Small Cell Lung Cancer

Seizing on Opportunities to Translate Recent Research into the Clinic for New Diagnostics and Interventions

The Small Cell Lung Cancer Working Group

Clinical Trials and Translational Research Advisory Committee

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A. The Workshop

(1) Origin of the Workshop

The Recalcitrant Cancer Research Act of 2012 (H.R. 733) requires the National Cancer Institute (NCI) to “develop scientific frameworks” that will assist in making “progress against recalcitrant or deadly cancers.” Small cell lung cancer (SCLC) is a recalcitrant cancer as defined by its five-year relative survival rate of less than 7 percent and the loss of approximately 30,000 lives per year. The NCI convened a group of experts in the field of SCLC for a workshop held in Bethesda, Maryland on July 8-9, 2013 to evaluate research opportunities that could improve the scientific understanding and medical control of SCLC. The group, chaired by Drs. John Minna and Charles Rudin, included laboratory scientists, medical oncologists, surgeons, radiation oncologists, pathologists, biostatisticians, patient advocates, and NCI staff (see Addendum 1 – SCLC Working Group Roster).

The goals of the workshop were to identify key scientific opportunities and critical areas where focused research efforts could have the greatest impact on prevention, detection, or disease outcome for patients with SCLC. Workshop participants were asked to discuss recent advances in "omics", molecular pathology, and the prospects for early detection of SCLC; key developments in animal models for SCLC; and putative new drug targets and other areas of vulnerability of SCLC that may lead to new therapeutic approaches.

The findings and recommendations arising from the workshop are to be discussed with the NCI’s Clinical Trials and Translational Research Advisory Committee (CTAC) and to
inform the NCI in the development of a scientific framework for SCLC in accordance with the Recalcitrant Cancer Research Act of 2012.

(2) Overview of the Workshop Program

The workshop agenda topics included three thematic scientific sessions, a special session focused on attracting investigators to SCLC research, and a series of smaller breakout sessions designed to identify top research priorities and opportunities related to each of the three scientific sessions. A final session summarized the outcomes of the breakout sessions and prioritized recommendations. (See Addendum 2 – SCLC Workshop Agenda)

The first session focused on emerging opportunities in “omics”, molecular pathology, and early detection for SCLC. In a series of presentations and discussions, workshop participants reviewed the classification of neuroendocrine lung cancer molecular pathology and epidemiology, focusing on approaches to molecular characterization and early pathogenesis of putative precursor lesions of SCLC; current data and gaps in knowledge about the SCLC genome and transcriptome, with emphasis on known and suspected driver oncogenes and tumor suppressors\(^1,2\); recent and ongoing studies of the SCLC proteome, including potential therapeutic targets identified through this approach\(^3\); and new data on the SCLC epigenome, defining additional putative targets for intervention\(^4\).

The second session addressed emerging opportunities in preclinical models and on targeting cancer stem cells in SCLC. Workshop participants reviewed and discussed patient-derived xenograft (PDX) models as a platform for enhancing the biological
understanding of SCLC and for therapeutic testing\textsuperscript{5}; recent and ongoing genomic studies of genetically engineered mouse models (GEMMs) of SCLC\textsuperscript{6-8}; recent and ongoing studies using SCLC GEMMs as a platform for defining putative cells of origin for SCLC; developmental signaling pathways in SCLC; and a relatively unbiased approach to identifying critical oncogenic drivers in lung cancer through the use of synthetic lethal siRNA/shRNA screens.

The third session focused on emerging therapeutic opportunities, and new drug targets. Workshop participants discussed an ongoing study at the NCI Frederick National Laboratory assessing the relative activity of 103 oncology drugs and 420 investigational compounds of interest against a panel of approximately 60 SCLC cell lines characterized by genomic and gene expression profiles; recent studies and novel opportunities for immunotherapy in SCLC, including vaccine approaches as well as agents targeting immune checkpoints\textsuperscript{9}; and recent clinical data using temozolomide both as a single agent\textsuperscript{10} and with a poly-(ADP-ribose)-polymerase (PARP) inhibitor\textsuperscript{11}. Finally, promising opportunities for targeting Bcl-2 in SCLC\textsuperscript{12} were discussed.

In addition to the three scientific sessions, a fourth session focused on the scientific workforce in the field of SCLC. The group discussed barriers to entry to the field, noting that despite the relatively high incidence of SCLC, a relatively small number of scientists and clinicians are attracted to the study of this disease. A number of ideas were proposed to attract both new and established investigators to the study of SCLC.

This was followed by individual breakout sessions during which workshop participants proposed specific recommendations to address scientific opportunities that had been
identified during the aforementioned discussions. On the second day of the workshop, the entire group was reconvened to summarize the outcomes of the breakout sessions and prioritize a final set of recommendations.

