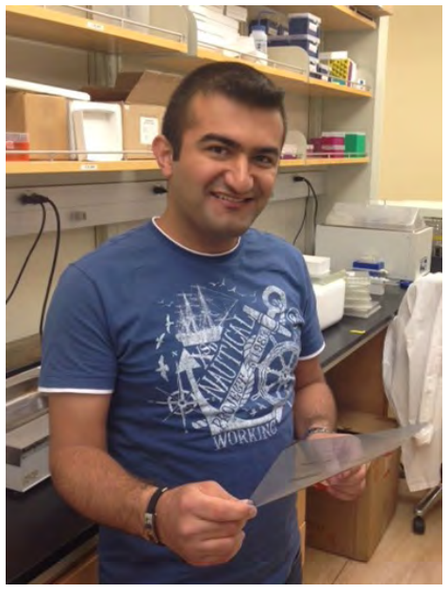
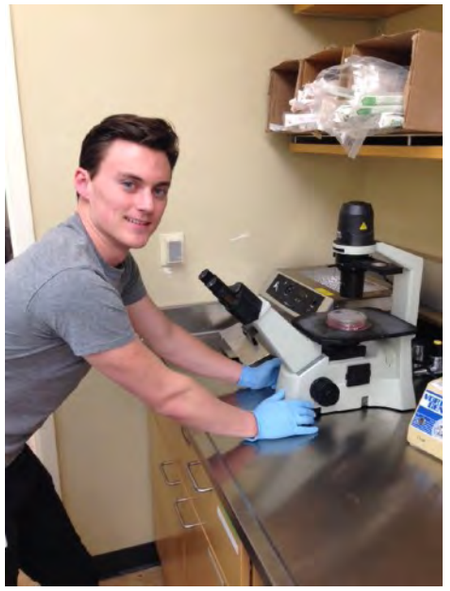
MYC drives a unique molecular and therapeutically-relevant subset of SCLC

