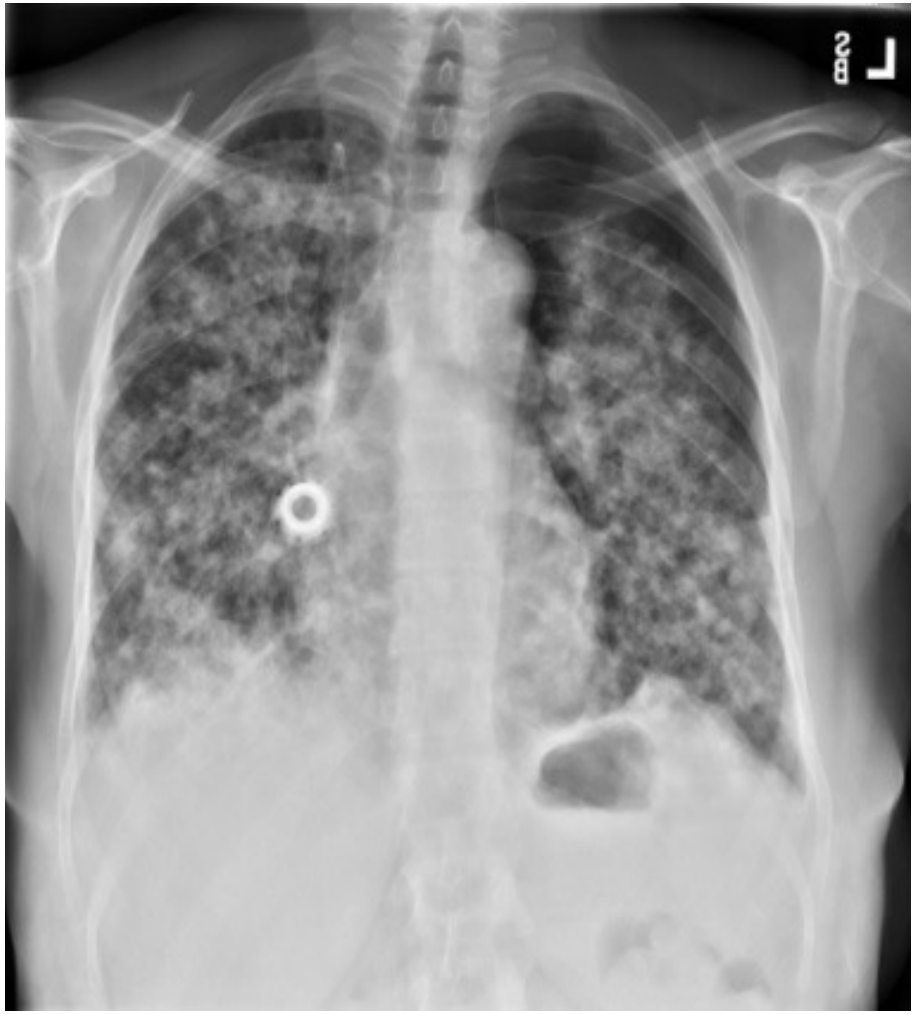
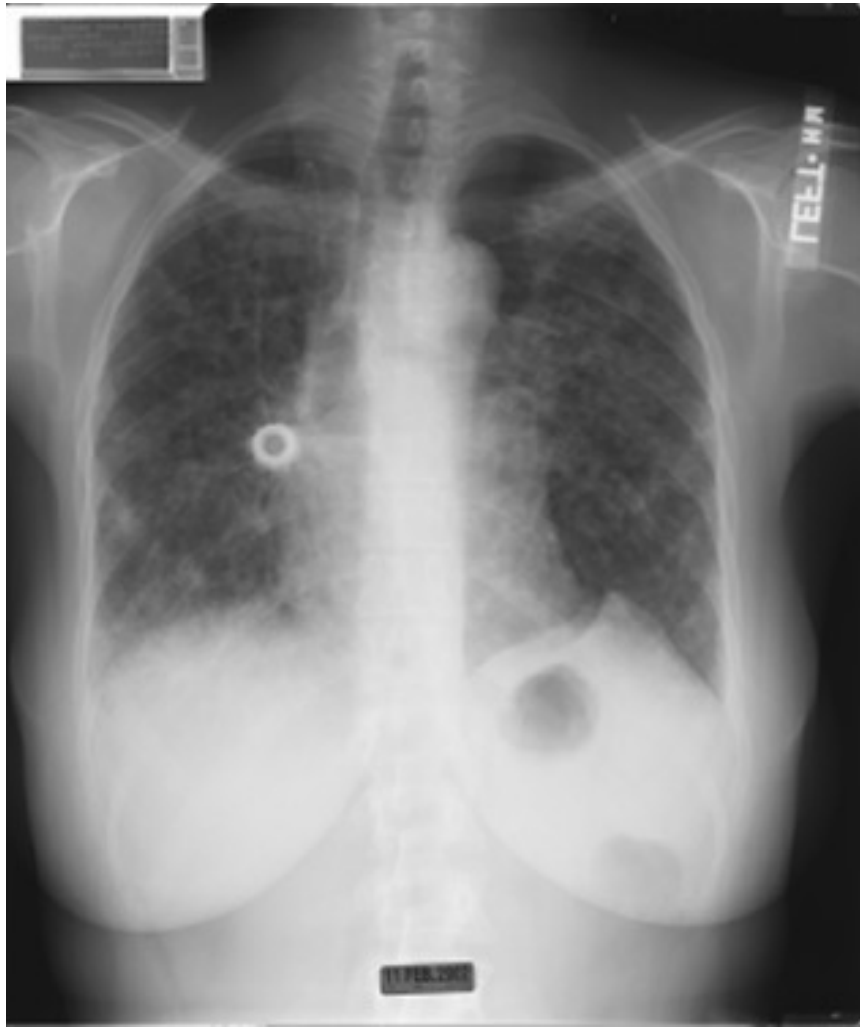
Future Directions

Getting to know the enemy well

Ramaswamy Govindan M.D.
Alvin J Siteman Cancer Center
Washington University School of Medicine
St. Louis



6 FEB 2002

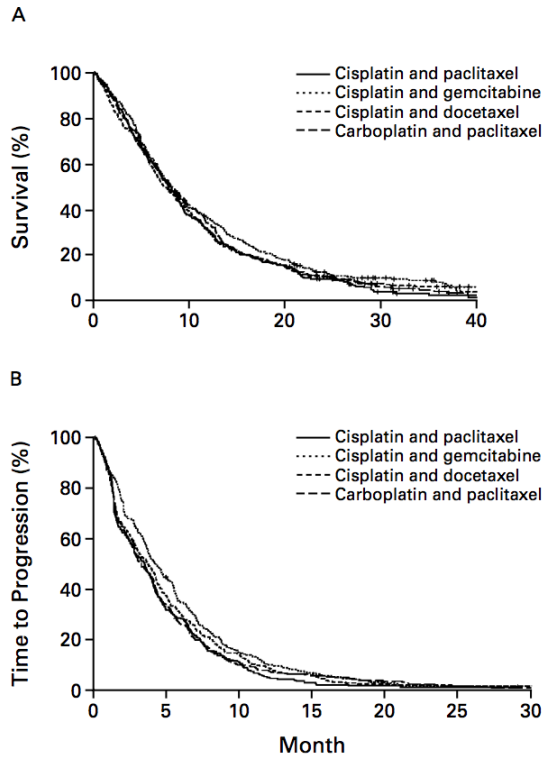


11 FEB 2002

The New England Journal of Medicine

COMPARISON OF FOUR CHEMOTHERAPY REGIMENS FOR ADVANCED NON–SMALL-CELL LUNG CANCER

JOAN H. SCHILLER, M.D., DAVID HARRINGTON, PH.D., CHANDRA P. BELANI, M.D., COREY LANGER, M.D., ALAN SANDLER, M.D., JAMES KROOK, M.D., JUNMING ZHU, PH.D., AND DAVID H. JOHNSON, M.D., FOR THE EASTERN COOPERATIVE ONCOLOGY GROUP



2002

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 20, 2004 VOL. 350 NO. 21

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

MEMORIAL SLOAN-KETTERING CANCER CENTER · ESTABLISHED 1884 ·

SITEMAN CANCER CENTER

BARNES-JEWISH Hospital at BJC HealthCare | Washington University in St. Louis SCHOOL OF MEDICINE

EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy

J. Guillermo Paez,[1,2*] Pasi A. Jänne,[1,2*] Jeffrey C. Lee,[1,3*] Sean Tracy,[1] Heidi Greulich,[1,2] Stacey Gabriel,[4] Paula Herman,[1] Frederic J. Kaye,[5] Neal Lindeman,[6] Titus J. Boggon,[1,3] Katsuhiko Naoki,[1] Hidefumi Sasaki,[7] Yoshitaka Fujii,[7] Michael J. Eck,[1,3] William R. Sellers,[1,2,4†] Bruce E. Johnson,[1,2†] Matthew Meyerson[1,3,4†]

Receptor tyrosine kinase genes were sequenced in non–small cell lung cancer (NSCLC) and matched normal tissue. Somatic mutations of the epidermal growth factor receptor gene *EGFR* were found in 15 of 58 unselected tumors from Japan and 1 of 61 from the United States. Treatment with the EGFR kinase inhibitor gefitinib (Iressa) causes tumor regression in some patients with NSCLC, more frequently in Japan. *EGFR* mutations were found in additional lung cancer samples from U.S. patients who responded to gefitinib therapy and in a lung adenocarcinoma cell line that was hypersensitive to growth inhibition by gefitinib, but not in gefitinib-insensitive tumors or cell lines. These results suggest that *EGFR* mutations may predict sensitivity to gefitinib.

Protein kinase activation by somatic mutation or chromosomal alteration is a common mechanism of tumorigenesis (*1*). Inhi- bition of activated protein kinases th the use of targeted small molecule dru antibody-based strategies has emerg

EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib

William Pao*†‡, Vincent Miller†§, Maureen Zakowski¶, Jennifer Doherty*, Katerina Politi*, Inderpal Sarkaria‖, Bhuvanesh Singh‖, Robert Heelan**, Valerie Rusch‖, Lucinda Fulton††, Elaine Mardis††, Doris Kupfer††, Richard Wilson††, Mark Kris†§, and Harold Varmus*

*Program in Cancer Biology and Genetics and Departments of †Medicine, §Surgery, ¶Pathology, and **Radiology, Memorial Sloan–Kettering Cancer Center, 1275 York Avenue, New York, NY 10021; and ††Genome Sequencing Center, Washington University School of Medicine, 4444 Forest Park Boulevard, St. Louis, MO 63108

Contributed by Harold Varmus, July 19, 2004

Somatic mutations in the tyrosine kinase (TK) domain of the epidermal growth factor receptor (EGFR) gene are reportedly associated with sensitivity of lung cancers to gefitinib (Iressa), kinase inhibitor. In-frame deletions occur in exon 19, whereas point mutations occur frequently in codon 858 (exon 21). We found from sequencing the *EGFR* TK domain that 7 of 10 gefitinib-sensitive tumors had similar types of alterations; no mutations were found in eight gefitinib-refractory tumors ($P = 0.004$). Five of seven tumors sensitive to erlotinib (Tarceva), a related kinase inhibitor for which the clinically relevant target is undocumented, had analogous somatic mutations, as opposed to none of 10 erlotinib-refractory tumors ($P = 0.003$). Because most mutation-positive tumors were adenocarcinomas from patients who smoked <100 cigarettes in a lifetime ("never smokers"), we screened *EGFR* exons 2–28 in 15 adenocarcinomas resected from untreated never smokers. Seven tumors had TK domain mutations, in contrast to 4 of 81 non-small cell lung cancers resected from untreated former or current smokers ($P = 0.0001$). Immunoblotting of lysates from cells transiently transfected with various *EGFR* constructs demonstrated that, compared to wild-type protein, an exon 19 deletion mutant induced diminished levels of phosphotyrosine, whereas the phosphorylation at tyrosine 1092 of an exon 21 point mutant was inhibited at 10-fold lower concentrations of drug. Collectively, these data show that adenocarcinomas from never smokers comprise a distinct subset of lung cancers, frequently containing mutations within the TK domain of *EGFR* that are associated with gefitinib and erlotinib sensitivity.

Tyrosine kinases (TKs) regulate signaling pathways that control critical cellular activities (1). When overexpressed or activated by mutations, TKs can contribute to the development of cancers. If tumor cells depend on a mutant TK for survival, as illustrated by certain mouse models of cancer (2, 3), the mutated enzyme can fortuitously serve as an Achilles' heel for cancer therapy (4). Human examples include BCR-ABL-dependent chronic myelogenous and acute lymphoblastic leukemias (5), *KIT*- and *PDGFRA*-dependent gastrointestinal stromal tumors (6), and *PDGFRA*-dependent hypereosinophilic syndrome (7). In each disease, activated oncogenes encode TKs; inhibition by imatinib mesylate (Gleevec) leads to rapid and durable clinical responses.

EGFR is a TK of the ErbB family that is the presumptive target (e.g., ref. 13), similar to those seen in the murine and human examples noted above. Assuming that the drug did affect a kinase, these kinds of responses suggested that at least some lung tumors depended on a specific genetic lesion for tumor survival. However, when gefitinib was approved as second- or third-line treatment for patients with non-small cell lung cancer (NSCLC), the clinically relevant target(s) of the drug in human tumors were unknown. Analyses of both preclinical xenograft models (14) and specimens from gefitinib-sensitive and -refractory tumors (15) did not reveal any obvious relationship between EGFR expression levels and tumor sensitivity. Retrospective epidemiologic analyses suggested that gefitinib is more likely to be effective in Japanese patients (11), individuals with adenocarcinomas of the bronchioloalveolar carcinoma (BAC) subtype, and "never smokers" (16).

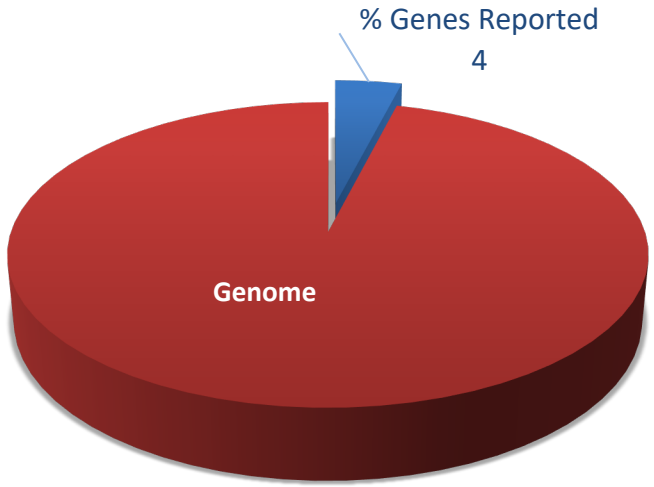
Recently, two groups have shown that mutations in the TK domain of *EGFR* are associated with sensitivity of NSCLC to gefitinib (17, 18). In total, deletions or amino acid substitutions in exons 18, 19, and 21 of *EGFR* were found in 13 of 14 tumors sensitive to the drug, but in none of 11 tumors with no response. Lynch and colleagues (17) found mutations in another 2 of 25 primary NSCLCs, and Paez *et al.* (18) found *EGFR* mutations in 16 of 119 unselected tumors, with a striking predominance of mutations found in 15 of 58 (28%) specimens from Japan as compared to 1 of 61 from the U.S. (2%).

To confirm and extend data on gefitinib sensitivity, we examined the status of the TK domain of *EGFR* in tumors that were sensitive and refractory to the drug. To determine whether a related but distinct TKI, erlotinib (Fig. 5), "targets" a similar subset of NSCLCs, we also profiled erlotinib-sensitive and -refractory tumors. The clinically relevant target of erlotinib has not yet been documented. To examine whether smoking history is predictive of the likelihood of *EGFR* mutations, we determined the incidence of *EGFR* TK domain mutations in 96 resected NSCLCs from never smokers, as well as former and current smokers who had never received a TKI. Finally, in an effort to explain the selective advantage of cells with mutant EGFR and the drug sensitivity conferred upon mutant-bearing tumors, we began to characterize some biochemical properties of EGFR mutants *in vitro*.

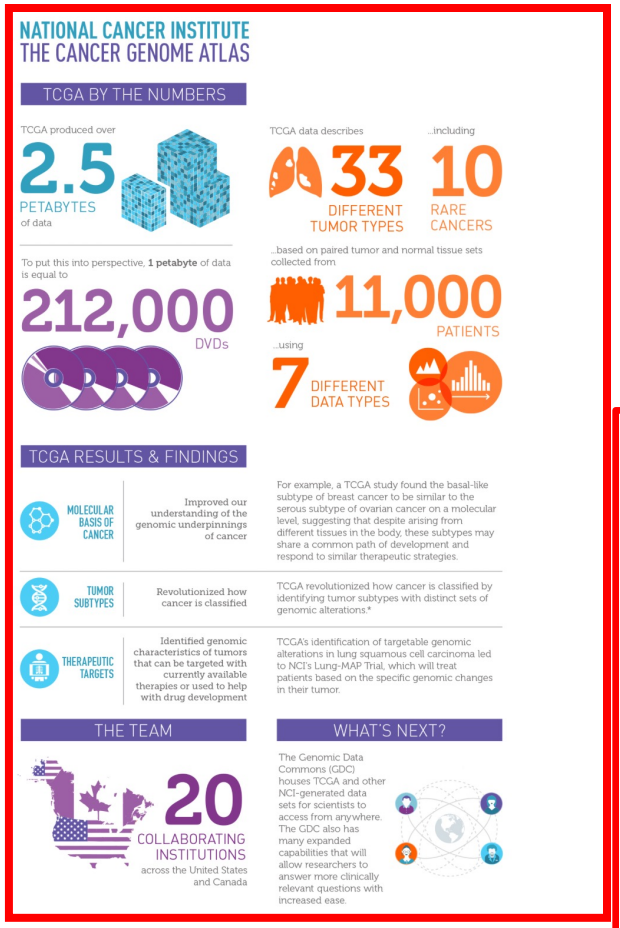
2004

Gene Mutations in Lung Cancer

As reported in COSMIC



2011



Study	Histology	WES	WGS	RNA-seq	Comments
TCGA LUSC 2012	LUAD	178	19	178	
Imielinski et al. 2012	LUAD	183	23		
Govindan et al. 2012	LUAD and large cell		17	17	
Rudin et al. 2012	SCLC	36	1	24	
Peifer et al. 2012	SCLC	27	2	15	
Park et al. 2013	LUSC	104		26	
TCGA LUAD 2014	LUSC	230	36	230	
Zhang et al. 2014	LUAD	11			Multi-regional
DeBruin et al. 2014	LUAD and LUSC	7	2		Multi-regional
George et al. 2014	SCLC		110	71	
Brastianos et al. 2015	NSCLC	38			Trios with brain metastases
*TCGA Pan-Lung 2016**	LUAD	274			
*TCGA Pan-Lung 2016**	LUSC	308			
TRACERx 2017	LUAD and LUSC	100			Multi-regional

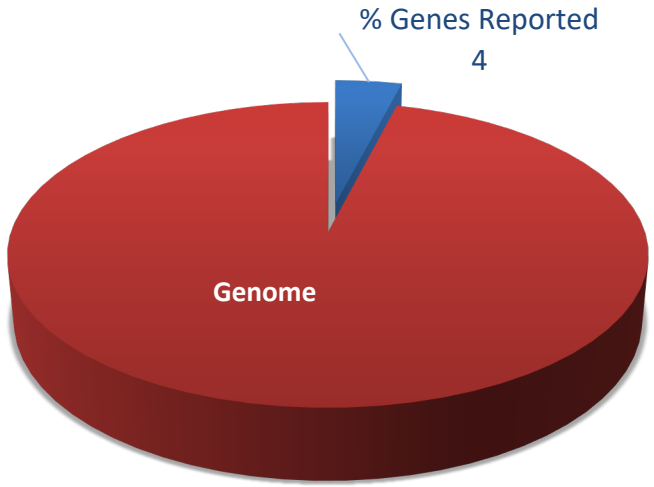
NSCLC	1433	97	451
SCLC	63	111	95

* Additional samples

2018

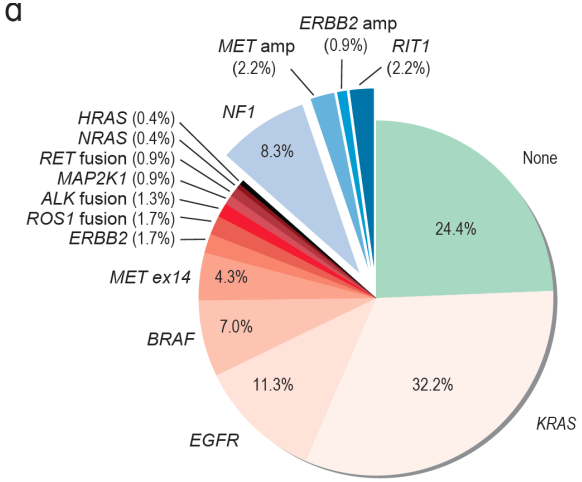
Gene Mutations in Lung Cancer

As reported in COSMIC



2011

a



TCGA adenocarcinoma, Nature 2014

Study	Histology	WES	WGS	RNA-seq	Comments
TCGA LUSC 2012	LUAD	178	19	178	
Imielinski et al. 2012	LUAD	183	23		
Govindan et al. 2012	LUAD and large cell		17	17	
Rudin et al. 2012	SCLC	36	1	24	
Peifer et al. 2012	SCLC	27	2	15	
Park et al. 2013	LUSC	104		26	
TCGA LUAD 2014	LUSC	230	36	230	
Zhang et al. 2014	LUAD	11			Multi-regional
DeBruin et al. 2014	LUAD and LUSC	7	2		Multi-regional
George et al. 2014	SCLC		110	71	
Brastianos et al. 2015	NSCLC	38			Trios with brain metastases
*TCGA Pan-Lung 2016**	LUAD	274			
*TCGA Pan-Lung 2016**	LUSC	308			
TRACERx 2017	LUAD and LUSC	100			Multi-regional

NSCLC	1433	97	451
SCLC	63	111	95

* Additional samples

2018

NATIONAL CANCER INSTITUTE
THE CANCER GENOME ATLAS

TCGA BY THE NUMBERS

TCGA produced over

2.5 PETABYTES of data

To put this into perspective, **1 petabyte** of data is equal to

212,000 DVDs

TCGA data describes

33 DIFFERENT TUMOR TYPES

...including

10 RARE CANCERS

...based on paired tumor and normal tissue sets collected from

11,000 PATIENTS

...using

7 DIFFERENT DATA TYPES

TCGA RESULTS & FINDINGS

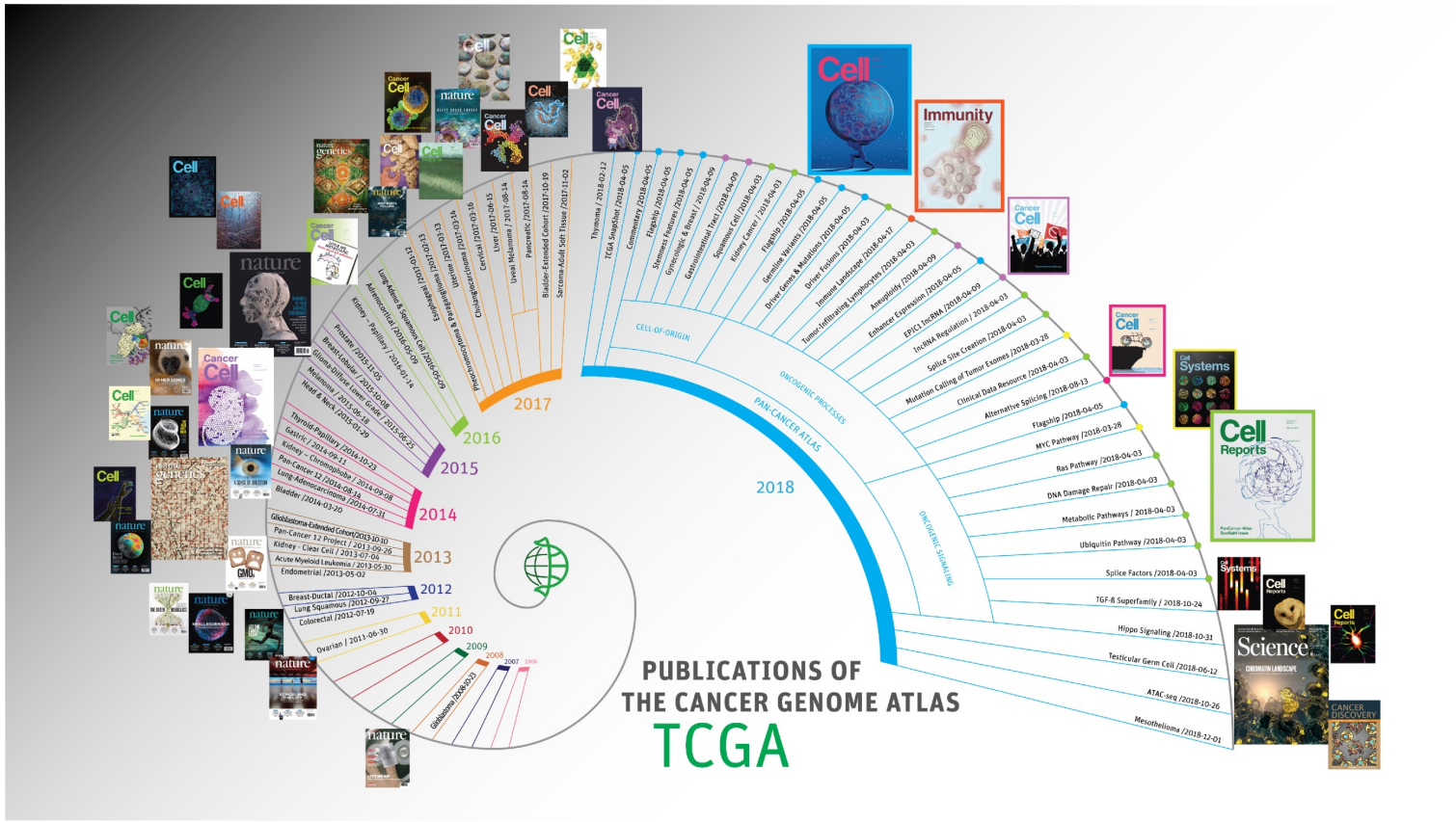
MOLECULAR BASIS OF CANCER	Improved our understanding of the genomic underpinnings of cancer	For example, a TCGA study found the basal-like subtype of breast cancer to be similar to the serous subtype of ovarian cancer on a molecular level, suggesting that despite arising from different tissues in the body, these subtypes may share a common path of development and respond to similar therapeutic strategies.
TUMOR SUBTYPES	Revolutionized how cancer is classified	TCGA revolutionized how cancer is classified by identifying tumor subtypes with distinct sets of genomic alterations.*
THERAPEUTIC TARGETS	Identified genomic characteristics of tumors that can be targeted with currently available therapies or used to help with drug development	TCGA's identification of targetable genomic alterations in lung squamous cell carcinoma led to NCI's Lung-MAP Trial, which will treat patients based on the specific genomic changes in their tumor.