B. Current Approaches to SCLC

Clinical approaches to SCLC have not advanced significantly in three decades. Although the focus of the workshop was on the identification of critical scientific advances and the prioritization of research opportunities, the current standard of care provides a necessary backdrop to the group's findings and is described in brief in this section.

(1) Risk Assessment and Screening

Although SCLC is, in most cases, a disease associated with tobacco use, little is known about predisposing genetic or non-genetic factors that lead to the development of the disease in certain current or former smokers but not in others. Somatic mutations accumulate during the lifetime of an individual exposed to the carcinogens in tobacco smoke. There is a need for further study of the germline (i.e., heritable) traits that contribute to the development of SCLC as well as the interactions between environmental exposures and individual inherited predispositions to SCLC.

Screening for SCLC is also a challenge. There are currently no validated biomarkers that can be measured in blood or other tissues to detect SCLC at an early stage. Furthermore, the recent NCI-sponsored National Lung Screening Trial\textsuperscript{13-15} that proved
the value of screening individuals at high risk of developing lung cancer with low-dose helical computed tomography (CT) also demonstrated that screening did not improve survival for the subset of SCLC patients detected by CT screening, unlike those with adenocarcinoma or squamous cell cancer of the lung. The majority of patients with SCLC detected by CT screening (86% of the 125 patients) were diagnosed with advanced stage disease, similar to the percent seen in the absence of dedicated screening. Consistent with this distribution of stages, subsequent therapy did not evidently prolong the survival of screened patients. These results suggest that metastatic dissemination and/or resistance to systemic therapy may develop early in the natural history of SCLC.

(2) Diagnosis, Staging, and Monitoring

The diagnosis of SCLC, whether the patient is symptomatic or not, usually begins with histologic confirmation of an abnormality detected on imaging studies, typically by fine needle aspirate biopsy. Immunohistochemical evaluation employing a variety of neuroendocrine or other markers confirms the diagnosis of SCLC. Medical history, physical examination, routine laboratory tests, and computed tomographic scans of the chest and abdomen with infusion of contrast material, and magnetic resonance imaging of the brain complete the initial evaluation. For patients without evidence of disease outside one hemithorax on these studies, 18Fluoro-deoxyglucose positron emission tomography (PET) is useful for optimal staging, and can detect bone metastases. Staging for patients with SCLC is most commonly categorized using the Veterans Administration Lung Study Group system; limited-stage disease (LD), which occurs in approximately one third of patients, is defined as SCLC confined to the hemithorax of
origin, the mediastinum, or the supraclavicular nodes, which can be encompassed within a tolerable radiation therapy port. Extensive-stage disease (ED) SCLC has spread beyond the supraclavicular areas and is too widespread to be included within the definition of LD. Patients with distant metastases by definition have ED\textsuperscript{16}.

Monitoring of response to therapy is usually performed by imaging techniques capable of providing accurate measurements of tumor size; these size measurements are interpreted by Response Evaluation Criteria In Solid Tumors (RECIST) criteria that define categories of response to treatment\textsuperscript{16}. PET staging now approaches a 100% level of sensitivity and greater than 90% specificity\textsuperscript{17-20}. The use of PET scanning to both stage and follow the effect of treatment for patients with SCLC has enhanced the accuracy by which the effectiveness of new treatment modalities can be examined.

(3) Therapy and Resistance

Current therapeutic approaches for SCLC are of modest long-term benefit despite the exceptionally good response to first-line therapy. Treatment for LD includes a standard first line chemotherapy regimen\textsuperscript{21,22} with concomitant radiation that can be encompassed in a single radiation port\textsuperscript{23,24}. Treatment for ED includes the same chemotherapy options, without concomitant radiation\textsuperscript{22}. In some instances, particularly for small peripheral lung nodules, surgery can also be considered\textsuperscript{25}.

Treatment programs for SCLC have changed little over the past three decades; the most important advances have improved the precision of radiation therapy and have introduced better supportive care measures, such as more effective antiemetic regimens. The generally accepted standard for first-line systemic therapy, etoposide
combined with either cisplatin or carboplatin, has been in use since the early 1980s\textsuperscript{23, 26-28}. An alternative first-line chemotherapy regimen, cisplatin and irinotecan, appeared to be superior in a Phase III study conducted in Japan\textsuperscript{29}, but these results could not be confirmed in subsequent US comparative trials\textsuperscript{22}. SCLC is an unusually chemosensitive and radiosensitive disease, at least initially, resulting in objective response rates of 60 to 80\% in patients without substantive co-morbid conditions. However, essentially all patients with ED, and most patients with LD, experience disease progression within months of completing first-line therapy. A recent genome-wide association study suggested that germline genetic variations may affect resistance to irinotecan, and thus may be associated with decreased overall survival of SCLC patients treated with chemotherapy\textsuperscript{30}. Certain single nucleotide polymorphisms (SNPs) that were associated with shorter overall survival may affect the expression of transcription factors involved in the epithelial-to-mesenchymal transition, a process by which epithelial cells lose their cell polarity and cell-cell adhesion, and gain migratory and invasive properties that may be involved in the development of metastases.

