Progress in Small Cell Lung Cancer (SCLC): Working Group Update 2019

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Outline

- Primer on SCLC
- 2014 Scientific Framework for SCLC
- Recent Scientific and Clinical Advances
- Feb 4, 2019 SCLC Progress Working Group Meeting
- Conclusions and Discussion of Next Steps

Incidence rates of Lung Cancer United States between 2010 – 2014

- 61.3 lung cancer cases per 100,000 persons
- Decreased 2.2% per year
- Incidence rates higher among
  - Men
  - Non-Hispanics
  - Nonmetropolitan counties
  - Regions other than West

Tumor characteristic**	No.	%
Total	**942,919**	**100.0**
Histology		
Non–small cell carcinoma	764,914	81.1
Adenocarcinoma	448,320	47.5
Squamous cell carcinoma	230,569	24.5
Non–small cell carcinoma, NOS	70,142	7.4
Large cell carcinoma	15,883	1.7
Small cell carcinoma	133,192	14.1
Epithelial carcinoma	23,319	2.5
All other histologies	21,494	2.3
Stage††		
Localized	189,113	20.1
Regional	227,876	24.2
Distant	495,671	52.6
Unknown	30,259	3.2

Gallaway MS et al, MMWR 2018;67(12)

SCLC is still a recalcitrant cancer in 2019

- US mortality ~ 30,000 lives/year (m/w ratio 1:1)
- 5-year survival <7%
- Treatment of SCLC (etoposide + platinum and radiation) has changed only in 2018 after 35 years with the addition of checkpoint inhibitors
- Initial responses to chemotherapy are short-lived and followed by aggressive recurrence
- Increased, but still limited availability of materials for research
- Limited early diagnostic approaches
- Avoidance of the use of tobacco is the only known way to prevent the disease

2014 Scientific Framework for SCLC: Recommendations

- **Better Research Tools for the Study of SCLC**

  Build better research tools for the study of SCLC by
  (a) optimizing the collection of tumor tissue specimens representing distinct phases of SCLC
  (b) developing new tumor models (conditionally-reprogrammed cell lines, patient-derived xenografts, and genetically-engineered mouse models) that reflect the phases of SCLC found in the clinic.

- **Comprehensive Genomic Profiling of SCLC**

  Expand comprehensive genomic profiling studies of clinically-annotated SCLC specimens to improve the basic understanding of the frequency, distribution, and range of molecular abnormalities that exist both at diagnosis and following therapeutic relapse.

- **New Diagnostic Approaches for SCLC**

  Investigate new diagnostic approaches for populations at high risk of developing SCLC.

- **Therapeutic Development Efforts**

  Focus therapeutic development efforts on specific molecular vulnerabilities of SCLC (tumor suppressor genes, unique genetic drivers and their pathways, neuronal characteristics, and immunotherapy).

- **Mechanisms Underlying Both High Rate of Initial Response and Rapid Emergence of Drug and Radiation Resistance**

  Examine the mechanisms underlying both the high initial rate of response to primary SCLC therapy and the rapid emergence of drug and radiation resistance following completion of treatment.

2018 SCLC Progress Working Group Members

Co-Chairs: Alex Adjei and Laurie Gaspar

Members

Lauren Averett Byers

David Carbon

Steven Dubinett

Janet Freeman-Daily

Ramaswamy Govindan

Christine Hann

Eric Haura

John Minna

David Mankoff

Roman Perez-Soler

Charles Rudin

Julien Sage

David Schrump (ex officio)

Ignacio Wistuba

NIH Liaisons

James Doroshow

Suzanne Forry

Wolf Lindwasser

Shakun Malik

Yves Pommier

Sheila Prindiville

Eva Szabo

Peter Ujhazy

Anish Thomas

2019 Update

- Reconvened the SCLC Progress WG via a series of webinars in January 2019 and an in-person meeting on February 4, 2019 to:
  - Provide update of key scientific advances (last five years) and assess the continued scientific relevance of the initiatives in light of current gaps and opportunities
  - Discuss progress made by the NCI (are we on track?)
- Information provided by NCI
  - FY 2018 SCLC Extramural Grants
  - SCLC Clinical Trials
  - SCLC 2014-2018 Publications
- WG report will provide basis for 5-year update of scientific framework due to Congress by June 30, 2019

