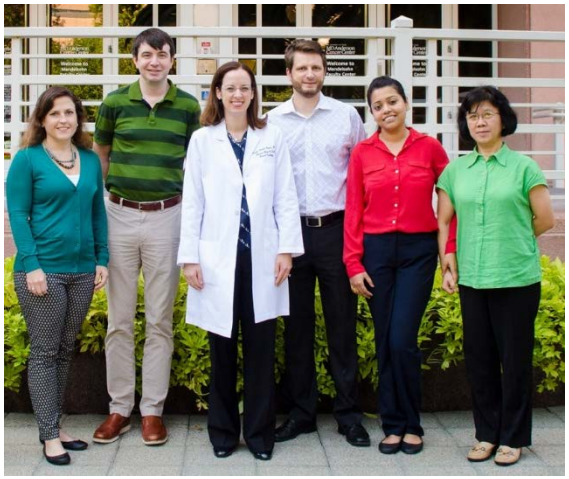
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

DDR and cell cycle vulnerabilities

Lauren Averett Byers, MD

SCLC Research Consortium Meeting
National Cancer Institute
16 March 2018



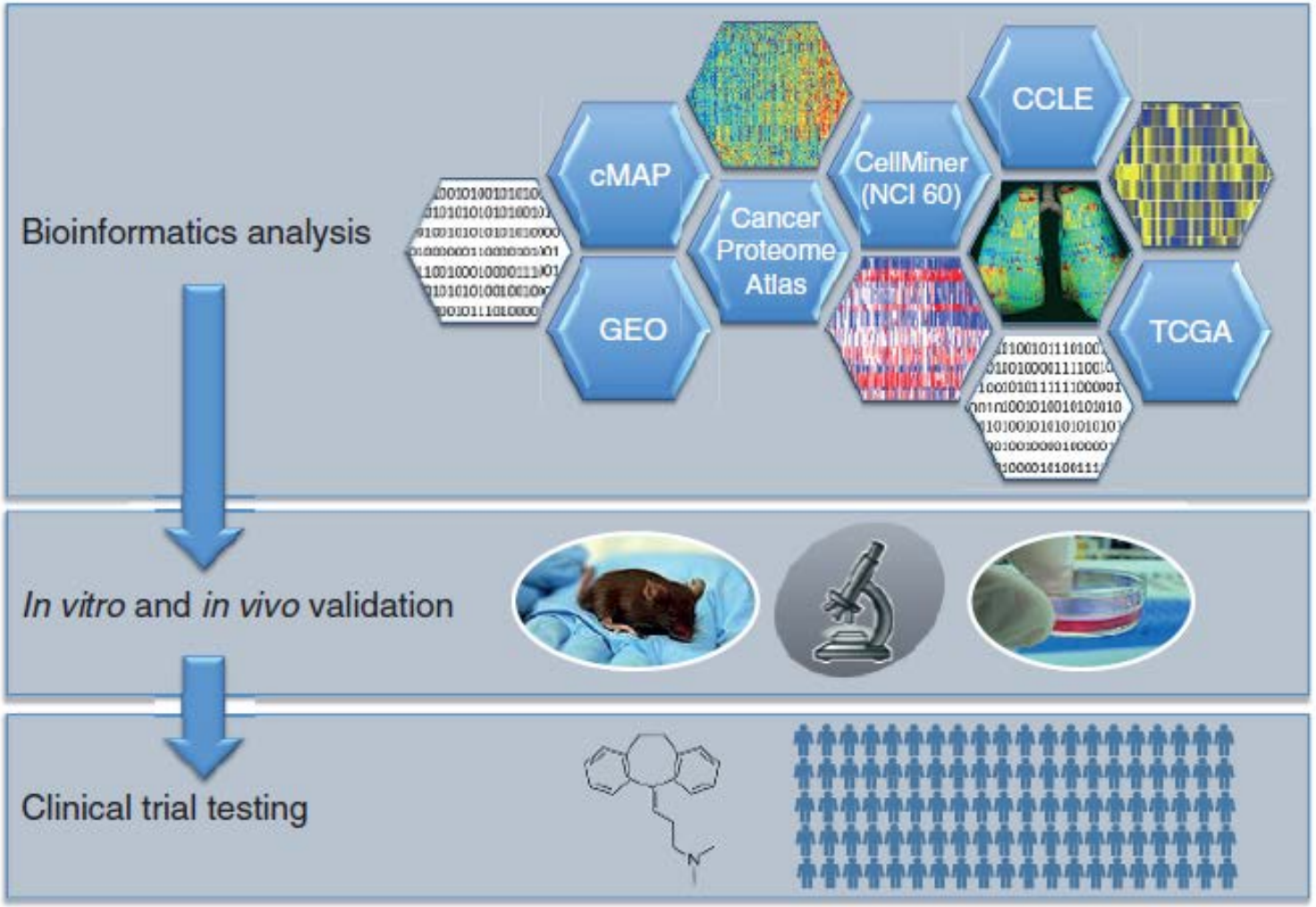
NCI Funded SCLC Projects

- NIH/NCI R01-CA207295
  - ***Therapeutic strategies for targeting PARP1 in small cell lung cancer***

- NIH/NCI U01-CA213273
  - ***Novel therapeutic approaches for enhancing antitumor immunity and overcoming PD-1/PD-L1 inhibitor resistance in SCLC***
    - Project 1: DNA damage response (DDR) inhibition to enhance anti-PD1/PDL1 response

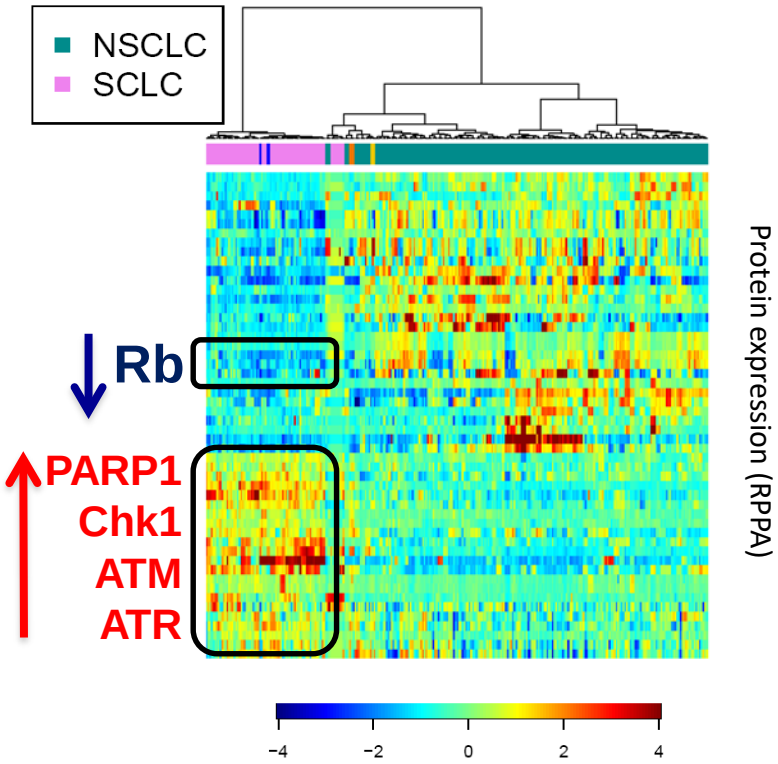
- UTSW/MDACC Lung SPORE

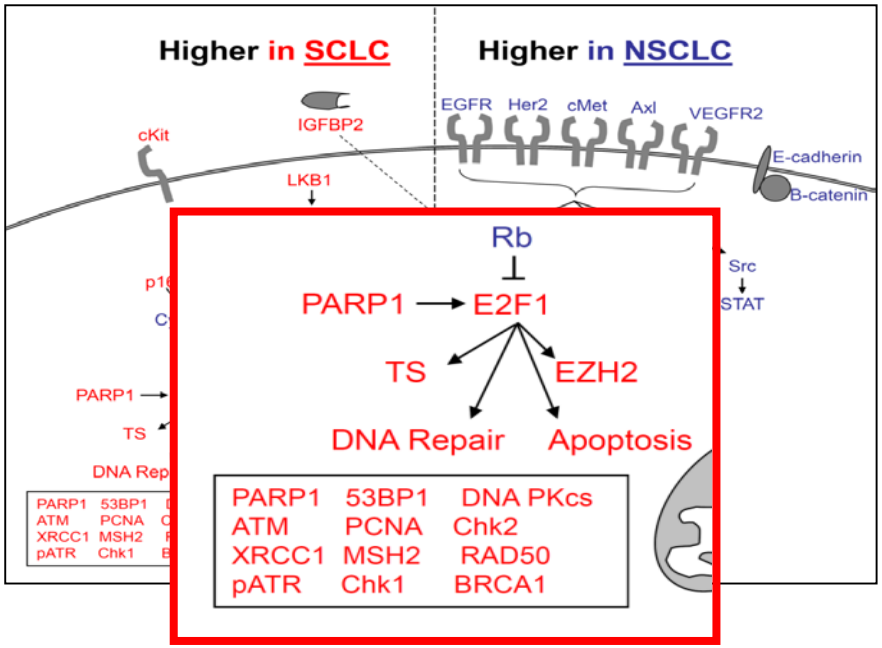
Are there distinct molecular profiles that translate into specific therapeutic vulnerabilities?