There is only one FDA-approved therapy for recurrent SCLC: topotecan, a topoisomerase 1 inhibitor\textsuperscript{31-33}. Recurrent SCLC is substantially less responsive to therapy than primary disease. Response rates for topotecan are approximately 25\% for relapses occurring at least 3 months after completion of first-line therapy, and as low as 3 – 6\% for progressive disease occurring at the time of or shortly after completion of first-line therapy. Objective responses to a third line of chemotherapy are uncommon\textsuperscript{34}. Hence, no consensus has been reached on treatment regimens for patients whose disease has progressed after first- and second-line therapy.
Prophylactic whole brain irradiation, in the absence of detectable brain metastases, is an important component of therapy for most limited stage, and some extensive stage, patients with SCLC. It is typically administered to those individuals who respond well to initial treatment shortly after completion of first-line combined modality therapy\(^35\), \(^36\). Prophylactic cranial radiation therapy decreases the risk of subsequent, clinically significant brain metastases and improves survival in patients with LD and ED\(^24\), \(^37\).

Approximately 100 SCLC interventional clinical trials have been registered in the ClinicalTrials.gov database since December 2007; about one-third of which are supported by the NCI\(^38\). These studies include efforts to target the neuroendocrine character of SCLC, its dependence on the (PARP) pathway\(^11\), and the use of immunological interventions including therapeutic vaccines\(^39\), antibody radio-immunoconjugates\(^40\), or checkpoint inhibitors intended to stimulate anti-cancer immune responses\(^28\).

### C. Recent Scientific Advances and Emerging Research Questions

The workshop participants discussed recent advances in SCLC research across many areas including genomics and proteomics, molecular pathology, animal models, cancer stem cells, and new drug targets. A number of critical scientific advances and emerging research questions were defined in the discussion.
Characterization of the SCLC Genome, Transcriptome, and Epigenome

Two recent studies have assessed the genomic landscape of SCLC using next generation sequencing approaches, including full exome sequencing, transcriptome profiling by RNASeq, copy number analyses, and limited whole genome sequencing to identify translocations\(^1,2\). In large part because of its association with smoking, SCLC has one of the highest densities of mutation per tumor\(^1\). Most of the mutations are of the *passenger* type, which means that they do not necessarily contribute to the initiation or progression of the disease. More important are *driver* mutations that directly contribute to carcinogenesis. These two reports confirmed what had been previously proposed in smaller studies, namely that the most prevalent inactivated tumor suppressor genes in SCLC are *TP53* and *RB*\(^{40-42}\). Concomitant inactivation of these tumor suppressors is nearly universal in SCLC. Novel mutations were also found, such as those in genes controlling epigenetic regulators, stem cell genes, as well as other driver mutations within established proto-oncogene and tumor suppressor gene families (including *MYC* family genes, *Bcl-2, PTEN, CREBBP, FGFR1, SLIT2*, and *EPHA7*, among others).

The number of primary SCLCs for which data have been reported at the level of full exome sequencing comprises only 82 samples (compared with the baseline number of 500 specimens per disease used in The Cancer Genome Atlas [TCGA] initiative) and is inadequate to characterize the spectrum of potential oncogenic driver mutations in SCLC to include those alterations with a frequency of occurrence below 10% with statistical significance. To highlight this, *FGFR1* amplification was detected at a rate of 6% in one study\(^1\), while such alterations were not observed at all in the other\(^2\). Another
limitation of these investigations is that many of the samples analyzed were from surgically resected early stage and chemo-naïve patients, and do not represent the full natural history of the disease with regard to development of metastases and changes induced by therapeutic intervention.

Critical research questions that emerged from these discussions included: What are the critical driver mutations present in SCLC beyond TP53 and RB inactivation? Are there molecularly defined subsets of SCLC with distinct clinical outcomes and distinct therapeutic vulnerabilities? Are there important molecular differences between primary SCLC and metastatic disease? Can drivers of metastasis, the dominant cause of death in SCLC patients, be specifically targeted?

(2) Analysis of Acquired Chemotherapy Resistance in SCLC

SCLCs possess a set of specific biological characteristics. They are often fast growing and rapidly metastatic, initially highly responsive to both chemotherapy and radiation, but often rapidly recurrent, with recurrent disease that is markedly more resistant to therapy. Recurrent SCLCs are rarely biopsied. Recurrence is expected in SCLC, and repeat biopsy is not known to be useful in guiding decisions regarding second-line therapy. Hence, remarkably little is known, at the molecular level, about the evolution of disease with treatment.