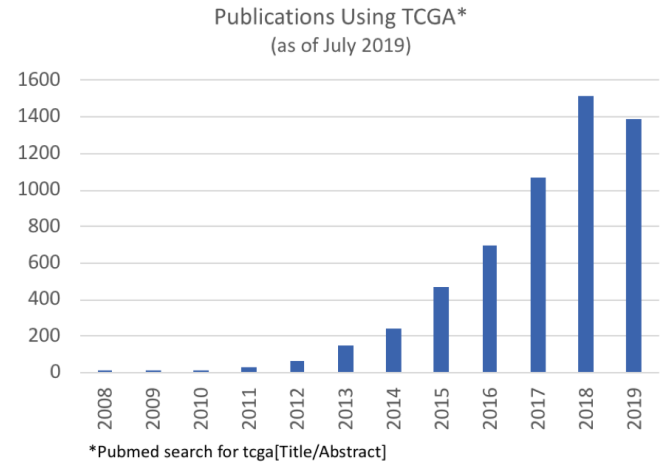
THE TEAM

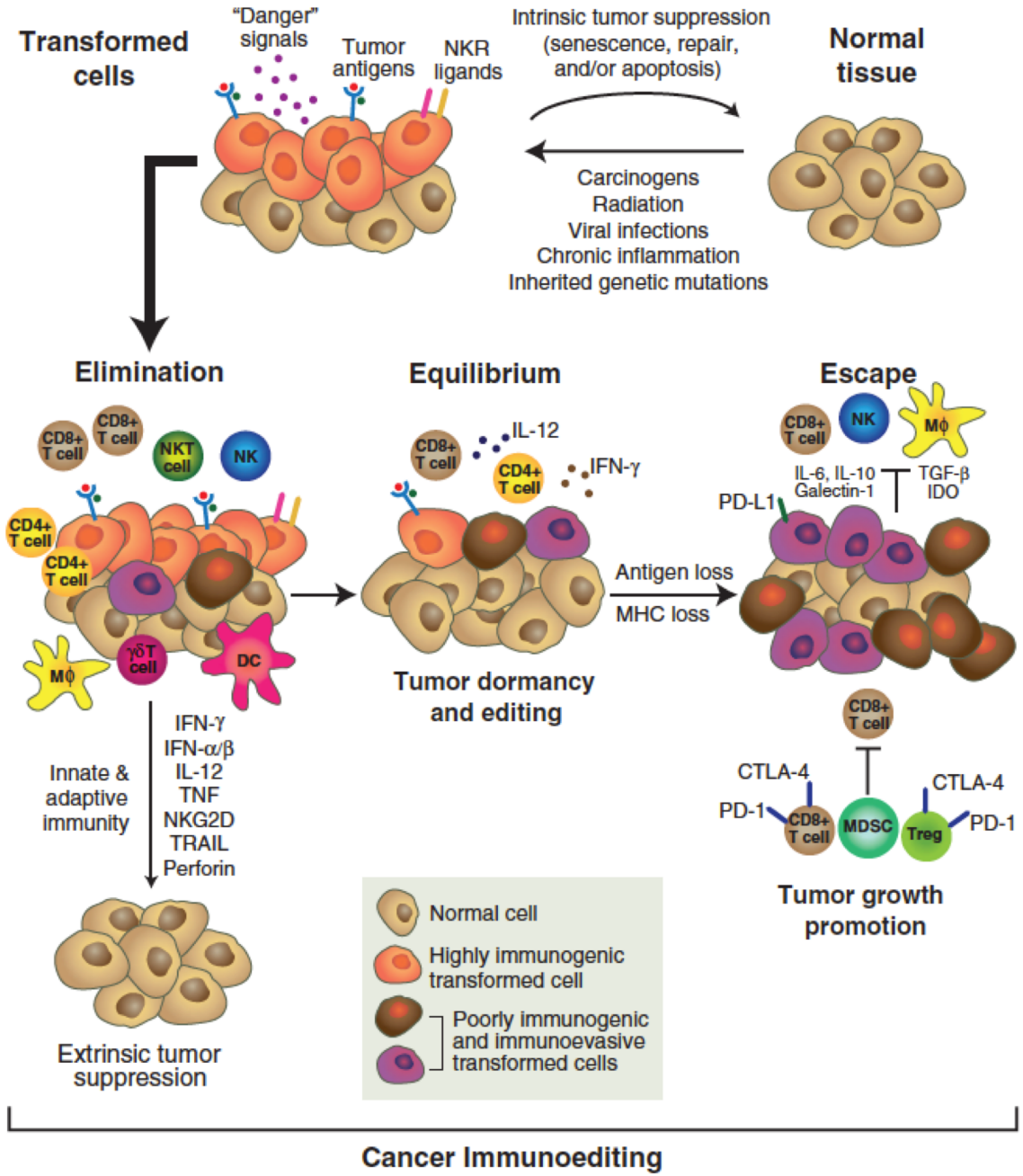
20 COLLABORATING INSTITUTIONS across the United States and Canada

WHAT'S NEXT?

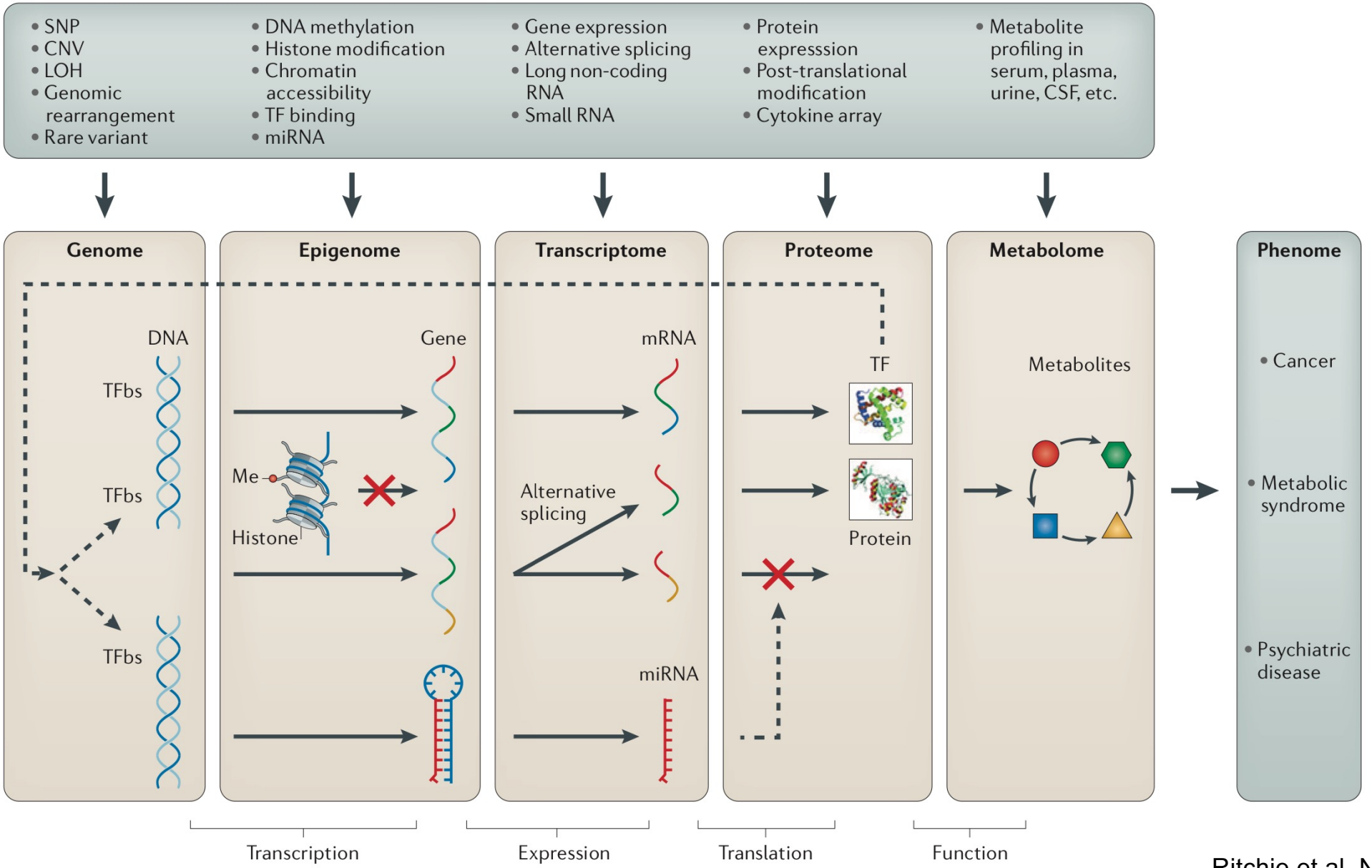
The Genomic Data Commons (GDC) houses TCGA and other NCI-generated data sets for scientists to access from anywhere. The GDC also has many expanded capabilities that will allow researchers to answer more clinically relevant questions with increased ease.



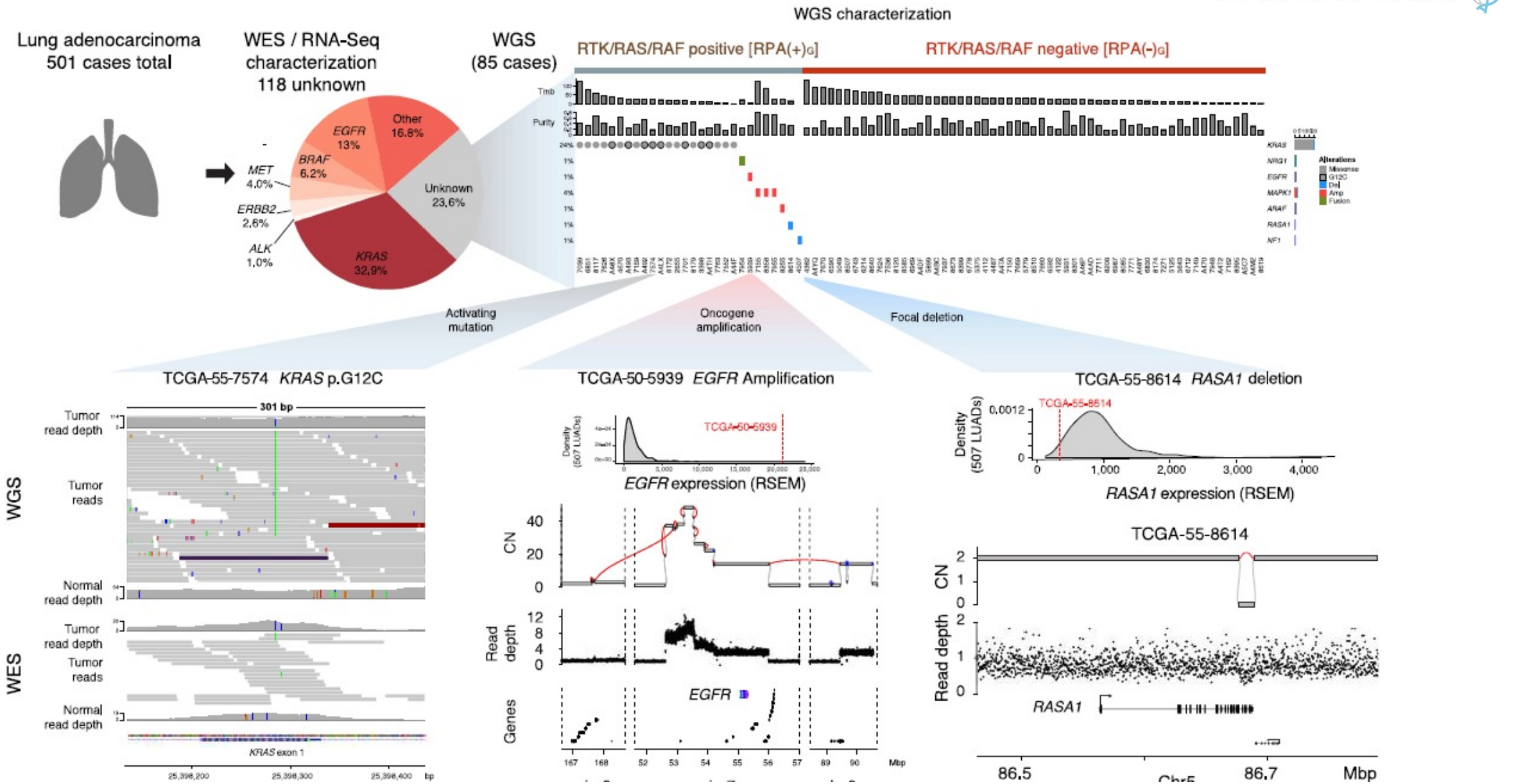




Schreiber, R. D et al, *Science* 2011

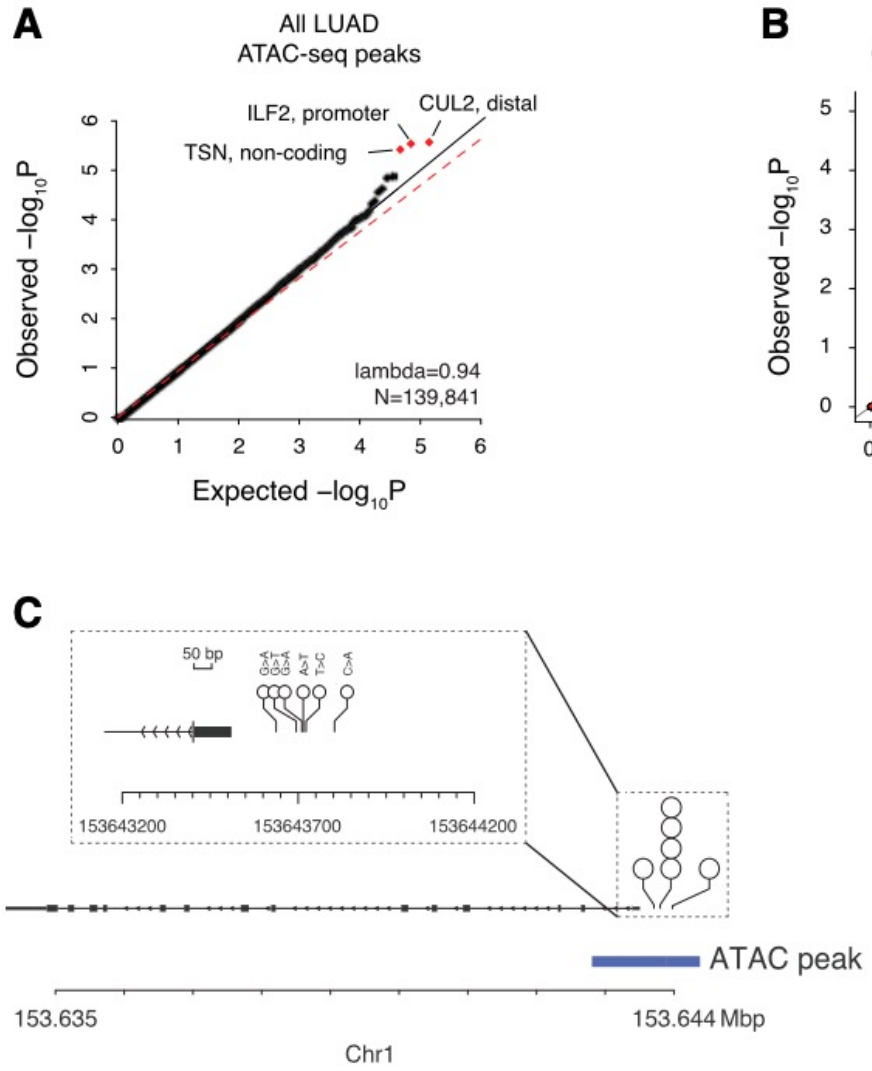


Ritchie et al. Nat Rev Gen, 2015



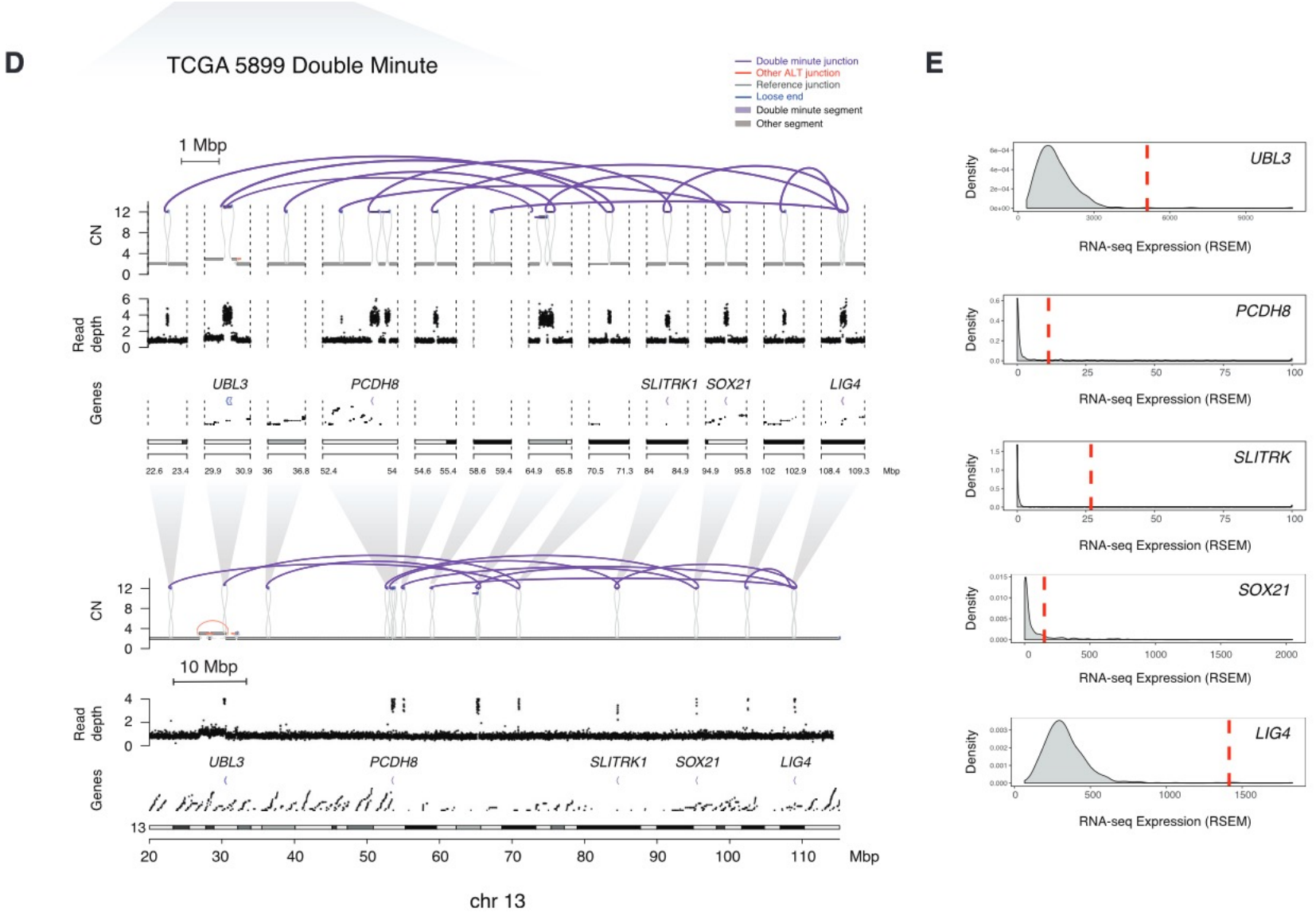
Carrot-Zhang. et al. Cell Reports (in print), 2021

Detecting driver alterations in “oncogene negative” lung adenocarcinoma



Carrot-Zhang. et al. Cell Reports, 2021

Detecting driver alterations in “oncogene negative” lung adenocarcinoma



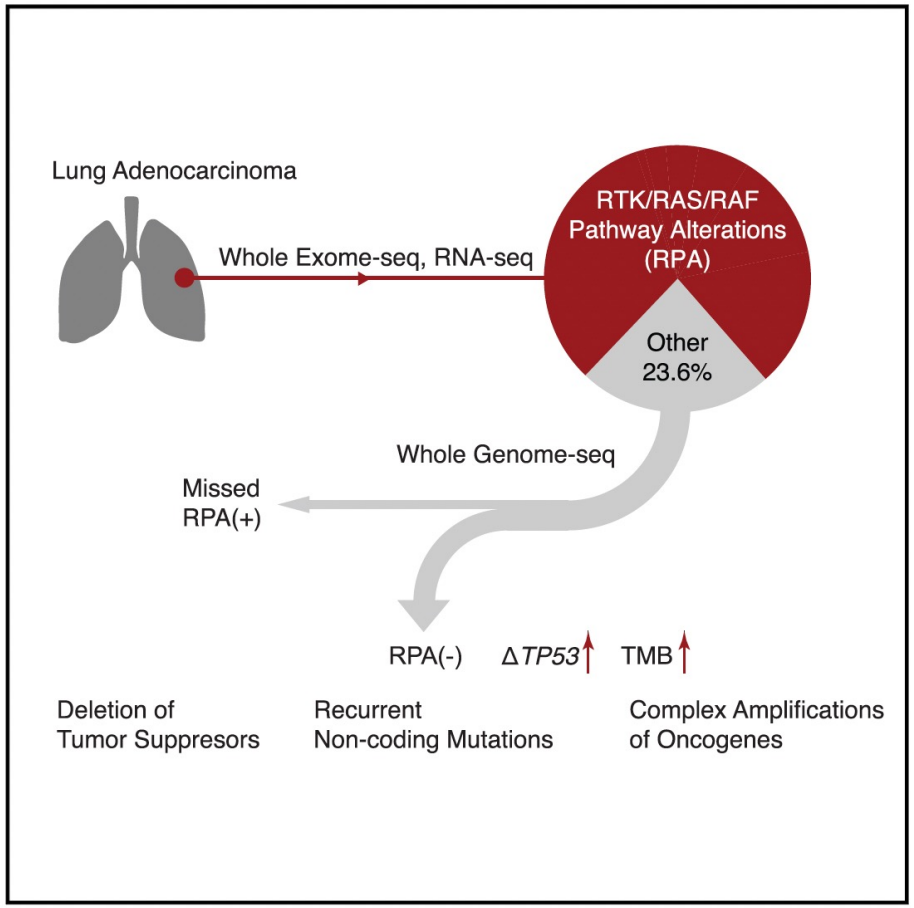
Carrot-Zhang. et al. Cell Reports, 2021

Cell Reports

Article

Whole-genome characterization of lung adenocarcinomas lacking the RTK/RAS/RAF pathway