Wang and Byers, Cancer Discovery 2013

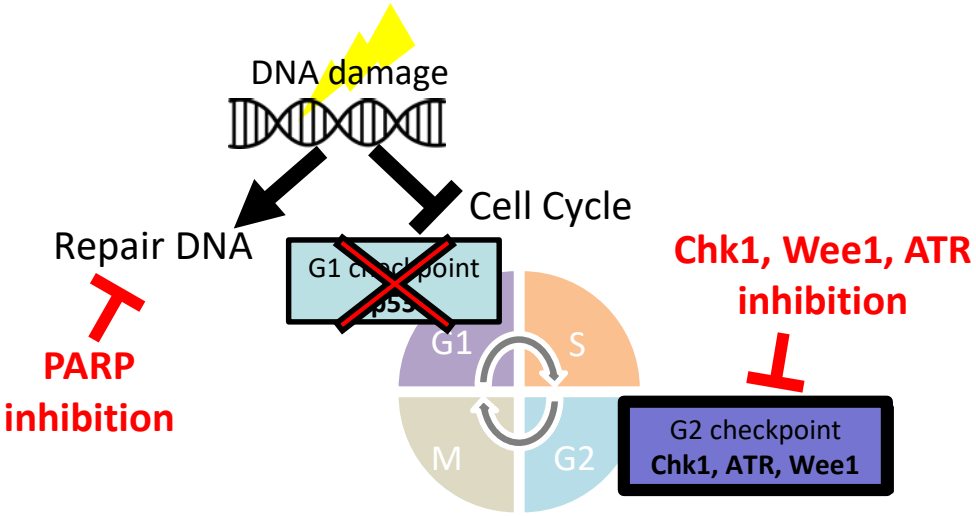
Rewiring of Small Cell Lung Cancer promotes increased expression of DDR proteins



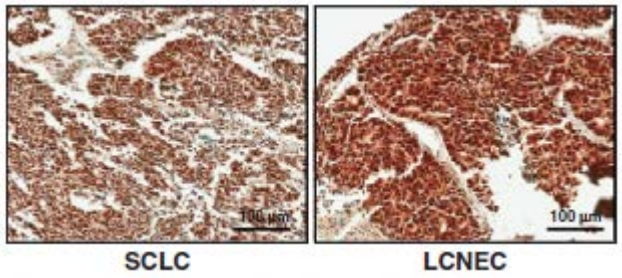


Byers et al. Cancer Discovery, 2012

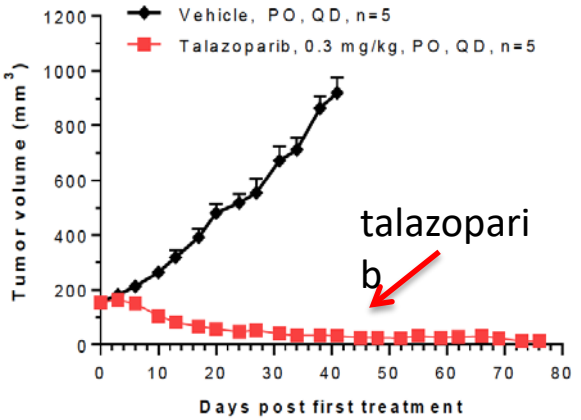
DNA Damage Response (DDR) – a therapeutic vulnerability in SCLC?



PARP IHC (patient tumors)



PARP inhibition -- PDX



Byers et al. Cancer Discovery, 2012
Cardnell et al. CCR, 2013
Feng et al AACR-NCI-EORTC 2014

Published OnlineFirst May 10, 2017; DOI: 10.1158/0008-5472.CAN-16-3409

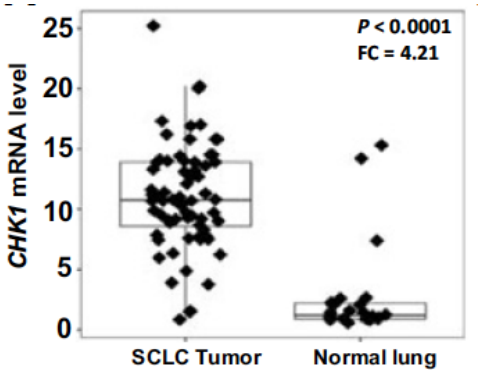
Therapeutics, Targets, and Chemical Biology

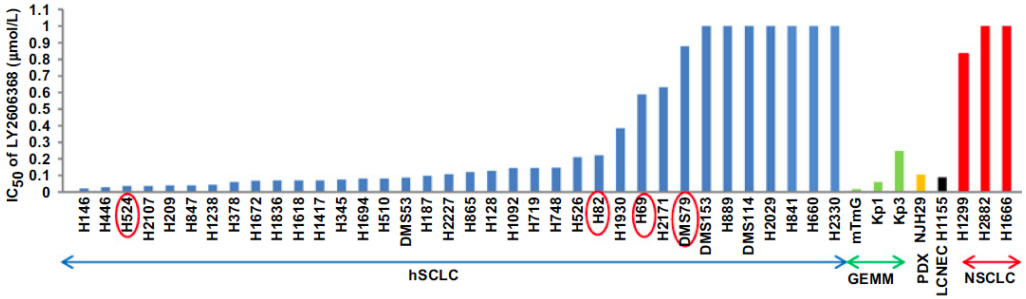
Cancer Research

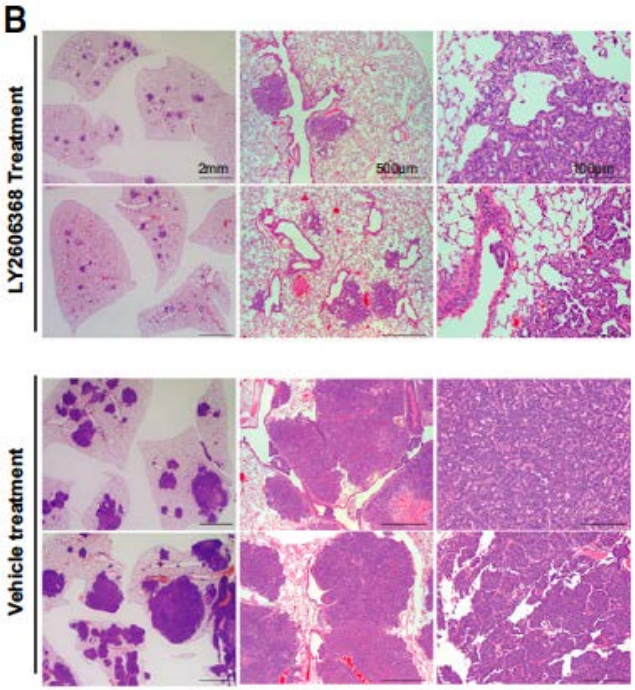
CHK1 Inhibition in Small-Cell Lung Cancer Produces Single-Agent Activity in Biomarker-Defined Disease Subsets and Combination Activity with Cisplatin or Olaparib

Triparna Sen[1], Pan Tong[2], C. Allison Stewart[1], Sandra Cristea[3,4], Aly Valliani[1], David S. Shames[5], Abena B. Redwood[6], You Hong Fan[1], Lerong Li[2], Bonnie S. Glisson[1], John D. Minna[7], Julien Sage[3,4], Don L. Gibbons[1,8], Helen Piwnica-Worms[6], John V. Heymach[1,9], Jing Wang[2], and Lauren Averett Byers[1]

Triparna Sen







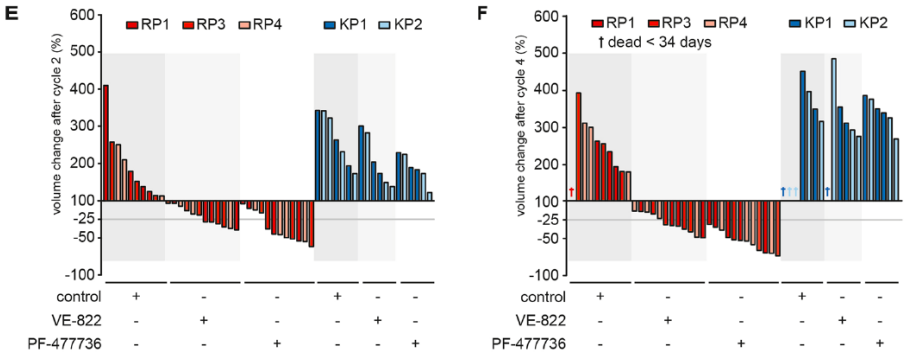
THE M Cancer Center
Making Cancer History®

Collaborators: Julien Sage, Trudy Oliver

Targeting a non-oncogene addiction to the ATR/CHK1 axis for the treatment of small cell lung cancer

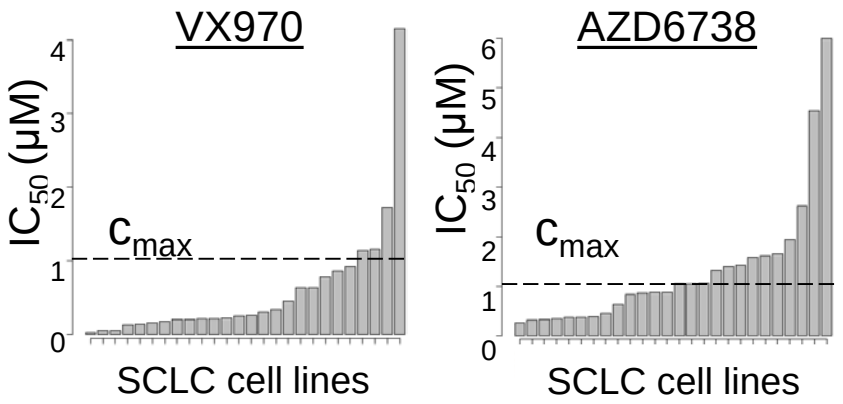
Fabian Doerr[1,2,3], Julie George[4], Anna Schmitt[1,2], Filippo Beleggia[1,2], Tim Rehkämper[1,2], Sarah Hermann[1,2], Vonn Walter[5,6], Jean-Philip Weber[7], Roman K. Thomas[4,8,9], Maike Wittersheim[8], Reinhard Büttner[8], Thorsten Persigehl[7] & H. Christian Reinhardt[1,2]