SCLC Progress WG Meeting – Feb 4, 2019

- Working Group Co-Chairs: Alex Adjei and Laurie Gaspar

- NCI Updates
  - Suzanne Forry, Eva Szabo, Peter Ujhazy: SCLC Consortium
  - Yves Pommier, Anish Thomas: Intramural Projects

- Planning Group Chairs (separate webinars and panel discussions)
  - Biology and Genetics: Lauren Byers
  - Models: Julien Sage
  - Prevention, Screening, & Diagnosis: Laurie Gaspar
  - Treatment and Resistance: Alex Adjei

SCLC Scientific Initiative 1	Key Scientific Advances
Better Research Tools for the Study of SCLC	**CTCs to profile SCLC and generate CDX** (Hodgkinson et al, Nat Med 2014) **Comprehensive drug screen in SCLC cell lines** (Polley et al, J Natl Cancer Inst 2016) **GEMMs for MYC-driven SCLC** (Mollaoglu et al, Cancer Cell 2017), **Cell of origin and metastatic potential in SCLC** (Yang, et al, Cancer Discovery 2018), **Crebbp** (Jia, et al, Cancer Discovery 2018) **Reprogrammed basal cells – SCLC and SCPC** (Park et al, Science 2018) and **hES cell model of SCLC** (Chen et al, J Exp Med 2019)

SCLC Scientific Initiative 2	Key Scientific Advances
Comprehensive Genomic Profiling of SCLC *(at diagnosis and after therapeutic relapse)*	**Genomic profiles of SCLC** (George et al, Nature 2015) **SCLC subsets, defined by lineage transcription factors – ASCL1, NEUROD1, POU2F3** (POU2F3 – Huang et al, Genes Dev 2018; multiple labs)

SCLC Scientific Initiative 3	Key Scientific Advances
New Diagnostic Approaches for SCLC	**ctDNA for early detection of SCLC** (Fernandez-Cuesta et al, EBioMedicine 2016)

SCLC Scientific Initiative 4	Key Scientific Advances
Therapeutic Development Efforts *(especially for specific therapeutic vulnerabilities, includes immunotherapy)*	**Role of DNA repair pathway alterations for targeting (PARP, Wee1, Chk1, ATR, etc)** (Sen et al/Byers lab and others) **Aurora kinase targeting** (Oliver lab, others) **Immunotherapy advances in the clinic, TMB as candidate biomarker** (Hellmann et al), **novel immune targets** (e.g., CD47) (Weiskopf/Sage) **Recognition of DLL3 as a potential target** (ADC, CAR-T, BiTE)

SCLC Scientific Initiative 4	Key Scientific Advances (cont.)
Therapeutic Development Efforts *(especially for specific therapeutic vulnerabilities, includes immunotherapy)*	**CheckMate-032: nivo for 3rd line treatment of metastatic SCLC** (Antonia et al., Lancet Oncol 2016; accel approval by FDA in 2018) **IMpower133: new frontline standard of care for extensive stage using chemo + atezo** (Horn et al., NEJM 2018; FDA priority review)

SCLC Scientific Initiative 5	Key Scientific Advances
Mechanisms Underlying High Rate of Initial Response and Rapid Emergence of Drug and Radiation Resistance	**SLFN11 as a predictive biomarker for PARPi, chemotherapy** (Byers, Rudin, others) **Role of WNT signaling in mediating resistance** (Wagner, Nat Comm2018)

Overall Summary

- The NCI has responded to all five initiatives with the formation of the SCLC Consortium.
- The number of grants for SCLC research has increased approximately three-fold over the past five years, including projects within the SCLC Consortium as well as other research awards.
- The increased number of genomic studies, greater understanding of SCLC biology, and emerging approaches to therapy, including targeted therapies and immunotherapy, have created new research opportunities.
- The current set of initiatives remain important and many grants have been funded to address them, these grants are in early stages and it is not possible to report on specific progress at this stage.