Questions that emerged during discussions of acquired resistance to SCLC therapy included: What are the molecular differences between de novo chemosensitive and subsequent chemo-resistant disease? Are these differences distinct from those in patients whose SCLCs are resistant to initial therapy? Are the mechanisms of acquired
resistance targetable using existing drugs? To what extent can the mechanisms of acquired resistance in patients with SCLC be phenocopied in animal models?

(3) TP53 and RB as Gatekeeper Mutations in SCLC

One of the major advances in the preclinical modeling of SCLC was the demonstration that targeted disruption of both TP53 and RB led to the development of lung cancer closely resembling human SCLC in a GEMM. This model has been subsequently refined and revalidated, and used by a number of groups to investigate critical questions including the molecular heterogeneity of metastases. These models have also been used to explore the biology of SCLC, including cell of origin studies and examinations of the development of metastases in SCLC. As described above, recent genomic sequencing studies of SCLC have identified a number of genes of interest that may be important in subsets of SCLC but also reconfirmed that these two critical tumor suppressors, TP53 and RB, were jointly disrupted in the large majority of SCLC.

Important questions that arose in discussions concerning gatekeeper mutations in SCLC: What effects do joint loss of TP53 and RB have on the signaling circuitry of the cell, distinct from loss of either single gene? Does concurrent loss of these two genes result in unique vulnerabilities in SCLC (i.e. are there synthetic lethalities associated with their joint disruption)? Can these vulnerabilities be targeted by existing or novel drugs?

(4) MYC Family Members in SCLC

Altered MYC signaling in SCLC (like that of TP53 and RB) was originally described many years ago. It was confirmed and further refined in recent genomic sequencing.
studies of SCLC\textsuperscript{1,2}. New observations included identification of a recurrent in-frame fusion involving \textit{RLF} and \textit{MYCL1} in a primary SCLC tumor and four SCLC cell lines, and that siRNA targeting \textit{MYCL1} in such lines inhibited proliferation\textsuperscript{2}. In contrast to the tumor suppressors \textit{TP53} and \textit{RB}, \textit{MYC} family members are activated oncogenes in SCLC and other cancers\textsuperscript{46}. Previous efforts to design specific inhibitors of \textit{MYC} signaling have been, broadly speaking, disappointing, but many new research tools and approaches are emerging\textsuperscript{47}.

Questions regarding the role of \textit{MYC} signaling in SCLC: Could a reinvigorated effort focused on inhibition of \textit{MYC} family members create novel \textit{MYC}-directed therapeutics? Are there common dependencies among \textit{MYC}-driven tumors? Could \textit{MYC}-targeting lead to durable responses in SCLC?

(5) Developmental and Stem Cell Signaling Pathways in SCLC

SCLC is unusual in that it seems to appear fully formed in the lung epithelium: no defined histologic precursor of SCLC has been described. \textit{ASCL1}-dependent embryonic developmental signaling and Hedgehog stem cell signaling pathways in particular have been implicated in SCLC clonogenic potential\textsuperscript{48,49}. Despite disappointing results of a randomized clinical trial of a Hedgehog pathway inhibitor in extensive stage SCLC\textsuperscript{50}, these pathways continue to be attractive potential targets as are other agents that target SCLC progenitor cells.

Questions regarding developmental signaling in SCLC: In which clinical context would targeting embryonic signaling pathways have the most impact? How should such strategies be optimally integrated with cytotoxic chemotherapy, radiation, and surgery?
D. Attracting Investigators to the Field of SCLC

Despite the frequency of SCLC, few scientists and clinicians are attracted to the study of this disease. Lack of improvement in the clinical course of SCLC over several decades may be a major barrier to attracting and retaining clinical investigators. The difficulties in obtaining sufficient quantities of human tissue for in-depth studies may also have reduced enthusiasm for further investigative efforts in the field.

To attract both new and established investigators to the study of SCLC, the NCI is encouraged to consider: 1) establishing dedicated funding opportunities for SCLC; 2) modifying the grant criteria for the Specialized Programs of Research Excellence (SPOREs) to promote the study of SCLC; 3) forming a Task Force on cross-institutional standardized tissue acquisition, utilization, and sharing; and 4) collaborating with scientific associations such as the International Association to Study Lung Cancer (IASLC) to co-sponsor a meeting dedicated to SCLC in which critical collaborative projects could be proposed and planned. Moreover, making SCLC a higher priority at national lung cancer meetings and workshops could enhance the interest of new investigators to the disease.

E. Recommended Initiatives

In the final session the workshop participants recommended five initiatives for the NCI to consider incorporating within its scientific framework for SCLC:
(1) Develop Better Research Tools for the Study of SCLC

There is a critical need to acquire better biospecimens to enhance the biological understanding of SCLC, as well as mechanisms of drug and radiation sensitivity and resistance. Moreover, the complex biology of SCLC could be understood at greater depth by developing new tumor models that better mirror the human disease.

