Scientific Framework for
Small Cell Lung Cancer (SCLC)

National Cancer Institute

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Scientific Framework For Small Cell Lung Cancer

Executive Summary

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. While it is true that the outcomes for the other common forms of lung cancer (squamous cell and adenocarcinoma) need to be greatly improved, each of the three major types of cancer that originate in the lung present very different problems, requiring different solutions. As the Scientific Framework describes, treatment of SCLC has not changed in the last 30 years; avoidance of the use of tobacco is the only known way to prevent the disease; no screening method has proved effective; responses to chemotherapy are not durable and are difficult to understand; and life expectancy after diagnosis tends to be very short. Consensus within the scientific community regarding the limited early diagnostic and therapeutic approaches available for patients with SCLC, as well as the limited availability of materials for research, have provided an impetus for the evaluation of new and missed opportunities that could build upon the existing portfolio of SCLC research to make additional progress against this disease.

Scientific progress has been made in the last decade in understanding some of the molecular and cellular biology characteristics of SCLC. This progress includes: identifying critical oncogenic changes found in nearly all SCLCs (such as inactivation of the *TP53* and *RB* genes; overexpression of Bcl-2 and Myc family members); developing genetically-engineered mouse models that closely mimic human SCLC, leading to the identification of a pulmonary neuroendocrine cell as the probable cell of origin for SCLC; creating patient-derived SCLC xenografts and tumor lines for preclinical studies and drug testing; and identifying essential stem cell signaling pathways (Hedgehog and Notch) and lineage oncogenes (*ASCL1*) driving the growth of SCLC with its characteristic neuroendocrine phenotype.

In contrast to these basic research findings, there have been few therapeutic advances in the systemic treatment of this cancer over the past 30 years. Standard therapeutic interventions used today, which combine chemotherapy (etoposide plus platinum compounds) and radiation therapy, reflect the prevailing state-of-the-art from the early 1980s.

SCLC is highly associated with cigarette smoking; the mutations that occur in SCLCs display a mutational signature consistent with exposure to carcinogens found in tobacco, and the decrease in cigarette smoking in the US population is reflected in the substantial decrease in the incidence of SCLC over the past 30 years. Additional public health efforts to prevent smoking initiation and to increase smoking cessation will decrease the incidence of this disease further.

Many patients who develop SCLC today stopped smoking years before their diagnosis. Thus, the first major obstacle to progress against SCLC is the continuing risk of developing the disease that remains for decades after smoking cessation. The second obstacle to progress is that for most patients the tumor is already widely metastatic at the time SCLC is diagnosed; therefore, curative surgery is rarely an option. Indeed, while SCLCs have been identified by computed

tomography (CT)-based screening efforts, including those of the NCI's National Lung Screening Trial (NLST), the vast majority of SCLCs found during these efforts were already metastatic, severely limiting any benefit CT screening might have on patient survival. Therefore, earlier detection methods are urgently needed. SCLCs are initially quite sensitive to chemotherapy and radiation therapy to a degree unlike most other common solid tumors (prostate cancer, colon cancer, or adenocarcinoma of the lung). However, the third obstacle to progress is the rapid development of resistance to chemotherapy in more than 95% of SCLC patients. Median survival from the time of diagnosis is less than 2 years. Because patients with SCLC rarely undergo surgical resection of their tumors, compared with patients with other forms of lung cancer, the histologic diagnosis of SCLC is most often made using needle biopsies that yield only small numbers of tumor cells. Hence, the fourth obstacle to progress is the lack of tumor tissue for clinical, molecular, and cell biologic studies, and in particular the lack of SCLC tissue obtained when resistance to chemotherapy develops, which would permit studies of the molecular mechanisms of acquired resistance.