Overall Summary (cont.)

- Recommendations for continued or more concentrated scientific efforts include:
  - Coordinated mechanisms for sample acquisition, storage, and characterization
  - Coordinated mechanisms for storage and sharing of cell and mouse models, beyond what is currently supported within the SCLC Consortium.
  - Increased sample collection for late stage disease, metastases, pre- and post-therapy, and exceptional responders.
  - Greater efforts to investigate the transcriptome, epigenome, metabolome, and microenvironment of SCLC.
  - Continued efforts to develop blood-based and imaging approaches for screening and diagnosis and new approaches to prevention.

NCI Initiatives - SCLC Consortium

1. Better Research Tools for the Study of SCLC
2. Comprehensive Genomic Profiling of SCLC
3. New Diagnostic Approaches for Populations at High Risk of Developing SCLC
4. Focusing Therapeutic Development Efforts on Specific Molecular Vulnerabilities of SCLC
5. Mechanisms Underlying Both High Rate of Initial Response and Rapid Emergence of Drug and Radiation Resistance

SCLC Consortium

- PAR-16-049 Therapeutic Development and Mechanisms of Resistance (U01)

1. Better Research Tools for the Study of SCLC
2. Comprehensive Genomic Profiling of SCLC
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5. Mechanisms Underlying Both High Rate of Initial Response and Rapid Emergence of Drug and Radiation Resistance

SCLC Consortium

- PAR-16-051 Innovative Approaches to the Prevention and Early Detection of Small Cell Lung Cancer (U01)

- PAR-16-049 Therapeutic Development and Mechanisms of Resistance (U01)

1. Better Research Tools for the Study of SCLC
2. Comprehensive Genomic Profiling of SCLC
3. New Diagnostic Approaches for Populations at High Risk of Developing SCLC
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SCLC Consortium

- PAR-16-050 Coordinating Center (U24)

- PAR-16-051 Innovative Approaches to the Prevention and Early Detection of Small Cell Lung Cancer (U01)

- PAR-16-049 Therapeutic Development and Mechanisms of Resistance (U01)

1. Better Research Tools for the Study of SCLC
2. Comprehensive Genomic Profiling of SCLC
3. New Diagnostic Approaches for Populations at High Risk of Developing SCLC
4. Focusing Therapeutic Development Efforts on Specific Molecular Vulnerabilities of SCLC
5. Mechanisms Underlying Both High Rate of Initial Response and Rapid Emergence of Drug and Radiation Resistance