Trudy G. Oliver, PhD
SCLC Consortium
March 15, 2018

Gurkan Mollaoglu

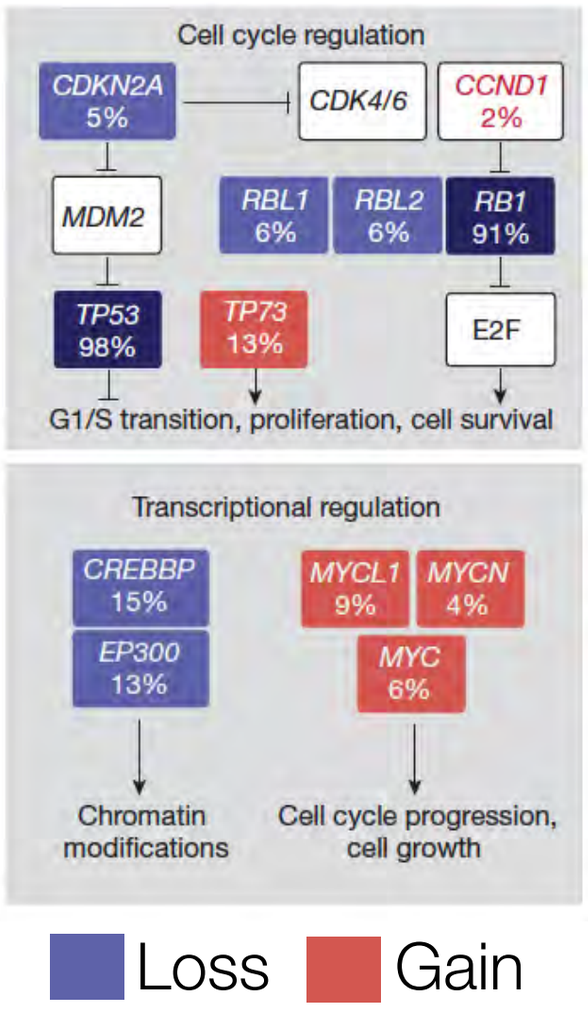


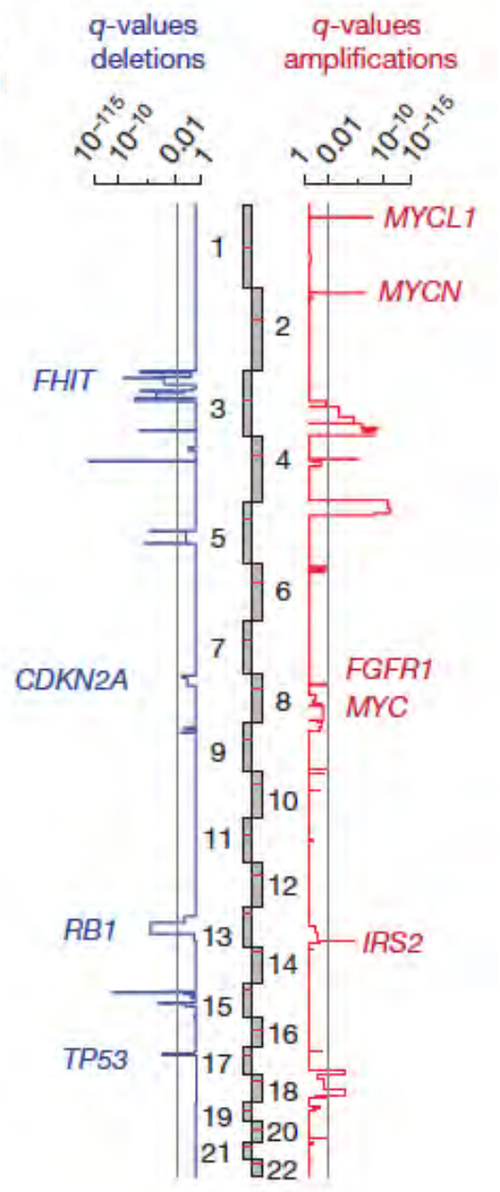
Matt Guthrie



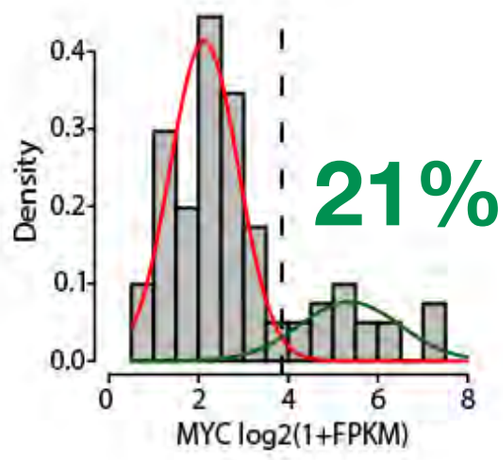
Genomics of human SCLC

Loss of RB1 and P53, plus mutually exclusive gain of MYC family members



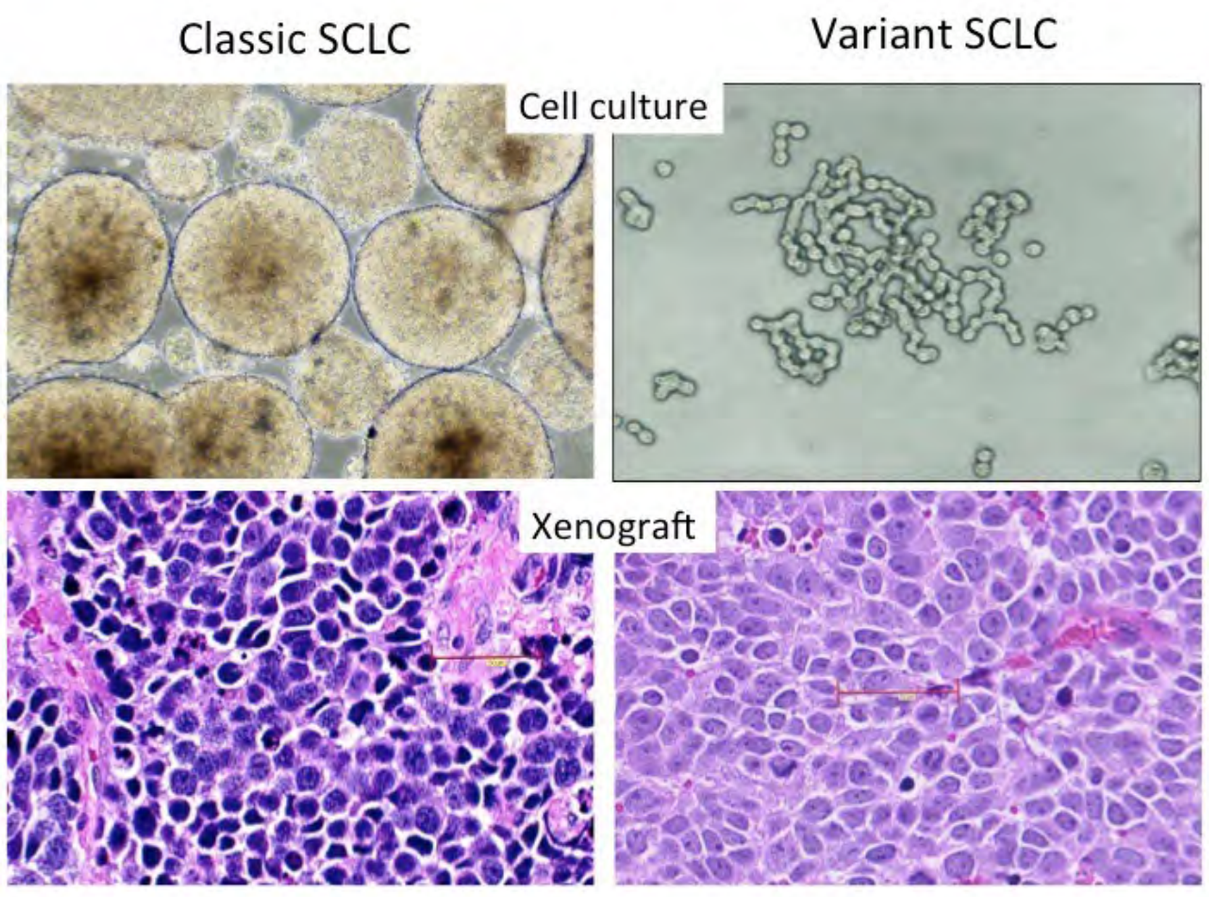


MYC mRNA



George et al, Nature, 2015

In the 1980's……classic and variant SCLC

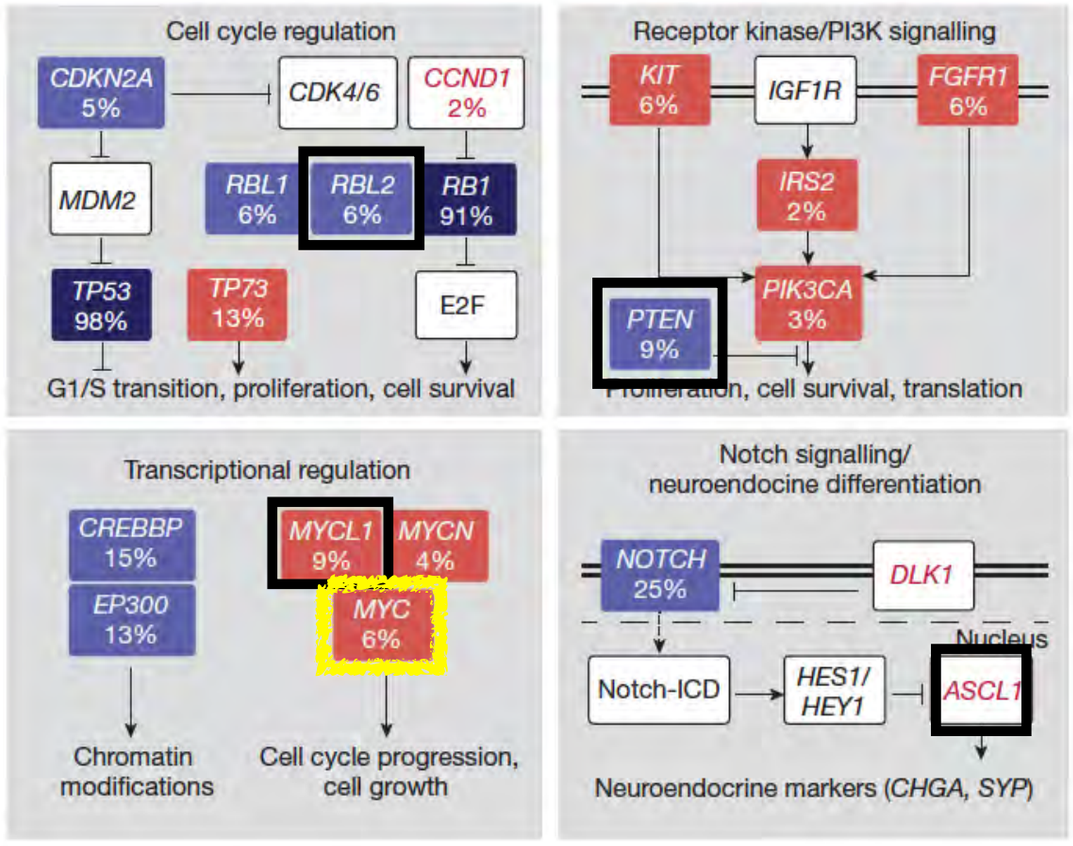


Provided by Drs. Adi Gazdar and John Minna

Variant SCLC

- More commonly derived from relapsed patients / at autopsy
- Associated with shorter survival time
- Reduced expression of neuroendocrine markers
- Faster proliferation
- More radio-resistant
- Associated with *c-MYC* amplifications

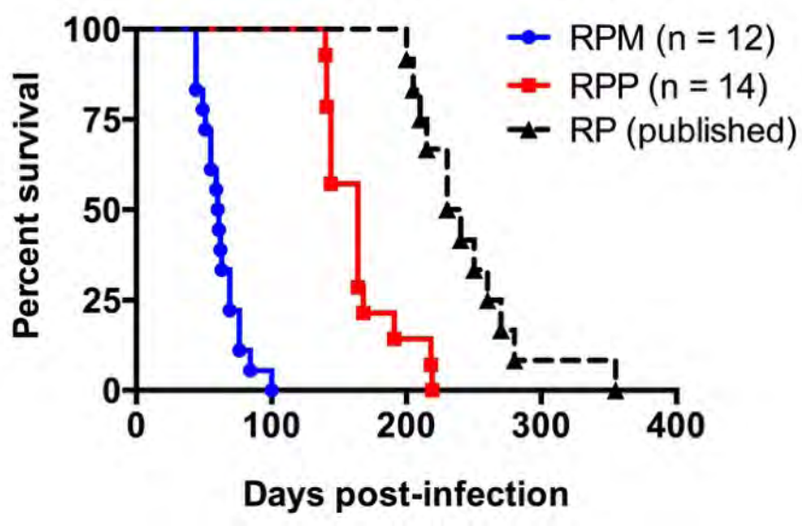
Mouse models of SCLC based on *Rb1/p53* loss



George et al Nature, 2015

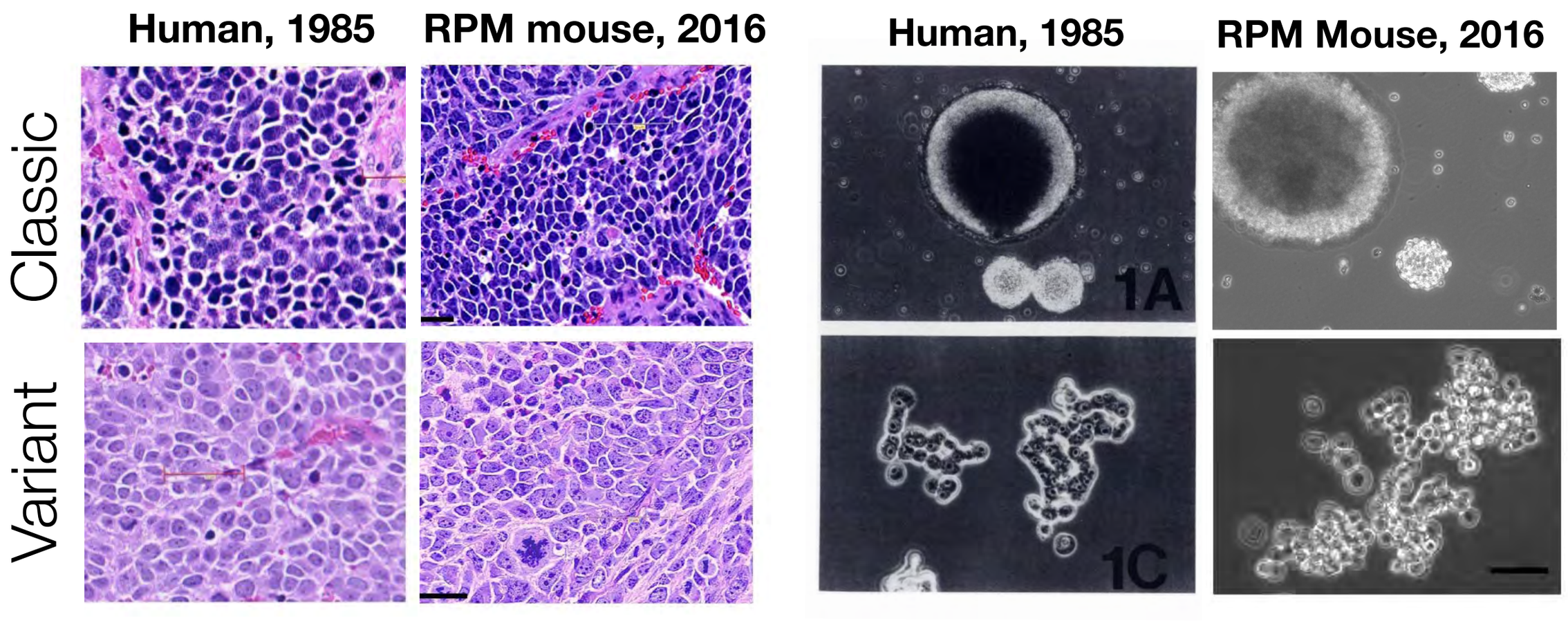
Rb1/p53 (RP, Berns)
Rb1/p53/Rbl2 (RPR2, Sage)
Rb1/p53/Pten (RPP, Jacks, MacPherson)
Rb1/p53/L-myc (Berns)
SV40 + Ascl1 (Linnoila)

Rb1/p53/Myc^{T58A} (RPM, Oliver)



Classic SCLC, LCNEC or other NSCLC phenotypes often with high *L-Myc* expression and latencies of ~5-12 months (Gazdar et al, JTO, 2015)