In view of the obstacles limiting progress toward understanding the biology, early diagnosis, and treatment of SCLC, the NCI assembled an expert panel of extramural scientists to identify new scientific opportunities, resources, or technologies
that could advance our knowledge of SCLC, and, in so doing, improve outcomes for patients with this disease or for those individuals at risk of developing SCLC. To expand the scope of SCLC research, five initiatives were developed by this group of experts for consideration by the NCI. It was recommended that the NCI: 1) develop better research tools for the study of SCLC by optimizing the collection of tumor tissue specimens representing distinct phases of SCLC (from initial diagnosis to disease recurrence following radio-chemotherapy) and by 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) expand comprehensive genomic profiling studies of clinically-annotated SCLC specimens to improve basic understanding of the frequency, distribution, and range of molecular abnormalities that exist both at diagnosis and following therapeutic relapse; 3) investigate new diagnostic approaches for populations at high risk of developing SCLC; 4) focus therapeutic development efforts on specific molecular vulnerabilities of SCLC (tumor suppressor genes, unique genetic drivers and their pathways, neuronal characteristics, and immunotherapy); and 5) investigate 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.

The NCI is developing plans to implement these recommendations. In addition, the means to evaluate progress and provide oversight of the NCI's SCLC research portfolio will be implemented to meet the goals of the Recalcitrant Cancer Research Act (H.R. 733) of 2012.

Introduction

H.R. 733, The Recalcitrant Cancer Research Act of 2012 (RCRA), enacted on January 2, 2013, calls upon the National Cancer Institute (NCI) to "develop scientific frameworks that will help provide the strategic direction and guidance needed to make true progress against recalcitrant or deadly cancers." Recalcitrant cancers are defined as those cancers with a five-year relative survival rate below 50 percent. The Act requires the NCI to identify two or more recalcitrant cancers that have a five-year relative survival rate of less than 20% and are estimated to cause at least 30,000 deaths per year in the United States.

This report, prepared by the NCI, National Institutes of Health (NIH), for submission to Congress focuses on the NCI's approach to small cell lung cancer (SCLC). The report reviews the current state-of-the-art in SCLC research and incorporates recommendations for new scientific initiatives provided by experts in the disease who met at a workshop held at the NCI on July 8-9, 2013 (Appendix 2). The workshop was attended by the NCI Director and senior NCI scientific staff; it was conducted to evaluate research opportunities that could improve the scientific understanding and medical control of SCLC. This report fulfills, in part, the provision of the RCRA that the NCI develop a scientific framework for two identified recalcitrant cancers (the other is pancreatic ductal adenocarcinoma) within 18 months of enactment of the RCRA (by July 2, 2014). Each scientific framework will be sent to Congress and made available publicly on the Department of Health and Human Services (DHHS) website within 30 days of completion.

Background

As our knowledge about cancer biology has increased over the last several years, scientists have come to understand that the classification of cancers used in the past – grouping all cancers that arise in one organ, such as the lung, as one kind of cancer with multiple subtypes – is no longer appropriate. There are three relatively common forms of lung cancer. Of these, SCLC arises from neuroendocrine cells; squamous cell lung cancer from the squamous epithelium in the large, central airways of the bronchial system; and adenocarcinoma of the lung from the pneumocytes in the lung periphery. It is recognized that these are three distinct kinds of cancer arising from three distinct cell lineages. These tumor types exhibit mostly different mutational profiles and have different clinical histories and treatment options; and often different scientific investigators. In addition, the amount of research progress has varied for these three cancers. As a consequence, each of the three major types of cancer that originate in the lung present very different problems and require different solutions.

Fifty years after issuance of the *Report on Smoking and Health by the United States Surgeon General*, tobacco use has changed dramatically: In the United States, the prevalence of current cigarette smoking among adults has declined from 42% in 1965 to 18% in 2012[1]. However, the consequences of smoking or ever-having smoked still affect many individuals. SCLC is one of the diseases that is directly related to smoking[2]. Currently, SCLC accounts for approximately 13-15% of all lung cancers diagnosed in the United States[2, 3]. With changes in cigarette filter design, and with a steady decline in the number of smokers in the United States, an encouraging

decline (of 20-25% of all lung cancers) in SCLC incidence has been observed. Nonetheless, approximately 30,000 individuals are diagnosed with SCLC yearly in this country. Median survival for patients with limited stage disease (tumor that has not spread beyond the hemi-thorax and related supraclavicular lymph nodes) is approximately 18 months; while survival for the two thirds of patients who are diagnosed with more advanced (extensive stage) disease is 9 months[4, 5]. Accordingly, only 3 to 6% of patients are alive 5 years following diagnosis of SCLC[3].