Scientific Reports, Nov 2017



ATRi (VE-822), Chk1i (PF-477736)

ATRi sensitivity in human cell lines



Carl Gay, IASLC Targeted Therapy Mtg 2018

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Published OnlineFirst July 11, 2017; DOI: 10.1158/1078-0432.CCR-17-1284

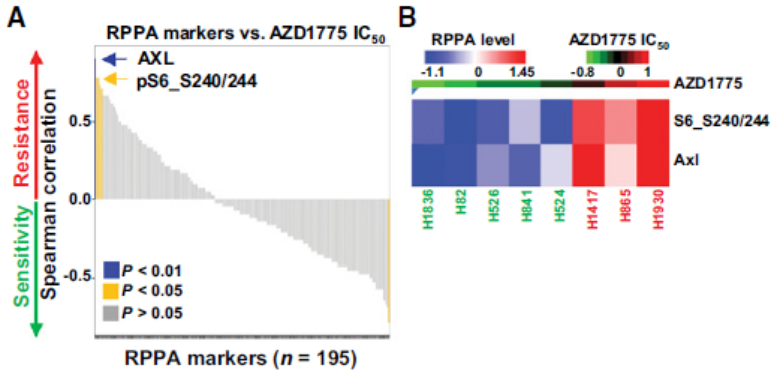
Cancer Therapy: Preclinical

Clinical Cancer Research

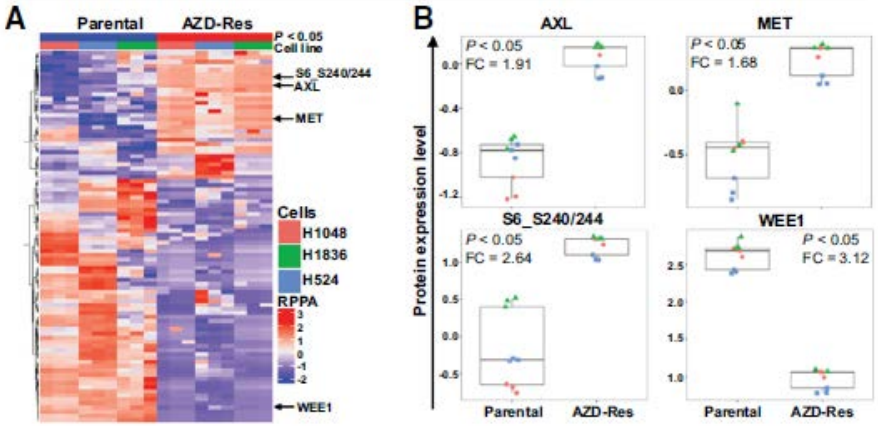
Targeting AXL and mTOR Pathway Overcomes Primary and Acquired Resistance to WEE1 Inhibition in Small-Cell Lung Cancer

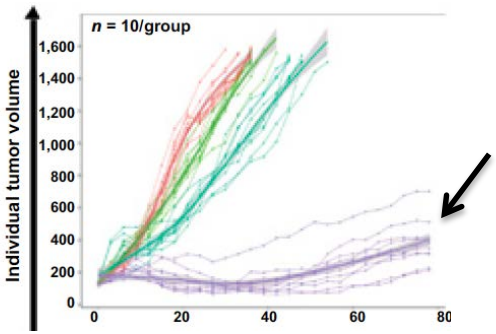
Triparna Sen[1], Pan Tong[2], Lixia Diao[2], Lerong Li[2], Youhong Fan[1], Jennifer Hoff[1], John V. Heymach[1,3], Jing Wang[2], and Lauren Averett Byers[1]

Biomarkers of Primary Wee1i resistance



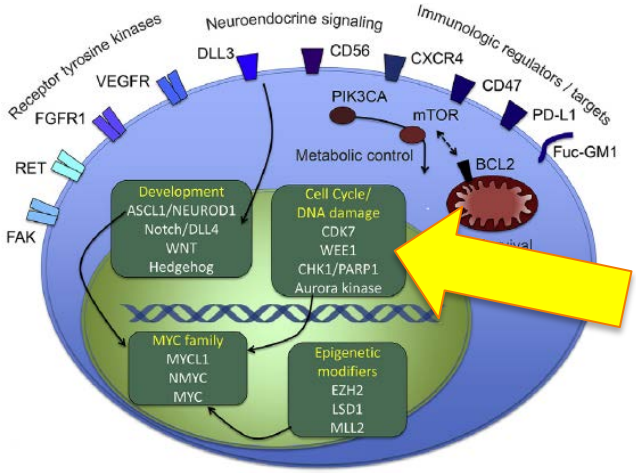
Biomarkers of Acquired Wee1i resistance





Wee1 + AXL inhibition combination (Wee1i resistant model)

Growing number of PARP, ATR, Chk1, Wee1 and other DDR inhibitors in clinical trials



Bunn, J Thorac Oncol 2016

Table 1 DDR-targeted therapy clinical trials in SCLC (list includes ongoing trials as of 12/2017)

Trial	Treatment	Indication
PARP inhibitor trials in SCLC		
NCT03227016	Phase 1: veliparib alone; phase 2: veliparib + topotecan	Relapsed/refractory ES-SCLC
NCT02734004	Phase 1/2: MEDI4736 (anti-PD-L1) in combination with olaparib	Advanced solid tumors including ES-SCLC cohort
NCT02289690	Phase 2: carboplatin/etoposide +/– veliparib	Treatment-naïve ES-SCLC
NCT02769962	Phase 1/2: CRLX101 (camptothecin nanoparticle) + olaparib	Relapsed/refractory ES-SCLC
NCT01642251	Phase 1/2: cisplatin/etoposide +/– veliparib	Treatment-naïve ES-SCLC
NCT02498613	Phase 2: olaparib + cediranib (anti-VEGFR TKI)	Advanced solid tumors including ES-SCLC cohort
NCT02446704	Phase 1/2: olaparib + TMZ	Relapsed/refractory ES-SCLC
NCT03009682	Phase 2: olaparib monotherapy	Relapsed/refractory ES-SCLC harboring HR mutations
NCT02511795	Phase 1b: olaparib + AZD1775 (WEE1 inhibitor)	Advanced solid tumors including ES-SCLC cohort
ATR inhibitor trials including SCLC		
NCT02487095	Phase 1/2: topotecan + VX970	Advanced small cell cancers
NCT02589522	Phase 1: VX-970 + WBRT	Brain metastases from tumors
NCT02223923	Phase 1: AZD6738 +/– RT	Advanced solid tumors
NCT02723864	Phase 1: veliparib + VX-970 + cisplatin	Advanced solid tumors
NCT02595931	Phase 1: VX-970 + irinotecan	Advanced solid tumors
NCT02157792	Phase 1: VX-970 + chemotherapy	Advanced solid tumors
NCT03188965	Phase 1: BAY1895344 monotherapy	Advanced solid tumors
CHK inhibitor trials including SCLC		
NCT02735980	Phase 2: prexasertib monotherapy	Relapsed/refractory ES-SCLC
NCT02797964	Phase 1: SRA737 monotherapy	Advanced solid tumors
NCT02797977	Phase 1: SRA737 + gemcitabine +/– cisplatin	Advanced solid tumors
NCT02873975	Phase 2: prexasertib monotherapy	Advanced solid tumors with HR deficiency or replicative stress
NCT03057145	Phase 1: prexasertib + olaparib	Advanced solid tumors
Wee1 inhibitor trials including SCLC		
NCT02482311	Phase 1: AZD1775 monotherapy	Advanced solid tumors including ES-SCLC cohort
NCT02511795	Phase 1b: AZD1775 + olaparib	Advanced solid tumors including ES-SCLC cohort
NCT02593019	Phase 2: AZD1775 monotherapy	Relapsed/refractory ES-SCLC
NCT02688907	Phase 2: AZD1775 monotherapy	Relapsed/refractory ES-SCLC with MYC amplifications or CDKN2A + TP53 mutations

Sen, Gay, and Byers. TLCR 2018

Combination of Temozolomide with the PARP inhibitor Veliparib improves outcomes in relapsed SCLC