C-MYC-driven tumors and cell lines resemble variant SCLC

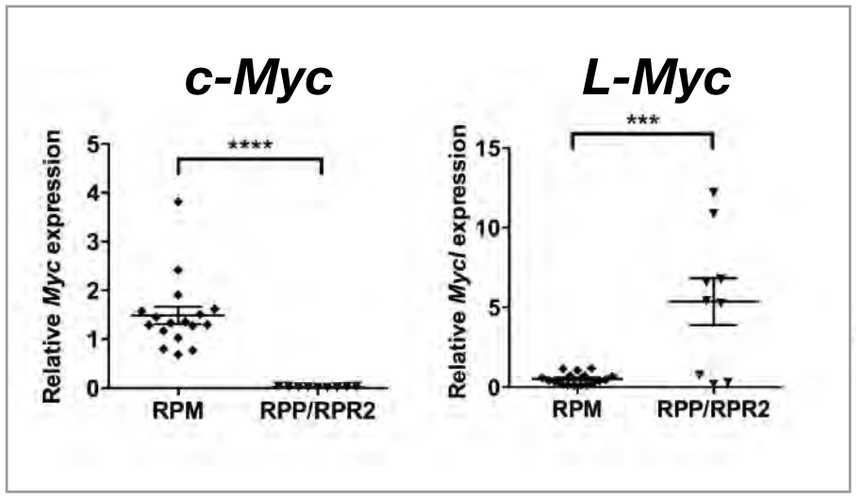


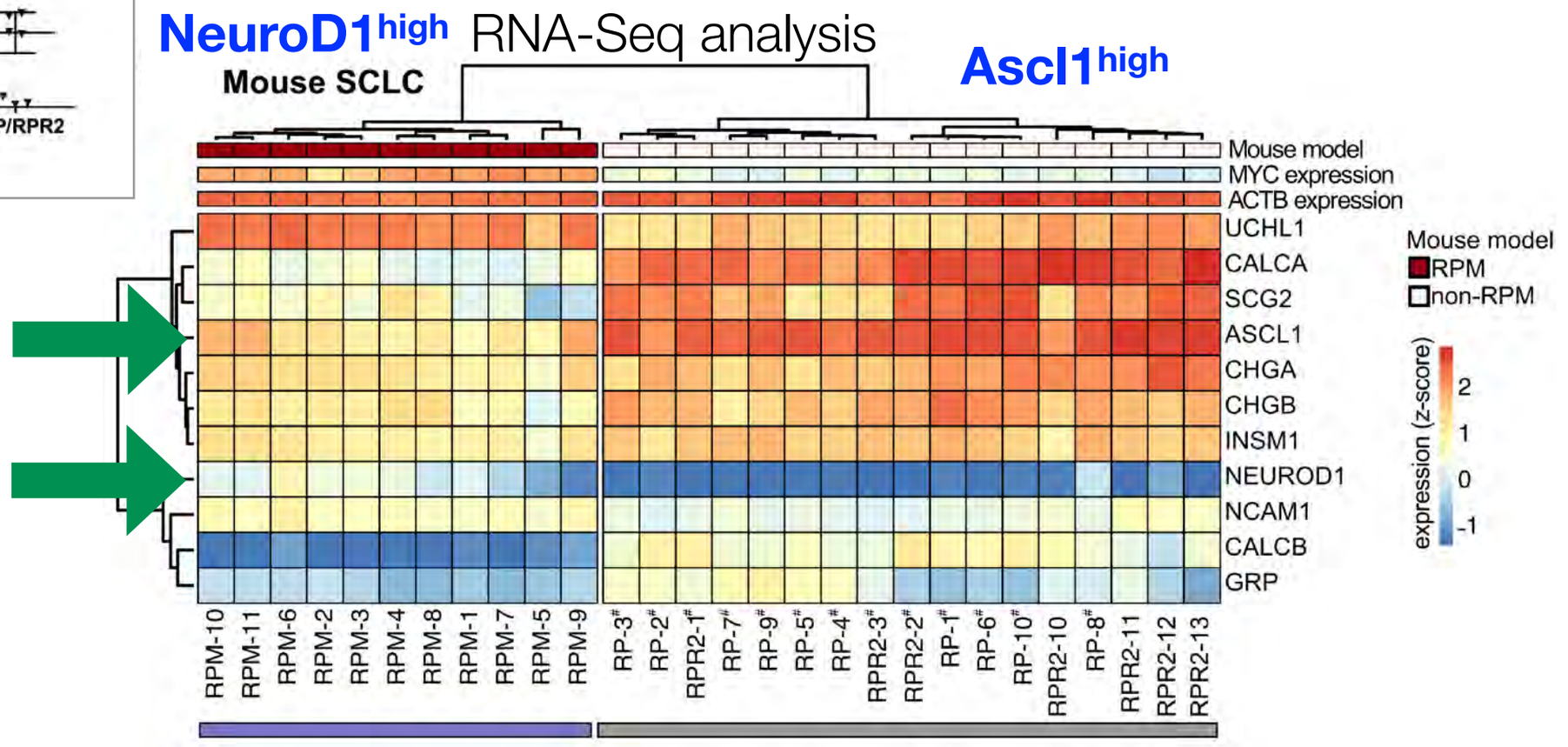
Are they neuroendocrine?

Mollaoglu & Guthrie et al, *Cancer Cell*, 2017

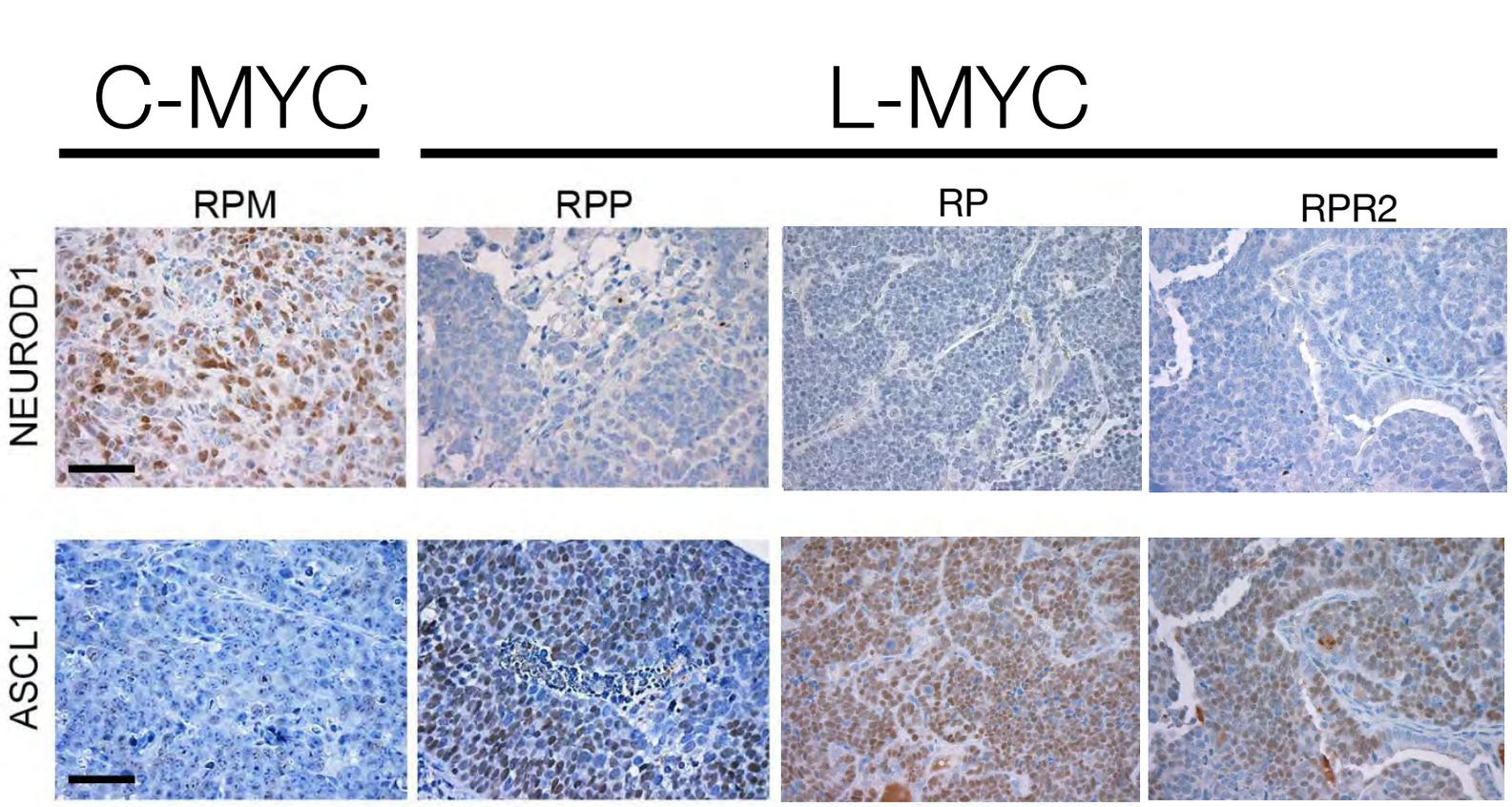
Carney et al, Can Res, 1985

MYC-driven tumors are neuroendocrine-low, with reduced *Ascl1*, and increased *NeuroD1*