Despite positive epidemiologic trends in the United States, the worldwide incidence of lung cancer, including SCLC, is still rising[6]. The highest incidence and mortality rates among males are currently in Central and Eastern Europe. In many developing countries, lung cancer rates are predicted to increase because of tobacco usage patterns that continue to broaden.

While recent progress has occurred in the understanding of SCLC biology, the clinical application of this knowledge is still in its infancy. Thus, there is currently an opportunity to consider how to hasten the control of SCLC by expanding our comprehension of SCLC at the molecular level, by fostering new diagnostic approaches for individuals at high risk of developing SCLC, by focusing the development of new treatments on recently-discovered molecular vulnerabilities in SCLC, and by understanding why rapid, initial responses to systemic therapy are almost always followed by a drug- and radiation-refractory state that cannot be ameliorated with further treatment.

Summary of the Literature and Recent Advances

Etiology, Epidemiology, Prevention:

Based on considerable evidence from population and experimental studies, it is clear that smoking is the most frequent cause of SCLC. Heavy smokers (for example, those who have smoked on average at least one pack of cigarettes a day for 30 years) have approximately a 110 times greater chance of developing SCLC than individuals who have never smoked tobacco. Although refraining from ongoing tobacco smoking reduces the risk of developing SCLC, the relative risk of developing the disease does not equal that of a non-smoker despite 35 years of smoking abstinence[7]. Still, within 2 years of smoking cessation a lowered risk can be observed, and a rapid decline in the risk of developing SCLC continues over the next 10 years[8]. However, the declining risk of SCLC slows thereafter; 35 years following smoking cessation, depending on the amount smoked before quitting, an approximate 3-fold higher risk remains. Other less prevalent risk factors include occupational or environmental exposures to uranium, radon, beryllium, cadmium, silica, vinyl chloride, nickel compounds, and diesel exhaust[9].

The age-adjusted incidence rate for SCLC in the US peaked in the early 1990s (11.29 cases per 100,000) and is currently 6.74 cases per 100,000 (2010 data[10]). The decrease is primarily due to reduced rates of smoking and to the use of filtered cigarettes. Today's filters absorb larger carcinogenic particles, but still allow smaller particles to enter the lungs. However, filter use also prompts smokers to inhale more deeply. The result is a shift toward a higher incidence of peripheral lung adenocarcinomas (arising from alveolar tissues deeper in the lung) rather than the

previously more prevalent squamous cell cancers and SCLCs that arise centrally[11]. Among all patients diagnosed with SCLC, the proportion of women with the disease increased from 28% in 1973 to 50% in 2002[2]. Most cases of SCLC occur in individuals aged 60-80 years[12], and the estimated overall death rate for SCLC is 30,000 per year[13-15]. The best known preventive measure against SCLC is smoking abstinence. A small percentage of SCLC patients have never smoked, and their disease may be caused by other environmental factors or as yet unknown causes[16]. A healthy lifestyle that includes a balanced diet and adequate physical activity can also decrease the risk of SCLC[17-19].

Biology and Genetics:

The unique histologic features of SCLC were first described by Barnard in 1926 as "oat cell sarcoma" because of the appearance of the cells under the microscope[20]. The biology of SCLC differs from that of adenocarcinoma or squamous cell carcinoma of the lung in that its cell of origin has neuroendocrine characteristics: the cells express features of neuronal as well as endocrine cells[21, 22]. These features, such as the expression of the ASCL1 molecule, assist in the diagnosis of the disease[23]. Patients with SCLC may also display symptoms derived from an increased release of certain hormones (for example, antidiuretic hormone) produced by SCLC cells[24].