Recurrent SCLC patients

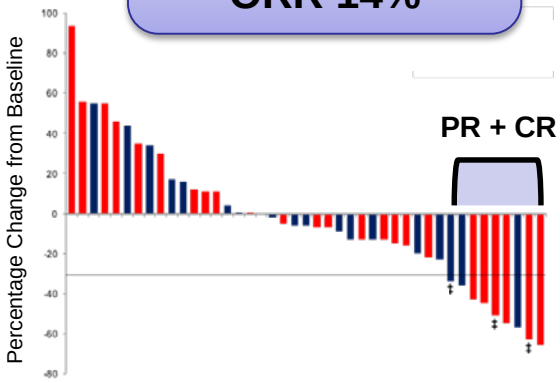
- 1-2 prior regimens
- 104 pts treated

Clinical Outcomes

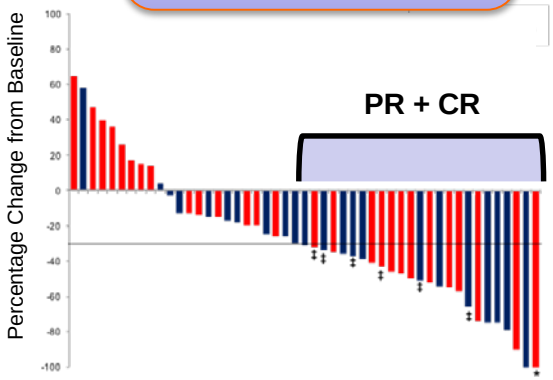
- **Higher Response Rate** in Veliparib/TMZ arm (39% vs. 14%)
- **Higher Overall Survival** with combination in patients with biomarker-positive (SLFN11 ≥ 1%) tumors

Pietanza and Byers, et al, ASCO 2016; World Lung Cancer Conference 2017

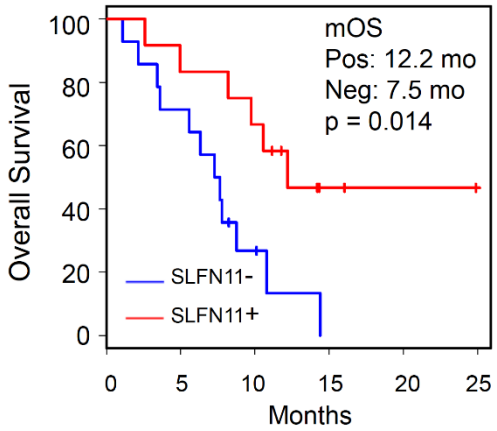
Placebo/TMZ
(n=44)
ORR 14%



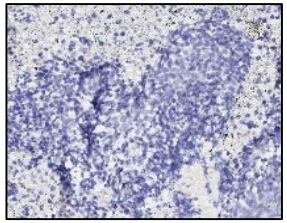
Veliparib/TMZ
(n=49)
ORR 39%



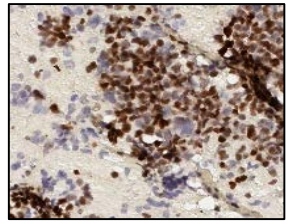
Veliparib/TMZ



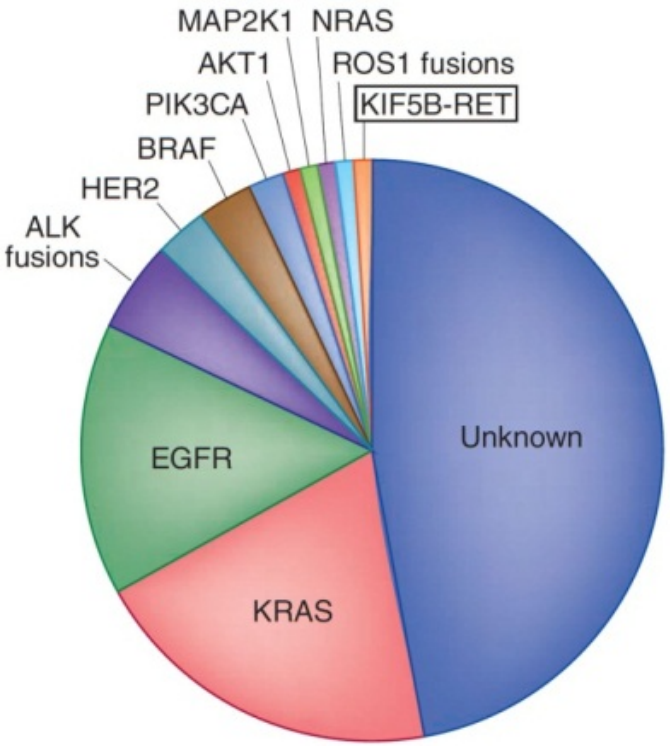
SLFN11 Negative



SLFN11 Positive

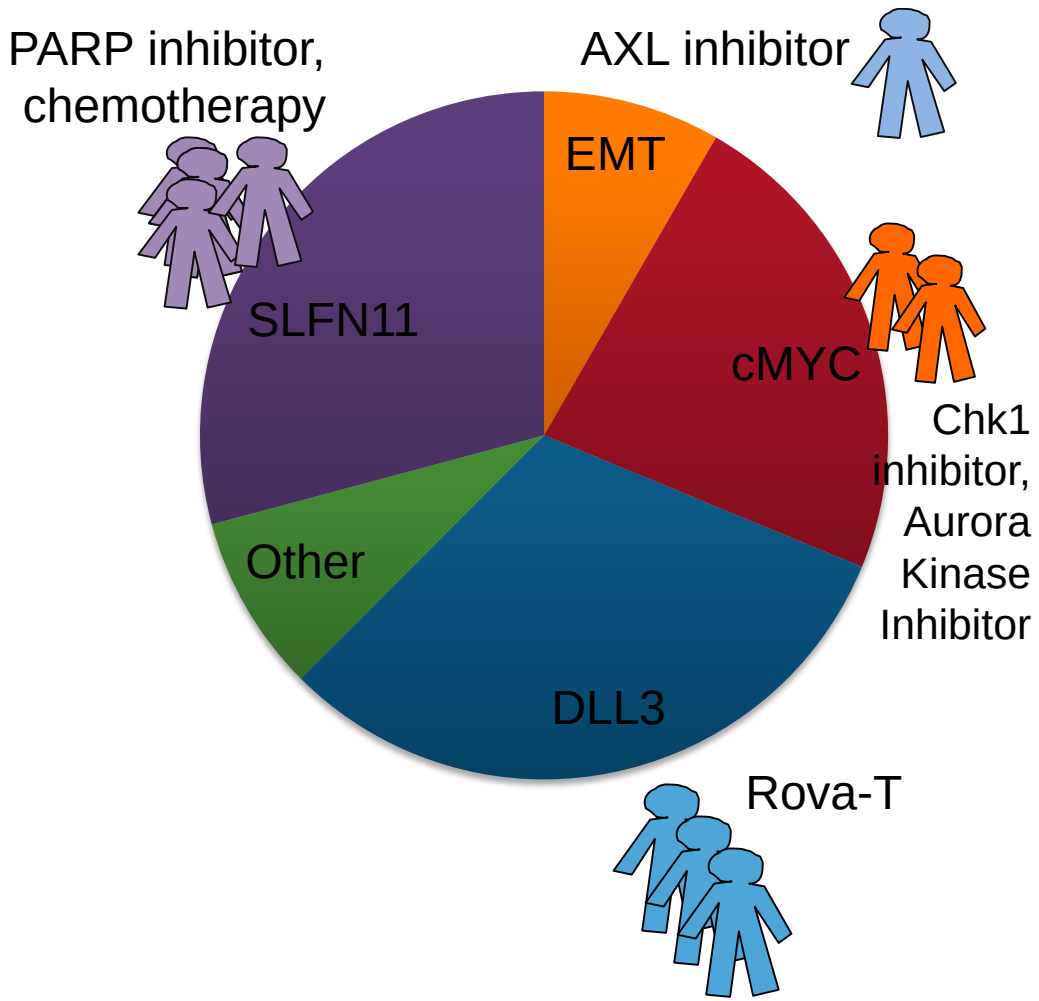


NSCLC – Genomic Pie Slices



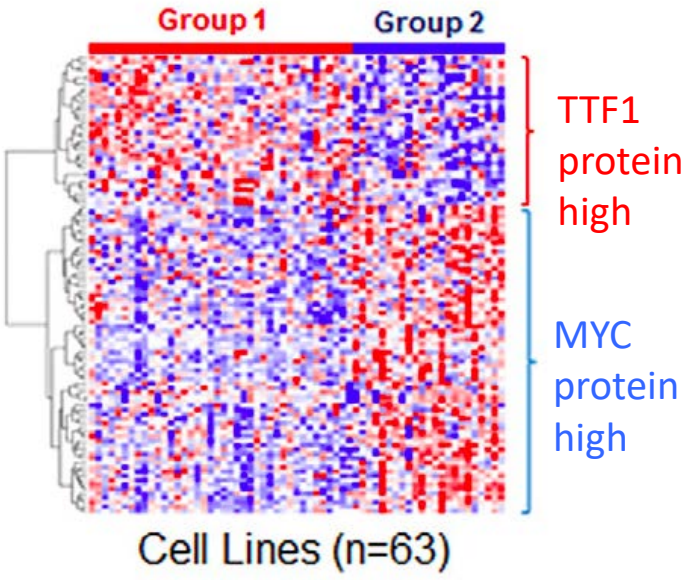
Pao, Hutchinson; Nat Med 2012

SCLC – Evolving Proteomic Landscape

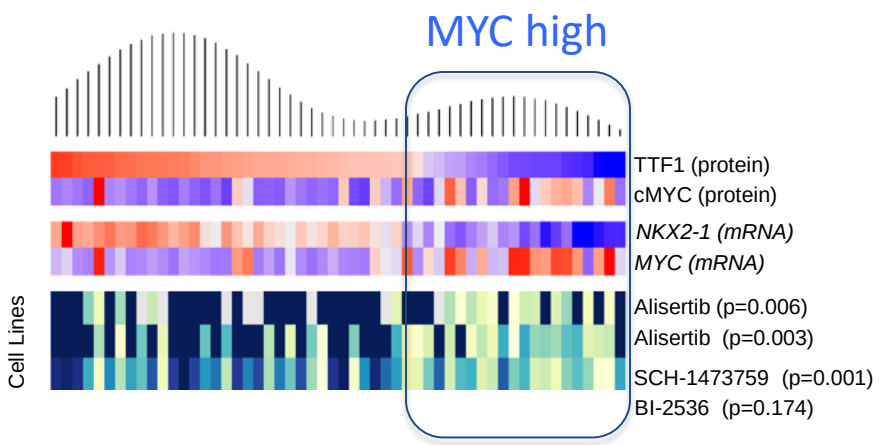


Protein expression of TTF1 and cMYC define distinct molecular subgroups of small cell lung cancer with unique vulnerabilities to aurora kinase inhibition, DLL3 targeting, and other targeted therapies