Detecting driver alterations in “oncogene negative” lung adenocarcinoma



Carrot-Zhang. et al. Cell Reports, 2021

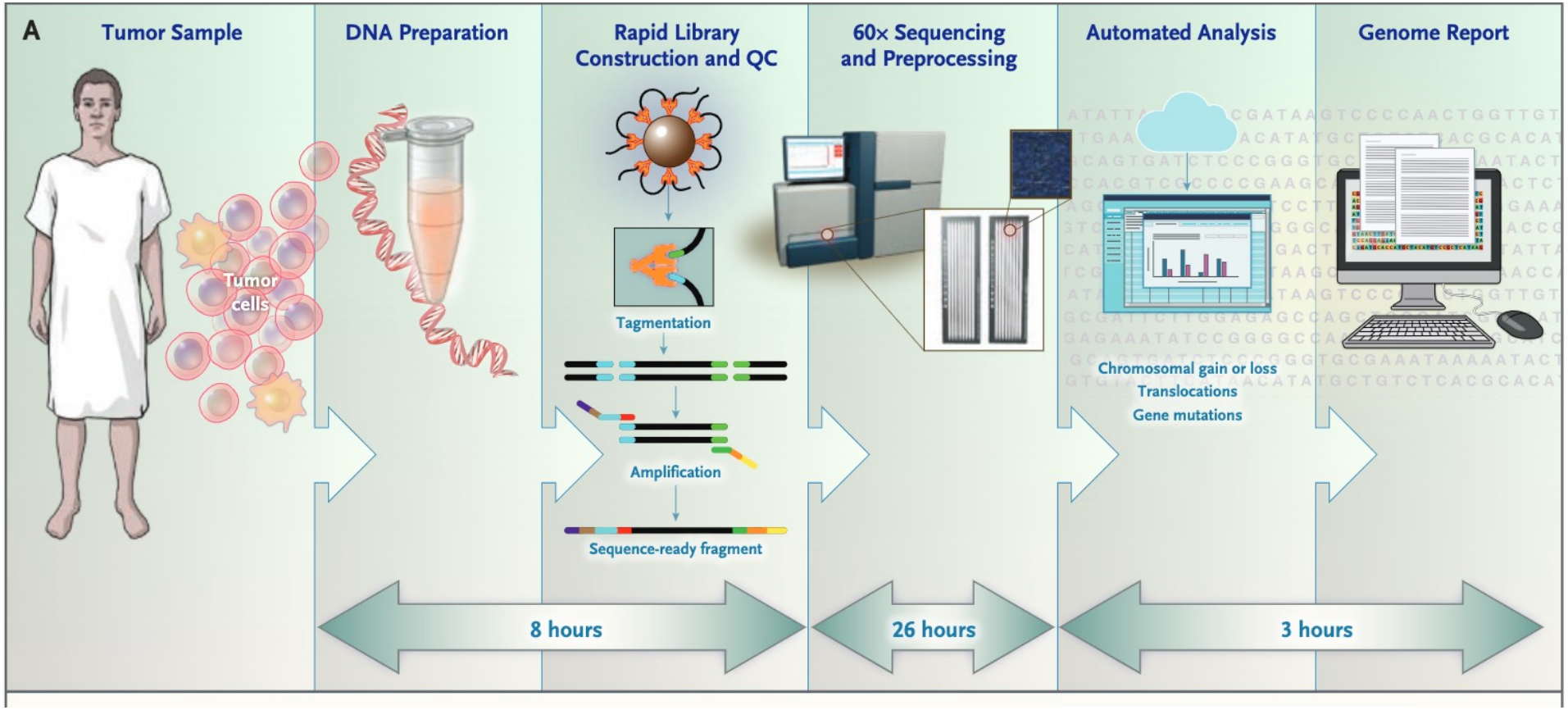
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Genome Sequencing as an Alternative to Cytogenetic Analysis in Myeloid Cancers

Eric J. Duncavage, M.D., Molly C. Schroeder, Ph.D., Michele O'Laughlin, B.S., Roxanne Wilson, B.S., Sandra MacMillan, B.S., Andrew Bohannon, B.S., Scott Kruchowski, B.S., John Garza, B.S., Feiyu Du, M.S., Andrew E.O. Hughes, M.D., Ph.D., Josh Robinson, B.A., Emma Hughes, B.S., Sharon E. Heath, Jack D. Baty, B.A., Julie Neidich, M.D., Matthew J. Christopher, M.D., Ph.D., Meagan A. Jacoby, M.D., Ph.D., Geoffrey L. Uy, M.D., Robert S. Fulton, M.S., Christopher A. Miller, Ph.D., Jacqueline E. Payton, M.D., Ph.D., Daniel C. Link, M.D., Matthew J. Walter, M.D., Peter Westervelt, M.D., Ph.D., John F. DiPersio, M.D., Ph.D., Timothy J. Ley, M.D., and David H. Spencer, M.D., Ph.D.

Harnessing the power of Whole Genome Sequencing

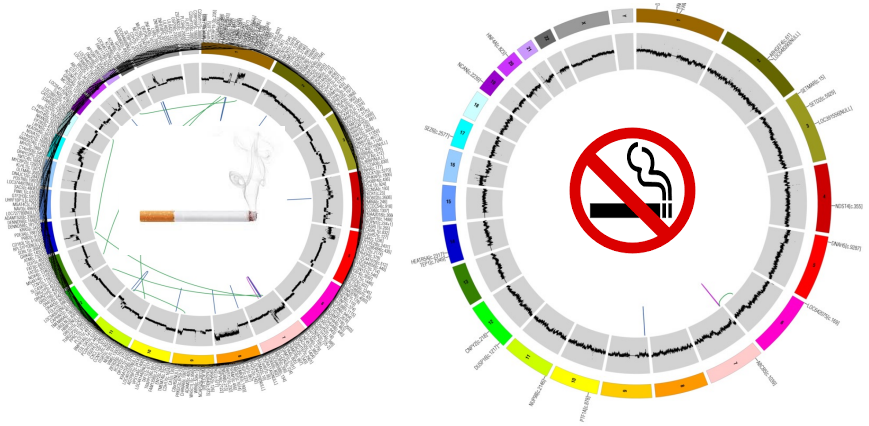


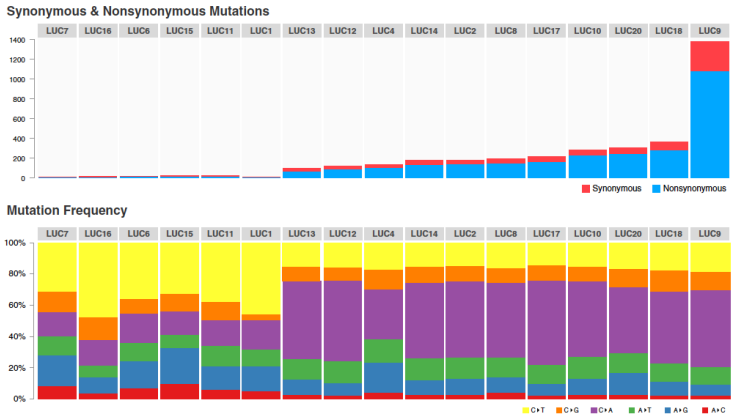
N Engl J Med 2021;384:924-35.

SITEMAN CANCER CENTER

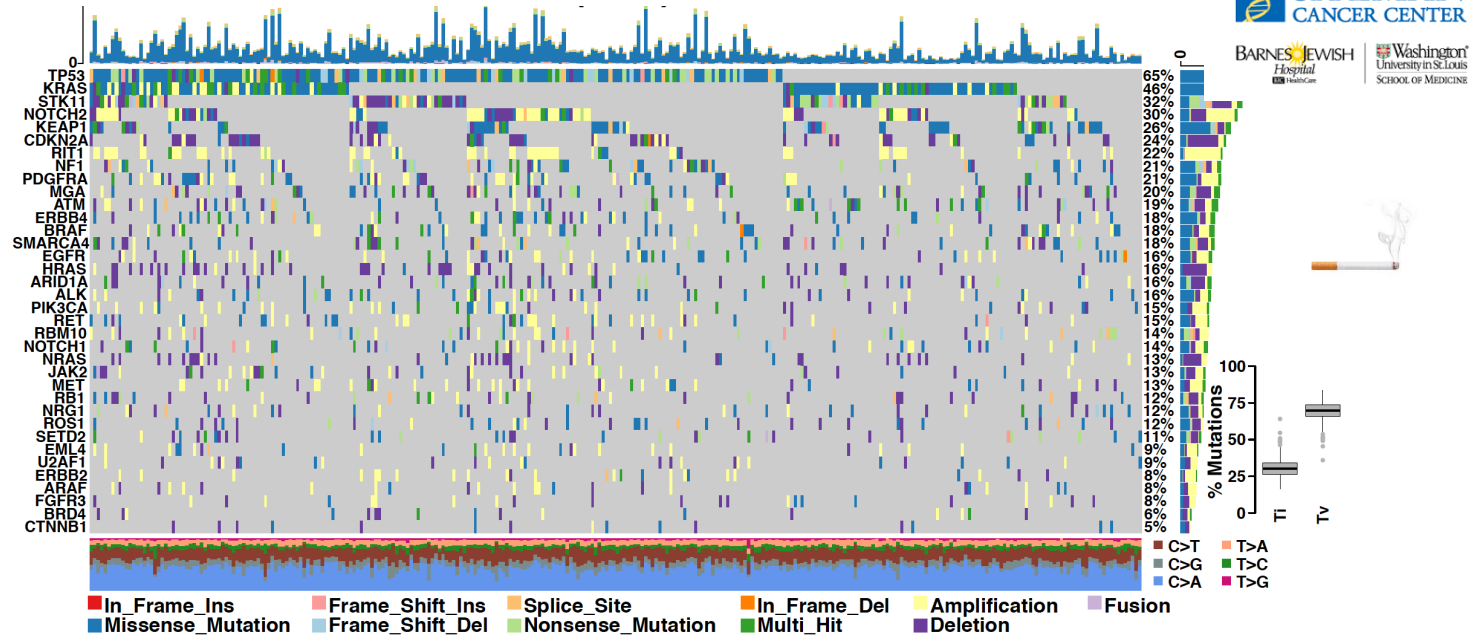
BARNES-JEWISH Hospital BJC HealthCare | Washington University in St. Louis SCHOOL OF MEDICINE

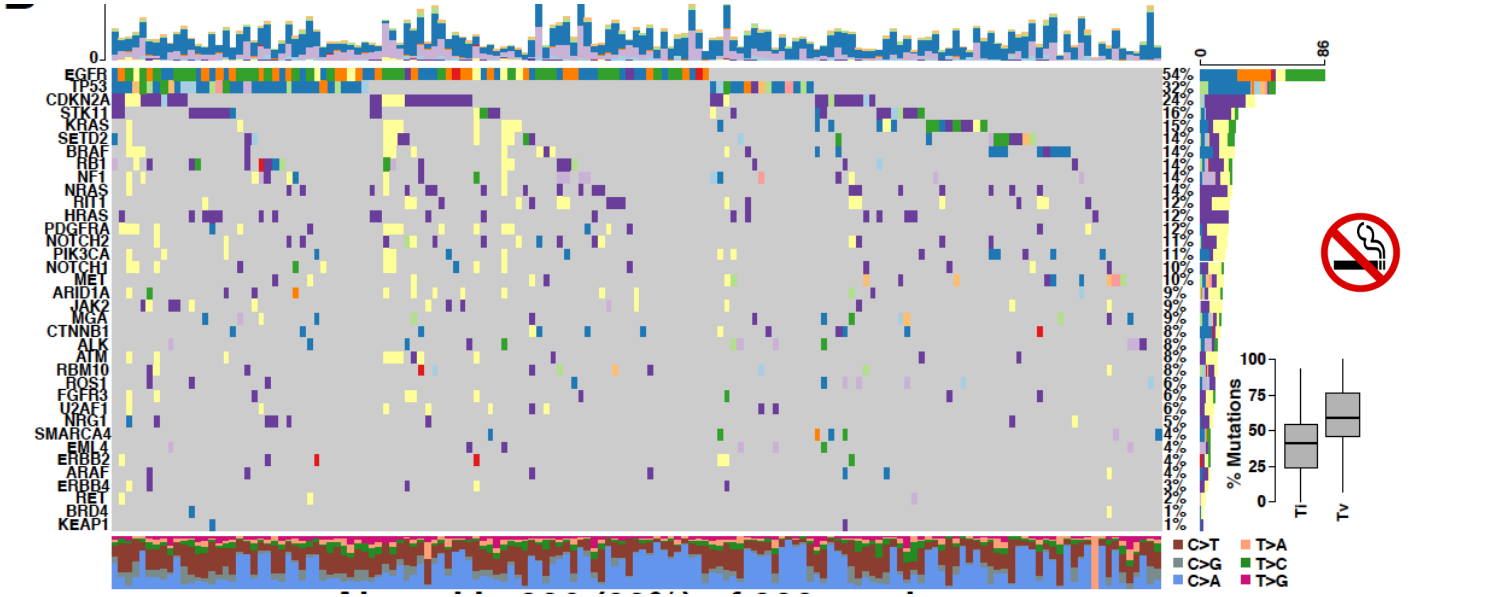
Genomic Landscape of Non-Small Cell Lung Cancer in Smokers and Never-Smokers





Govindan et al .Cell. 2012

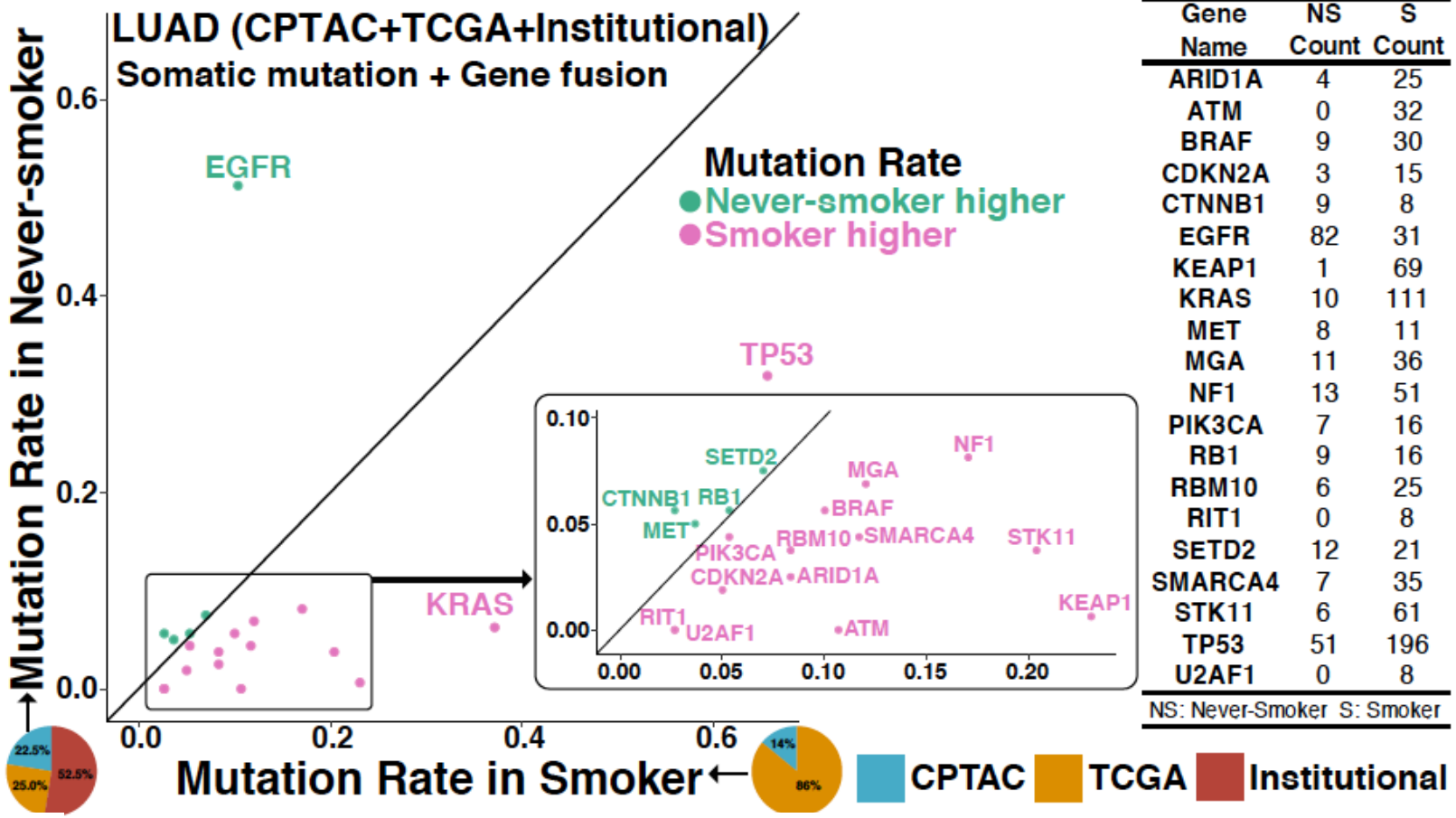




Devarakonda S et al, JCO 2021

Lung adenocarcinoma in never smokers

Somatic alterations



Gene Name	NS Count	S Count
ARID1A	4	25
ATM	0	32
BRAF	9	30
CDKN2A	3	15
CTNNB1	9	8
EGFR	82	31
KEAP1	1	69
KRAS	10	111
MET	8	11
MGA	11	36
NF1	13	51
PIK3CA	7	16
RB1	9	16
RBM10	6	25
RIT1	0	8
SETD2	12	21
SMARCA4	7	35
STK11	6	61
TP53	51	196
U2AF1	0	8

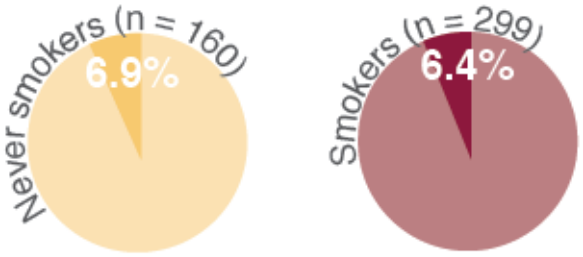
NS: Never-Smoker S: Smoker

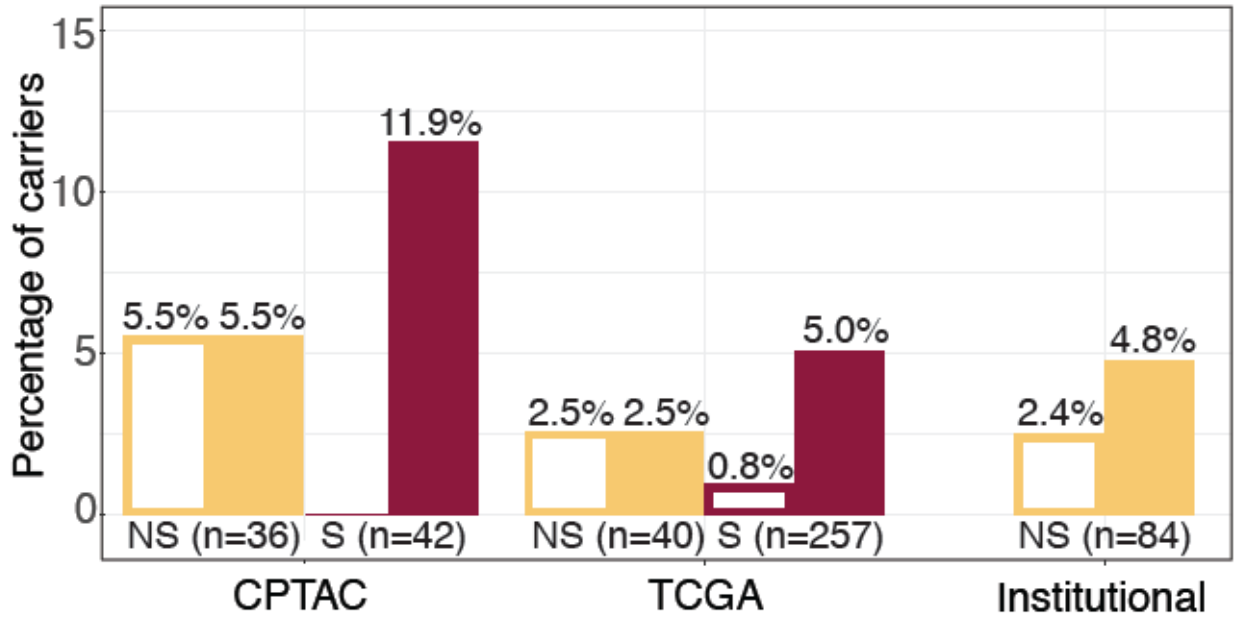
Devarakonda S et al, JCO 2021

Lung adenocarcinoma in never smokers

Germline alterations

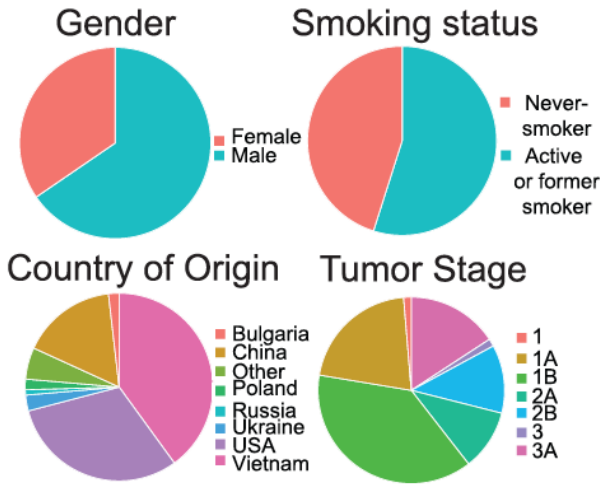
Classification	Variant count		
	CPTAC	TCGA	Institutional
Pathogenic	7	14	4
Likely Pathogenic	2	3	2
Prioritized VUS	5	24	5

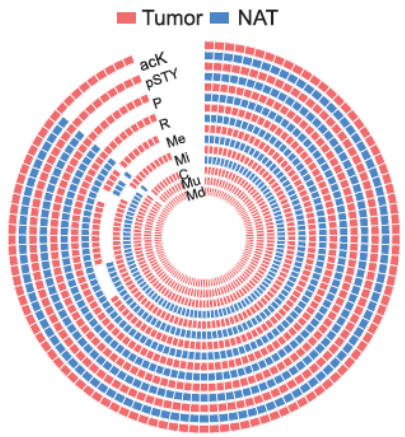




Devarakonda S et al, JCO 2021

Proteogenomic alterations in lung adenocarcinoma

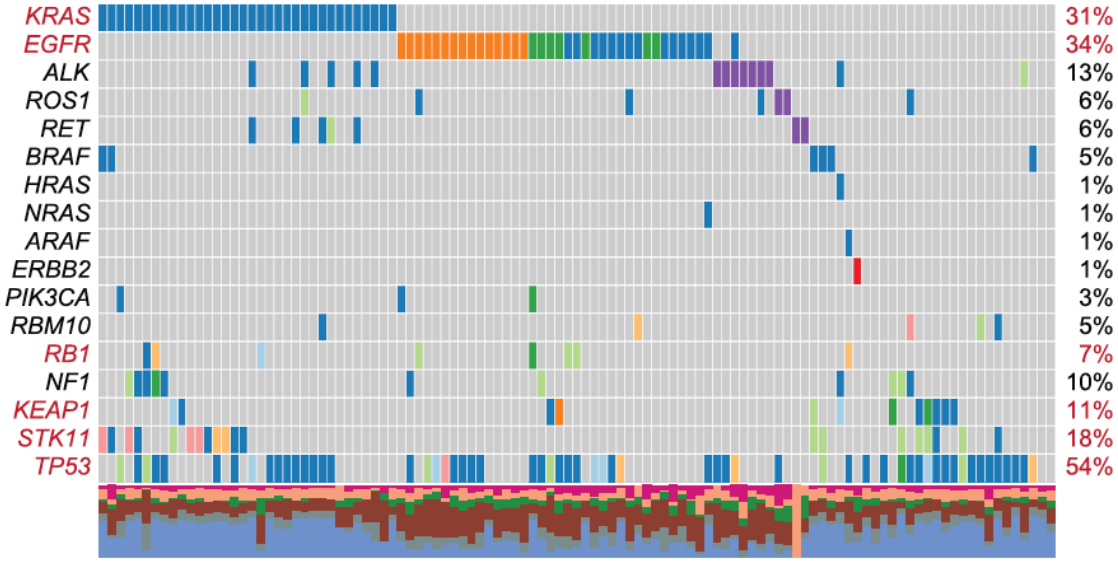


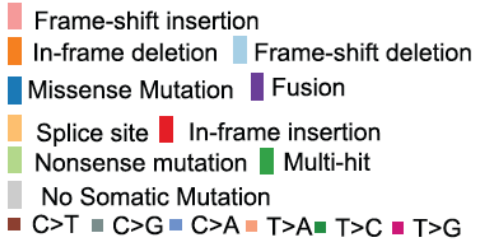


Dataset (T/NAT)

acK (acetylome) 110/101
pSTY (phospho) 110/101
P (proteome) 110/101
R (RNA) 110/101
Me (Methylation) 100/87
Mi (miRNA) 107/100
C (CNA) 109
Mu (Mutation) 109
Md (Metadata) 110