According to the current World Health Organization classification, SCLC belongs in the larger group of neuroendocrine tumors of the lung. This group consists of low-grade typical carcinoid tumors, intermediate-grade atypical carcinoid tumors, and high-grade neuroendocrine tumors including large-cell neuroendocrine carcinoma and SCLC[25, 26]. Typical carcinoid tumors are relatively benign with 90% 5-year survival rates; atypical carcinoid tumors can be more aggressive with a 50-60% 5-year survival rate. Large cell neuroendocrine carcinomas and SCLC represent the most aggressive of this class of malignancies with 5-year survival rates of 27% and 3-6%, respectively. While differing from adenocarcinomas, which are epithelial in origin, SCLC has, in some cases, been demonstrated to develop in parallel with adenocarcinoma, or may emerge in a patient treated for adenocarcinoma of the lung (in this case the tumor is classified as a combined SCLC/adenocarcinoma). The simultaneous presence of two histologic types of lung cancer may be due to a shared carcinogenic insult[27], and may be related to *field cancerization*, i.e., histologically normal-appearing tissue adjacent to neoplastic tissue that displays molecular abnormalities, some of which are the same as those of the tumor[28].

Two reports published in 2012 provided a detailed characterization of 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[29, 30]; these investigations expanded understanding of the range of genetic alterations in this disease. In large part because of its association with smoking, SCLC has one of the highest densities of mutation per tumor (an average of 7.4 mutations per mega base pair), surpassing another highly mutated cancer, melanoma, with a density of 6.29[29]. 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 studies that examined a smaller number of tumors, namely that the most

prevalent inactivated tumor suppressor genes in SCLC are *TP53* and *RB-1*[31-33]. 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 (*Myc* family genes, *Bcl-2, PTEN, CREBBP, FGFR1, SLIT2, EPHA7*, for example; see Table 1 in the addendum for a current list). 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[29], while such alterations were not observed at all in the other[30]. 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. As noted previously, the use of needle biopsies as the initial diagnostic approach for patients with presumed SCLC has limited the availability of tumor specimens for genetic analyses. A renewed effort to obtain such specimens will be needed to fully assess genomic changes in this malignancy.

Recently, considerable attention has been devoted to evaluating epigenetic changes in SCLC, including altered methylation patterns and the discovery of variations in microRNA expression[34, 35]. One study found that 73 genes were methylated in >77% of primary SCLCs; most of the methylated genes had not been previously linked to aberrant methylation in other tumor types. Gene ontology analyses indicated a significant enrichment of methylated genes encoding transcription factors related to the process of neuronal differentiation. Another investigation demonstrated that expression of the microRNA, miR-886-3p, is down-regulated by DNA hypermethylation in SCLC; its downregulation is closely correlated with shorter patient survival. miR-866-3p is a potent repressor of cell proliferation, migration, and cancer cell invasion. Finally, another investigation suggested that overexpression of the polycomb repressive complex 2 (PRC2) may contribute to poorer prognosis for patients with SCLC[36]. PRCs are known to modify the epigenetic status of tumors and repress target genes that establish and maintain cell fate. An improved understanding of these epigenetic alterations may facilitate the development of new biomarkers for early detection and prognosis, and may lead to the development of better therapies for patients with SCLC.

The search for prognostic markers for patients with SCLC led to the discovery of the neuroendocrine marker, pro-opiomelanocortin (POMC), the expression of which has been shown to predict liver metastases and poor survival in SCLC[22]. Other therapeutic targets and prognostic markers [such as poly-(ADP-ribose)-polymerases (PARP) —critical DNA repair proteins] have been discovered by proteomic approaches[37]. In addition, the identification and characterization of SCLC stem cells, detectable by expression of CD44 and CD90 surface markers, may reveal hidden vulnerabilities in this disease[38]. SCLC cells expressing these surface proteins have increased expression of the mesenchymal markers N-cadherin and vimentin, increased mRNA levels of the embryonic stem cell-related genes *NANOG* and *OCT4*, and increased resistance to irradiation compared to other sub-populations studied.