Robert J. Cardnell[1], Lerong Li[2], Triparna Sen[1], Rasha Bara[1], Pan Tong[2], Junya Fujimoto[3], Abbie S. Ireland[4], Matthew R. Guthrie[4], Sheila Bheddah[5], Upasana Banerjee[1], Nene N. Kalu[1], You-Hong Fan[1], Scott J. Dylla[5], Faye M. Johnson[1,6], Ignacio I. Wistuba[3], Trudy G. Oliver[4], John V. Heymach[1], Bonnie S. Glisson[1], Jing Wang[2,4,*] and Lauren A. Byers[1,6,*]



MYC-high SCLC sensitive to Aurora Kinase inhibition

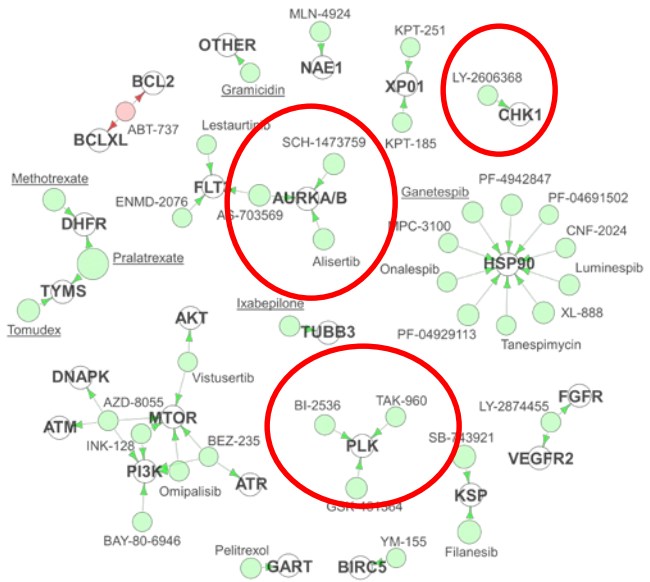


Protein expression of TTF1 and cMYC define distinct molecular subgroups of small cell lung cancer with unique vulnerabilities to aurora kinase inhibition, DLL3 targeting, and other targeted therapies

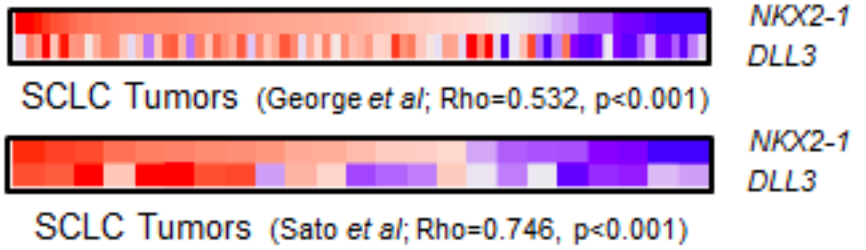
Robert J. Cardnell[1], Lerong Li[2], Triparna Sen[1], Rasha Bara[1], Pan Tong[2], Junya Fujimoto[3], Abbie S. Ireland[4], Matthew R. Guthrie[4], Sheila Bheddah[5], Upasana Banerjee[1], Nene N. Kalu[1], You-Hong Fan[1], Scott J. Dylla[5], Faye M. Johnson[1,6], Ignacio I. Wistuba[3], Trudy G. Oliver[4], John V. Heymach[1], Bonnie S. Glisson[1], Jing Wang[2,4,*] and Lauren A. Byers[1,6,*]

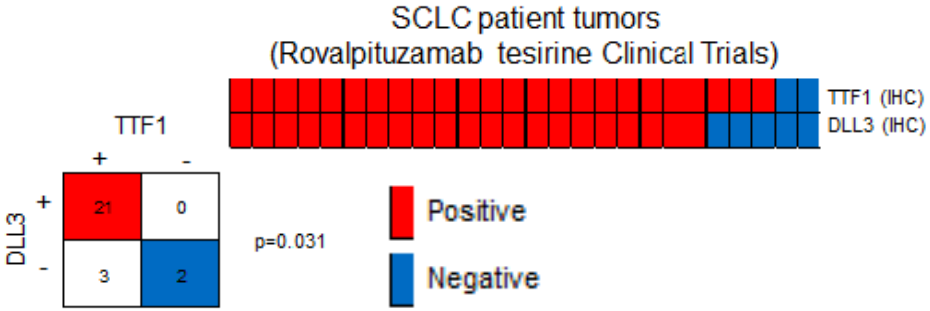
Targets for **non-NE** SCLC (TTF1-low/MYC-high)

e.g., Aurora, PLK, Chk1



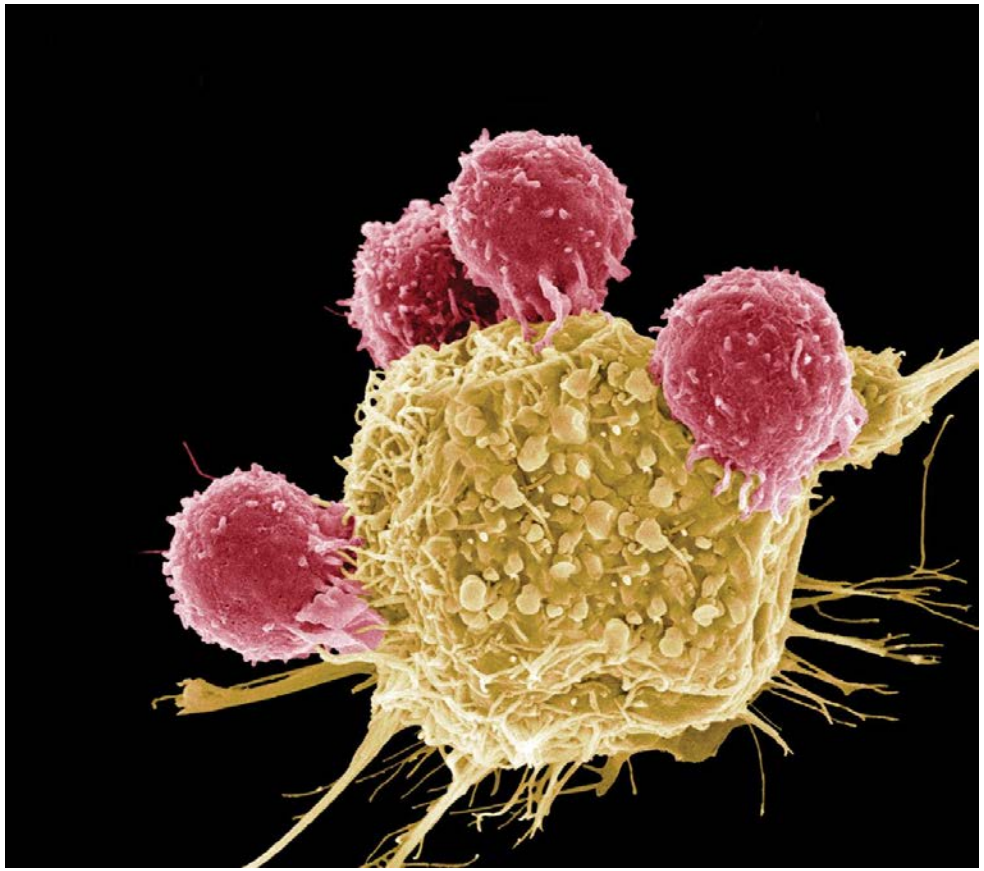
Low DLL3 expression in **TTF1-low** SCLC





Immunotherapy = Bacon?

National Geographic Magazine, March 2018



New kinds of cancer treatments help the immune system's T cells (pink) find and attack cancer cells (yellow).

PHOTOGRAPH BY STEVE GSCHMEISSNER, SCIENCE SOURCE (COLORIZED SEM)

Eventually, …doctors will be able to target more types of cancer with combination treatments, including antibodies that remove immunological barriers.

"I think they will be like bacon…Bacon is good on everything."