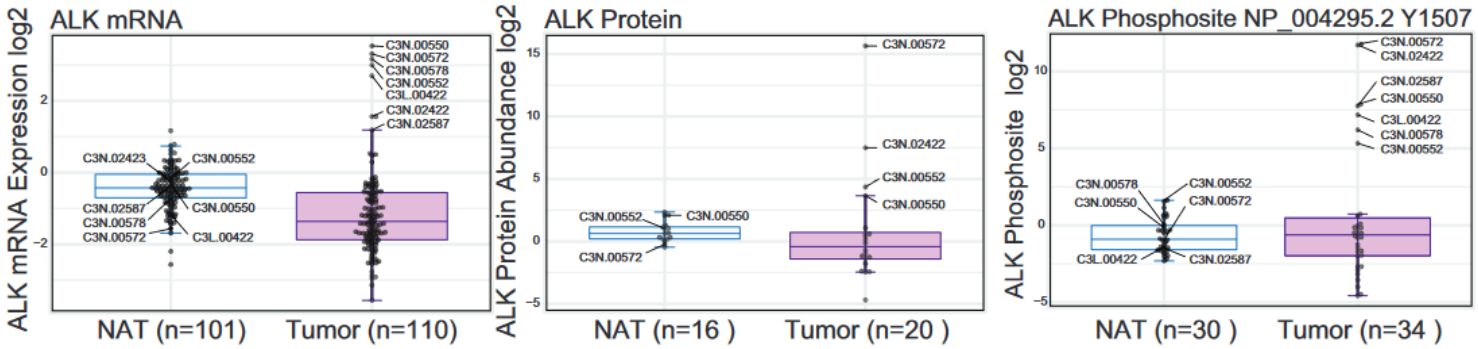
Platform	Data type	Features
Clinical metadata		15
WXS WGS	Germline mutations	16,660
	Somatic mutations	32,250
	CNA	19,267
Methylation array	DNA methylation	16,478
RNA-seq	mRNA	18,099
miRNA-seq	miRNA	2,585
TMT Proteomics	Proteins	10,699
	Phosphorylation	41,188
	Acetylation	6,906

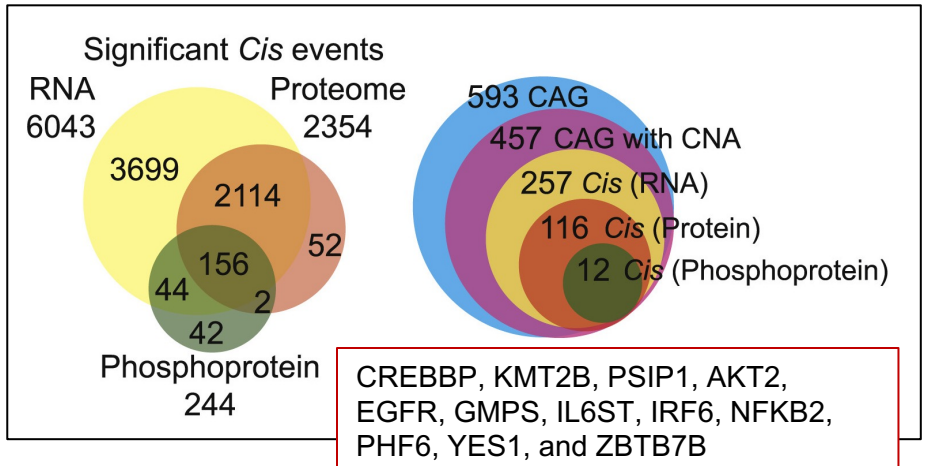


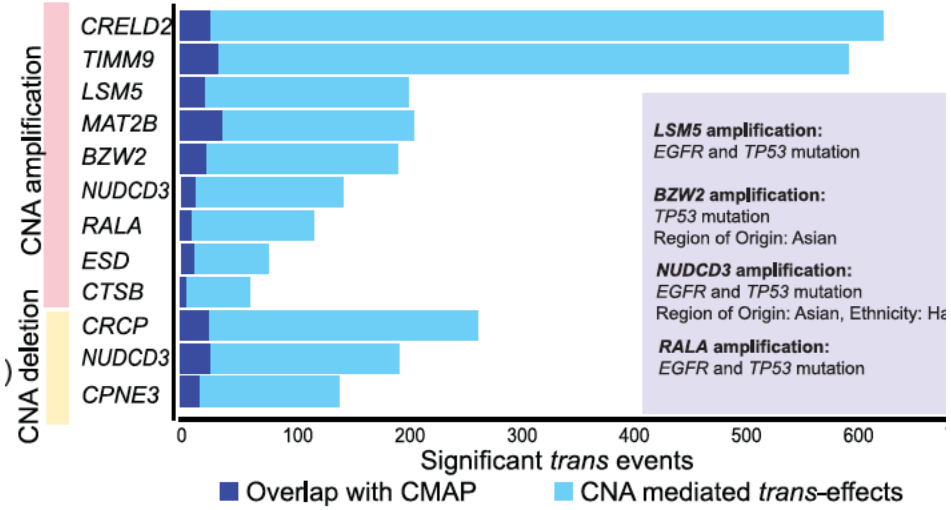


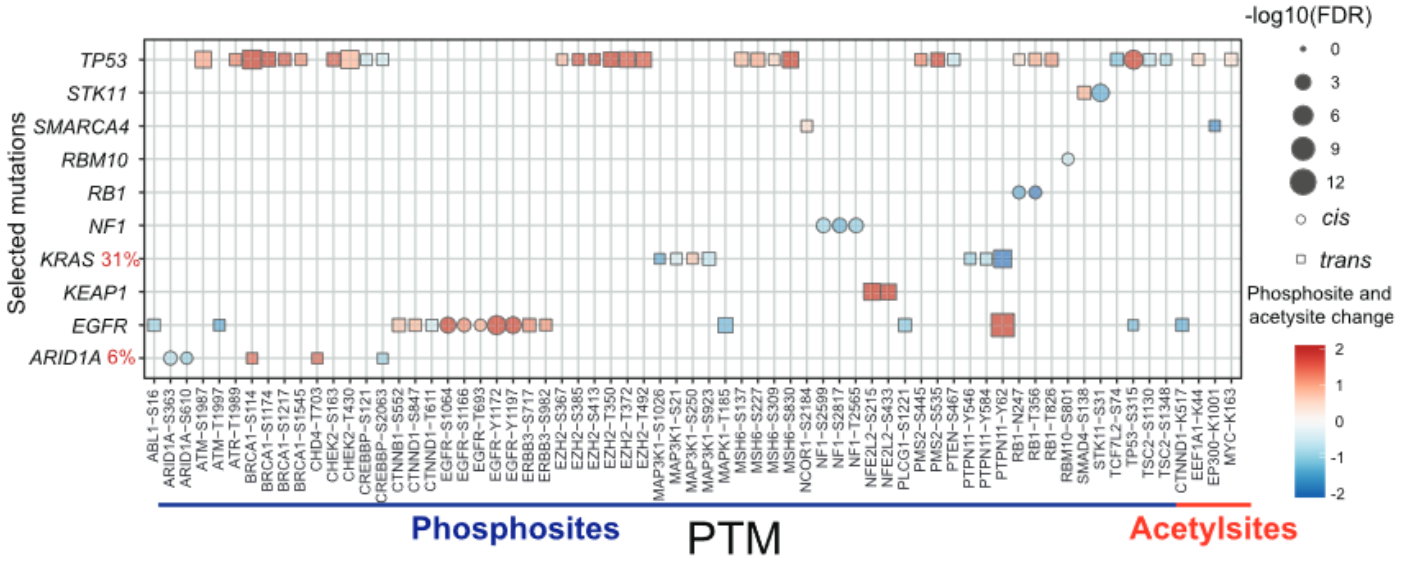
Mike Gillette et al. Cell 2020

Proteogenomic alterations in lung adenocarcinoma



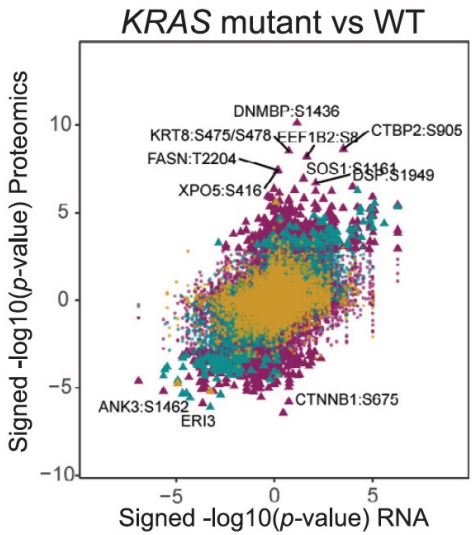


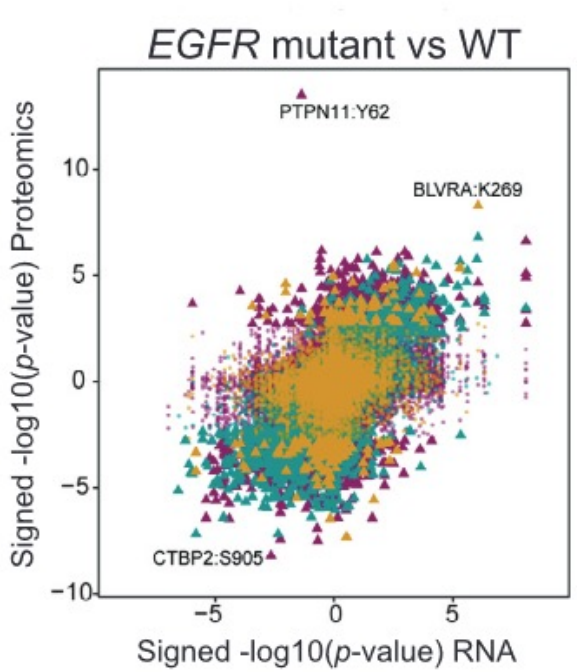


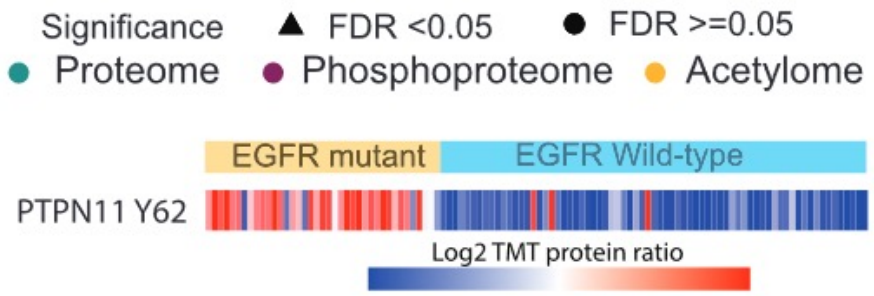


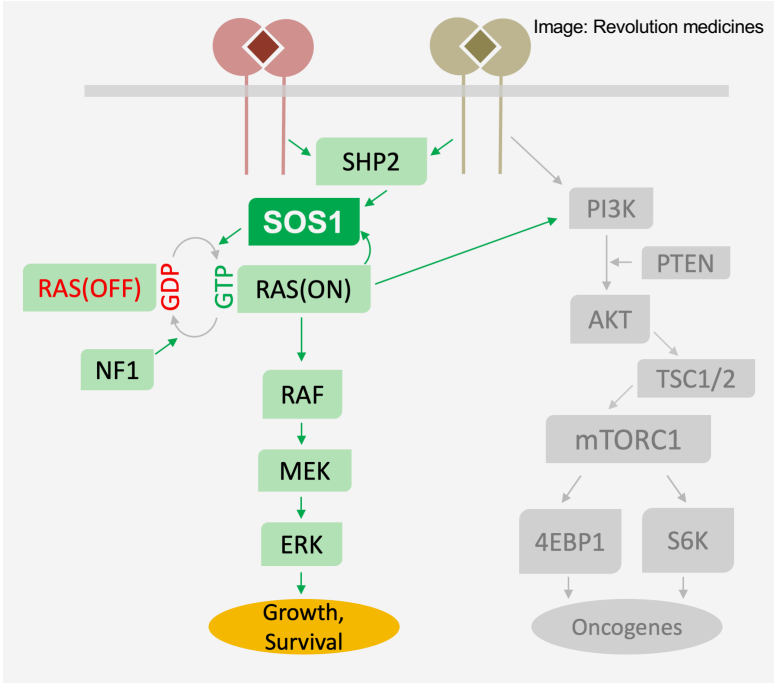
Mike Gillette et al. Cell 2020

Proteogenomic alterations in lung adenocarcinoma





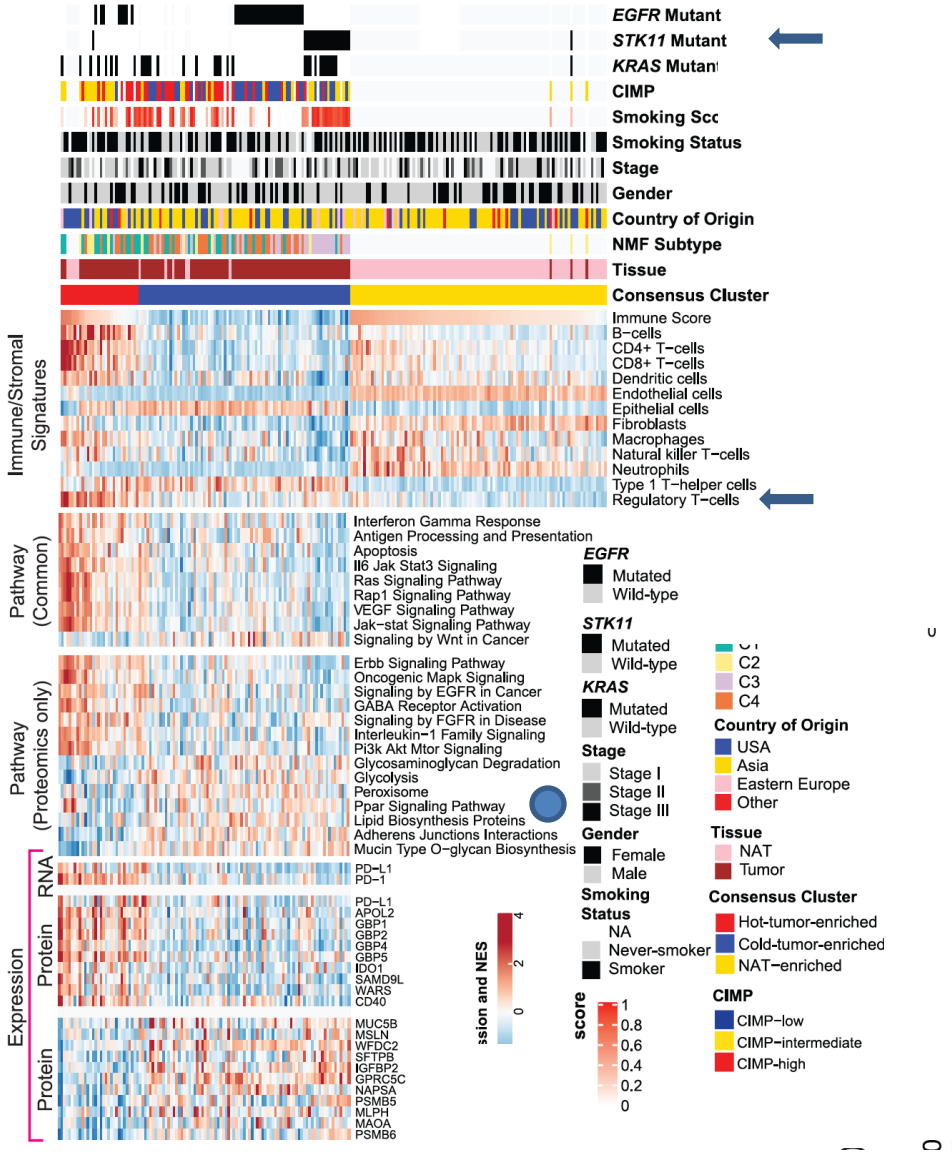




Mike Gillette et al. Cell 2020

Proteogenomic alterations in lung adenocarcinoma

Immune landscape



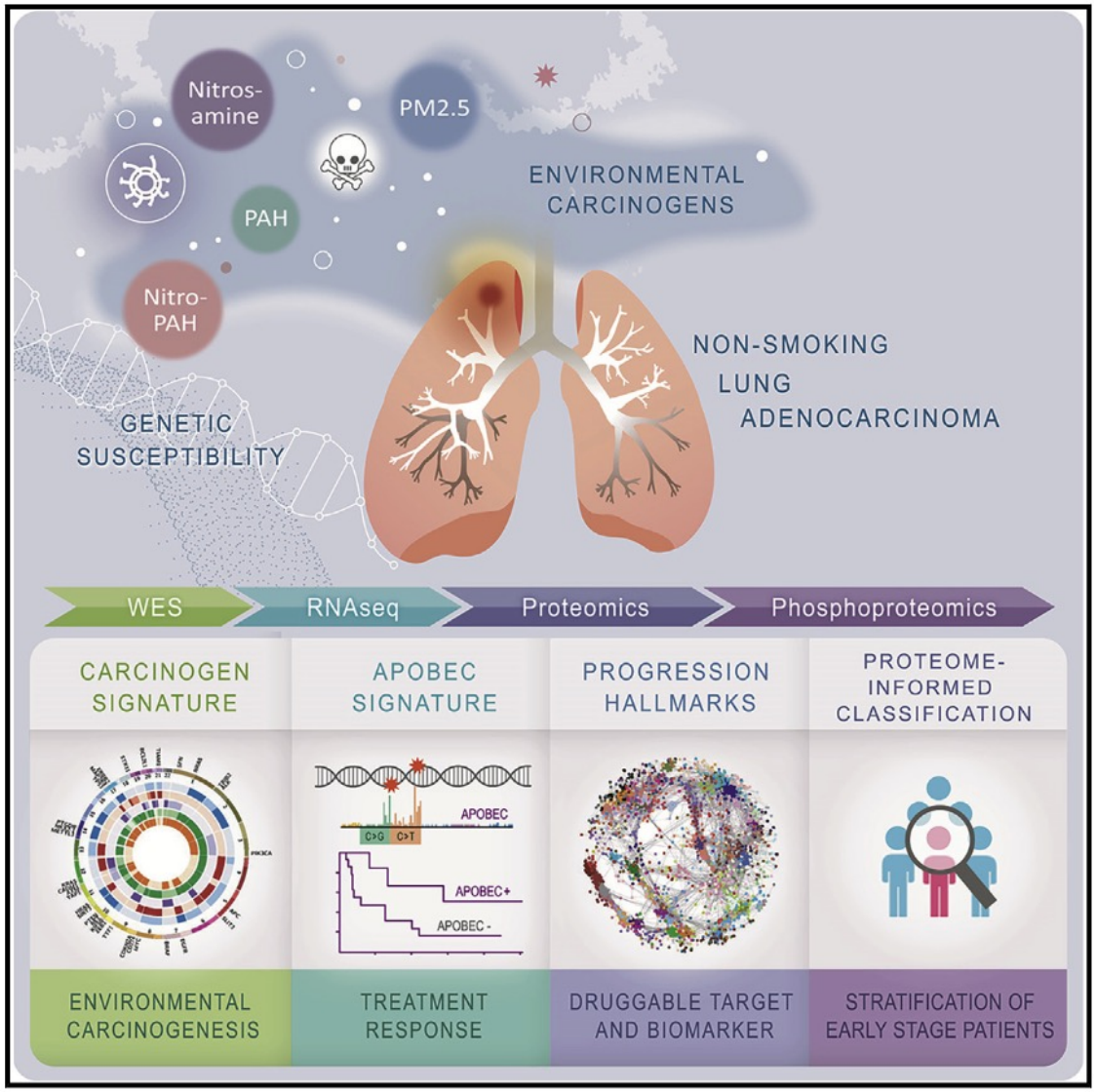
Mike Gillette et al. Cell 2020

Proteogenomic alterations in lung adenocarcinoma

Cell

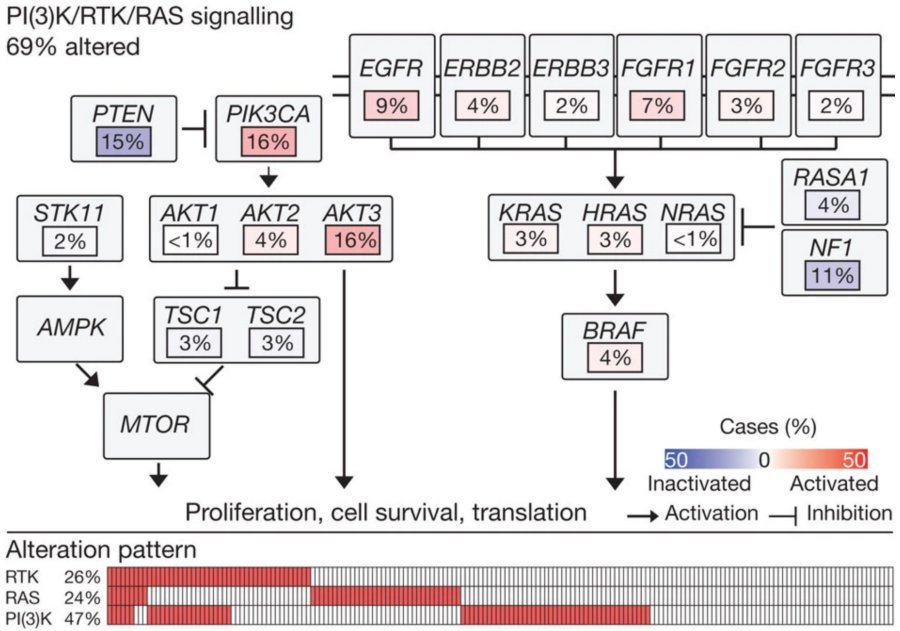
Resource

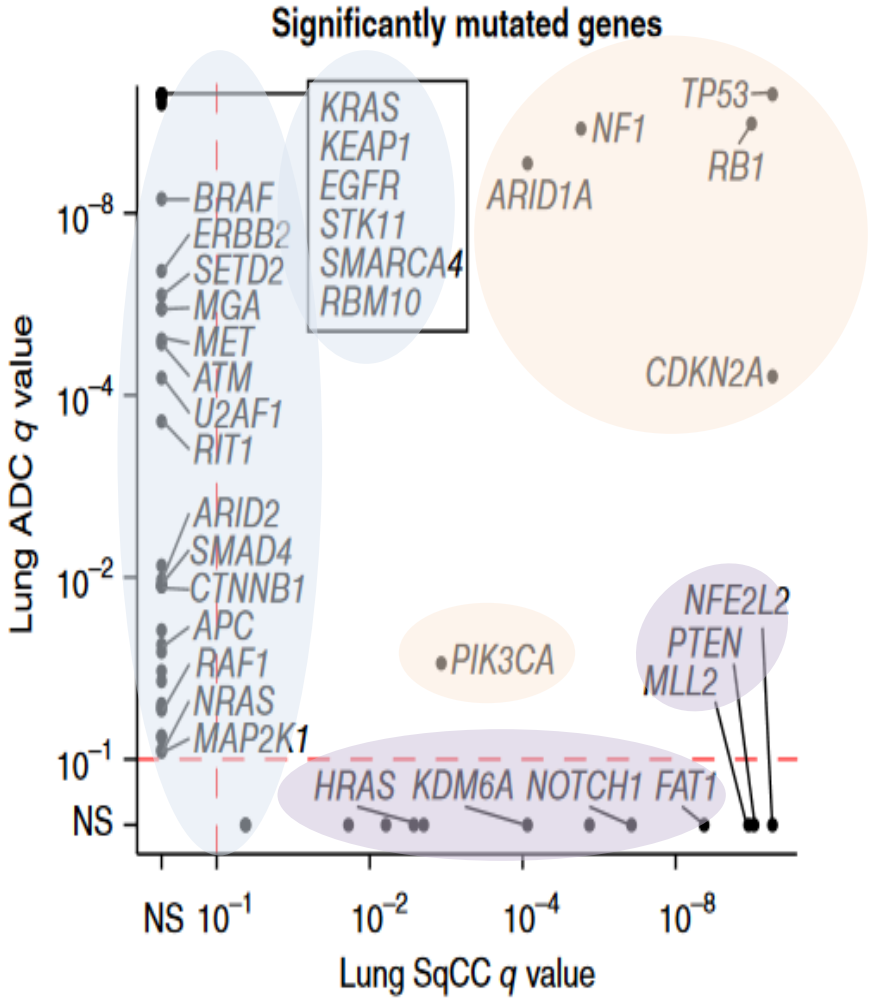
Proteogenomics of Non-smoking Lung Cancer in East Asia Delineates Molecular Signatures of Pathogenesis and Progression

