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

Laurie E Gaspar MD MBA
Alex Adjei MD PhD
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

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
<table>
<thead>
<tr>
<th>SCLC Scientific Initiative 1</th>
<th>Key Scientific Advances</th>
</tr>
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<tbody>
<tr>
<td>Better Research Tools for the Study of SCLC</td>
<td>CTCs to profile SCLC and generate CDX (Hodgkinson et al, Nat Med 2014)</td>
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<td><strong>Comprehensive drug screen in SCLC cell lines</strong> (Polley et al, J Natl Cancer Inst 2016)</td>
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<td><strong>GEMMs for MYC-driven SCLC</strong> (Mollaoglu et al, Cancer Cell 2017), <strong>Cell of origin and metastatic potential in SCLC</strong> (Yang, et al, Cancer Discovery 2018), <strong>Crebbp</strong> (Jia, et al, Cancer Discovery 2018)</td>
</tr>
<tr>
<td>SCLC Scientific Initiative 2</td>
<td>Key Scientific Advances</td>
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<tr>
<td>Comprehensive Genomic Profiling of SCLC</td>
<td>Genomic profiles of SCLC (George et al, Nature 2015)</td>
</tr>
<tr>
<td><em>(at diagnosis and after therapeutic relapse)</em></td>
<td><strong>SCLC subsets, defined by lineage transcription factors – ASCL1, NEUROD1, POU2F3</strong> (POU2F3 – Huang et al, Genes Dev 2018; multiple labs)</td>
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<td>SCLC Scientific Initiative 3</td>
<td>Key Scientific Advances</td>
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<tr>
<td>New Diagnostic Approaches for SCLC</td>
<td>ctDNA for early detection of SCLC (Fernandez-Cuesta et al, EBioMedicine 2016)</td>
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<tr>
<td>SCLC Scientific Initiative 4</td>
<td>Key Scientific Advances</td>
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| **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)* |
<table>
<thead>
<tr>
<th>SCLC Scientific Initiative 4</th>
<th>Key Scientific Advances (cont.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Therapeutic Development Efforts</strong></td>
<td><strong>CheckMate-032: nivo for 3rd line treatment of metastatic SCLC</strong> (Antonia et al., Lancet Oncol 2016; accel approval by FDA in 2018)</td>
</tr>
<tr>
<td><em>(especially for specific therapeutic vulnerabilities, includes immunotherapy)</em></td>
<td><strong>IMpower133: new frontline standard of care for extensive stage using chemo + atezo</strong> (Horn et al., NEJM 2018; FDA priority review)</td>
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<tr>
<td>SCLC Scientific Initiative 5</td>
<td>Key Scientific Advances</td>
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<tr>
<td>Mechanisms Underlying High Rate of Initial Response and Rapid Emergence of Drug and Radiation Resistance</td>
<td>SLFN11 as a predictive biomarker for PARPi, chemotherapy (Byers, Rudin, others)</td>
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<td>Role of WNT signaling in mediating resistance (Wagner, Nat Comm2018)</td>
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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.
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

1. Better Research Tools for the Study of SCLC
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- PAR-16-049 Therapeutic Development and Mechanisms of Resistance (U01)
SCLC Consortium

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- 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)
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)

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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
John Minna, UT Southwestern Medical Center
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
Anna Farago, Massachusetts General Hospital
Beverly Teicher, National Cancer Institute
Peter Ujhazy, National Cancer Institute
Eva Szabo, National Cancer Institute
Suzanne Forry, National Cancer Institute
Yves Pommier, National Cancer Institute
Anish Thomas, National Cancer Institute
James Lee, Ohio State University
Kwok-Kin Wong, New York University
Nathanael Gray, Dana-Farber Cancer Institute
Camilla Christensen, Dana-Farber Cancer Institute
Jeffrey Kern, National Jewish Health
Kwon Park, University of Virginia
Julien Sage, Stanford University
David MacPherson, Fred Hutchinson Cancer Research Center