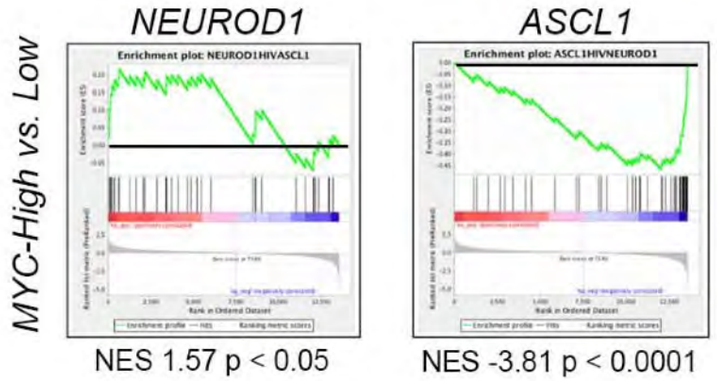


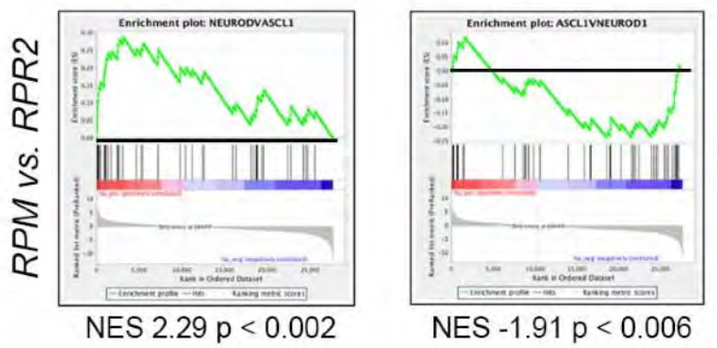


MYC-driven mouse and human tumors express NEUROD1 and its target genes



81 human tumors

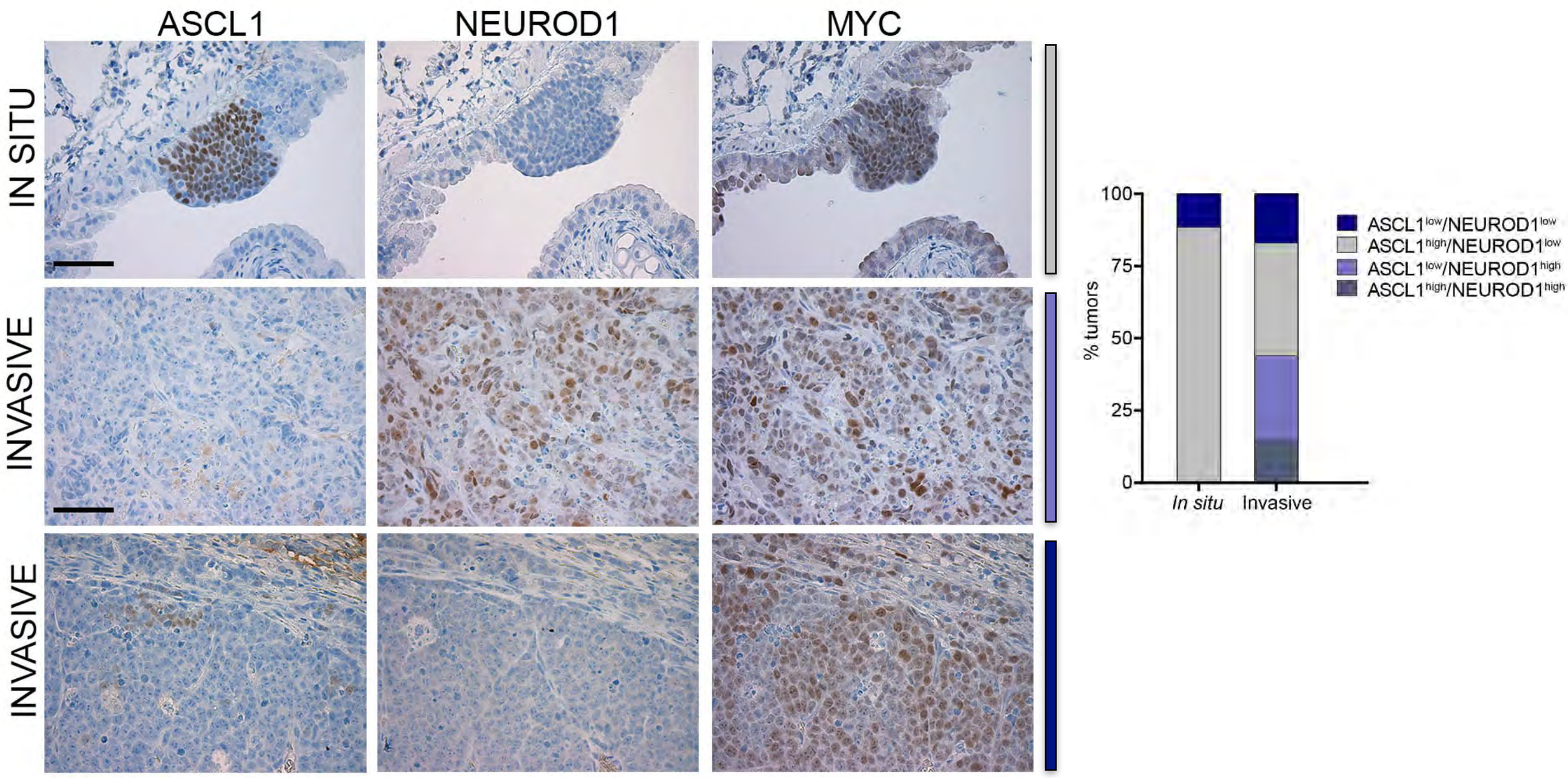




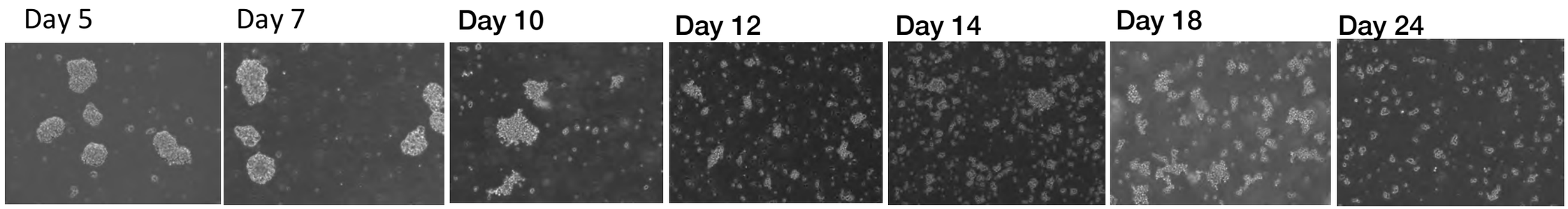
26 mouse tumors

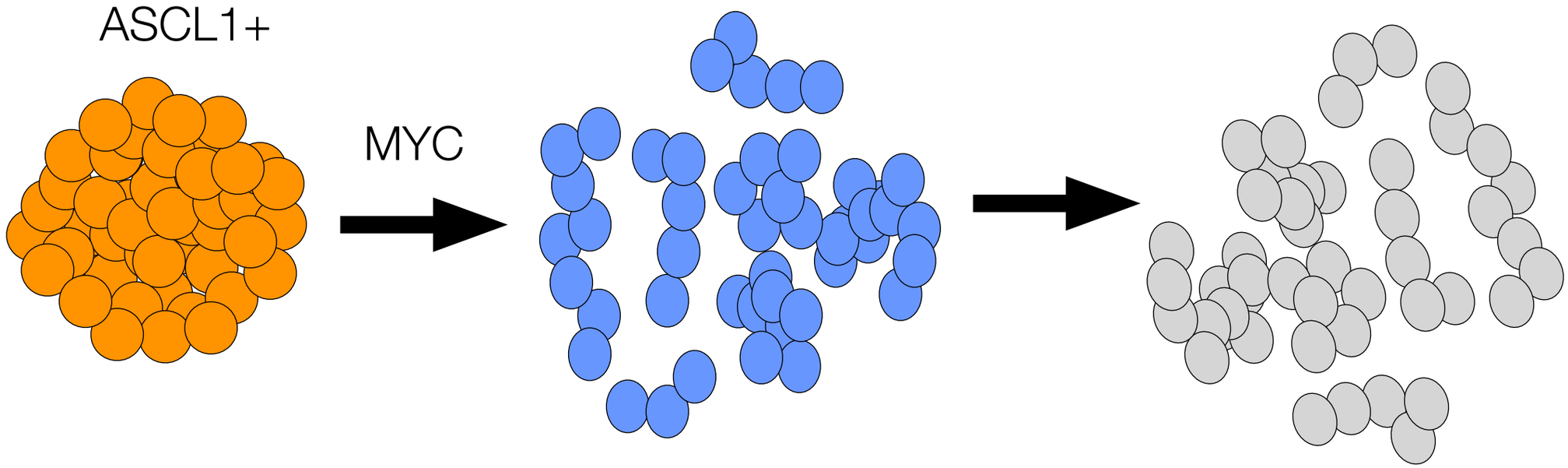
Borromeo et al, *Cell Reports*, 2016

Hypothesis: SCLC originates in ASCL1+ cells and progresses to NEUROD1+ or double-negative state



Hypothesis: MYC promotes transition of ASCL1+ cells to NEUROD1+ to double-negative