(A) Optimize Collections of Tumor Tissues

The diagnosis of SCLC is frequently made by cytological examination of biopsy material obtained by fine needle aspiration; repeat biopsies, performed during distinct stages of disease progression, are rarely attempted. The paucity of available biospecimens for this disease is striking, and is a primary barrier to progress in SCLC research. Newer image-guided diagnostic approaches, such as endoscopic bronchial ultrasound-guided core biopsies, can be safely performed and yield substantially more tumor for molecular characterization. The use of these newer biopsy approaches underscores the importance of incorporating specialists in pulmonary medicine, cardiothoracic surgeons, and interventional radiologists (who perform the diagnostic procedures) as active members of the multidisciplinary team of health care professionals who care for patients with SCLC.

Beyond changing standard of care approaches to diagnostics, investigators in the field should be encouraged to implement biopsy protocols to ensure that good quality biospecimens are obtained under optimized conditions for banking, molecular profiling, creating xenografts, and/or cell line derivation. Research protocols to permit well-controlled and standardized repeat biopsies over time (and during the multiple phases
of SCLC disease progression) should also be strongly encouraged. These will provide the tumor tissues with which to answer critical questions about SCLC regarding the range of driver mutations involved, mechanisms of progression, acquired resistance to therapeutics, and factors promoting metastasis.

(B) Develop New SCLC Models

The complex biology of SCLC could be understood at greater depth by developing new tumor models that better mirror the human disease. SCLC cell lines currently used for tissue culture studies have a number of potential deficiencies, including low growth fractions and a tendency to proliferate as multi-cell tumor aggregates, making their use for drug screening difficult. Furthermore, many SCLC lines do not have germline DNA available to permit certain identification somatic mutations, and most SCLC lines have been continuously propagated for years using standard methods that may drastically alter their molecular composition compared with the primary tumors from which they were derived. New techniques, including the development of conditionally reprogrammed tumor cell lines (developed with Rho kinase inhibitors), initiated from small tumor biopsies, offer the possibility of rapid establishment of SCLC cell lines with both germline DNA available and molecular pedigrees much closer to primary tumors. These models, especially if well-annotated clinically and developed using sequential tumor biopsies from individual patients, could be used to study mechanisms underlying the early evolution of drug resistance, a phenomenon that occurs regularly following initial therapy in patients with SCLC.
In addition to new, clinically-annotated cell lines from patients with SCLC, the need also exists for development of a larger collection of PDX models that have been derived from paired biopsies obtained before combined modality therapy is initiated, and then at the time of disease progression in the same patients. Such models would be of value for understanding mechanisms of both primary and acquired drug resistance.

Current GEMMs have elucidated the cell of origin for SCLC and essential driver mutations for this disease; however, the long latency period required for the development of SCLCs in GEMMs has limited the broad applicability of these models, in particular for drug screening. There is a need to improve such models by: 1) incorporating a greater degree of genetic heterogeneity during their elaboration; 2) producing GEMMs that integrate acquisition of drug resistance into the model development process (which would be useful for screening second line therapies) and, 3) evaluating the effects of tobacco smoke on the carcinogenic process in GEMMs. Recently, other models have been developed that may be suitable to study SCLC metastases. In these systems, newly-developed mouse strains that lack functional B-, T-, and NK cells (Pfp/Rag2 double-knockout) have been used to facilitate the production of mice carrying SCLC xenografts that undergo spontaneous metastases; this model more clearly mirrors the clinical course of SCLC.

(2) Assemble Comprehensive Genomic Profiling

The small number of SCLCs that have been analyzed by exome or whole genome sequencing is inadequate to define the full spectrum and distribution of driver mutations in this disease. Efforts to characterize a much larger set of tumors from patients with
SCLC, particularly from patients entered on clinical trials, for genomic, epigenetic, and transcriptome alterations, should be strongly encouraged. Furthermore, comparative analyses of paired biospecimens from single individuals, obtained from chemo-sensitive and chemo-resistant disease, or from primary and metastatic sites, should permit a more focused description of the driver alterations associated with changes in disease state. A comprehensive molecular analysis of specimens from the small subset of patients with long-term survival from SCLC would also be of substantial interest. Studies of the SCLC genomics should be accompanied by an evaluation of genetic changes in the germline of SCLC patients as well as individuals at high risk of developing SCLC to identify possible heritable predispositions to this disease. Finally, coordination of these complementary efforts with a comprehensive proteomic characterization of SCLC is necessary for the validation of novel diagnostic and therapeutic targets appropriate for intervention.