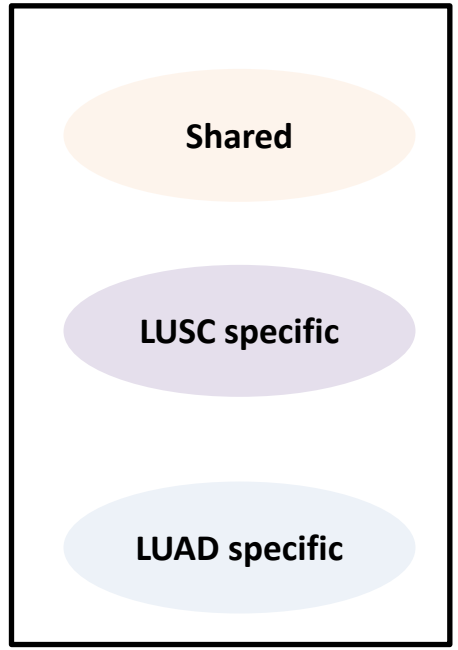


Yi-Ju Chen et al. Cell 2020

Squamous Cell Lung Cancer

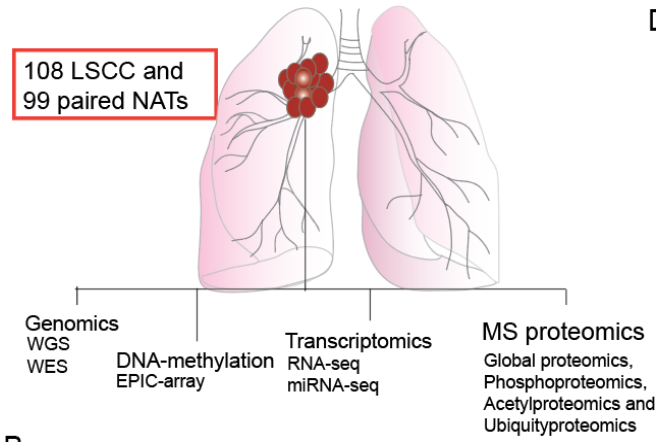


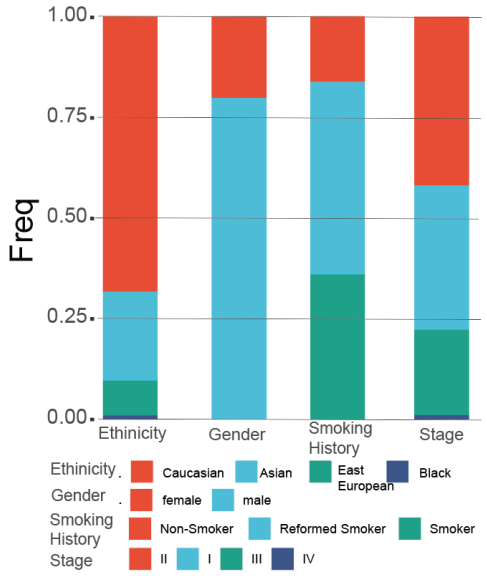




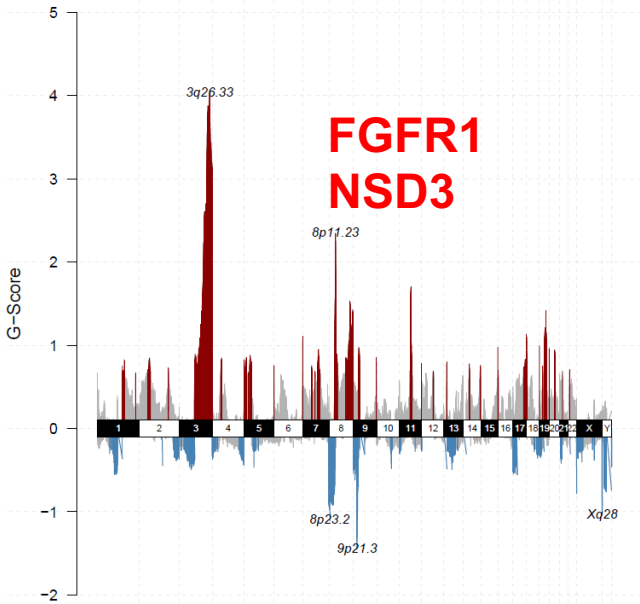
TCGA, Nature 2012; Nat Genet. 2016

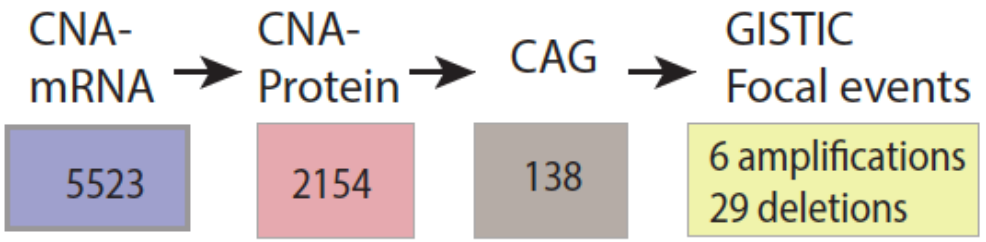
Proteogenomic alterations in lung squamous cell carcinoma



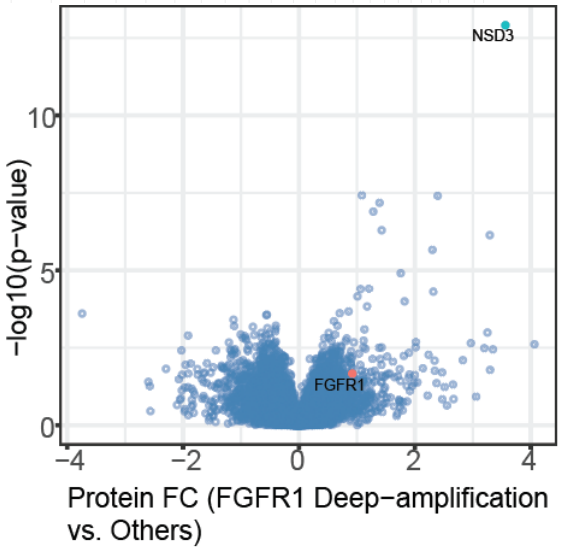


Most participants were Caucasian males smokers.
Females and Asians have moderate representation.



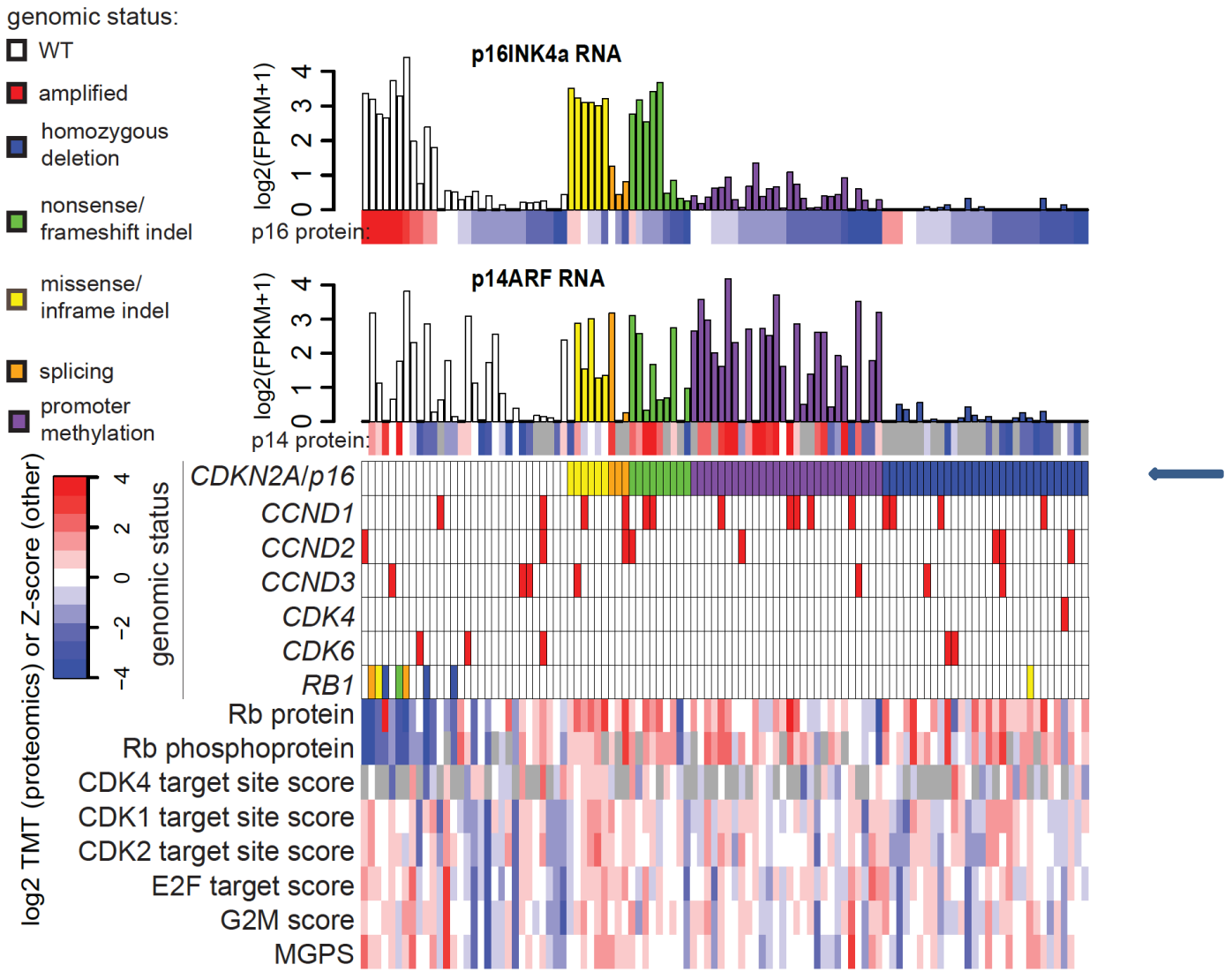


SOX2
NSD3
CCND1



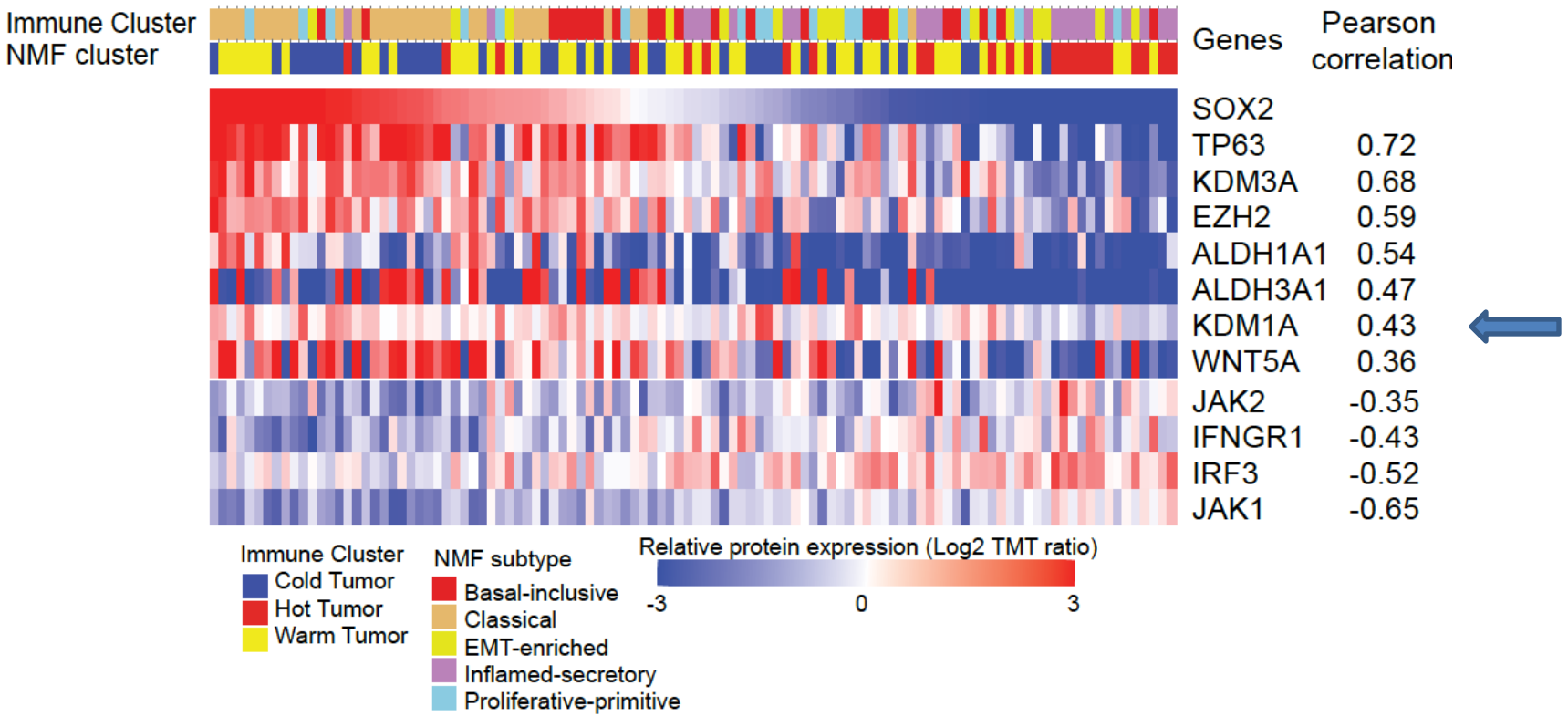
Satpathy et al Cell 2021

Proteogenomic alterations in lung squamous cell carcinoma
CDNK2A



Satpathy et al Cell 2021

Proteogenomic alterations in lung squamous cell carcinoma Targeting SOX2



Satpathy et al Cell 2021

nature COMMUNICATIONS

ARTICLE

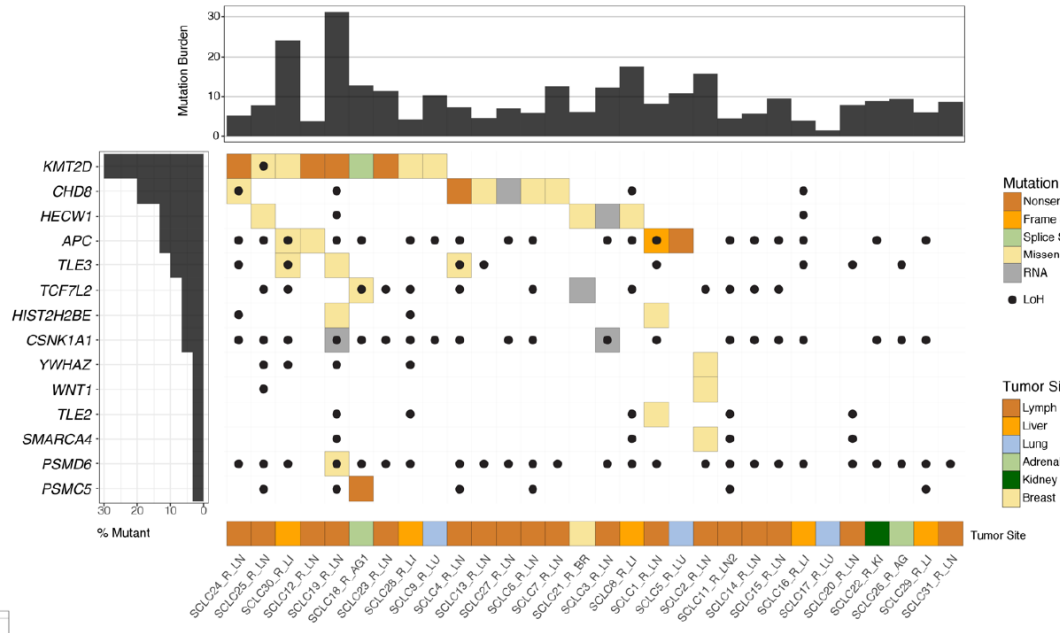
DOI: 10.1038/s41467-018-06162-9 OPEN

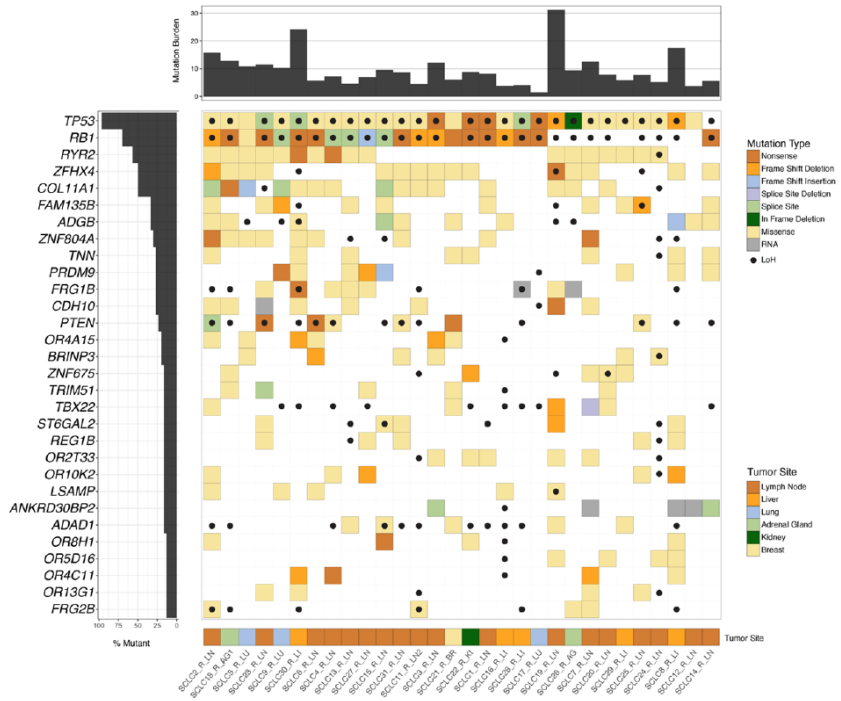
Recurrent WNT pathway alterations are frequent in relapsed small cell lung cancer

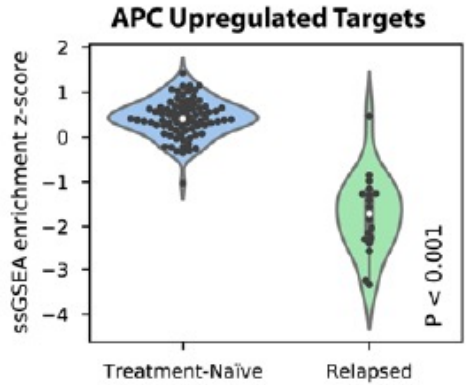
Alex H. Wagner[1], Siddhartha Devarakonda[2,3], Zachary L. Skidmore[1], Kilannin Krysiak[1,2], Avinash Ramu[1], Lee Trani[1], Jason Kunisaki[1], Ashiq Masood[2,3,9], Saiama N. Waqar[2,3], Nicholas C. Spies[1], Daniel Morgensztern[2,3], Jason Waligorski[1], Jennifer Ponce[1], Robert S. Fulton[1], Leonard B. Maggi Jr.[2,3,4], Jason D. Weber[2,3,4], Mark A. Watson[3], Christopher J. O'Conor[5], Jon H. Ritter[5], Rachelle R. Olsen[6], Haixia Cheng[6], Anandaroop Mukhopadhyay[6], Ismail Can[6], Melissa H. Cessna[7], Trudy G. Oliver[6], Elaine R. Mardis[1,3,8,10], Richard K. Wilson[1,3,8,10], Malachi Griffith[1,2,3,8], Obi L. Griffith[1,2,3,8] & Ramaswamy Govindan[2,3]

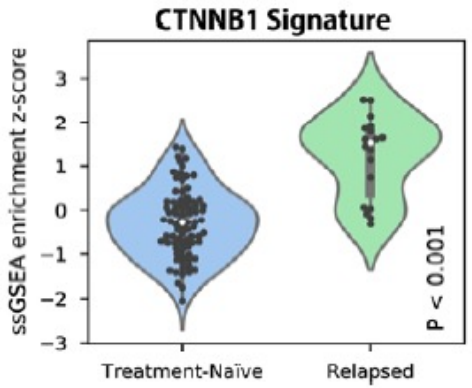
SITEMAN CANCER CENTER

BARNES-JEWISH Hospital BJC HealthCare | Washington University in St. Louis SCHOOL OF MEDICINE





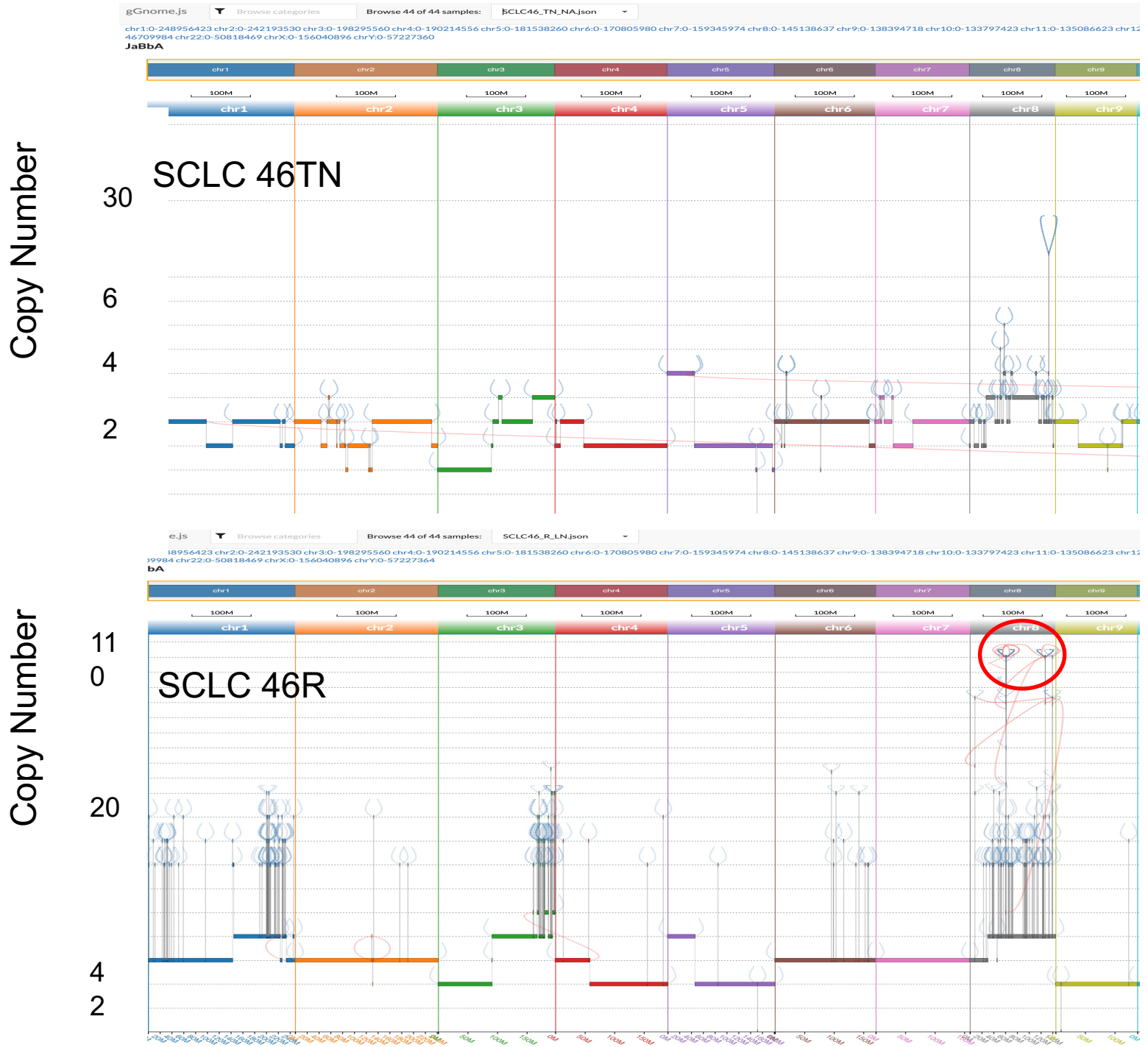




Wagner et al, Nature Comm. 2018

Amplification of MYC in Relapsed SCLC

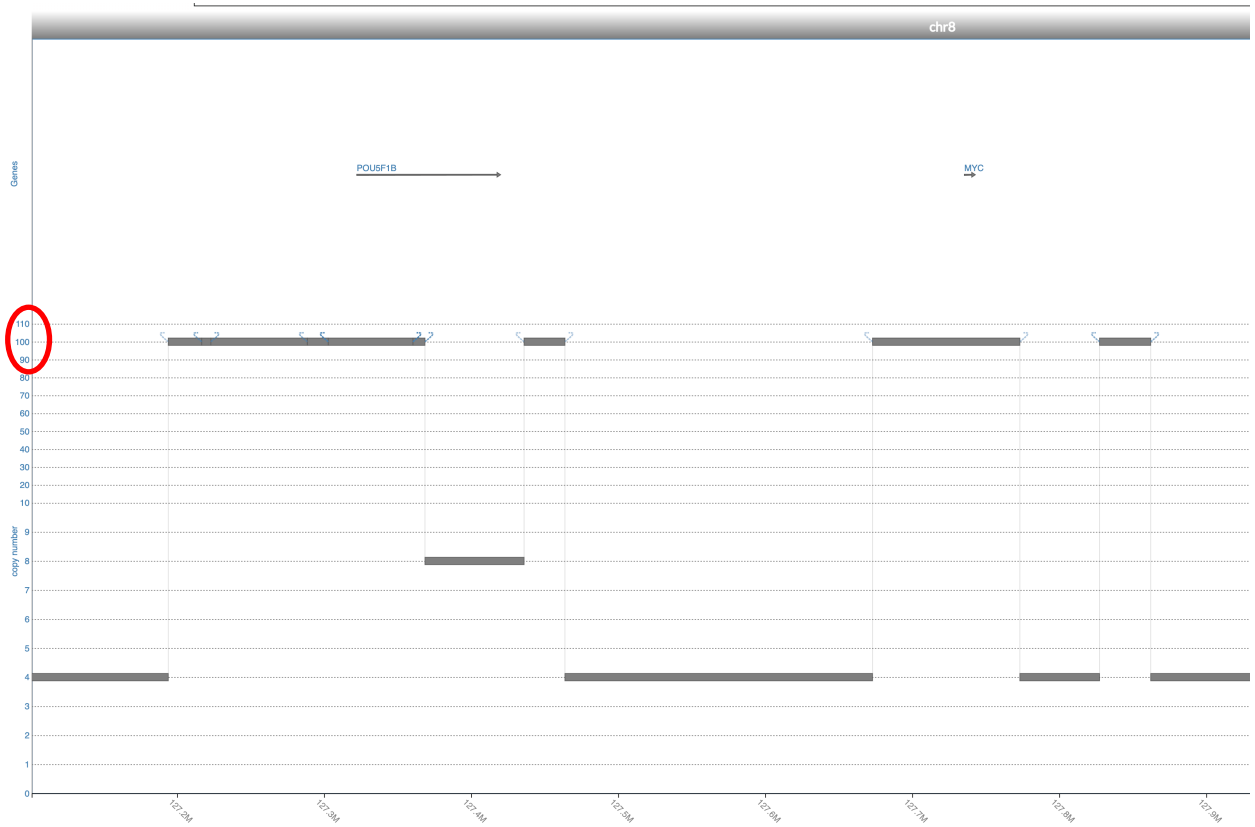
Copy number calls generated using JaBbA: **Hadi et al. *Cell*, 2021**