SCLC Consortium Members

Charles Rudin, Memorial Sloan Kettering
Michael Berger, Memorial Sloan Kettering
Nikolaus Schultz, Memorial Sloan Kettering
John Poirier, Memorial Sloan Kettering
Andrea Ventura, Memorial Sloan Kettering
Scott Lowe, Memorial Sloan Kettering
Kelly Clarke, Memorial Sloan Kettering
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+Adi Gazdar, UT Southwestern Medical Center
Yu Shyr, Vanderbilt University
Lynne Berry, Vanderbilt University
Patrick Nana-Sinkam, Virginia Commonwealth University
-Tyler Jacks, Massachusetts Institute of Technology
Afshin Dowlati, Case Western Reserve University
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Peter Ujhazy, National Cancer Institute
Eva Szabo, National Cancer Institute
Suzanne Forry, National Cancer Institute
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Kwon Park, University of Virginia
Julien Sage, Stanford University
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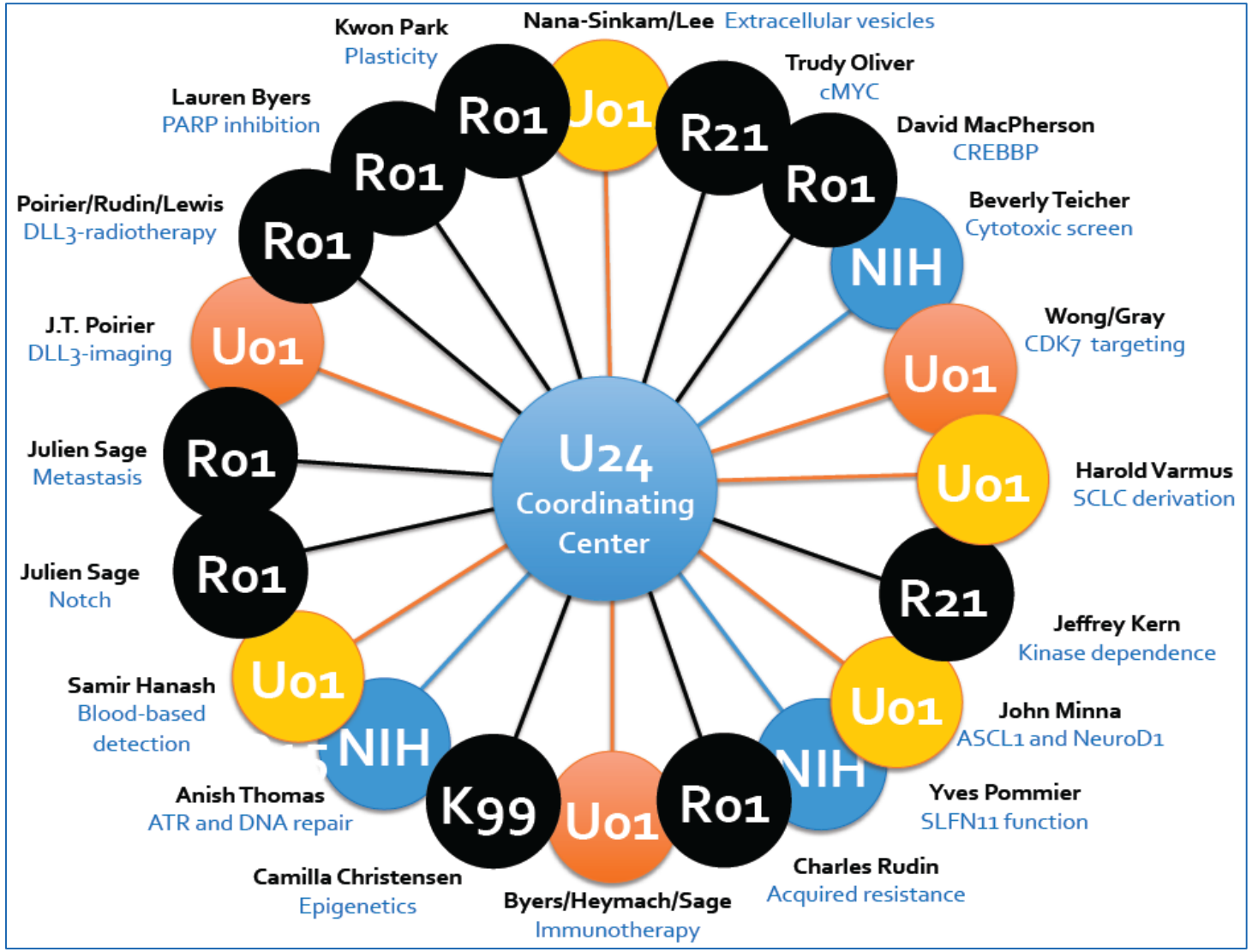
Massion Pierre, Vanderbilt University
Vito Quaranta, Vanderbilt University
Douglas Spitz, University of Iowa
Phuoc Tran, Johns Hopkins
Alissa Weaver, Vanderbilt University

SCLC Consortium



IASLC SCLC Meetings

COMPONENTS OF THE U24 COORDINATING CENTER

NIH NATIONAL CANCER INSTITUTE

Coordination
Forry
Szabo
Ujhazy

UT Southwestern Medical Center

Cell line resources
Minna
(Gazdar)