(3) Develop New Diagnostic Approaches

In view of the need for new approaches to the diagnosis and prevention of SCLC, the unique genetic dependencies that underlie the pathogenesis of SCLC, and the multiple genetic alterations found in the histologically “normal” lung epithelia of patients with SCLC, there is an opportunity to expand understanding of the critical molecular changes in the lung that precede the development of frank SCLC. Assessment of field cancerization in the normal epithelium surrounding tumors is already ongoing in patients with adenocarcinomas of the lung; preliminary data indicate a distinction between a noncancerous smoker’s transcriptome signature and that from a smoker with cancer. Further, the failure of spiral CT screening to detect SCLC early enough for successful treatment
intervention has focused attention on the potential to develop early tissue- or blood-based molecular predictors of SCLC; hence, molecular profiling efforts as described above should also include studies of tobacco-exposed but non-malignant lung tissues, including tissues adjacent to SCLCs.

Recent improvements in non-invasive diagnostic techniques that can use circulating tumor cells (CTCs) or DNA from blood to characterize genetic alterations specific for an individual patient’s tumor\textsuperscript{54, 55} suggest that more sensitive screening tests for SCLC, perhaps incorporating assessments of mutant \textit{RB} and \textit{TP53} in CTCs or circulating DNA, are possible. Validation of non-invasive methods to detect early stage SCLC or to more clearly identify molecular risk factors in individuals with a long history of smoking could provide critical insights into the natural history of SCLC. Using another non-invasive technique, preliminary studies indicate that measurement of volatile compounds and DNA abnormalities in the breath of patients with lung cancer may enable early diagnosis\textsuperscript{56}. Establishing the relevance of these tests for the early detection and/or monitoring of SCLC will require validation in prospective clinical studies.

Another opportunity to improve the early detection of SCLC lies in the use of improved quantitative and functional imaging with multi–detector CT, dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI), and combined PET and CT imaging\textsuperscript{19}. These techniques allow more reliable detection and staging of SCLCs; for example, PET-based staging appears to be superior to conventional staging, and can significantly alter patient management, particularly with regard to the design of radiotherapy fields\textsuperscript{20}. Major advances in the early diagnosis of SCLC may result from complementary
combinations of molecular and imaging tests designed for use in high-risk populations. New studies are needed for individuals at high risk of developing SCLC to ascertain, for example, whether molecular profiling of bronchial epithelial cells or sequencing circulating DNA from blood for the hallmarks of SCLC (such as mutations in RB or TP53) might permit early diagnosis of a pre-invasive stage of small cell neoplasia of the lung.

(4) Facilitate Therapeutic Development Efforts

The nearly universal loss of functional TP53 and RB tumor suppressor genes is a hallmark of SCLC. GEMMs developed by combined knockout of these tumor suppressor genes effectively mimic the pathologic features of this disease. Research to examine targetable vulnerabilities associated with loss of these two genes could lead to new therapeutic approaches focused on molecular pathways that are altered by the loss of RB and TP53 function. While it is currently not possible to restore the activity of malfunctioning tumor suppressor genes, synthetic lethality approaches could target multiple proteins that these suppressor genes regulate57, 58, potentially restoring control of cancer cell growth. An additional experimental approach involves local delivery of tumor suppressor genes via gene therapy59. MYC, ASCL1, and Hedgehog signaling pathways represent other important therapeutic targets in SCLC; preclinical models suggest that SCLCs demonstrate dramatic “addiction” to the function of these pathways. Despite prior difficulties in developing therapies directed against transcription factors such as MYC and ASCL1, renewed efforts to target these critical dependencies in SCLC may be appropriate because of recent advances in chemical biology and drug screening47.
In addition to small molecule therapeutics, new immunotherapy strategies, such as the use of checkpoint inhibitors targeting immune suppressor mechanisms in the tumor microenvironment, as well as therapeutic vaccine approaches, have recently been applied to the treatment of lung cancer\textsuperscript{60, 61}. Recent results from Phase II studies suggest that the human anti-CTLA-4 monoclonal antibody ipilumumab adds to the therapeutic benefit of chemotherapy in SCLC\textsuperscript{62}. An ongoing Phase III clinical trial that compares the etoposide/platinum combination plus or minus ipilumumab will help to define the role of immune suppressors in SCLC patients with extensive disease\textsuperscript{63}; results from this and other studies should be used to broaden the range of therapeutic approaches applicable to patients with SCLC. As part of this it will be important to define the targets of cytotoxic immune responses after breaking tolerance including whether the immune targets include oncopeptide mutations, and also defining mechanisms of escape from such immune surveillance.