-Elfriede Noessner, German Cancer Research Center for Environmental Health

PARP inhibition increases PDL1 expression and may activate innate immune response

Cancer Therapy: Preclinical

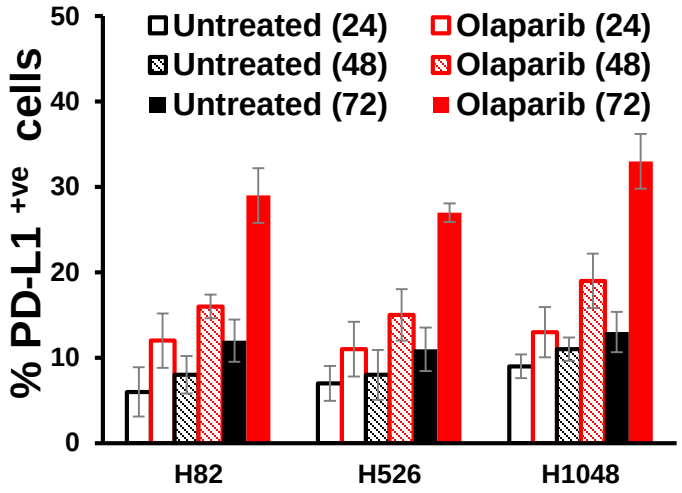
Clinical Cancer Research

PARP Inhibitor Upregulates PD-L1 Expression and Enhances Cancer-Associated Immunosuppression

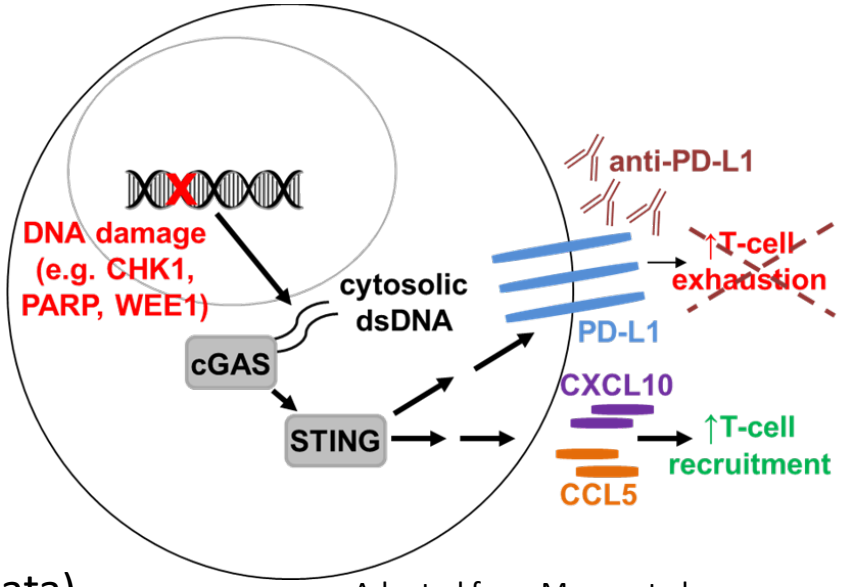
Shiping Jiao[1,2], Weiya Xia[1], Hirohito Yamaguchi[1], Yongkun Wei[1], Mei-Kuang Chen[1,2], Jung-Mao Hsu[1], Jennifer L. Hsu[1,3,4], Wen-Hsuan Yu[1,2], Yi Du[1], Heng-Huan Lee[1], Chia-Wei Li[1], Chao-Kai Chou[1], Seung-Oe Lim[1], Shih-Shin Chang[1], Jennifer Litton[5], Banu Arun[5], Gabriel N. Hortobagyi[5], and Mien-Chie Hung[1,2,3,4]

Jiao et al, CCR 2017

Olaparib increases PDL1 (SCLC)

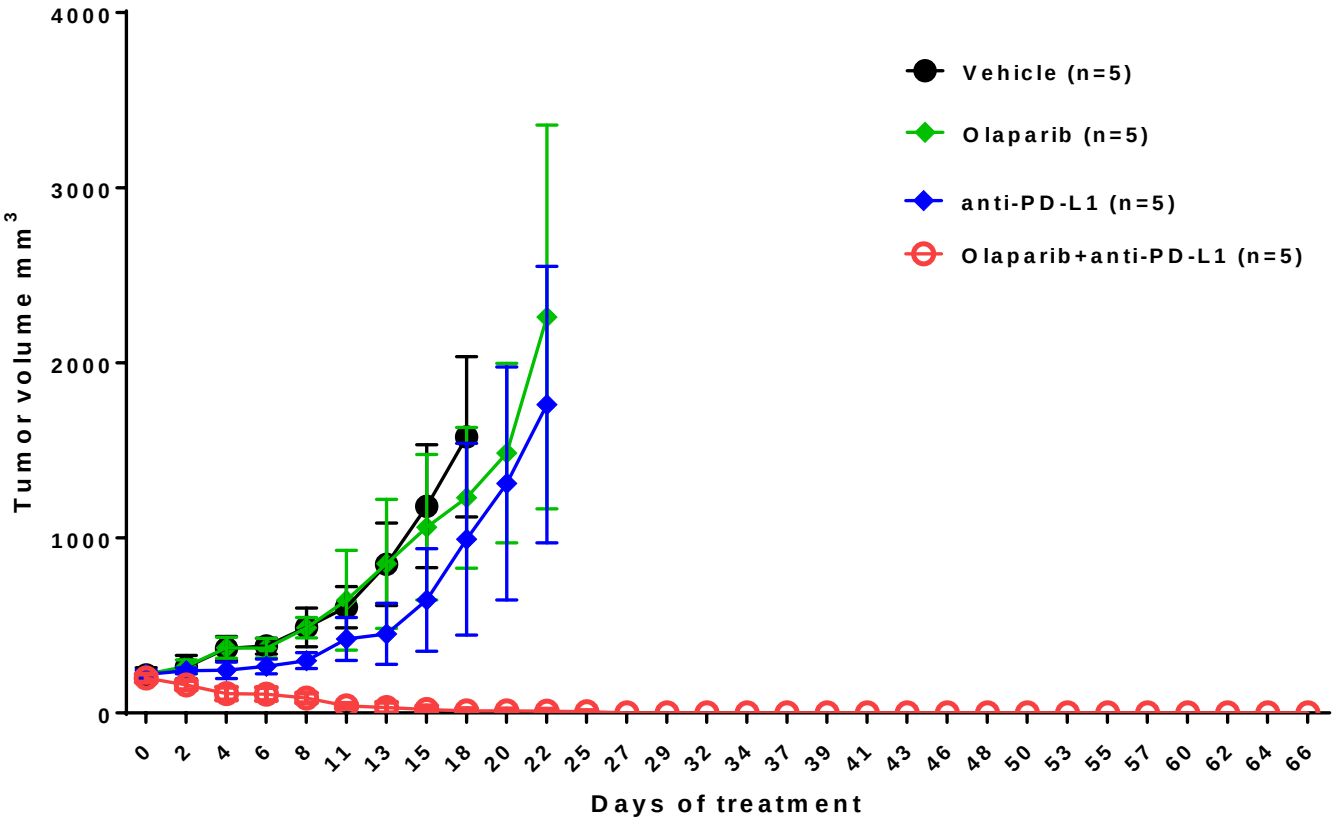


Byers, IASLC Santa Monica 2018 (unpublished data)



Adapted from Mouw et al.

Co-targeting PARP1 (olaparib) and PD-L1 causes significant tumor regression in SCLC model

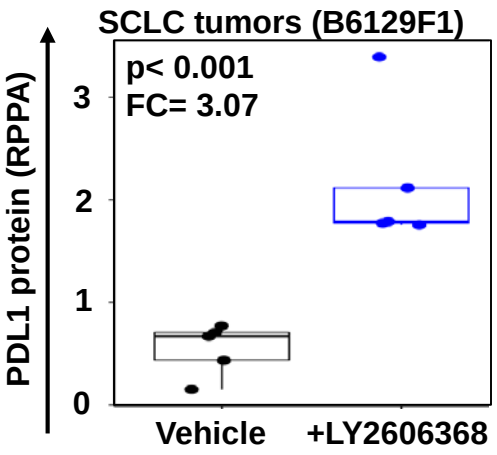


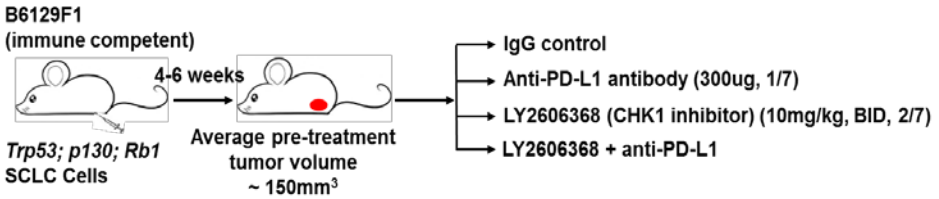
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