Lauren Byers, The University of Texas MD Anderson Cancer Center
Samir Hanash, The University of Texas MD Anderson Cancer Center
John Heymach, The University of Texas MD Anderson Cancer Center
Trudy Oliver, University of Utah
Harold Varmus, Weill Cornell Medicine
Haobin Chen, National Cancer Institute
Melanie Cobb, University of Texas Southwestern
Nicholas Dyson, Massachusetts General Hospital
Ramawamy Govindan, Washington University in St. Louis
Obi Griffith, Washington University in St. Louis
Christine Hann, Johns Hopkins
Jane Johnson, University of Texas Southwestern
Robert Jones, University of Guelph
Mark Krasnow, Stanford University
Christin Kuo, Stanford University
Johnathan Lehman, Vanderbilt University
Qi Liu, Vanderbilt University
Carlos Lopez, Vanderbilt University
Christine Lovly, Vanderbilt University
Luigi Marchionni, Johns Hopkins
Xianbing Meng, University of Iowa
Massion Pierre, Vanderbilt University
Vito Quaranta, Vanderbilt University
Douglas Spitz, University of Iowa
Phuoc Tran, Johns Hopkins
Alissa Weaver, Vanderbilt University
COMPONENTS OF THE U24 COORDINATING CENTER

Cell line resources
Minna (Gazdar)

Clinical correlates database
Shyr
Berry

Coordination
Forry
Szabo
Ujhazy

Tissue microarrays
Dowlati

PDX models
Rudin
Poirier

GEMMs
Ventura
Lowe

Molecular profiling
Berger
Taylor
Schultz
Shen

GEMM models
(Jacks)
PDX/CDX models
Farago
### PAR-16-051: Innovative approaches to the prevention and early detection of SCLC (Grants Funded, 4 cycles)

<table>
<thead>
<tr>
<th>PI(s)</th>
<th>Institutions</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nana-Sinkam, P; Lee, LJ</td>
<td>VCU, OSU, Institute for Systems Biology</td>
<td>Extracellular Vesicles in Small Cell Lung Cancer Early Detection</td>
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<tr>
<td>Hanash, S</td>
<td>MDACC</td>
<td>Development of Risk and Early Detection Biomarker for Small Cell Lung Cancer</td>
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<tr>
<td>Varmus, H</td>
<td>Weill Cornell</td>
<td>Studies of the Initiation and Progression of Small Cell Lung Cancer Using Cells Derived by Differentiation from Human Pluripotent Stem Cells</td>
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<tr>
<td>Weaver, A</td>
<td>Vanderbilt</td>
<td>Phenotype Interactions in SCLC Development and Detection</td>
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<tr>
<td>Krasnow, M</td>
<td>Stanford</td>
<td>Molecular mechanisms of SCLC initiation and detection in mice and humans</td>
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<tr>
<td>Park, K-S</td>
<td>UVA, Mayo, Des Moines U</td>
<td>Targeting BCAT1 and branched-chain amino acid metabolism for the detection and prevention of SCLC</td>
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<tr>
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<td>J.T. Poirier</td>
<td>Sloan-Kettering</td>
<td>Preclinical development of a DLL3-targeted theranostic for small cell lung cancer</td>
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<tr>
<td>K-K Wong, N.S. Gray</td>
<td>NYU; Dana-Farber</td>
<td>Targeting the transcriptional and epigenetic landscape in chemo-refractory Small-Cell Lung Cancer</td>
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<tr>
<td>J. Heymach, L. Byers, J. Sage</td>
<td>MDACC; Stanford University</td>
<td>Novel therapeutic approaches for enhancing anti-tumor immunity in SCLC</td>
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<tr>
<td>J. Minna</td>
<td>UT Southwestern</td>
<td>Developing ASCL1 and NeuroD1 lineage oncogene targeted therapy for small cell lung cancer</td>
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<td>L. Marchionni, C. Hann, P. Tran</td>
<td>Johns Hopkins University</td>
<td>Bioinformatic-Chemical Approach to Credential Molecular Targets to Combat Rapid Chemo-Radiation Resistance in SCLC</td>
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<td>N.J. Dyson, A. Farago</td>
<td>Massachusetts General Hospital</td>
<td>Using patient-derived models to understand drug responses in SCLC</td>
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<tr>
<td>R. Govindan, O. Griffith, T. Oliver</td>
<td>Washington University; University of Utah</td>
<td>Genomic and Functional Identification of Chemotherapy Resistance Mechanisms in Small Cell Lung Cancer</td>
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### NCI Grants in SCLC Awarded in 2018

<table>
<thead>
<tr>
<th>All</th>
<th>U54</th>
<th>U24</th>
<th>U01</th>
<th>U2C</th>
<th>P30</th>
<th>P50</th>
<th>R01</th>
<th>R21</th>
<th>R03</th>
<th>R35</th>
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- 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.