\textbf{(5) Understand Mechanisms Underlying Both High Initial Rate of Relapse and the Rapid Emergence of Drug and Radiation Resistance}

Patients with SCLC often respond very well to first-line chemo-radiotherapy; however, disease progression almost invariably occurs within months of achieving an initial remission\textsuperscript{22}. Recurrence is usually characterized by rapidly progressive, treatment-resistant disease. Understanding the mechanisms underlying early therapeutic sensitivity for most SCLC patients and the rapid molecular changes involved in the acquisition of resistance to drug and radiation treatment are critical to improving long-term outcomes. Recent studies suggest that the mechanisms of therapeutic response and resistance to chemo-radiotherapy for SCLCs are pleiotropic, and include: 1) altered
mRNA expression levels of several genes (ERCCI, BRCA1, ATP7B, PKM2, TOPOI, TOPOIIA, TOPOIIB, and C-MYC)\textsuperscript{64}; 2) the expression of certain cancer stem cell markers (CD133) that are associated with the overexpression of mitogenic neuropeptide receptors\textsuperscript{65, 66}; 3) elevated levels of DNA repair proteins and/or activation of the PI3K/mTOR pathway\textsuperscript{67}; and 4) overexpression of ATP-binding cassette transporters\textsuperscript{68}, among many. However, definitive studies to elucidate molecular mechanisms of resistance, including the genetic evolution of drug resistance patterns, await the ready availability of clinical SCLC tumor samples obtained before and after treatment, and the development of model systems more reflective of acquired drug and radiation resistance in patients. Until such tumor tissues and models are available, definitive interventions to overcome SCLC resistance, and predictive biomarkers to guide those interventions, will remain difficult to develop. Thus, the development of new approaches to understanding the rapid emergence of drug and radiation resistance in SCLC using new, clinically-annotated SCLC models is of central importance if the outcome for patients with this disease is to be improved.

**F. Summary**

A workshop of SCLC experts examined the recent advances in risk assessment, screening, diagnosis, staging, monitoring, therapy and resistance of SCLC and identified new scientific opportunities for investigation that have the potential to improve outcome for patients with this disease. Based on an appreciation of the current state of knowledge and standard of clinical care used in SCLC, workshop participants
recommended five research opportunities for expanding NCI’s research programs for SCLC:

(1) Building better research tools for the study of SCLC by (a) optimizing the collection of tumor tissue specimens representing distinct phases of SCLC (from initial diagnosis to disease recurrence following radio-chemotherapy) and (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;

(2) Expanding 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;

(3) Investigating new diagnostic approaches for populations at high risk of developing SCLC;

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

(5) Examining 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.
G. References


### H. List of Abbreviations

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<th>Abbreviation</th>
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<tr>
<td>ADP</td>
<td>adenosine diphosphate</td>
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<td>ATP</td>
<td>adenosine triphosphate</td>
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<td>CT</td>
<td>computed tomography</td>
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<td>CTAC</td>
<td>Clinical Trials and Translational Research Advisory Committee</td>
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<td>CTC</td>
<td>circulating tumor cell</td>
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<td>GEMM</td>
<td>genetically engineered mouse model</td>
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<td>IASLC</td>
<td>International Association to Study Lung Cancer</td>
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<td>LD</td>
<td>limited-stage disease</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>NCI</td>
<td>National Cancer Institute</td>
</tr>
<tr>
<td>NK cells</td>
<td>natural killer cells</td>
</tr>
<tr>
<td>PDX</td>
<td>patient-derived xenograft</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>RECIST</td>
<td>Response Evaluation Criteria In Solid Tumors</td>
</tr>
<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
</tr>
<tr>
<td>RNASEq</td>
<td>RNA sequencing</td>
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<tr>
<td>SCLC</td>
<td>small cell lung cancer</td>
</tr>
<tr>
<td>shRNA</td>
<td>short hairpin RNA</td>
</tr>
<tr>
<td>siRNA</td>
<td>small interfering RNA</td>
</tr>
<tr>
<td>SNP</td>
<td>single nucleotide polymorphism</td>
</tr>
<tr>
<td>SPORE</td>
<td>Specialized Programs of Research Excellence</td>
</tr>
<tr>
<td>TCGA</td>
<td>The Cancer Genome Atlas</td>
</tr>
</tbody>
</table>
ADDENDUM 1

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NCI Workshop on Small Cell Lung Cancer: Seizing on Opportunities to Translate Recent Research into the Clinic for New Diagnostics and Interventions

**Dates**: Monday, July 8 – Tuesday, July 9, 2013  
**Place**: Natcher Conference Center, NIH Main Campus, Bethesda, MD  
**General Session Room**: E1/E2