Models of SCLC:

Human SCLC-derived cell lines and animal models of SCLC have played an important role in SCLC research. Over the last decade, much has been learned about the nature of SCLC from studies based on cell lines[39-41]. This work revealed new molecular abnormalities in SCLC cells that have been used in diagnosis and therapy, as well as in the establishment of mutational profiles for this disease[29, 30]. SCLC cell lines demonstrate expression of cell surface receptors that play an important role in neuronal function, such as the vasopressin receptor and three bombesin receptors, as well as expression of transcription factors that play a role in the biology of tumor stem cells, such as SOX2, ASCL1, OCT4, and NANOG. Thus, cell models exist that, at least in part, mimic the molecular abnormalities observed in SCLC tumor specimens in vivo[41]. However, many currently available SCLC cell lines grow slowly in vitro, which is not representative of the proliferation rate of this tumor in vivo; slow growth in cell culture also limits the use of SCLC cell lines for high throughput drug screening[41].

Animal models employed to study SCLC include: xenografts produced from the subcutaneous implantation of established human SCLC cell lines into immune-deficient mice; patient-derived xenografts (PDXs) in which human tumors are implanted directly from a biopsy specimen into an immune-incompetent mouse without having been established first as a cell line in vitro; and genetically-engineered mouse models (GEMMs) in which gene knock-out and knock-in technologies have made it possible to reflect the genetic and biological evolution of human SCLC. Xenograft models derived from established SCLC cell lines, unfortunately, often do not resemble primary SCLCs at the molecular level. PDXs, on the other hand, mirror the heterogeneity of the primary tumor and can mimic some factors in the tumor microenvironment, excluding those of the immune system[42]. PDX models have facilitated next-generation DNA sequencing of SCLC specimens by allowing the expansion in vivo of a small, initial tumor specimen[43]. PDX models have also assisted in the proteomic characterization of SCLCs by establishing molecular signatures that reflect the neuroendocrine origin of this cancer[44].

Unfortunately, because of the difficulty obtaining SCLC specimens appropriate for direct xenografting, the number of SCLC PDX models available for investigation is quite modest[45]. GEMMs can develop spontaneous, autochthonous tumors and have the microenvironment required for tumor progression, including degradation of the extracellular matrix and angiogenesis; however, they may lack the genetic complexity that is typical of SCLC. SCLC GEMMs are usually developed based on the inactivation of 2 or 3 critical tumor suppressor genes (mimicking the situation in SCLC patients). The gene combinations include *TP53, RB1, p130,* and *PTEN*[46-49]. These models have been used to explore the biology of SCLC, including cell of origin studies and examinations of the development of metastases in SCLC[50]. For example, GEMMs were used to confirm the importance of the Hedgehog cell signaling pathway in SCLC. However, in view of the time required for the development of tumors in GEMMs, drug testing in these models, although valuable, can be laborious and expensive.

Another way to define critical proteins and signaling pathways in SCLC is through the use of synthetic lethality siRNA/shRNA screens in cell culture that can efficiently explore cooperating pathways and networks involved in the development of this cancer[51]. Two genes convey synthetic lethality if mutations in either, alone, are compatible with cell viability, but mutations

in both lead to cell death[52]. This technique can also be adapted for the selection of drugs that could be used in combination therapies or for targeting "undruggable" targets[53].

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 may contribute to the development of SCLC. In rare instances, an inherited p53 deficiency (Li-Fraumeni syndrome) may lead to the development of SCLC after radiation exposure[54], but additional studies will be required to fully understand 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[55-57] 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[55, 57]. 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 significantly 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.

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 (MRI) of the brain complete the initial evaluation. For patients without evidence of disease outside one hemithorax on these studies, ^{18}Fluoro-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[58].

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[58]. PET staging now approaches a 100% level of sensitivity and greater than 90% specificity[59-62]. 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.

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[63, 64] with concomitant radiation that can be encompassed in a single radiation port[65, 66]. Treatment for ED includes the same chemotherapy options, without concomitant radiation[64]. In some instances, particularly for small peripheral lung nodules, surgery can also be considered[67].