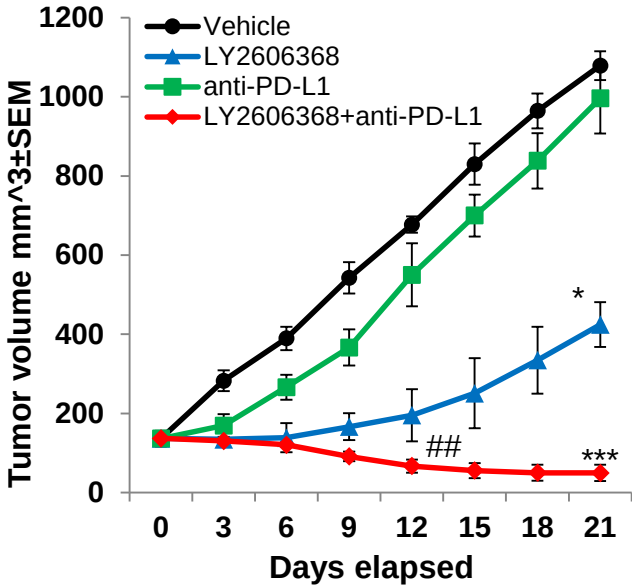
Naoto Morikawa, John Heymach

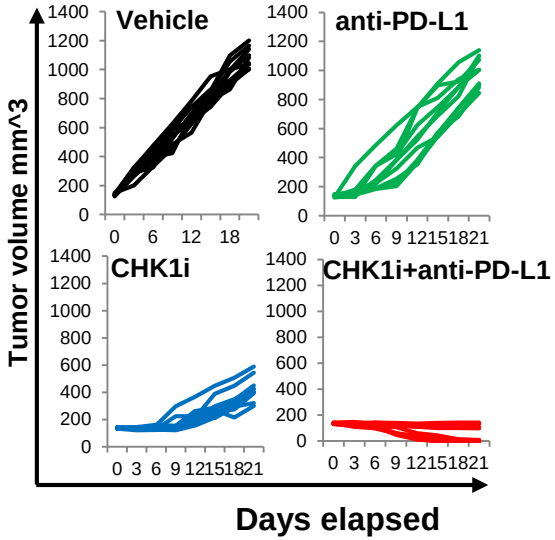
Co-targeting CHK1 and PD-L1 causes significant tumor regression in SCLC model

Chk1i increases PDL1







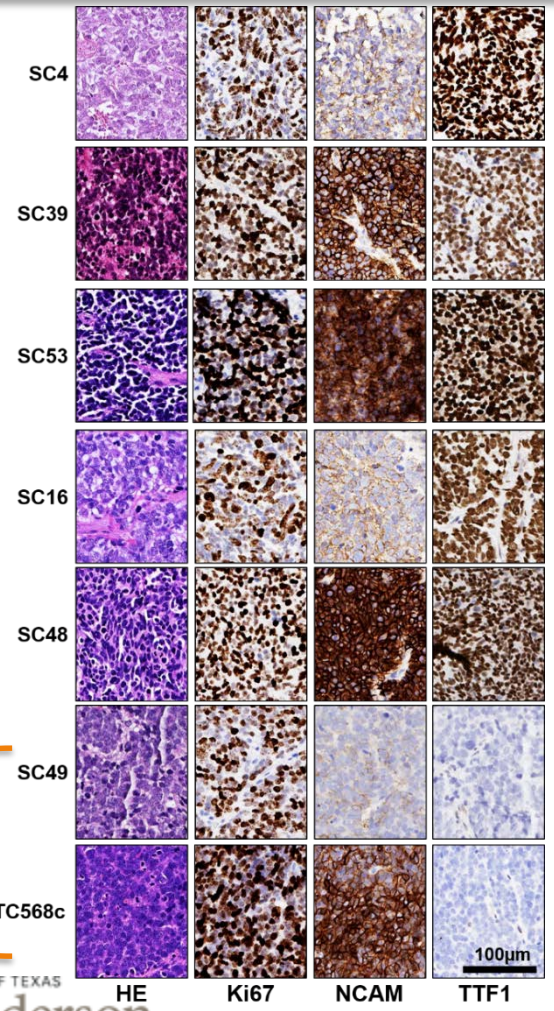


Complete tumor regression in 60% mice

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Sen et al, WCLC 2017

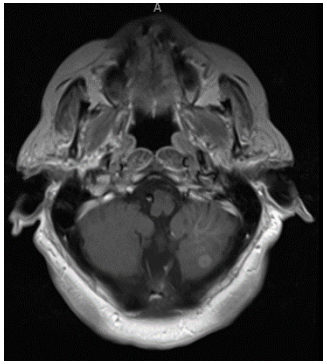
CTC-derived xenograft models (CDXs)

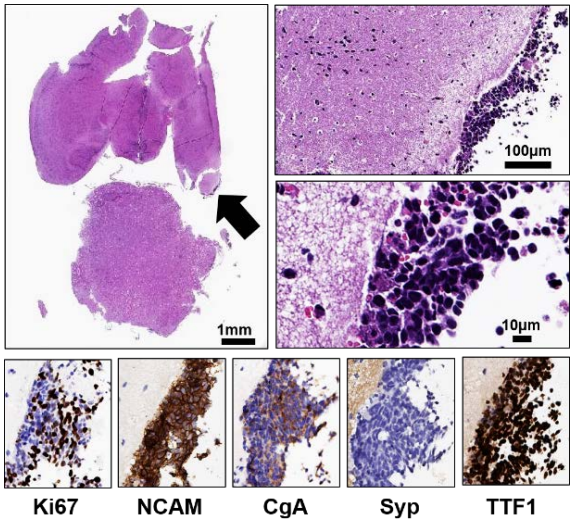


Allison Stewart

Carl Gay

Leptomeningeal Disease (SC39)

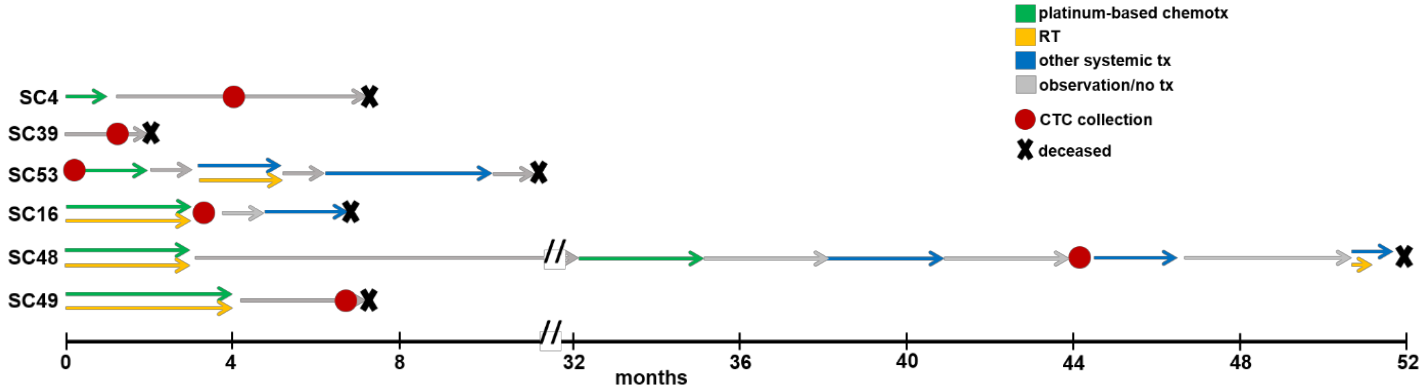


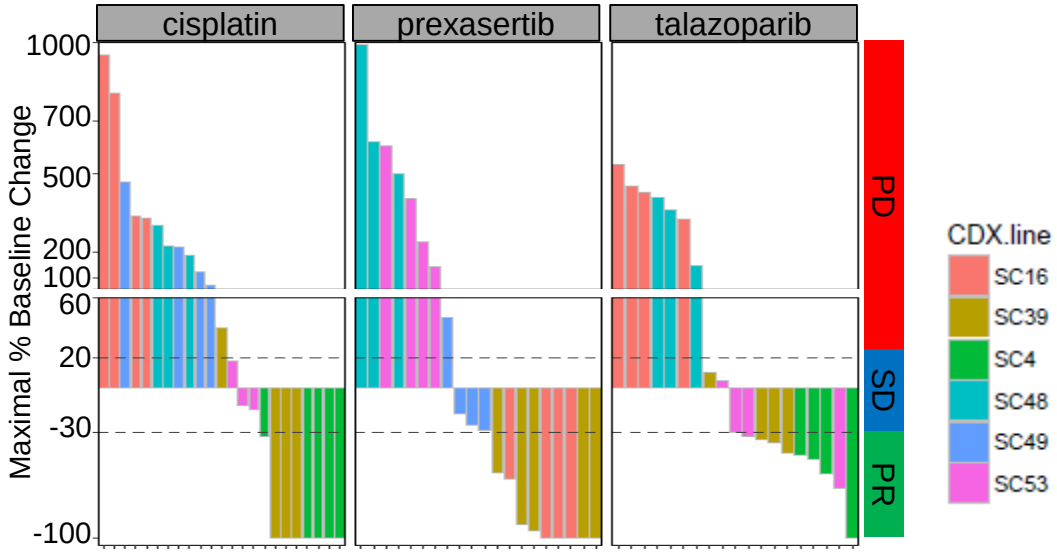


THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Junya Fujimoto, John Heymach, Hai Tran, Ignacio Wistuba
MDACC Lung Moon Shot Program
(unpublished)