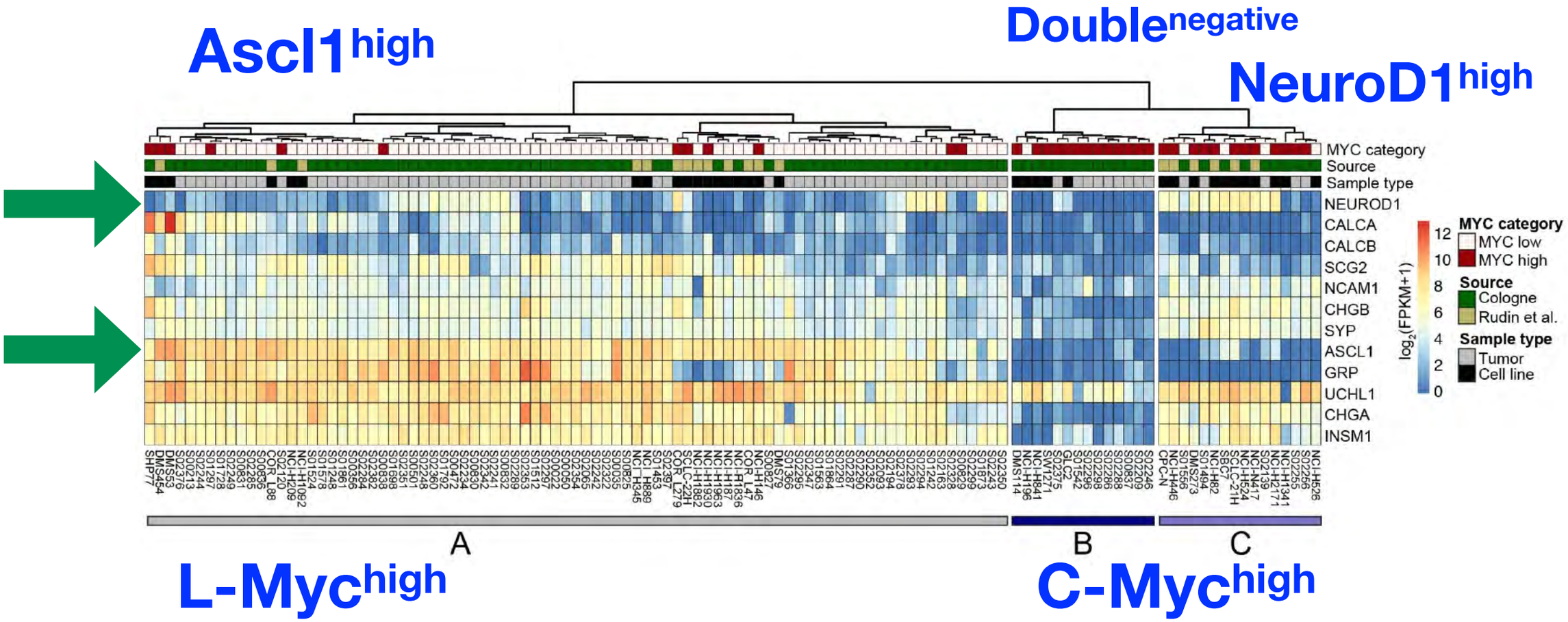




Unpublished data, Abbie Ireland

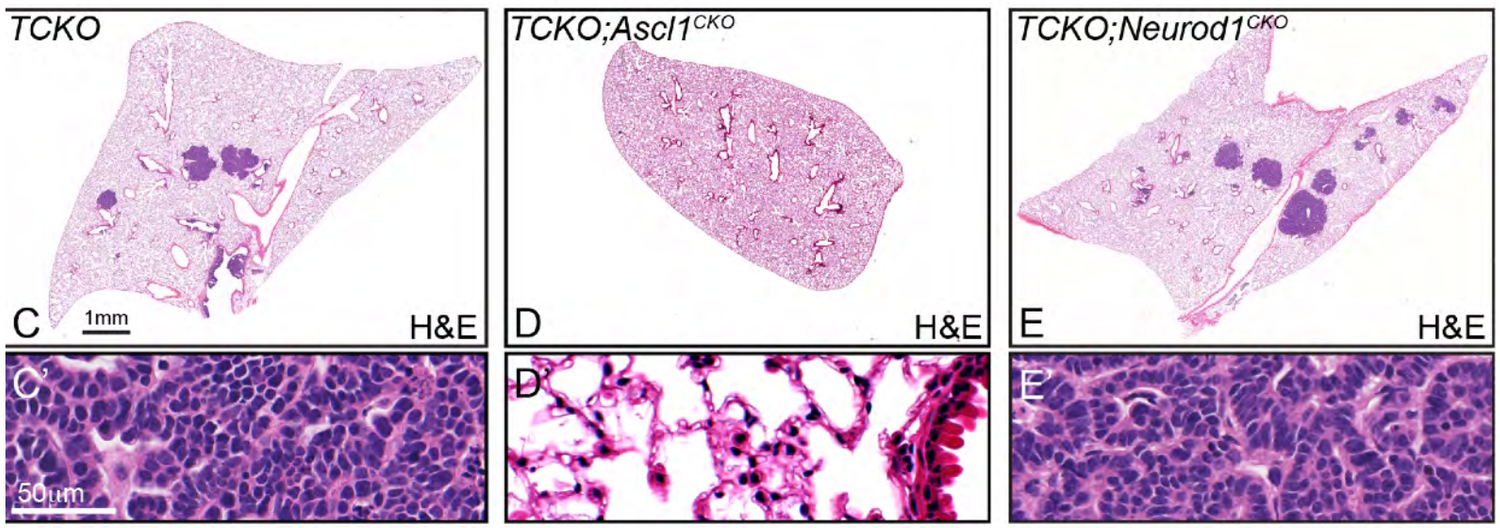
MYC-high human SCLC exhibits low neuroendocrine gene expression and a switch in ASCL1/NEUROD1

Unsupervised clustering of 81 human tumors and 34 human SCLC cell lines



ASCL1 is required for classic SCLC development

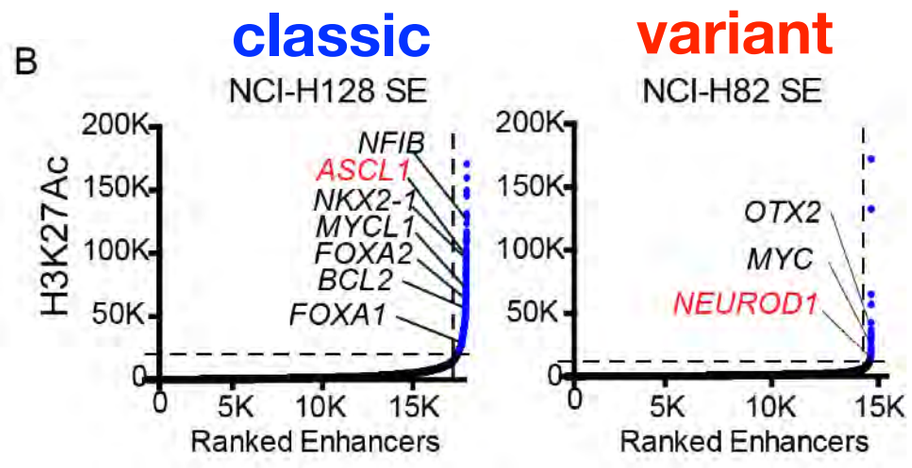
- ASCL1 is required, but NEUROD1 is not required for classic (L-MYC-associated) SCLC



RPR2 model (Sage)

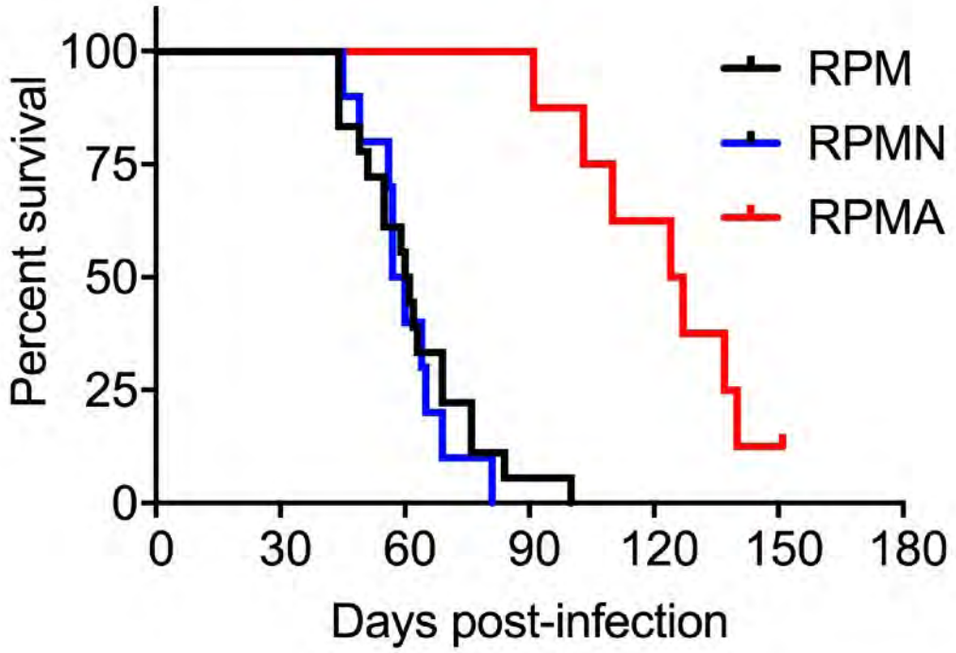
Are ASCL1 and NEUROD1 required for MYC-driven SCLC?