JaBbA output formatted to fit slide

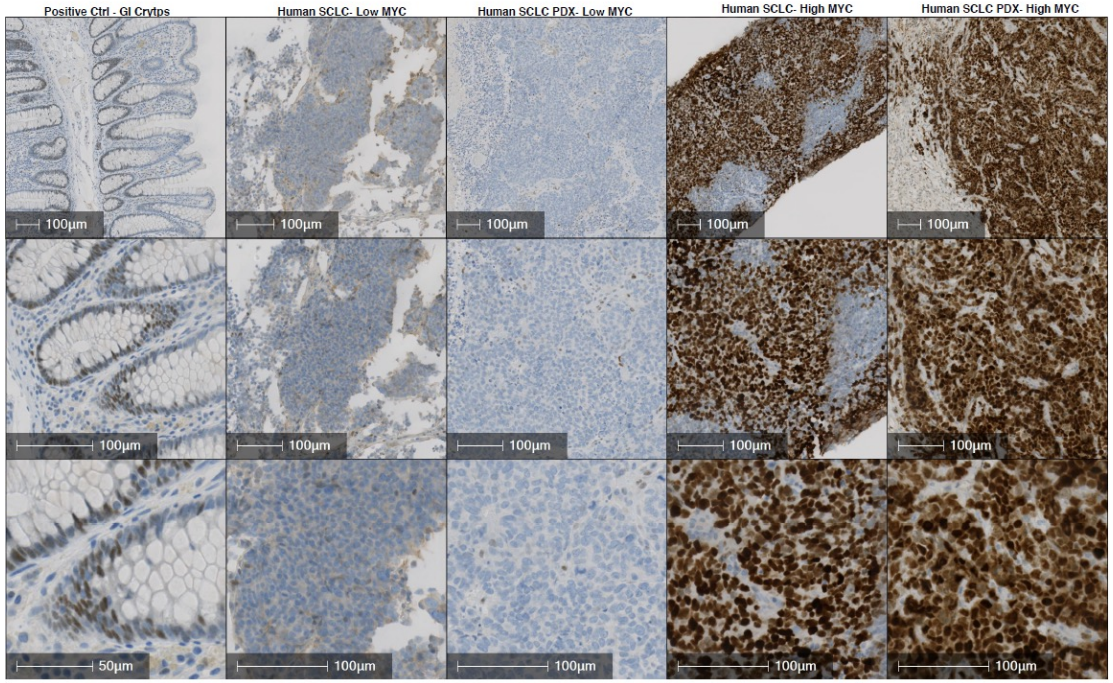
UNPUBLISHED

MYC amplified clones are selected at relapse in SCLC



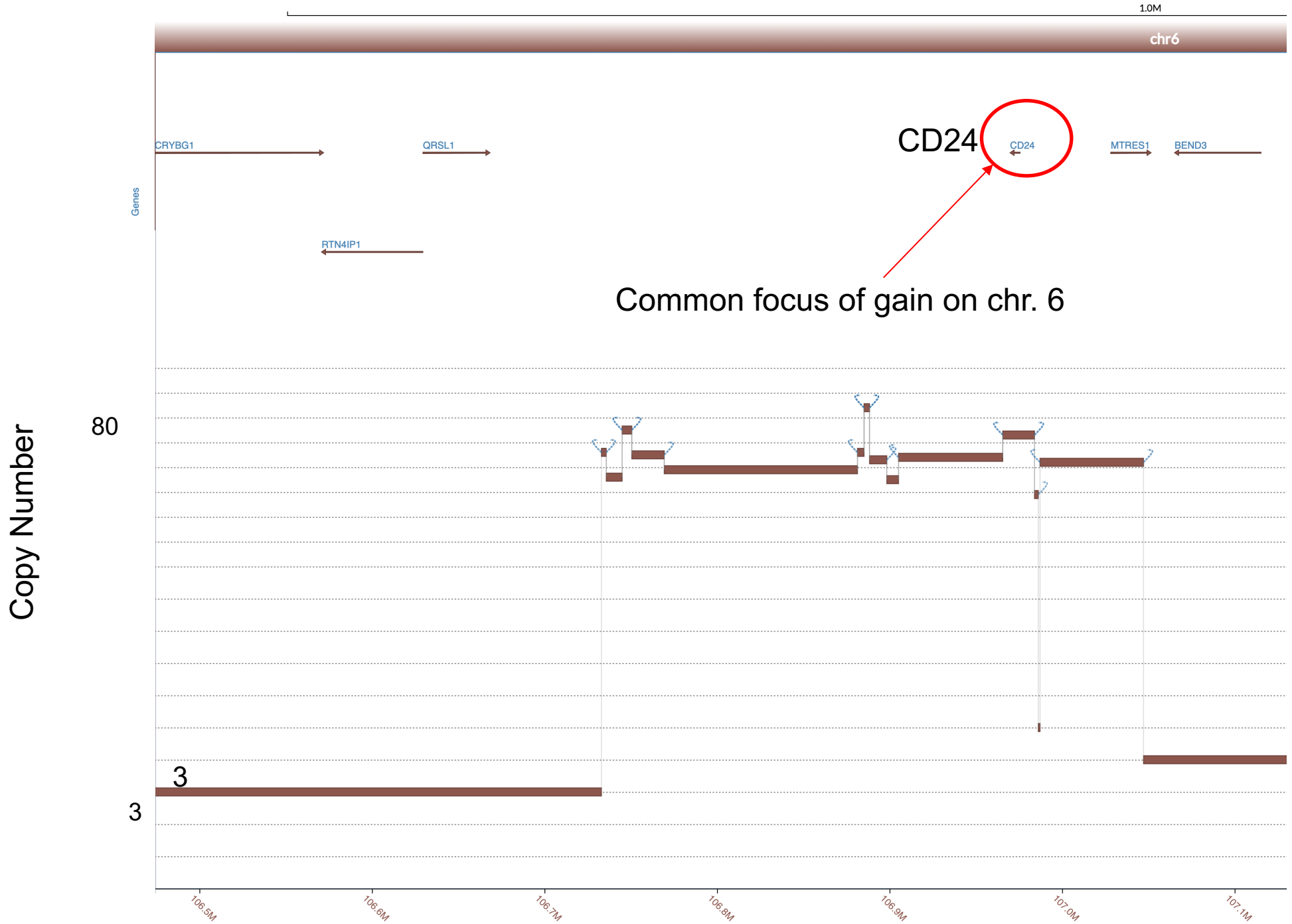
Copy number calls generated with JaBbA

Hadi et al. *Cell*, 2021



Validation with in-situ hybridization for *MYC*

UNPUBLISHED

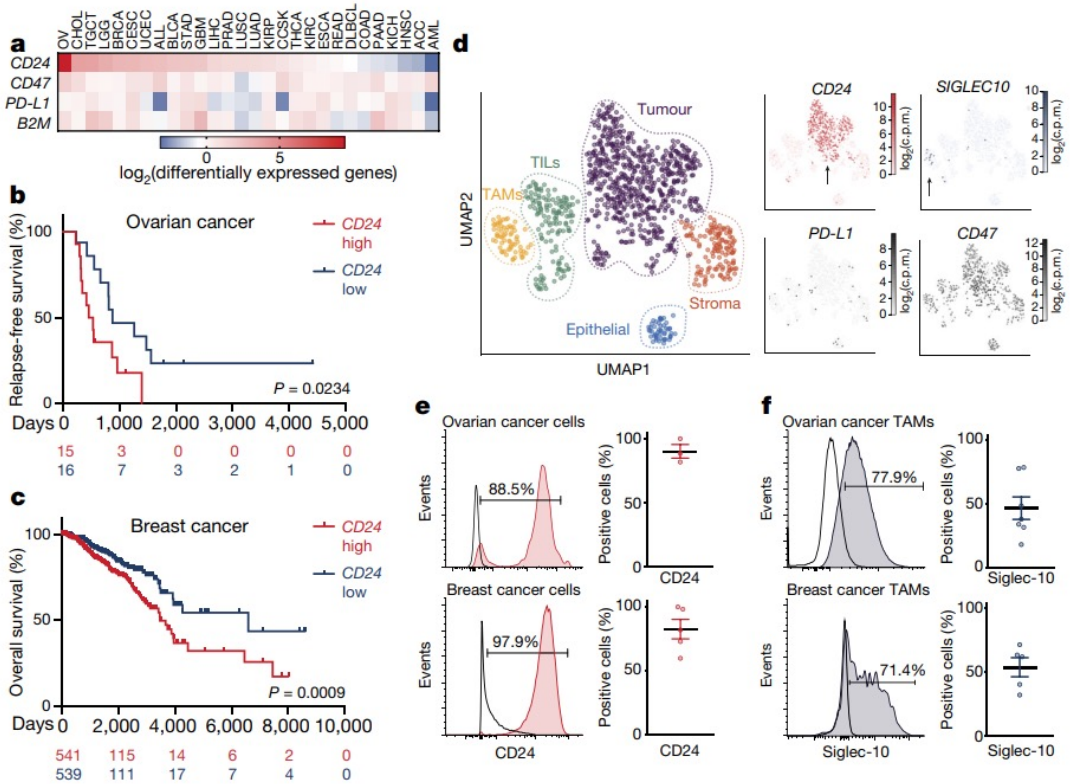

1.0M
chr6
CRYBG1
QRSL1
CD24
CD24
MTRES1
BEND3
Genes
RTN4IP1
Common focus of gain on chr. 6
Copy Number
80
3
3
106.5M
106.6M
106.7M
106.8M
106.9M
107.0M
107.1M

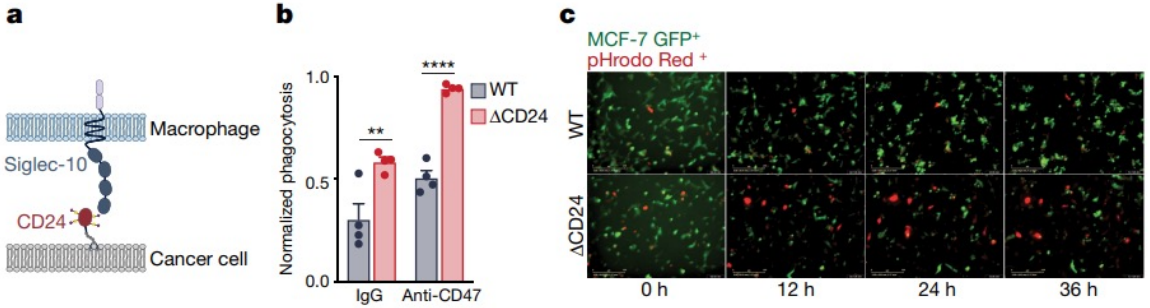
LETTER

https://doi.org/10.1038/s41586-019-1456-0

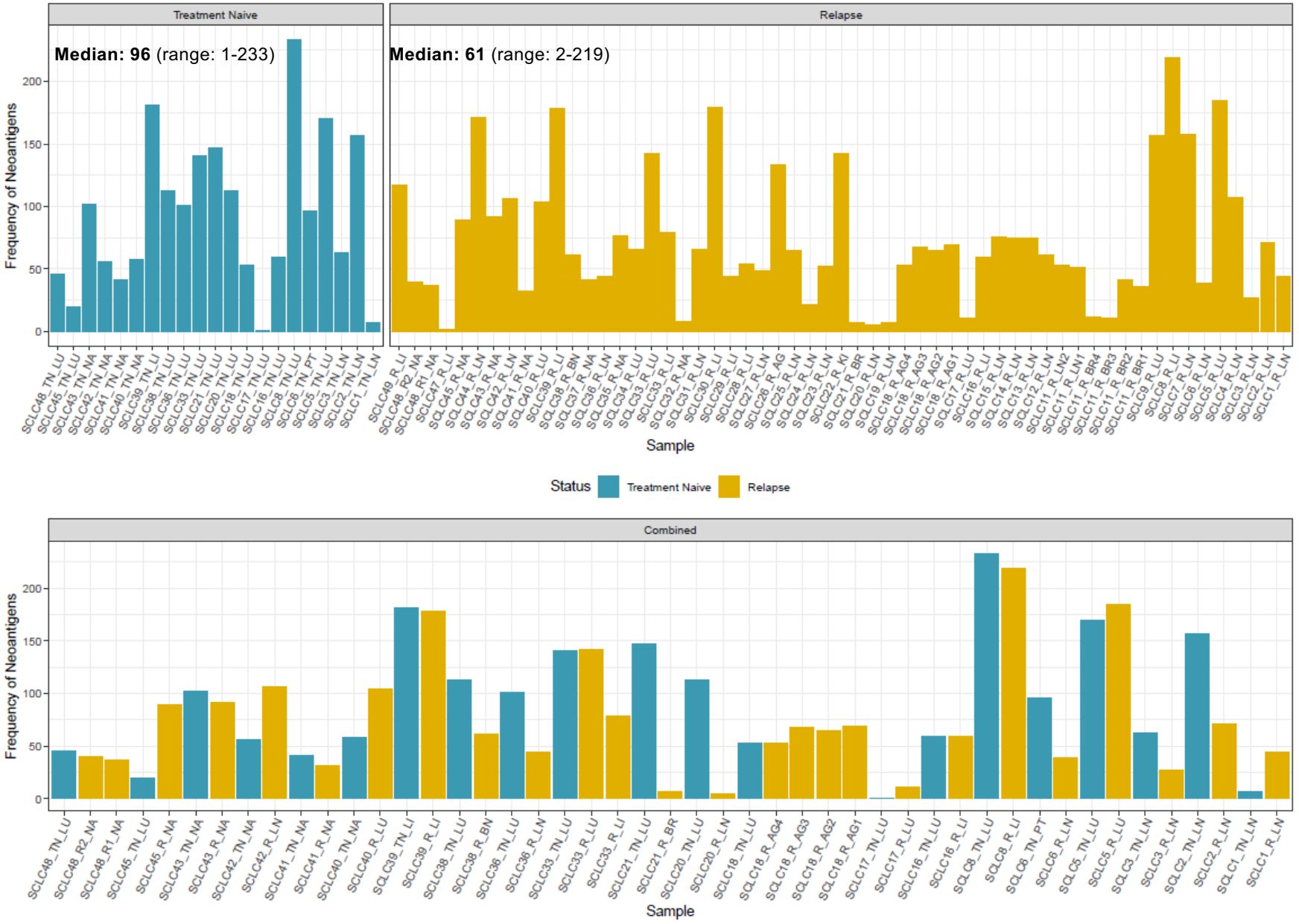
CD24 signalling through macrophage Siglec-10 is a target for cancer immunotherapy

Amira A. Barkal[1,2,3,4], Rachel E. Brewer[1,2,3], Maxim Markovic[1,2,3], Mark Kowarsky[5], Sammy A. Barkal[1], Balyn W. Zaro[1,2,3], Venkatesh Krishnan[6], Jason Hatakeyama[1,7], Oliver Dorigo[6], Layla J. Barkal[8] & Irving L. Weissman[1,2,3,9]*





Neo-epitope burden in SCLC

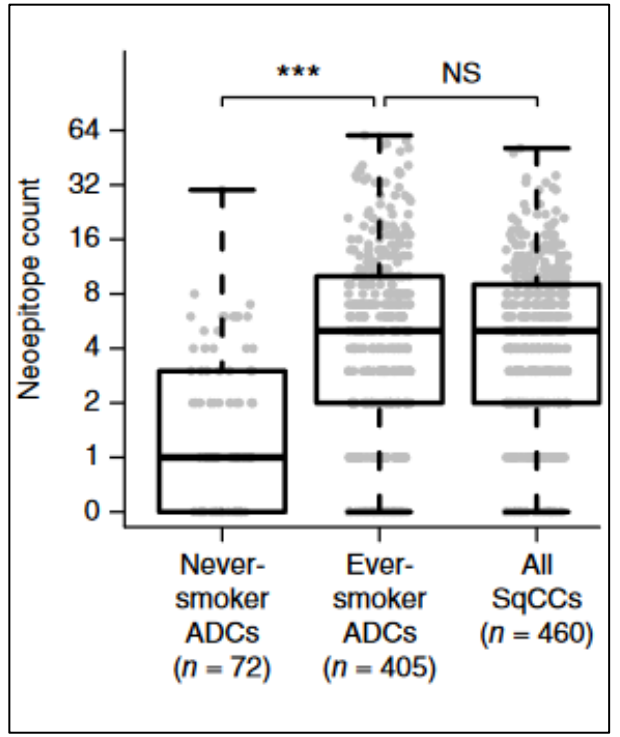


pVAC-Seq: Hundal et al. Genome Med, 2016

SITEMAN CANCER CENTER

BARNES-JEWISH Hospital | Washington University in St. Louis School of Medicine

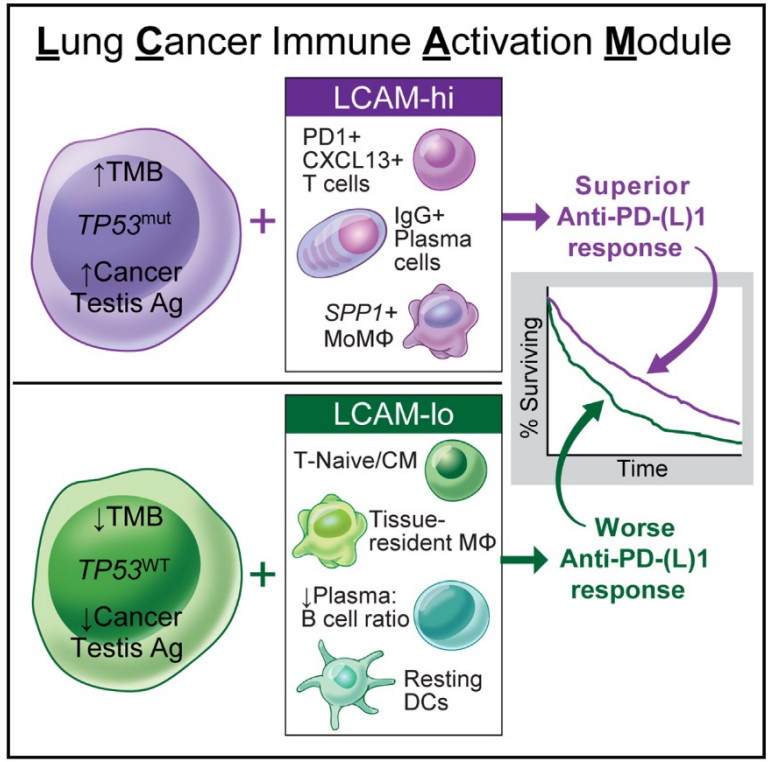
NSCLC - TCGA



Campbell et al. Nat Genetics, 2016

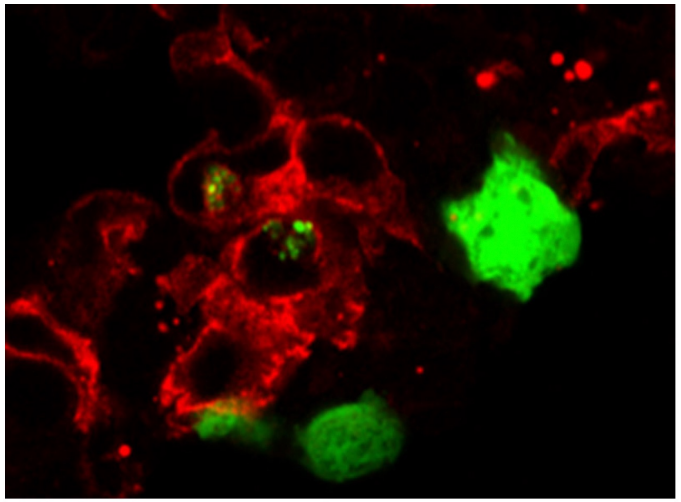
UNPUBLISHED DATA
PLEASE DO NOT POST

Single-cell analysis of human non-small cell lung cancer lesions refines tumor classification and patient stratification

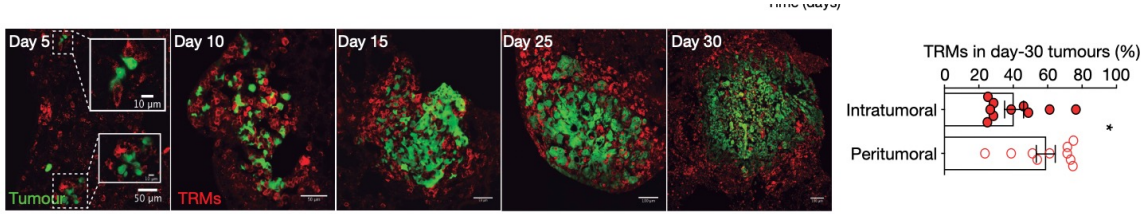


Cancer Cell *39*, 1594–1609, December 13, 2021

Tissue-resident macrophages provide a pro-tumorigenic niche to early NSCLC cells

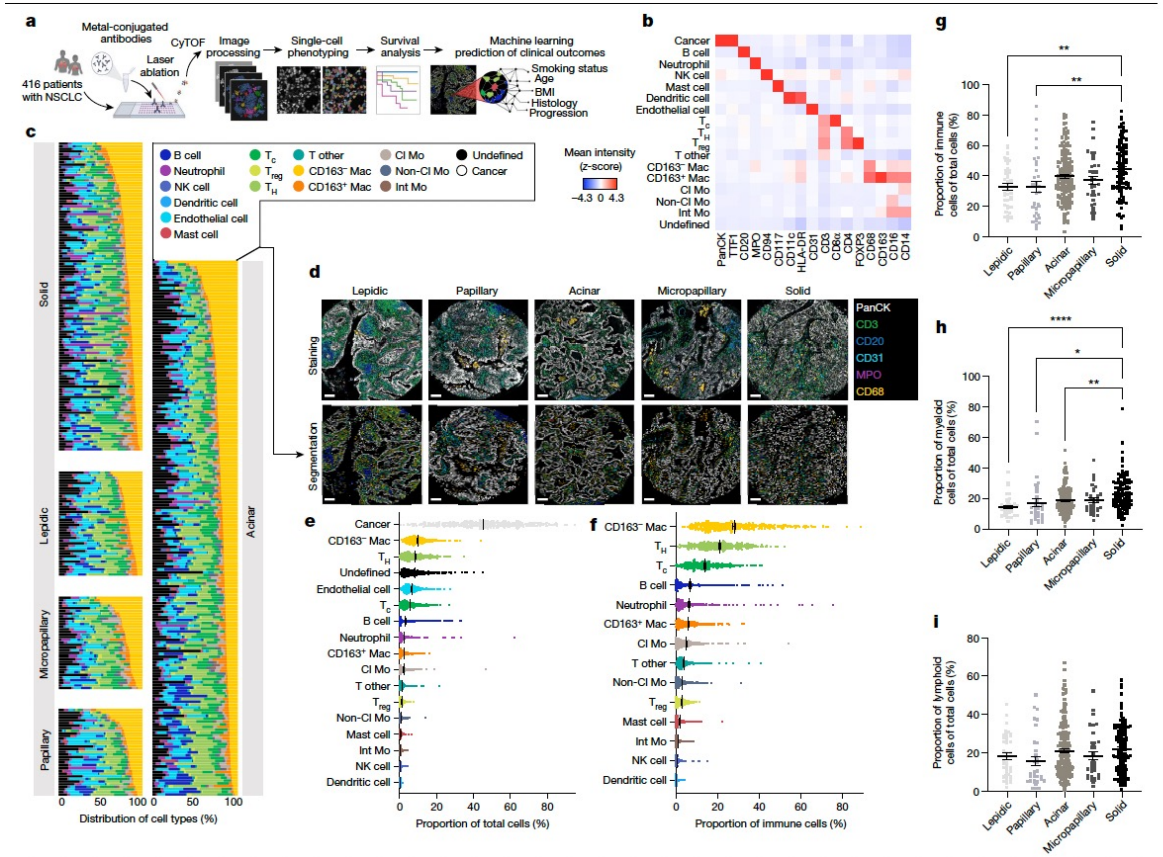


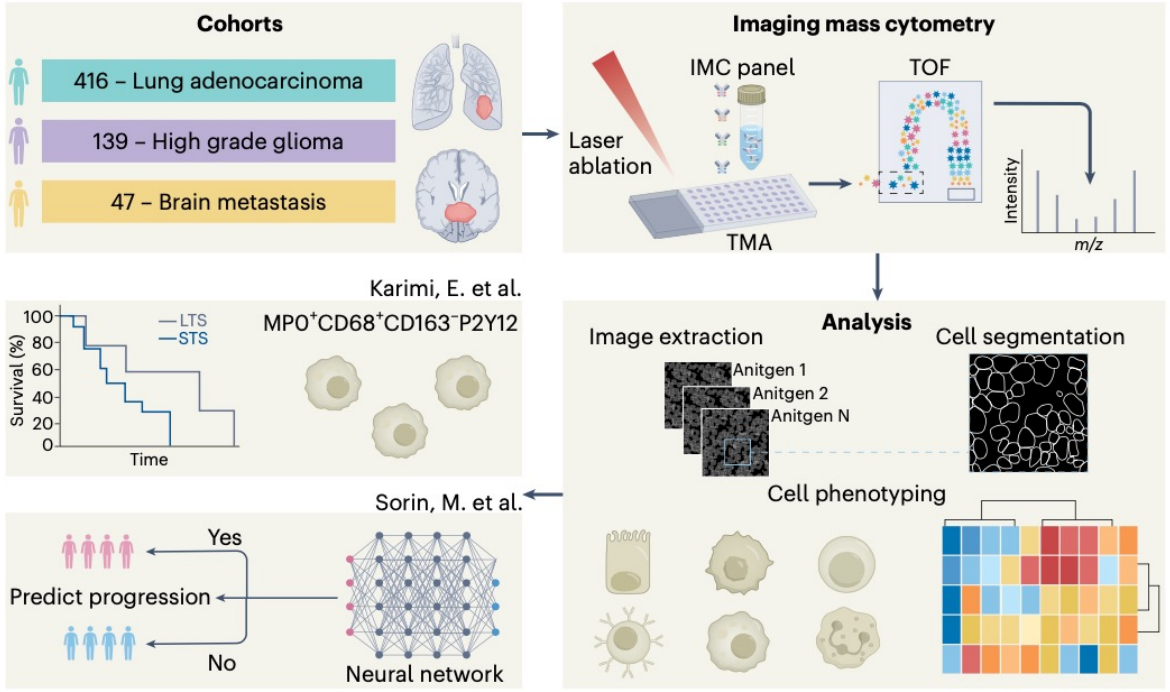
Tissue resident macrophages, in red, are shown eating tumor cells, in green.