CASE WESTERN RESERVE UNIVERSITY EST. 1826

Tissue microarrays
Dowlati

VANDERBILT UNIVERSITY

Clinical correlates database
Shyr
Berry

Memorial Sloan Kettering Cancer Center

cBioPortal for Cancer Genomics

PDX models
Rudin
Poirier

GEMMs
Ventura
Lowe

Molecular profiling
Berger
Taylor
Schultz
Shen

MIT

MGH 1811 MASSACHUSETTS GENERAL HOSPITAL

GEMM models
(Jacks)

PDX/CDX models
Farago

PAR-16-051: Innovative approaches to the prevention and early detection of SCLC (Grants Funded, 4 cycles)

PI(s)	Institutions	Title
Nana-Sinkam, P; Lee, LJ	VCU, OSU, Institute for Systems Biology	Extracellular Vesicles in Small Cell Lung Cancer Early Detection
Hanash, S	MDACC	Development of Risk and Early Detection Biomarker for Small Cell Lung Cancer
Varmus, H	Weill Cornell	Studies of the Initiation and Progression of Small Cell Lung Cancer Using Cells Derived by Differentiation from Human Pluripotent Stem Cells
Weaver, A	Vanderbilt	Phenotype Interactions in SCLC Development and Detection
Krasnow, M	Stanford	Molecular mechanisms of SCLC initiation and detection in mice and humans
Park, K-S	UVA, Mayo, Des Moines U	Targeting BCAT1 and branched-chain amino acid metabolism for the detection and prevention of SCLC

PAR16-049: Grants Funded as of Feb. 4, 2019

PI(s)	Institution(s)	Title
J.T. Poirier	Sloan-Kettering	Preclinical development of a DLL3-targeted theranostic for small cell lung cancer
K-K Wong, N.S. Gray	NYU; Dana-Farber	Targeting the transcriptional and epigenetic landscape in chemo-refractory Small-Cell Lung Cancer
J. Heymach, L. Byers, J. Sage	MDACC; Stanford University	Novel therapeutic approaches for enhancing anti-tumor immunity in SCLC
J. Minna	UT Southwestern	Developing ASCL1 and NeuroD1 lineage oncogene targeted therapy for small cell lung cancer
L. Marchionni, C. Hann, P. Tran	Johns Hopkins University	Bioinformatic-Chemical Approach to Credential Molecular Targets to Combat Rapid Chemo-Radiation Resistance in SCLC
N.J. Dyson, A. Farago	Massachusetts General Hospital	Using patient-derived models to understand drug responses in SCLC
R. Govindan, O. Griffith, T. Oliver	Washington University; University of Utah	Genomic and Functional Identification of Chemotherapy Resistance Mechanisms in Small Cell Lung Cancer

NCI Grants in SCLC Awarded in 2018

All	U54	U24	U01	U2C	P30	P50	R01	R21	R03	R35	K08	F31	F99	F30
47	1	1	16	1	1	1	14	4	1	1	2	2	1	1

- By comparison, there were only 17 grants with SCLC focus in 2012, including 5 R01s.

Gaps and Opportunities

- Coordinated mechanisms for sample acquisition, storage, and characterization beyond what is currently supported within the SCLC Consortium, including access to clinical trial specimens, mandating biopsies (possibly within a SCLC master protocol), funding for rapid autopsy programs, and enhanced bioinformatics resources modeled on TCGA
- Increased sample collection for late stage disease, metastases, pre- and post-therapy, and exceptional responders
- Greater efforts to investigate the transcriptome, epigenome, metabolome, and microenvironment of SCLC
- Increased resources for the storage and sharing of cell and mouse models, including increased molecular characterization with clinical annotation
- Development of models for immunotherapy
- Continued efforts to develop blood-based and imaging approaches for screening and diagnosis
- New approaches to prevention

Next Steps

- Finalize report of WG and circulate to CTAC members for acceptance (May 2019).

- NCI updates Scientific Framework for submission to Congress by June 30, 2019.