super enhancers

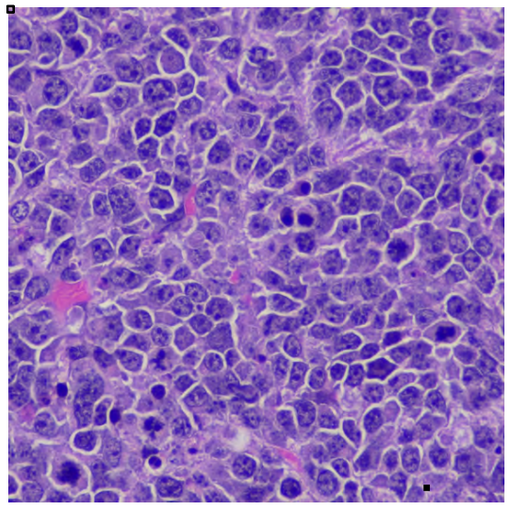


Borromeo et al, Cell Reports, 2016
Christensen, Cancer Cell, 2014

NEUROD1 is not required for MYC-driven SCLC



RPMN tumors



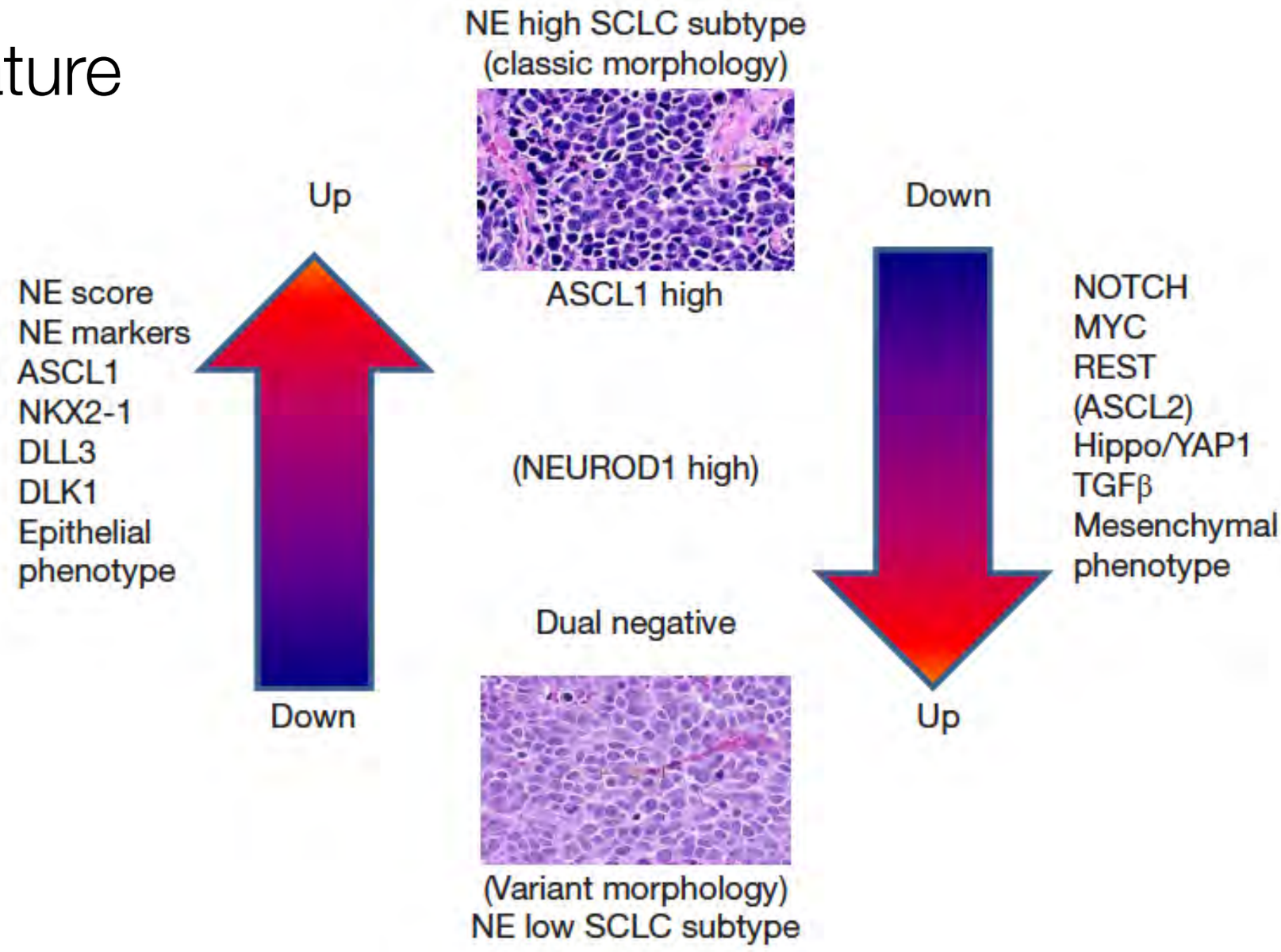
Scale, 25µm

MYC-driven tumors develop in the absence of ASCL1, but what are they?

Unpublished data, Rachelle Olsen, collaboration with Jane Johnson & Adi Gazdar

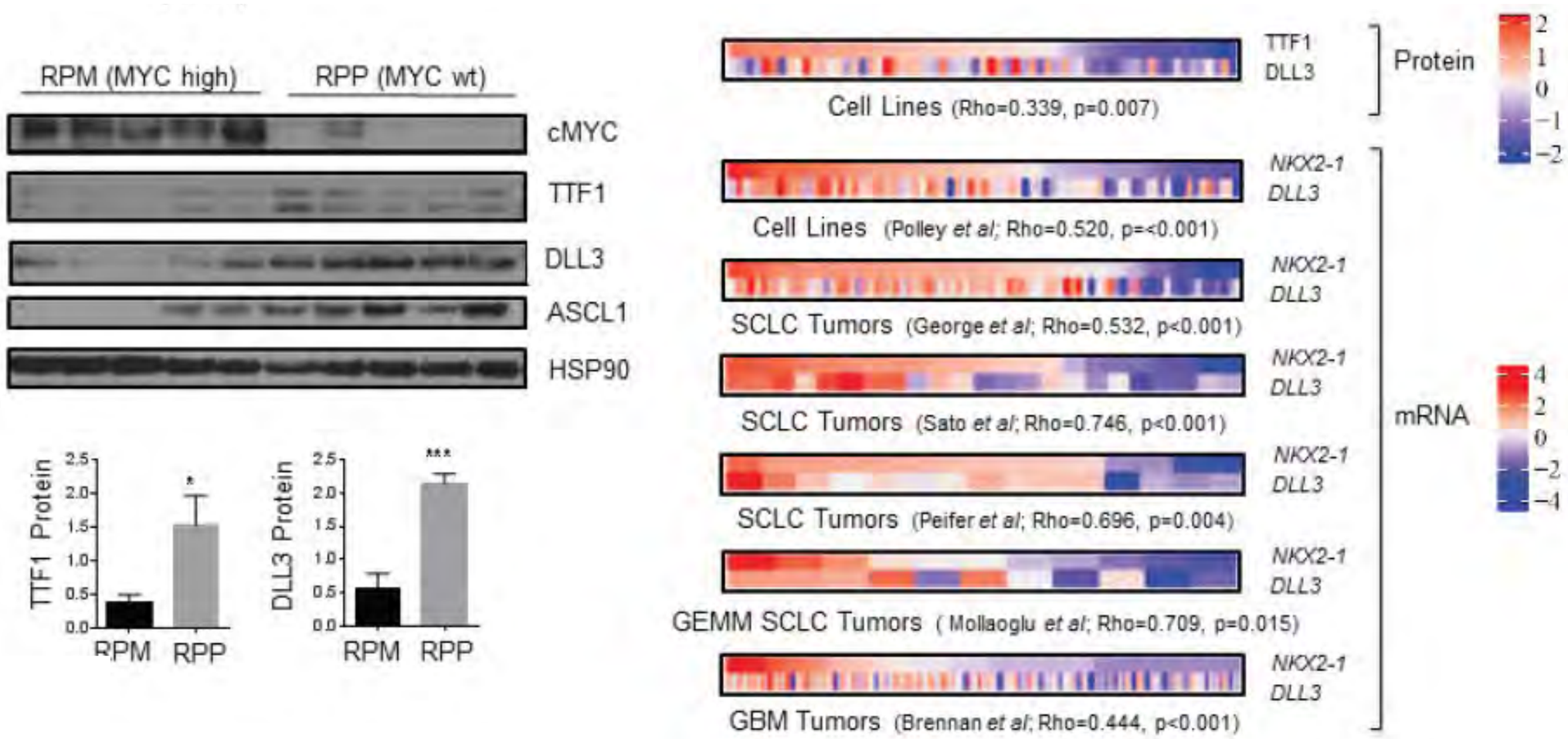
Features associated with the double-negative "NE-low" state in mouse and human

NE signature



Zhang et al, Transl Lung Cancer Res, 2018 (Girard, Gazdar, Minna)

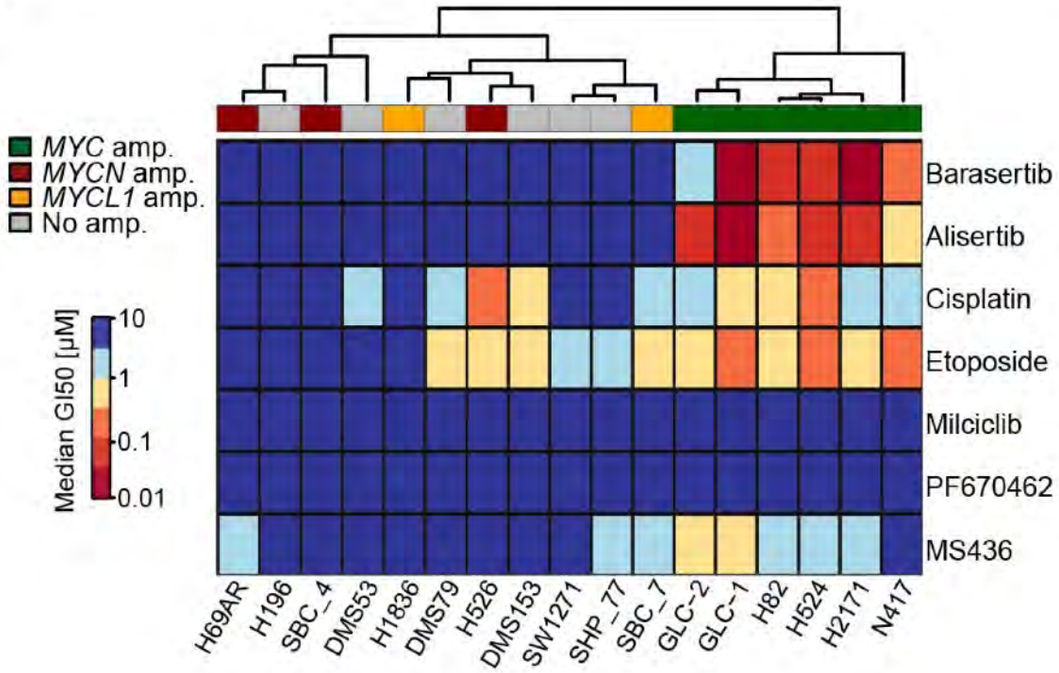
MYC-driven tumors have reduced NKX2-1/TTF1 and DLL3 (a new SCLC drug target, “Rova-T”)