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[65, 68-70]. An alternative first-line chemotherapy regimen, cisplatin and irinotecan, appeared to be superior in a Phase III study conducted in Japan[71], but these results could not be confirmed in subsequent US comparative trials[64]. 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[72]. Certain single nucleotide polymorphisms (SNPs) that were associated with shorter overall SCLC survival may affect the expression of transcription factors involved in the epithelial-to-mesenchymal transition (EMT), 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[73-75]. 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[76]. 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[77, 78]. Prophylactic cranial

radiation therapy decreases the risk of subsequent, clinically significant brain metastases and improves survival in patients with LD and ED[66, 79].

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[80]. These studies include efforts to target the neuroendocrine character of SCLC, its dependence on the PARP pathway[81], and the use of immunological interventions including therapeutic vaccines[82], antibody radio-immunoconjugates[83], or checkpoint inhibitors intended to stimulate anti-cancer immune responses[70].

SCLC Research Supported By The NCI

The NCI supports a range of research activities that are relevant to improving outcomes for patients with SCLC. A review of the portfolio of NCI and NIH grants that support basic and translational studies, clinical trials, and training programs related to SCLC is presented in Appendix 1.

Scientific Opportunities For SCLC Research And Plans To Implement Recommended Initiatives

Recent advances in SCLC research were examined during a multidisciplinary workshop convened to develop new scientific opportunities for this recalcitrant disease. The workshop report, *Small Cell Lung Cancer: Seizing on Opportunities to Translate Recent Research into the Clinic for New Diagnostics and Interventions*, was presented to and accepted by the NCI Clinical Trials and Translational Research Advisory Committee on June 18, 2014, and is available as Appendix 2 of this Report. Based on the unique features of SCLC and the urgent need to improve early diagnosis and treatment, as well as the recommendations of the experts attending the SCLC Workshop, the NCI plans to focus on five scientific opportunities that could improve the outlook for patients with SCLC:

1. Building <u>better research tools for the study of SCLC</u> 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 <u>comprehensive genomic profiling</u> 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 <u>new diagnostic approaches</u> for populations at high risk of developing SCLC;
4. Focusing <u>therapeutic development efforts</u> on specific molecular vulnerabilities of SCLC (tumor suppressor genes, unique genetic drivers and their pathways, neuronal characteristics, and immunotherapy); and
5. Examining the <u>mechanisms underlying both the high initial rate of response to primary SCLC therapy and the rapid emergence of drug and radiation resistance</u> following completion of treatment.

1. Better Research Tools for the Study of SCLC:

(A) Optimizing Collection 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. While there are ethical considerations related to performing biopsies strictly for research purposes, patients may, in fact, benefit from interim analyses of the spectrum of mutations in their tumors that could uncover clinically-actionable targets.

Recommendations for next steps: The NCI has recently re-issued an RFA (Support for Human Specimen Banking in NCI-Supported Clinical Trials) that will provide assistance for the collection of human tumor tissues from patients entered on the full range of NCI-supported clinical trials (both early therapeutics studies and comparative studies). The NCI's new Early Therapeutics Clinical Trials Network, furthermore, routinely collects formalin-fixed diagnostic specimens as well as fresh biopsy tissues during proof-of-mechanism studies of new agents. New resources from the Specimen Banking RFA can be focused to increase the number of SCLC specimens gathered at specific stages of SCLC including pre- and post-treatment samples from the same patient. Tailored administrative supplements to Specialized Programs of Research Excellence in Lung Cancer, translational programs that are already funded for disease-specific tumor banking, could also be developed to support the collection of SCLC specimens under defined clinical and tumor banking conditions, including optimization of protocols for collecting specimens from primary and metastatic sites as well as under informed consent conditions that would permit sharing of relevant pre-treatment and genomic information.

(B) 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 suffer from 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 of 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 or circulating tumor cells, offer the possibility of rapid establishment of SCLC cell lines with molecular pedigrees much closer to primary tumors[84]. 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. An SCLC PDX collection sized to provide sufficient genetic heterogeneity to reflect the variation in therapeutic response observed in the clinic could provide an attractive platform for in vivo studies of molecularly-guided, single agent and combination targeted therapies.

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[85]. 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.