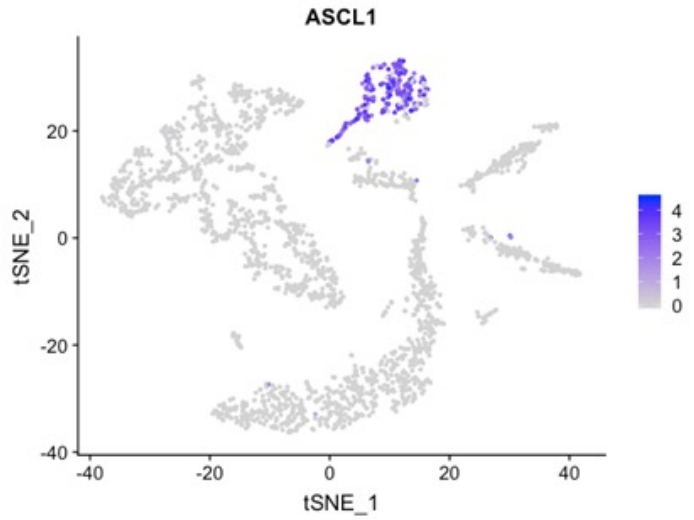
Nature | Vol 595 | 22 July 2021

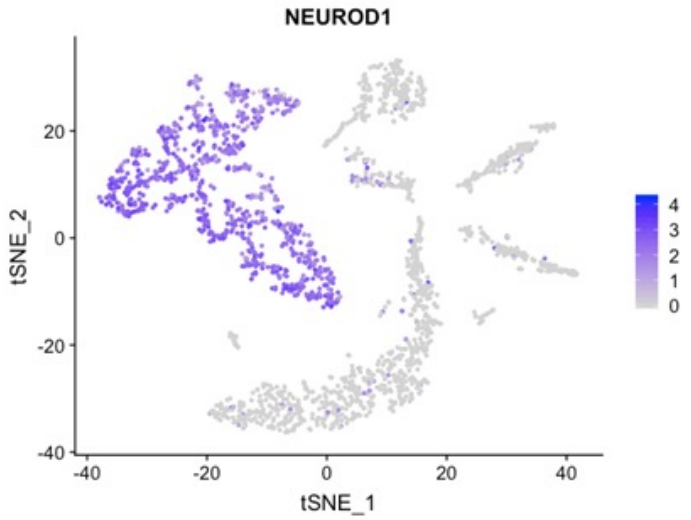
Single-cell spatial landscapes of the lung tumour immune microenvironment

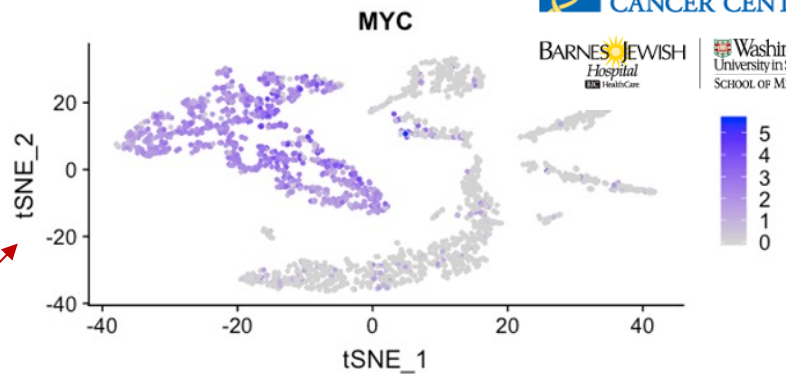


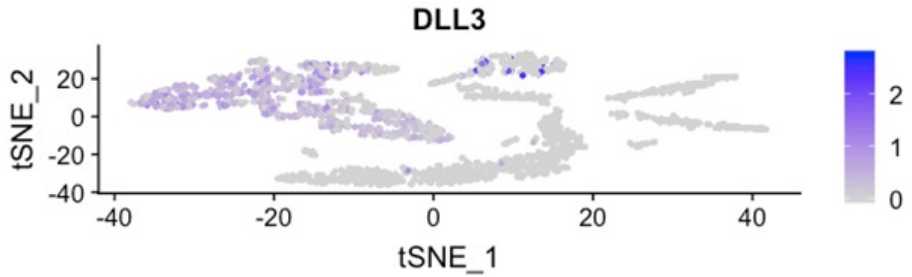


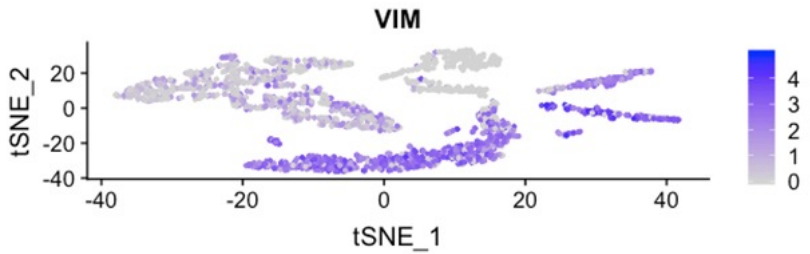
Intratumoral heterogeneity in SCLC

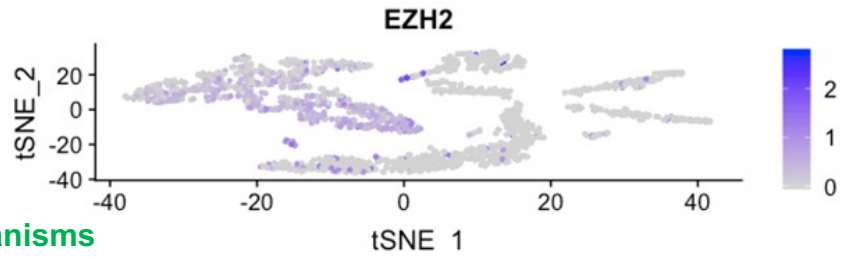




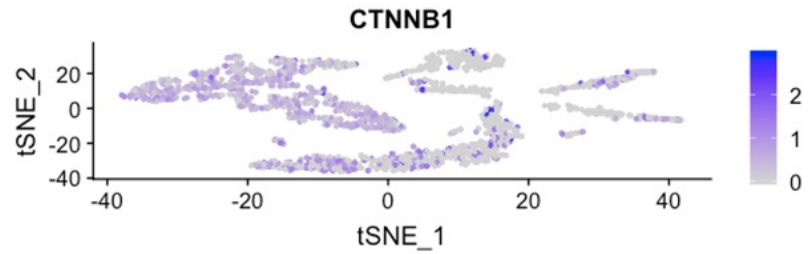


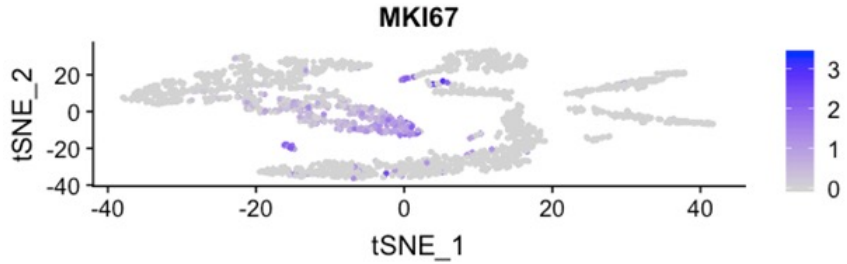






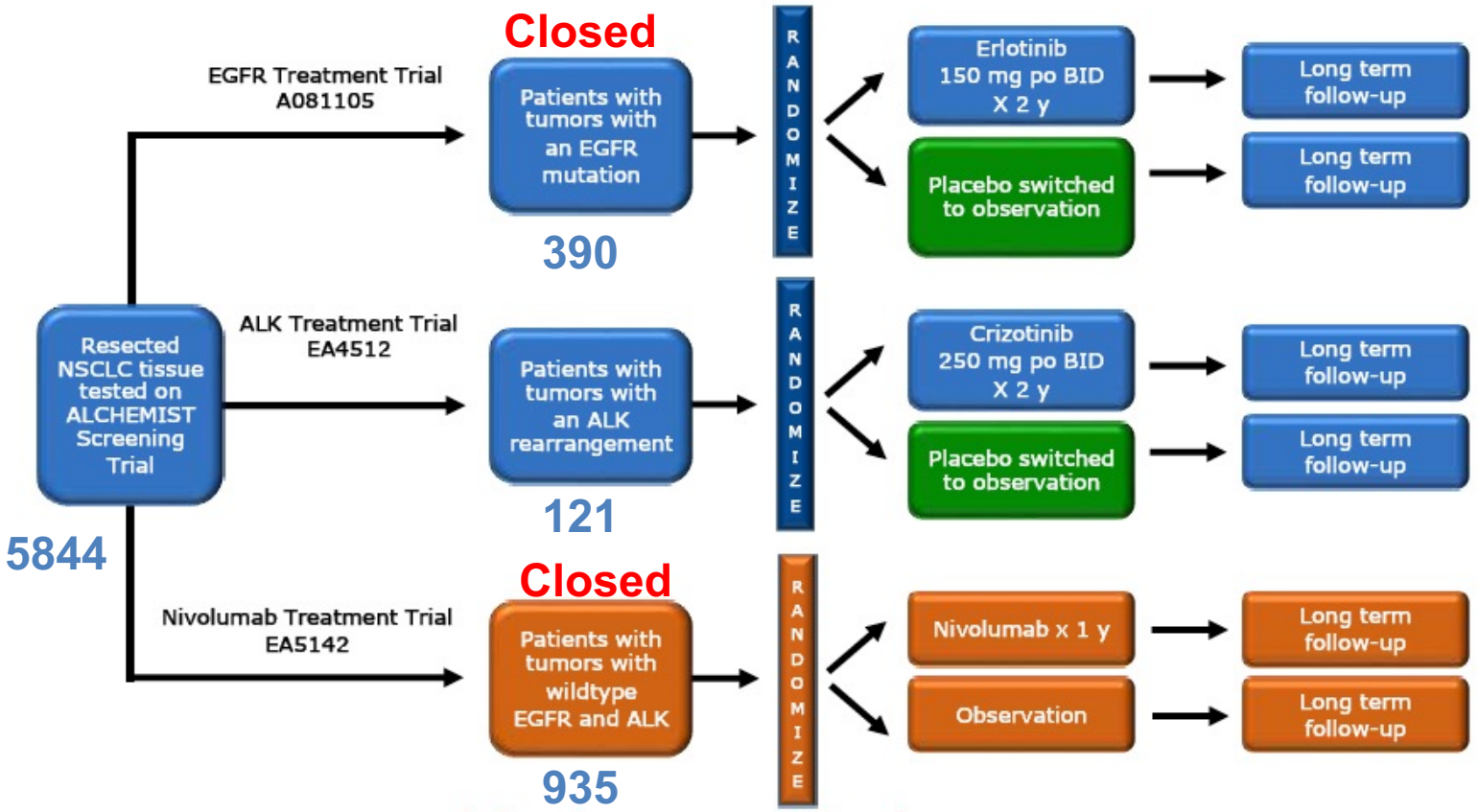
Heterogeneity in resistance mechanisms





UNPUBLISHED DATA
PLEASE DO NOT POST

ALCHEMIST 2.0



- Includes all squamous cell histology
- Additional Stratified Factor: PD-L1 ≥ 1% or <1%
- Co-Primary Endpoints: DFS and OS

Report generated as of Friday 4/26/2024 8:00 AM

Trial Metrics: ALCHEMIST

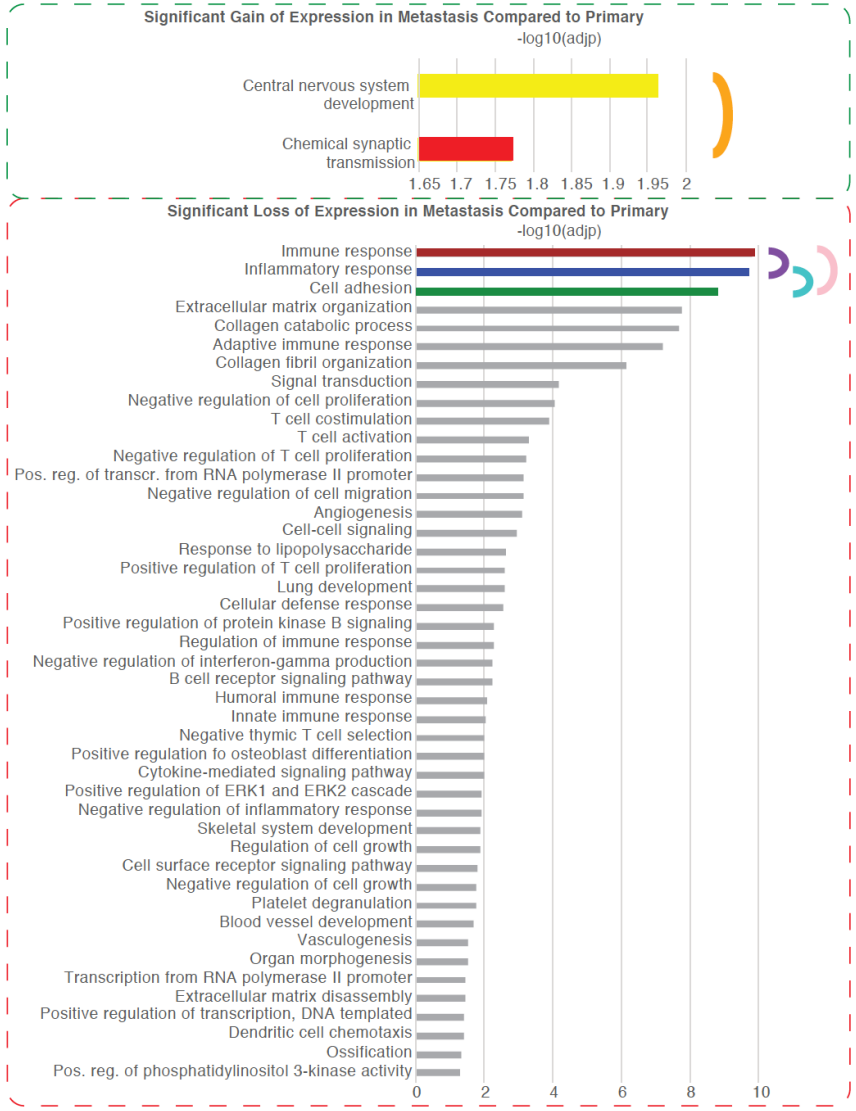
Metric	Value
Total site open for A151216	1212
Total pts registered to A151216	7166
Total pts registered to A081105	390
Total pts registered to E4512	166
Total pts registered to EA5142	935
Total pts registered to A081801	569