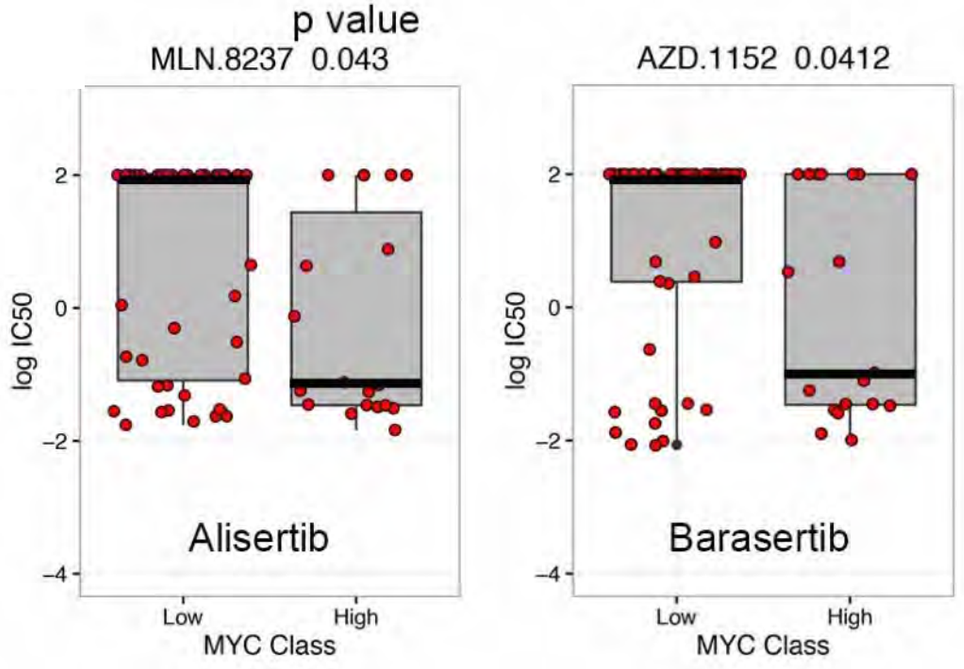
Collaboration with Dr. Lauren Byers
Cardnell et al, *Oncotarget*, 2017

MYC-high SCLC cell lines preferentially respond to Aurora kinase A/B inhibition

Human SCLC cell lines



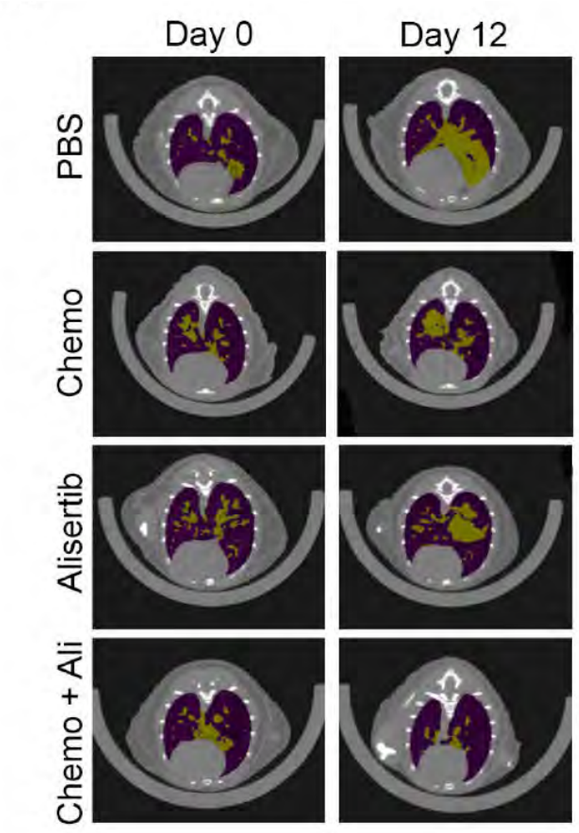
63 human SCLC cell lines



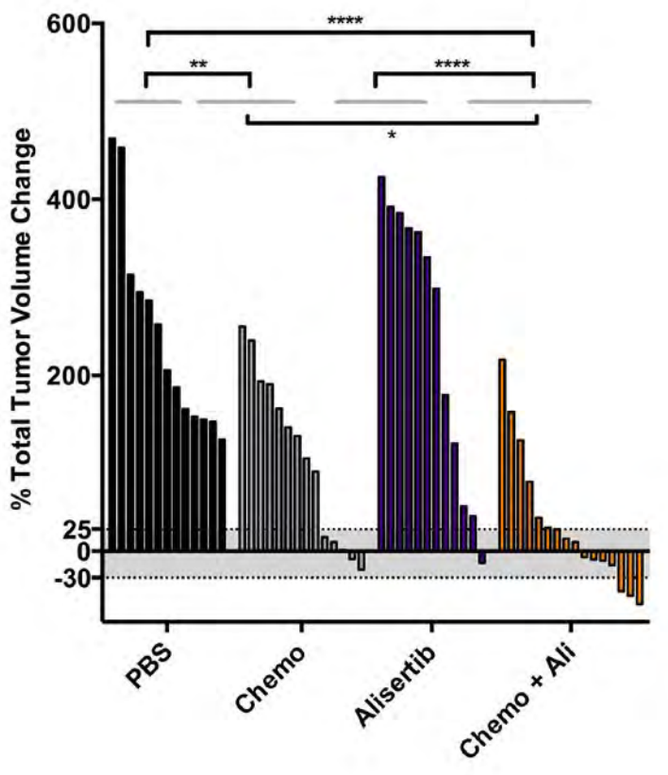
Polley et al, JNCI, 2016

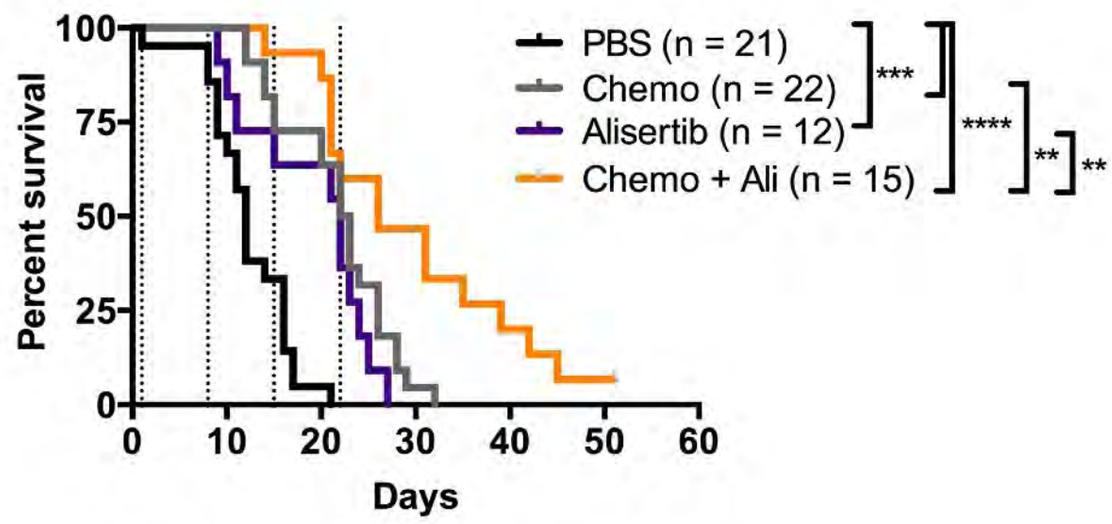
21% of relapsed SCLC responded to Alisertib monotherapy (Melichar et al, *Lancet Oncology*, 2015)

Alisertib in combination with chemotherapy significantly improves tumor control and survival



Tumor / Lung



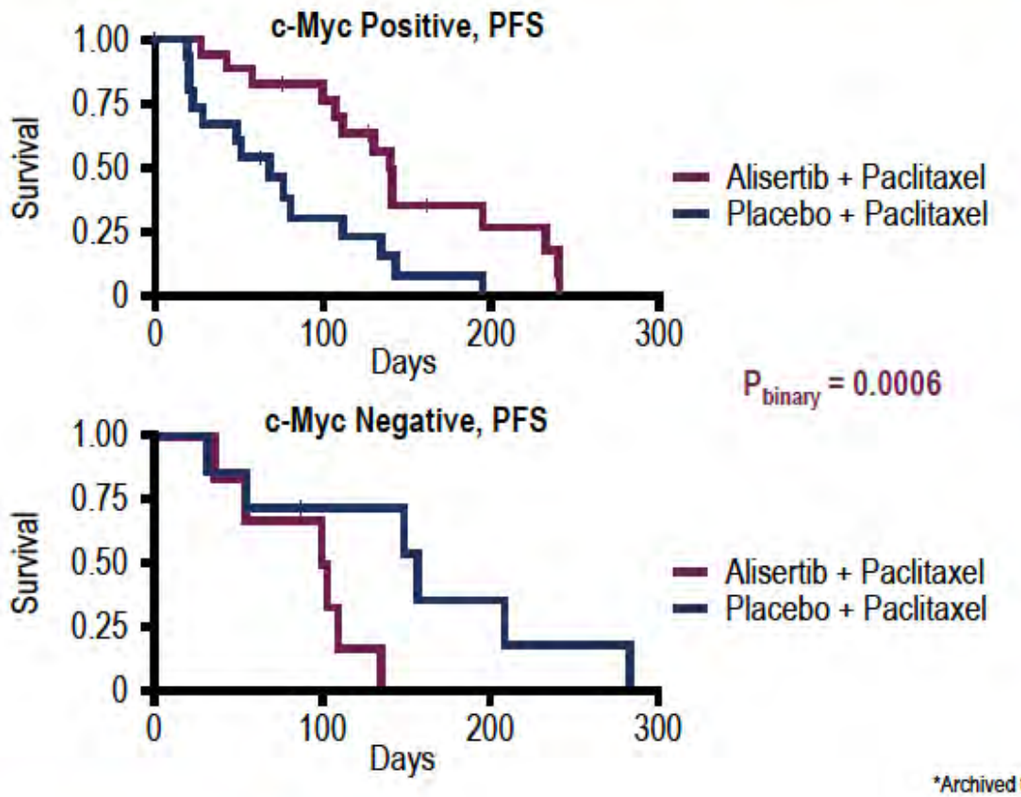


NCI-funded R21 related to MYC & Alisertib
RPM mice deposited into JAX #029971

Mollaoglu & Guthrie et al, *Cancer Cell*, 2017

Improved survival in patients with MYC-high tumors

n = 46 out of 89 patient samples assessed by MYC IHC



Arm	c-Myc positive	
	n	Median PFS (months)
Alisertib + Paclitaxel	17	4.64
Placebo + Paclitaxel	16	2.27
Hazard Ratio (95% CI)	0.29 (0.12–0.72)	

Arm	c-Myc negative	
	n	Median PFS (months)
Alisertib + Paclitaxel	6	3.32
Placebo + Paclitaxel	7	5.16
Hazard Ratio (95% CI)	11.8 (1.52–91.2)	

*Archived tumor tissue available from 46 patients. Modal intensity for c-Myc positive= 1+, 2+, 3+ IHC score. Modal intensity for c-Myc negative = 0 IHC score.