### Day 1: Monday, July 8, 2013

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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| 8:00 – 8:15 AM| **Welcome and Charge**  
Harold Varmus, M.D. and James Doroshow, M.D.  
John Minna, M.D. and Charles Rudin, M.D., Ph.D. (Co-Chairs) |
| 8:15-10:15 AM | **Session 1: Emerging Opportunities in Omics, Molecular Pathology, and Early Detection**  
Session Co-Chairs: Stephen Baylin, M.D. and Eric Haura, M.D.  
Speakers: Ilona Linnoila, M.D. – *Neuroendocrine Lung Cancer Molecular Pathology and Epidemiology*  
Ignacio Wistuba, M.D – *Molecular Characterization and Early Pathogenesis of SCLC*  
Roman Thomas, M.D. – *SCLC Genome Studies in US and Europe*  
Lauren Byers, M.D. – *Proteomic Analysis of SCLC*  
John Poirier, Ph.D. – *SCLC Epigenome* |
| 10:15-10:30 AM| Morning Break (on your own) |
| 10:30 AM-12:30 PM| **Session 2: Emerging Opportunities in Preclinical Models and Targeting Cancer Stem Cells**  
Session Co-Chairs: Anton Berns, Ph.D. and Tyler Jacks, Ph.D.  
Speakers: Craig Peacock, Ph.D. – *Patient Derived Xenograft Models*  
David McFadden, M.D. – *Genome Sequencing of Murine SCLC*  
Nadine Jahchan, Ph.D. – *Study of Murine Models of SCLC*  
Anton Berns, Ph.D. – *Defining Cell of Origin/Cancer Stem Cells for SCLC*  
Douglas Ball, M.D. – *Developmental Signaling Pathways in SCLC*  
Michael White, Ph.D. – *Synthetic Lethal siRNA, shRNA Screens* |
**Roundtable:** Paul Bunn, M.D., David Carbone, M.D., Ph.D., Jeffrey Engelman, M.D., Andrea Ferris, M.B.A., Adi Gazdar, M.D., William Pao, M.D., Ph.D., David Shames, Ph.D.

12:30-1:30 PM  **Lunch Break (on your own)**

1:30-3:30 PM  **Session 3: Emerging Opportunities in Therapeutics and New Drug Targets**

**Session Co-Chairs:** Bruce Johnson, M.D. and Joan Schiller, M.D.

**Speakers:**
- Beverly Teicher, Ph.D. – *Drug Library Screening*
- Lee Krug, M.D. – *Immunotherapy Strategies in SCLC – Vaccines and Immune Checkpoint Blockade*
- Catherine Pietanza, M.D. – *DNA Damage Repair, PARP, and Temozolomide*
- Christine Hann, M.D. – *Targeting Bcl-2 and mTOR in SCLC*
- Scott Dylla, Ph.D. – *Anti-Stem Cell Targeted Monoclonal Therapy*

**Roundtable:** Eli Glatstein, M.D., Glenwood Goss, M.D., Roy Herbst, M.D., Ph.D., Mark Kris, M.D., Taofeek Owonikoko, M.D., Ph.D., Suresh Ramalingam, M.D., Regina Vidaver, Ph.D., Everett Vokes, M.D.

3:30-3:45 PM  **Afternoon Break (on your own)**

3:45 -4:15 PM  **Special Session: Attracting Investigators to the Field of Small Cell Lung Cancer**

**Session Chair:** Paul Bunn, M.D.

**Roundtable:** Dara Aisner, M.D., Ph.D., Christine Hann, M.D., Roy Herbst, M.D., Ph.D., Nadine Jahchan, Ph.D., Lee Krug, M.D., David McFadden, M.D., William Pao, M.D., Ph.D., David Shames, Ph.D.

4:15-5:30 PM  **Breakout sessions on each of the 3 topics above**
Participants summarizing key opportunities and needs
- **Session 1 Breakout Room:** Room C1/C2
- **Session 2 Breakout Room:** Room D
- **Session 3 Breakout Room:** Room A

5:30-6:30 PM  **Session chairs (only) confer to develop session summaries, slides, outline of report**

6:30 PM  **Adjourn (End of Day One)**
Day 2: Tuesday, July 9, 2013

8:00-8:15 AM  **Review Charge**  
John Minna, M.D. and Charles Rudin, M.D., Ph.D.

8:15 AM-12:00 PM  **Summary and Recommendations**

  **Session Co-Chairs:** John Minna, M.D. and Charles Rudin, M.D., Ph.D.

  8:15-9:15 AM  **Emerging Opportunities in Omics, Molecular Pathology, and Early Detection: Recommendations**  
Stephen Baylin, M.D. and Eric Haura, M.D.

  9:15-10:15 AM  **Emerging Opportunities in Preclinical Models and Targeting Tumor Stem Cells: Recommendations**  
Anton Berns, Ph.D. and William Pao, M.D., Ph.D.

  10:15-11:15 AM  **Emerging Opportunities in Therapeutics and New Drug Targets: Recommendations**  
Bruce Johnson, M.D. and Joan Schiller, M.D.

  11:15-12:00 PM  **Summary of Recommendations and Next Steps**  
John Minna, M.D. and Charles Rudin, M.D., Ph.D.

  12:00 PM  **Adjourn**