CDX in vivo response matches clinical response of patient to chemotherapy

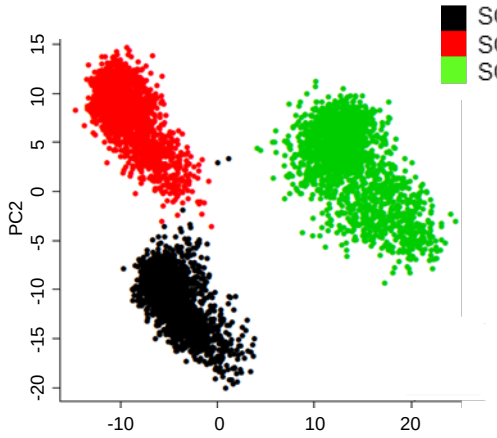


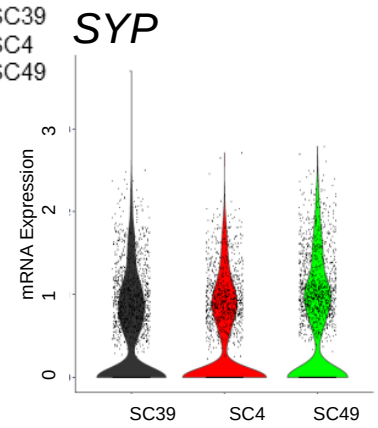


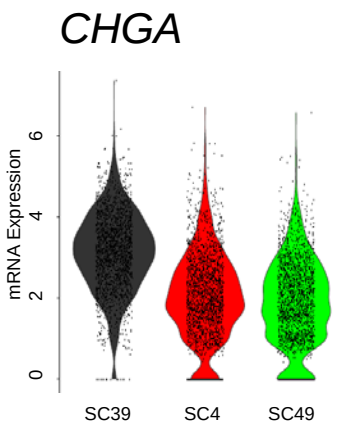
Allison Stewart, Carl Gay (Byers Lab), unpublished

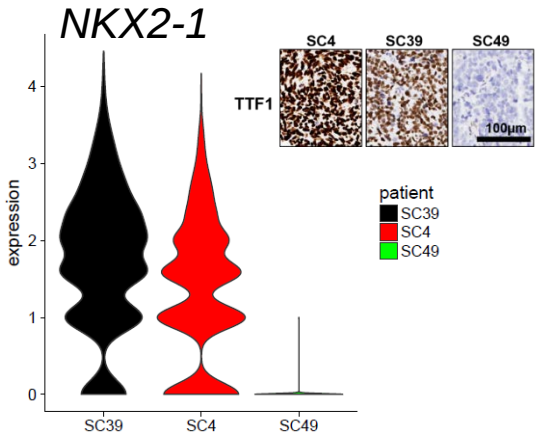
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

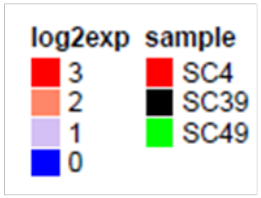
Single cell RNAseq analysis of CDX models to explore tumor heterogeneity

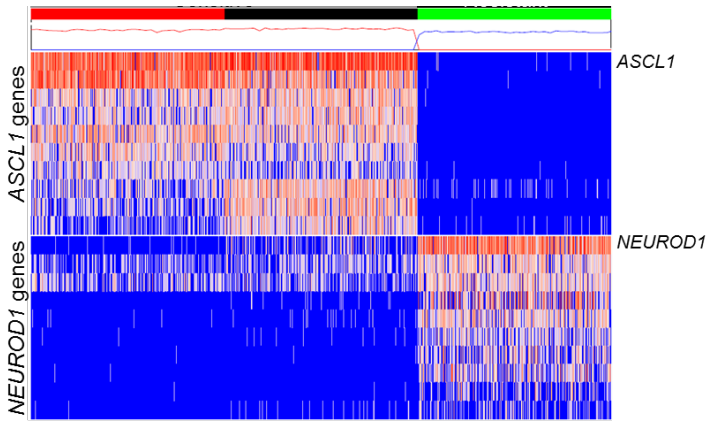


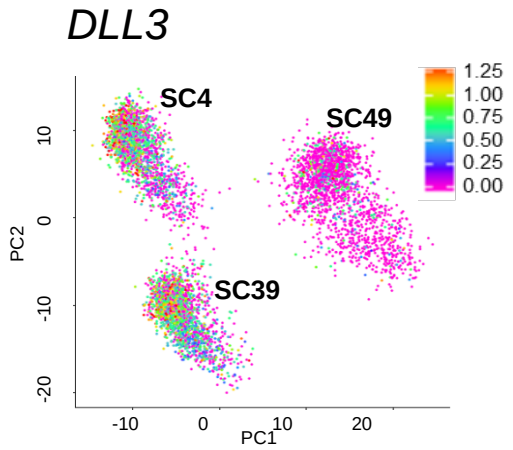








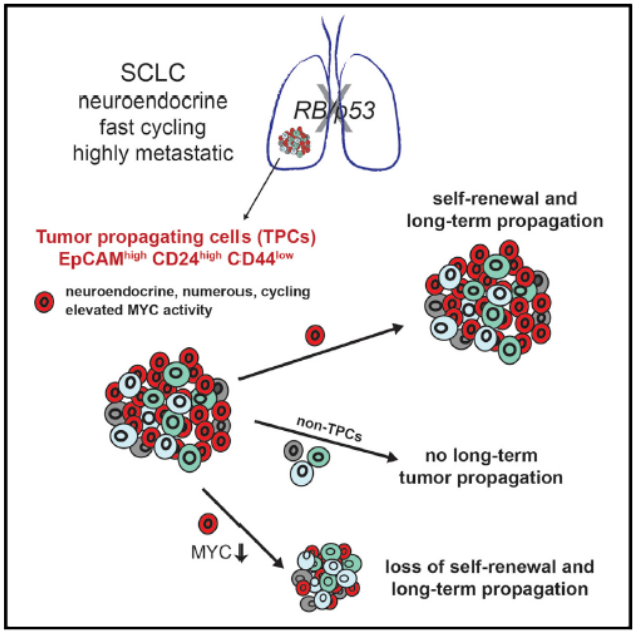




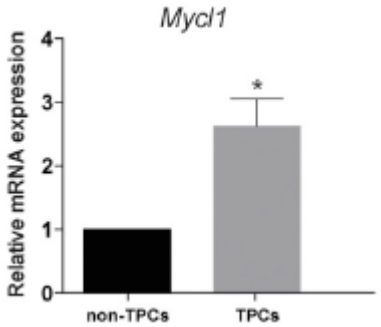
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Allison Stewart, Carl Gay, Yuanxin Xi, Jing Wang, unpublished; Funded by SWOG/JAX Pilot

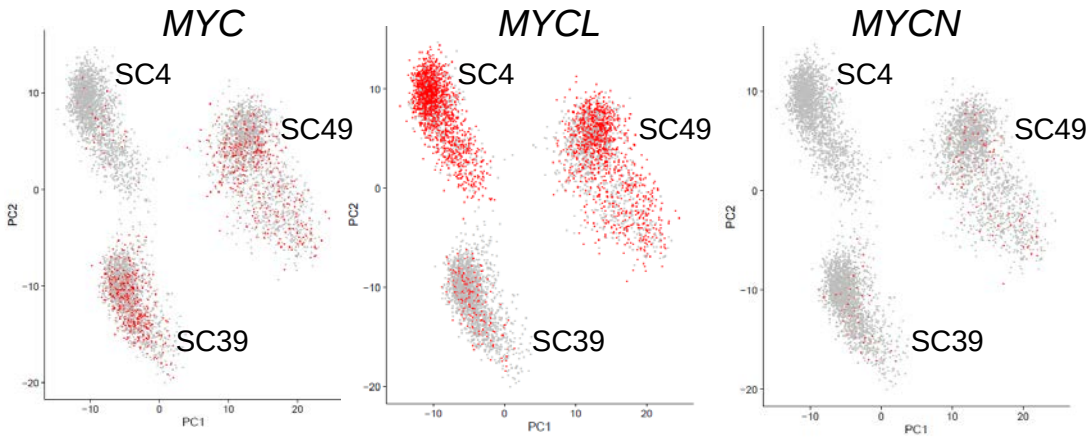
L-MYC is associated with tumor propagation in SCLC



Jahchan et al., 2016



CDX tumors - Single cell RNAseq



Allison Stewart, Carl Gay, Yuanxin Xi, Jing Wang, unpublished

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Conclusion

- Activity of DNA damage response (DDR) and cell cycle inhibitors observed in SCLC models (e.g., PARP1, Chk1, Wee1, ATR inhibitors), many now in the clinic
- Candidate biomarkers for specific DDR inhibitors identified, with initial validation of SLFN11 in TMZ-veliparib treated patients (CTEP/NCI trial)
- DDR-IO combinations enhance anti-tumor effect in syngeneic and spontaneous GEMM models, warrant further investigation in the clinic
- CTC-derived xenograft models (CDXs) provide an opportunity for increasing the number of drug resistant models for translational research
- Single cell RNAseq data reveals intra-tumoral heterogeneity. Contribution of tumor heterogeneity to resistance is being further investigated.

Acknowledgements

Byers Lab:
Triparna Sen
Carl Gay
Allison Stewart
Robert Cardnell
Kavya Ramkumar
Carminia Della Corte

Bioinformatics:
Jing Wang
Yuanxin Xi
Pan Tong
Lixia Diao
Lerong Li

Other MD Anderson:
John Heymach
Don Gibbons
Bonnie Glisson
Junya Fujimoto
Ignacio Wistuba
John De Groot
Bingliang Fang

Other Collaborators
Julien Sage
Trudy Oliver
John Minna
Adi Gazdar

Paul Robson Lab
--Siva Vijayakumar
--Mohan Bolisetty

Funding:
NIH/NCI 1-U01-CA213273
NIH/NCI 1-R01-CA207295
MDACC CCSG (P30-CA016672)
UTSW/MDACC SPORE (5-P50-CA070907)
SWOG ITSC Grant (single cell analysis)
Lung Cancer Research Foundation
LUNGevity Foundation
The University of Texas MD Anderson Lung Cancer Moon Shot Program
The Rexanna Foundation
MD Anderson Small Cell Lung Cancer Working Group

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®