COPENHAGEN 2016 ESMO congress

MYC-high SCLC is preferentially sensitive to Aurora kinase inhibition

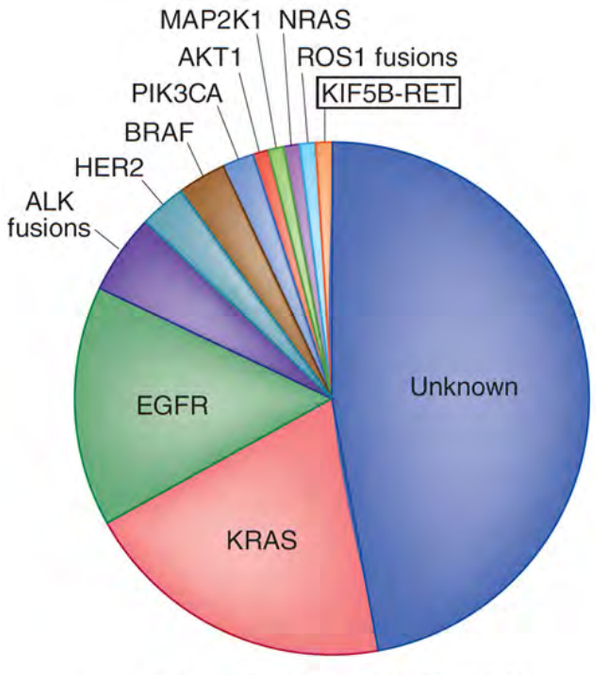
With permission from Owonikoko et al, ESMO, 2016

MYC promotes aggressive, neuroendocrine-low, “variant” subtype (NEUROD1^{+} or Double^{Negative}) of SCLC that is vulnerable to Aurora kinase inhibition

Molecular and functional subtypes of SCLC exist (MYC vs. L/N-MYC) **with clinical implications**

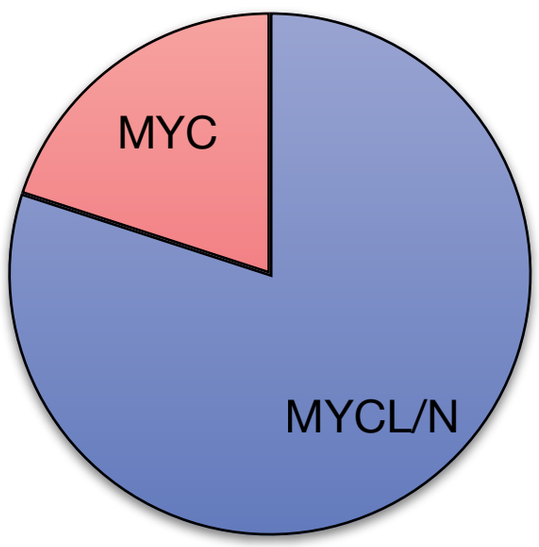
While subtype-specific therapies are not yet approved (and need to be improved), **preclinical and clinical trials** should examine these biomarkers to best determine subtype-specific therapies

NSCLC



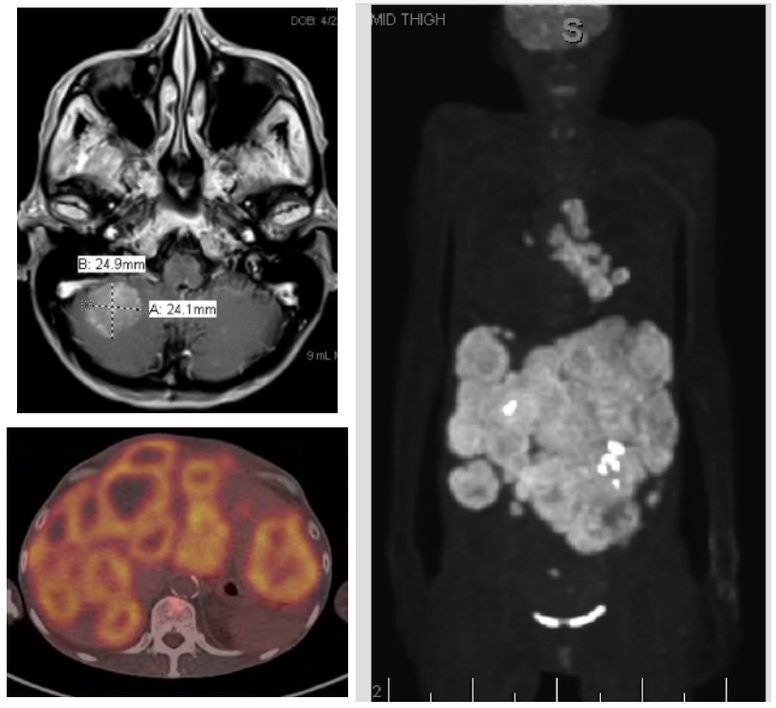
Source : Nature Medicine 18, 349–351 (2012)

SCLC

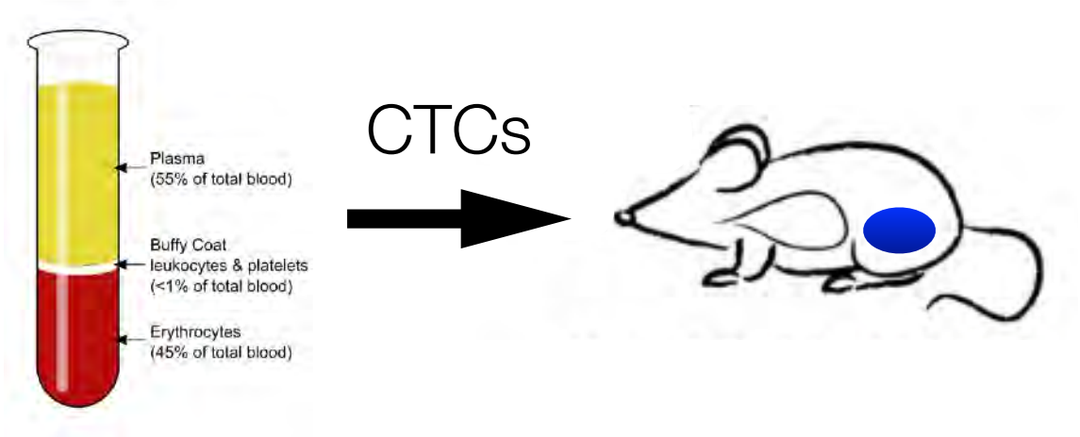


SCLC subset differences:
Metabolic profile
Apoptotic BH3 profile
Immune profile
Metastatic drivers

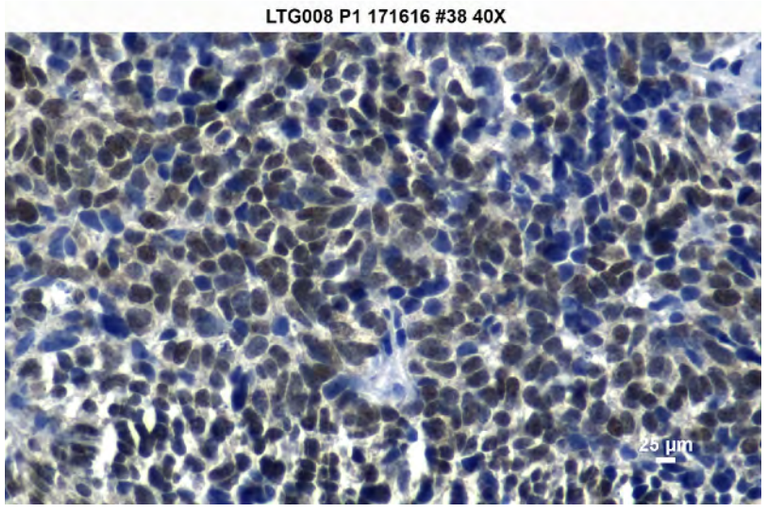
CDX models at Huntsman Cancer Institute, n = 11



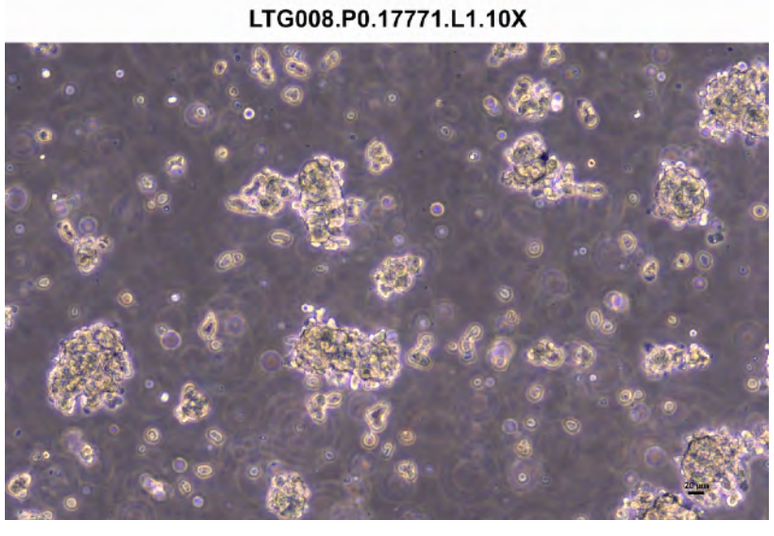
Female, 2/6/2018



CDX tumor, ASCL1+



CDX-derived cell line



With planned sequencing from Charlie Rudin, JT Poirier, Roman Thomas and Julie George…..
to be deposited into cBioportal

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Damon Runyon Cancer Research Foundation

Congressionally Directed Medical Research Programs
CDMRP
Department of Defense

NIH National Institutes of Health
Turning Discovery Into Health

Mini-grants from Cell Response & Regulation and UADOT