Recommendations for next steps: The NCI's Division of Cancer Treatment and Diagnosis began a Patient-Derived Models (PDM) Program approximately 12 months ago to develop a library of clinically- and genetically-characterized PDXs and conditionally-reprogrammed cell lines in support of the extramural community. Over 1000 human tumor specimens will be collected from biopsies of metastatic solid tumors of patients undergoing screening for eligibility in an NCI-supported clinical trial that matches targeted anticancer agents with specific mutations. Supplemental grants to 15 NCI-supported Cancer Centers in fiscal year 2013 were also placed to increase the number of surgical specimens and CTCs available for model development. Thus, the facilities and resources are in hand to conduct a focused effort to increase the number of PDX models and tumor cell lines from patients with SCLC. With further support from and to the NCI-supported Cancer Center community, it is likely that the collection of annotated SCLC specimens can be facilitated; based on the current tissue collection and PDX 'take' rate, approximately 50-75 new PDX and cell line models could be established over 3 years from 150 to 200 SCLC biopsies and/or surgical specimens.

2. 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[86]. Studies of 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.

Recommendations for next steps: Assuming the attempts described above to improve collection of clinically-annotated SCLC tissues from both the NCI Early Therapeutics Network and NCI-supported Cancer Centers are successful, it is likely that approximately 200 SCLCs could be accumulated (half from clinical trial activities and half directly from tissue acquisition efforts through the NCI Cancer Centers Program). Although not equivalent to the standard approach of studying approximately 500 tumors in any one tumor histology used by TCGA, comprehensive molecular profiling of 200 SCLCs would substantively increase (by a factor of 2-3) the number of these tumors evaluated to date; furthermore, it is likely that the approach outlined herein would provide a greater range of clinical information associated with the tumor tissues than has routinely been available for efforts of the TCGA consortium. Resources to perform the sequencing and molecular profiling of these specimens and the associated analyses of the correlative data would be made available through supplementation of ongoing activities at currently-funded TCGA sites.

3. 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 in bronchial epithelial cells and adenocarcinoma cells from smokers[87]. Further, the failure of spiral CT screening to detect SCLC early enough for successful 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[88, 89] suggest that more sensitive screening tests for SCLC, perhaps incorporating assessments of mutant *RB* and *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[90]. 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) MRI, and combined PET and CT imaging[60]. 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[62]. 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.

Recommendations for next steps: 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. The NCI's Early Detection Research Network has a strong lung cancer program that currently explores the use of non- and semi-invasive early diagnostic tools for lung cancers; it could serve as a platform for obtaining blood for DNA mutational analyses, as well as sputum and bronchoscopic biopsies for molecular profiling of pre-invasive disease. The molecular characterization of lesions that arise prior to frank SCLC in high-risk populations will be the focus of a new Program Announcement to stimulate improved early diagnostic approaches for SCLC.

4. 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 regulate[91, 92], potentially renewing control of cancer cell growth. An additional experimental approach involves local delivery of tumor suppressor genes via gene therapy[93]. 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 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 screening[94].

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 some types of lung cancer[95, 96]. Recent results from Phase II studies suggest that the human anti-CTLA-4 monoclonal antibody ipilimumab adds to the therapeutic benefit of chemotherapy in SCLC[97]. An ongoing Phase III clinical trial that compares the etoposide/platinum combination plus or minus ipilimumab will help to define the role of immune suppressors in SCLC patients with extensive disease[98]; results from this and other studies could begin 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.

Recommendations for next steps: The NCI has nearly completed screening a library of investigational single agents and targeted combinations against one of the largest panels of SCLC cell lines yet assembled. However, as described previously, the lack of clinical annotation of currently available human SCLC lines limits, in part, the general utility of these studies. New synthetic lethal approaches of specific relevance to the transcription factors and suppressor gene mutations known to control SCLC growth should be employed with the new SCLC model systems under development to advance the field of SCLC therapeutics. To expand pre-clinical studies of synthetic lethal screens against tumor suppressor pathways and small molecule targeting of the transcription factors or neuronal genes involved in the proliferation of SCLCs by individual investigators and multi-institutional teams, the NCI will announce its interest in supporting a Program Announcement focusing on SCLC therapeutics. As described below, this Program Announcement would also support studies to understand the rapid development of chemo-radioresistance in SCLC.