Proteogenomic Predictors of Recurrence in Non-small Cell Lung Cancer

1 U01CA271402-01	GOVINDAN, RAMASWAMY CARR, STEVEN A GILLETTE, MICHAEL A	WASHINGTON UNIVERSITY	2022	NCI	NCI

Brain Metastases from Lung Cancer

Differentially Expressed Genes



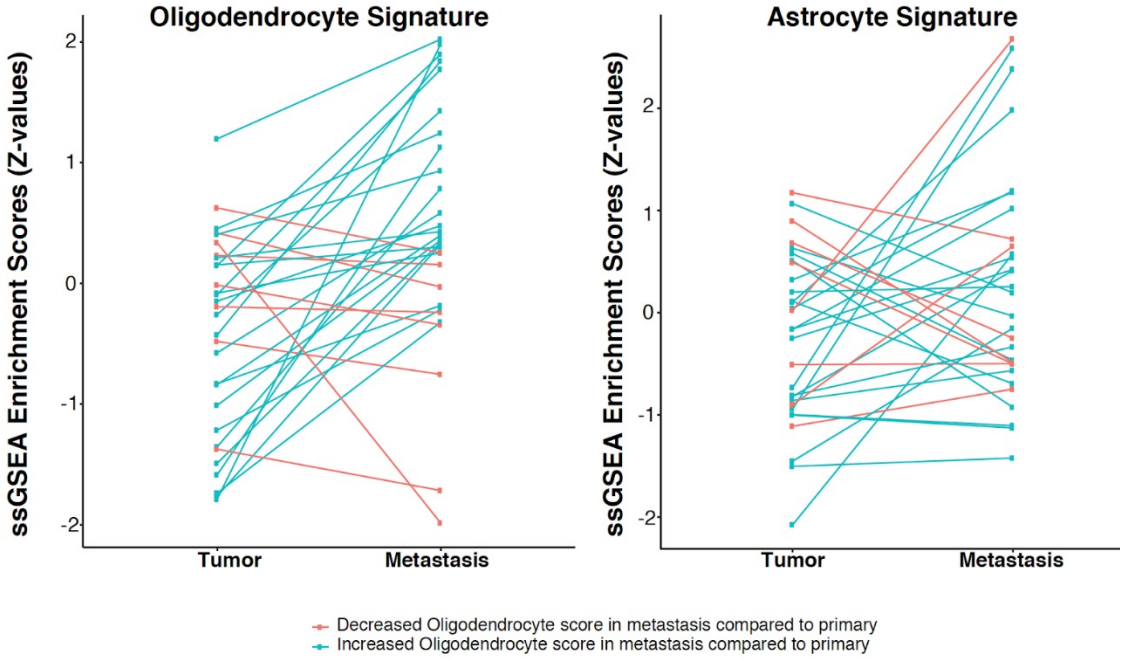
UNPUBLISHED DATA
PLEASE DO NOT POST

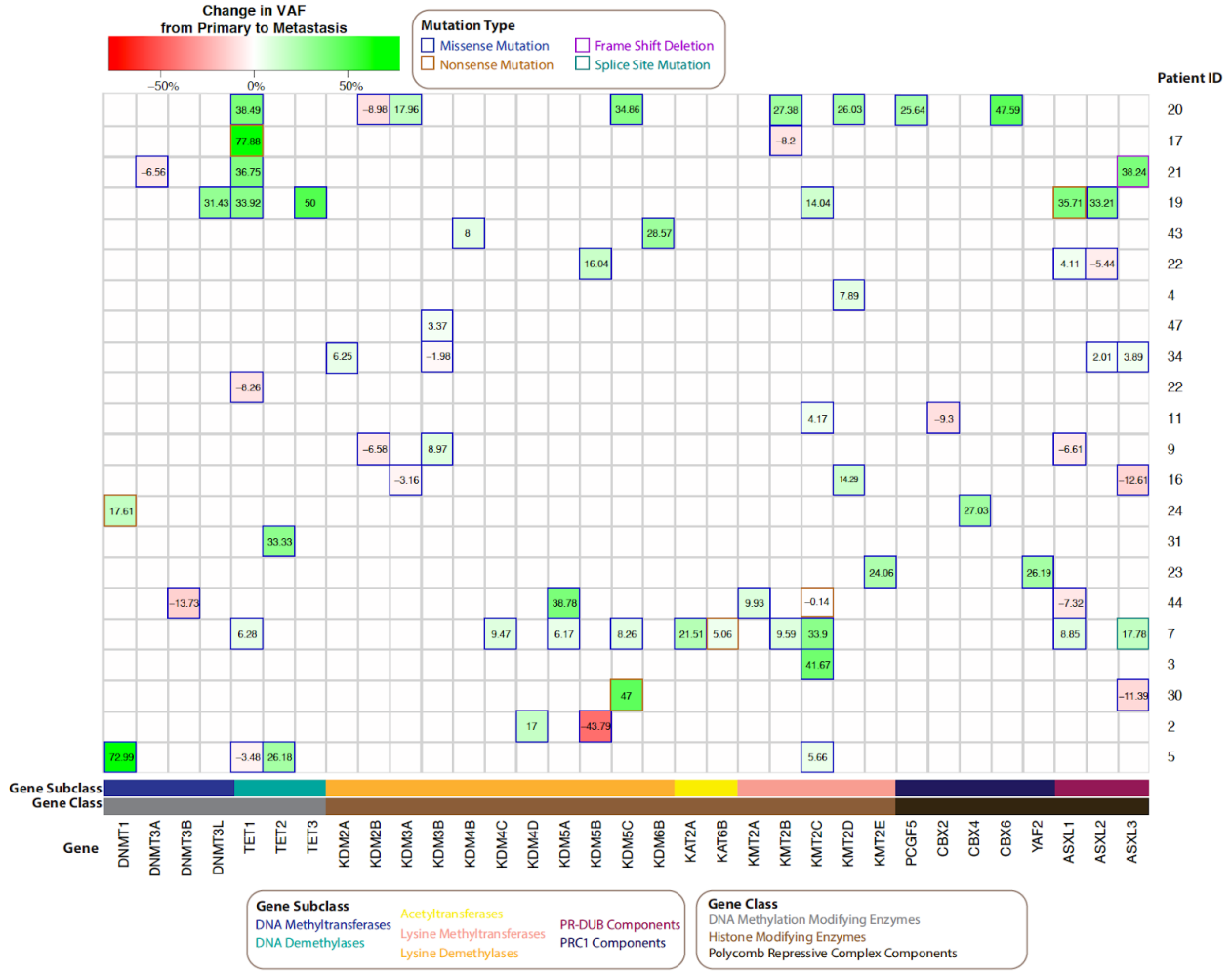
Brain Metastases from Lung Cancer

Enrichment of neural development pathway genes

SITEMAN CANCER CENTER

BARNES-JEWISH Hospital | Washington University in St. Louis SCHOOL OF MEDICINE



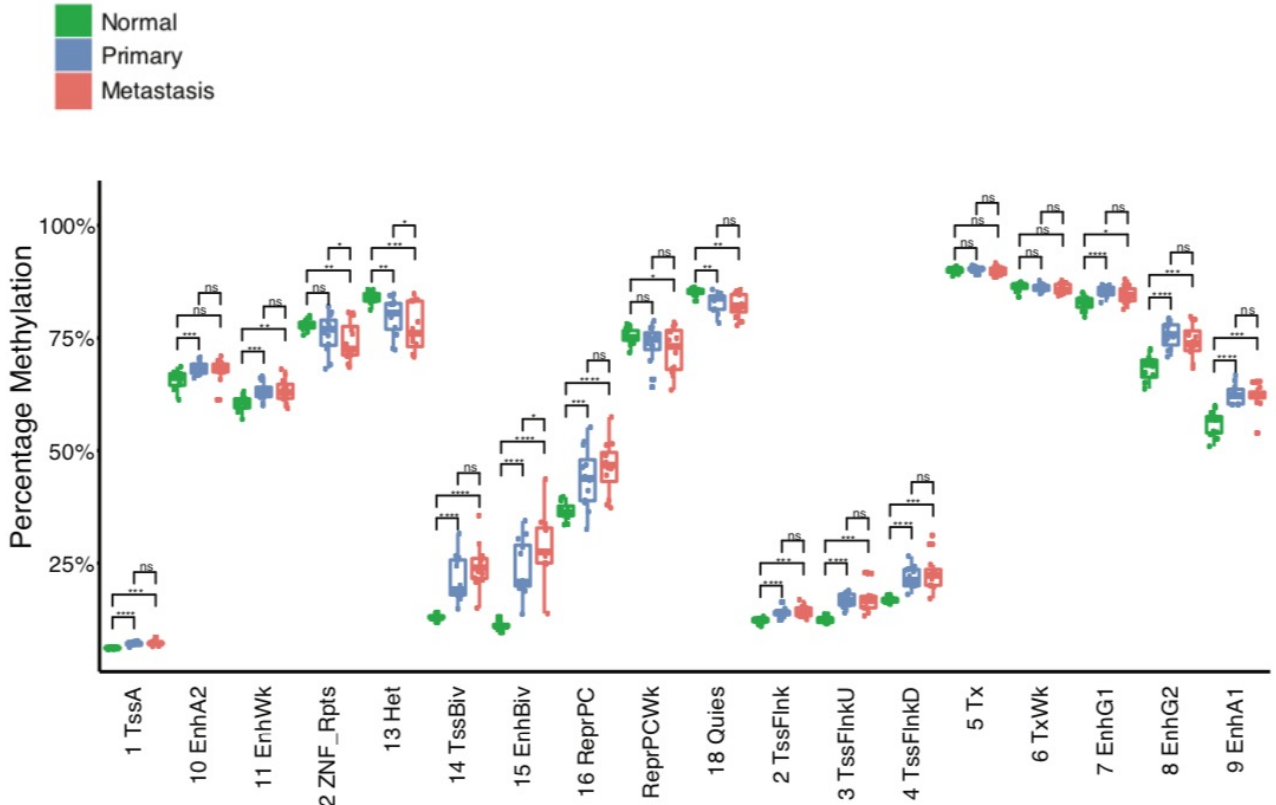


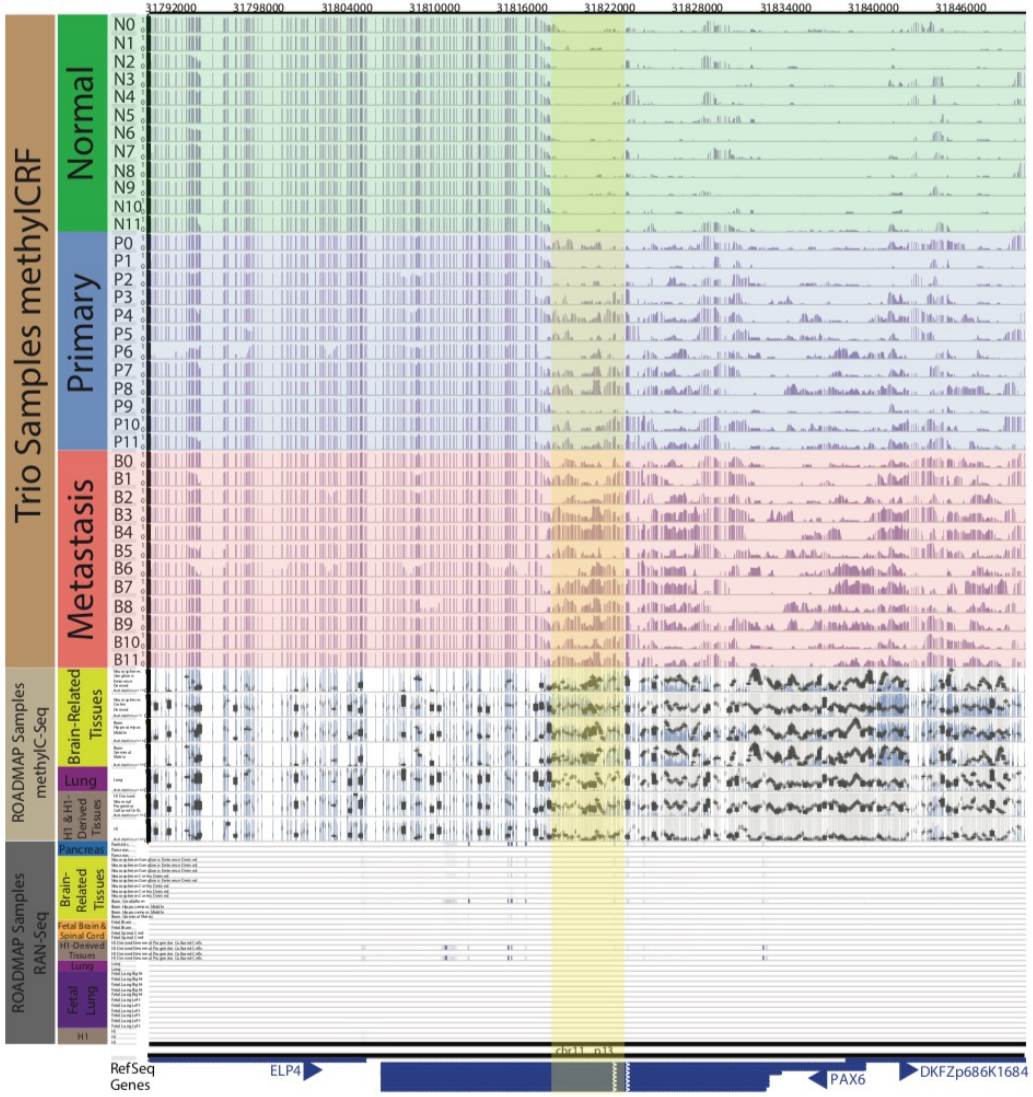
Brain Metastases from Lung Cancer

Enrichment of neural development pathway genes

SITEMAN CANCER CENTER

BARNES-JEWISH Hospital | Washington University in St. Louis SCHOOL OF MEDICINE





UNPUBLISHED DATA
PLEASE DO NOT POST

NIH NATIONAL CANCER INSTITUTE

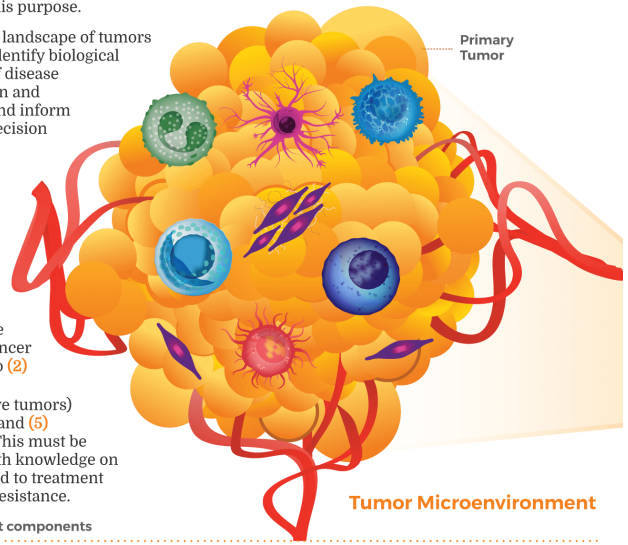
Cancer and the Human Tumor Atlas Network Infographic

Information mapped in human tumor atlases will provide a comprehensive understanding of the ecosystem of tumors and show important transitions in cancer.

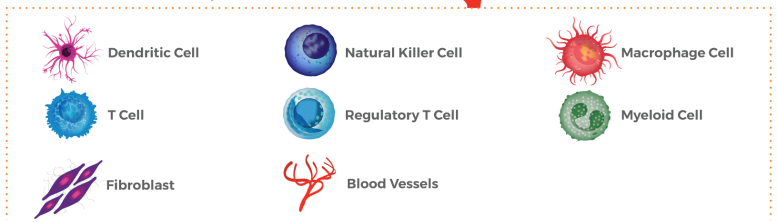
Cancer and the Human Tumor Atlas Network

The construction of human tumor atlases will provide a more comprehensive understanding of the ecosystems of tumors at the macro- and the micro-level. NCI has established the Human Tumor Atlas Network (HTAN) for this purpose.

Mapping the landscape of tumors will help identify biological markers of disease progression and treatment resistance and inform the development of precision risk-stratification, prevention, screening, diagnostic, and treatment strategies. To accomplish this, a better understanding of the molecular-, cellular-, and tissue-level communication networks that drive the major transitions in cancer from (1) normal cells to (2) dysplasia to (3) *in situ* carcinoma (noninvasive tumors) to (4) invasive disease and (5) metastasis is needed. This must be integrated with in-depth knowledge on how tumors (6) respond to treatment and (7) develop drug resistance.



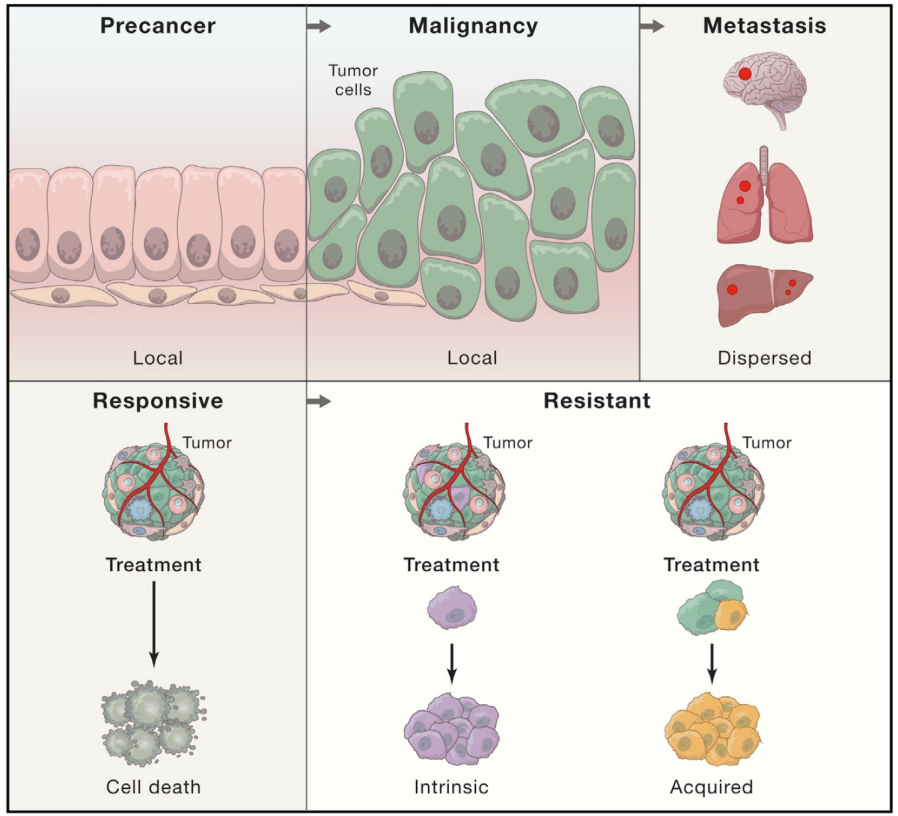
Tumor Microenvironment components



MEMORIAL SLOAN-KETTERING CANCER CENTER · ESTABLISHED 1884 ·

SITEMAN CANCER CENTER

BARNES-JEWISH Hospital BJC HealthCare | Washington University in St. Louis SCHOOL OF MEDICINE

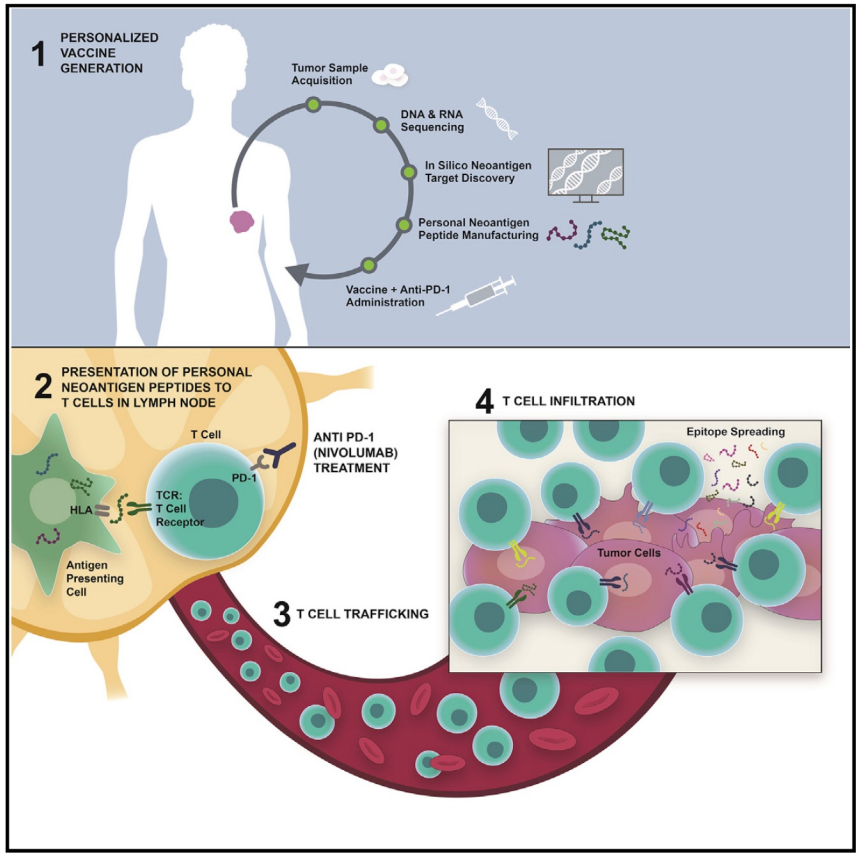


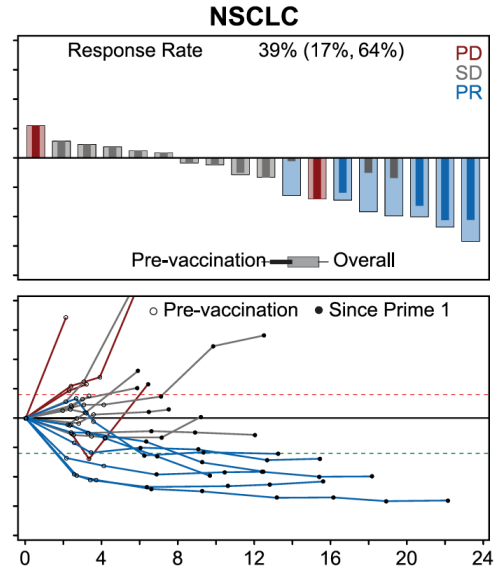
Molecular		Spatiomolecular	Histological	Anatomical
sc/snRNA-seq	RNA-seq	EM	H&E	MRI
sc/snEpigenomics	Epigenomics	Sequencing-based		CT
CITE-seq	WES	Fluorescence-based		PET
	Metabolomics	Antibody-based		
	Proteomics			
	Microbiome			

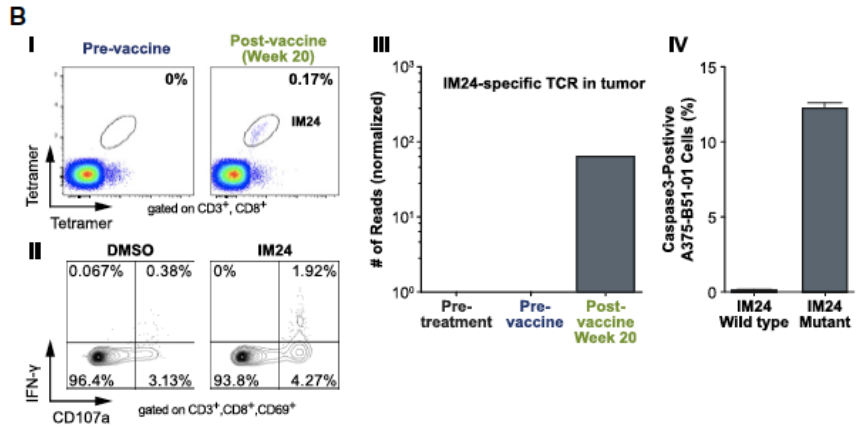
Single cell · Bulk · Multiplex transcriptomics · Multiplex proteomics

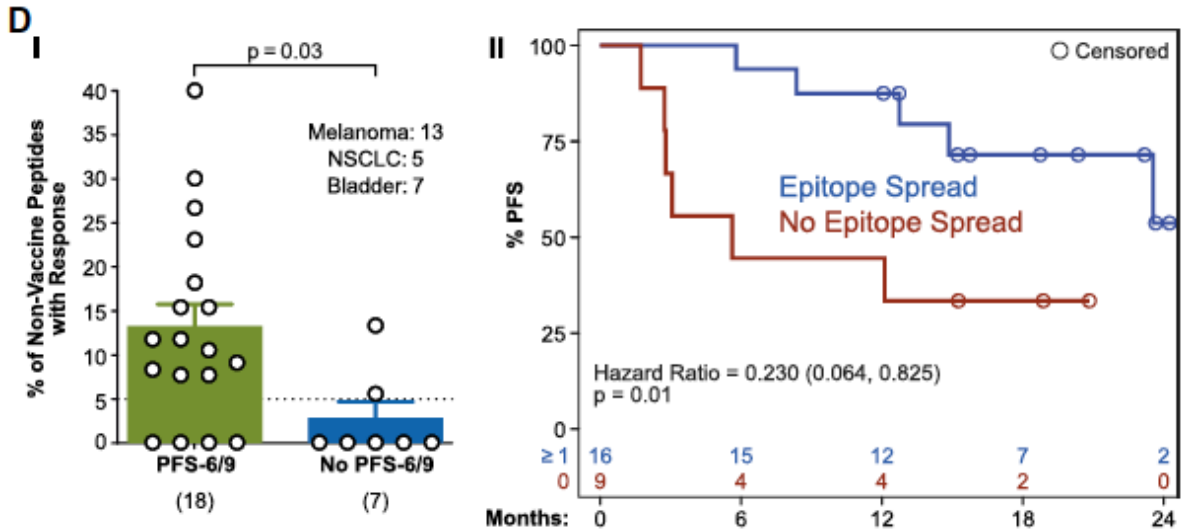
Cell

A Phase Ib Trial of Personalized Neoantigen Therapy Plus Anti-PD-1 in Patients with Advanced Melanoma, Non-small Cell Lung Cancer, or Bladder Cancer

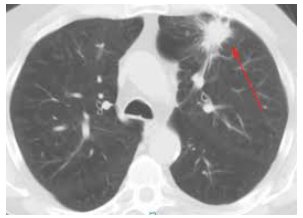








Prediction and Immunologic Validation of MHC Class I Neoepitopes



Tumor Biopsy

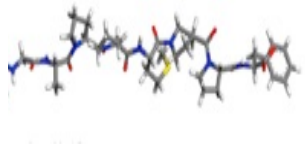
Whole Exome Sequencing plus RNA-Seq

Tumor vs Normal

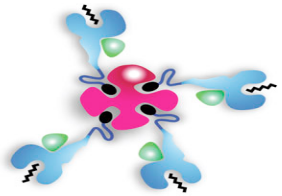
ID Expressed mutations

Epitope Prediction:

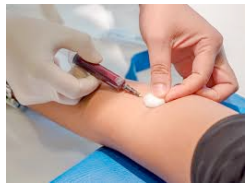
Use multiple algorithms to predict binding affinity to MHC I



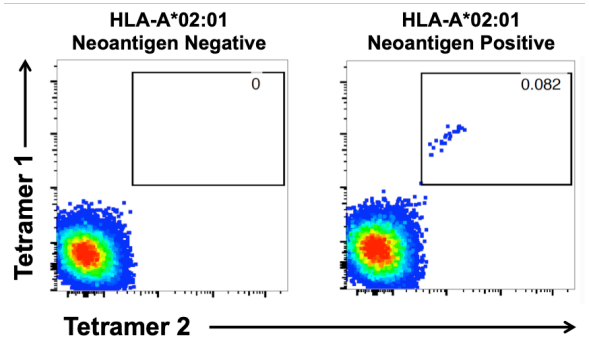
Synthesize Peptides



p-MHC-I Tetramers (44 alleles)



CD8⁺ TILs or Peripheral Blood



Analyze

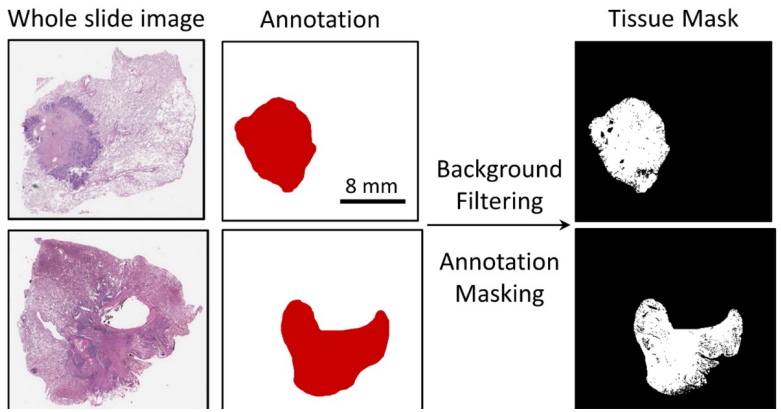
CHiPs

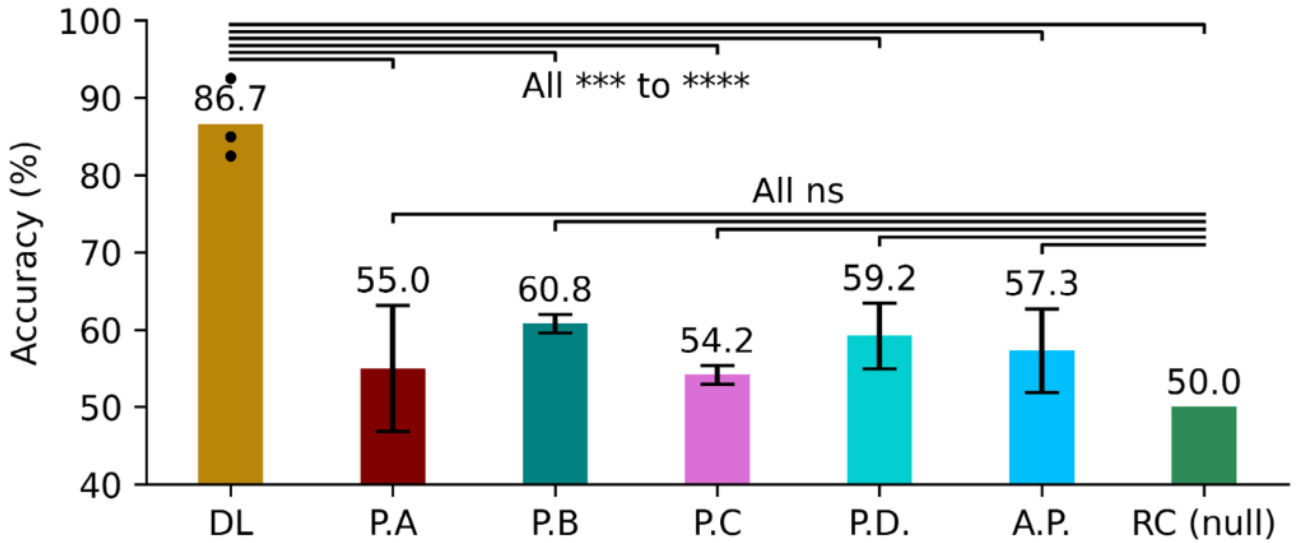
The Andrew M. and Jane M. Bursky Center for Human Immunology & Immunotherapy Programs

AI-guided histopathology predicts brain metastasis in lung cancer patients

Haowen Zhou[1†], Mark Watson[2†], Cory T Bernadt[2], Steven (Siyu) Lin[1], Chieh-yu Lin[2], Jon H Ritter[2], Alexander Wein[2], Simon Mahler[1], Sid Rawal[2], Ramaswamy Govindan[3], Changhuei Yang[1] and Richard J Cote[2*]

[1] *Department of Electrical Engineering, California Institute of Technology, Pasadena, CA, USA*
[2] *Department of Pathology and Immunology, Washington University School of Medicine, Saint Louis, MO, USA*
[3] *Department of Medicine, Washington University School of Medicine, Saint Louis, MO, USA*





Journal of Pathology
J Pathol May 2024; **263:** 89–98

And so in the military –

Knowing the other and knowing oneself,

In one hundred battles no danger.

Not knowing the other and not knowing oneself,

In every battle certain defeat.

The Art of War, Sun Tzu ~ 300 B.C.

Wu et al, Annual Rev Genet 2016

Acknowledgements

McDonnell Genome Institute at Wash U:

Rick Wilson (never smokers)

Li Ding **(**never smokers, CPTAC, PDX**)**

Obi and Malachi Griffith (small cell)

WUSM:

Mark Watson, Ting Wang (brain mets),

Sid Devarakonda (small cell, brain mets, never smokers)

NYU:

Harvey Pass (never smokers)

MD Anderson:

Ignacio Wistuba (never smokers)

U of Utah:

Trudy Oliver (small cell)

Broad/NYGC, Cornell: Matthew Meyerson/Marcin Imielinski and colleagues (TCGA)

Broad: Mike Gillette, Shankha Satpathy, Steve Carr and colleagues (CPTAC)

NCI: Ana Robles, ”JC” Zenklusen, Henry Rodriquez and colleagues

Funding: NCI, NHGRI, Lung Cancer Connection, Anheuser Busch Chair, IASLC, Alvin J Siteman Cancer Center, patients and families