5. Mechanisms Underlying Both High Initial Rate of Response 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[64]. 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*)[99]; 2) the expression of certain cancer stem cell markers (CD133) that are associated with the overexpression of mitogenic neuropeptide receptors[100, 101]; 3) elevated levels of DNA repair proteins and/or activation of the PI3K/mTOR pathway[102]; and 4) overexpression of ATP-binding cassette transporters[103] 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.

Recommendations for next steps: Although multiple experimental hypotheses to explain the development of drug resistance in SCLC have been advanced, these have primarily been derived from cell line models of acquired resistance that utilize step-wise, increasing exposures of tumor cells to chemotherapeutic agents in vitro. The relationship between resistance mechanisms discovered in this fashion to therapeutic resistance observed in the clinic is often incomplete. 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. The NCI will develop a Program Announcement devoted to elaborating new therapeutic approaches to SCLC. This call for grant applications will seek studies that interrogate specific molecular vulnerabilities in SCLC by synthetic lethal screening, and the discovery of new approaches to understanding and overcoming the mechanisms behind the rapid emergence of therapeutic resistance, using model systems developed from patient specimens obtained before and after the occurrence of drug-resistant, progressive disease.

Training a Highly Competent Research Workforce

As NCI implements the five recommended initiatives, progress in the development of a competent research workforce will be an intentional byproduct; these initiatives will serve as incentives for scientists to join the SCLC research community. NCI understands that a dedicated workforce is necessary to undertake SCLC research across a broad range of investigational topics, including basic and translational research involving the epidemiology, etiology, biology, genetics, and environmental factors that could lead to SCLC malignancies and/or its prevention. NCI also recognizes the importance of research training to sustain a workforce that takes advantage of the best research opportunities in the area of SCLC by supporting pre-doctoral and post-doctoral investigators, as well as independent early-career scientists and clinicians.

Barriers to entry into this field of study have been an issue in the past, and ideas to attract more scientists to study SCLC were proposed by the SCLC Working Group, including the establishment of dedicated funding opportunities (for the full report, see Appendix 2). Based on the recommendations developed by the Working Group, the Program Announcements noted above (recommendations four and five) and the joint workshop being co-sponsored with International Association of the Study of Lung Cancer (IASLC; further described below) intend to draw scientists to this field of study. Additionally, NCI is supporting many researchers in cross-cutting fields that aim to significantly impact SCLC, such as immunotherapy, radiology, genomics, and prevention research.

Oversight and Benchmarks for Progress

Lack of complete understanding of the biology of the SCLC has slowed the development of successful therapeutic interventions. Limited access to adequate tumor specimens and the aggressive character of SCLC has also played a role in slowing progress. Recognizing the importance of the disease, the NCI will establish a SCLC Action Planning Group (SCLCAPG) composed of NCI staff scientists and extramural advisors to oversee the implementation of the recommendations proposed in this report The NCI also plans to co-sponsor, with the IASLC, a joint workshop on SCLC early in 2015. The workshop will be built around the proposed research opportunities highlighted in this report; it will serve as a platform to conceptualize opportunities to support SCLC investigations in each of the research areas that have been described. Reports to the Clinical Trials and Translational Research Advisory Committee (CTAC) at regular intervals will inform the public of progress in this disease and fulfill requirements of the RCRA.

Summary and Scientific Recommendations and Implementation Timelines

Recommendations:

1. 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 (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. 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.

3. New Diagnostic Approaches for SCLC

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

4. 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).

5. 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.

Implementation Timelines

1. Support infrastructure for SCLC specimen collection via collaborative projects over the next 3 years across NCI's research networks to expand the generation of PDX and conditionally-reprogrammed cell lines from biopsies of SCLC patients enrolled on clinical trials or for whom detailed clinical information is available.
2. Characterize the genetic and molecular features of the SCLC specimens that have been collected at diagnosis and relapse over the next 3 to 5 years.
3. Issue a Program Announcement in the second half of 2015 supporting studies focused on discovering early molecular changes in histologically normal lung, blood (including circulating DNA), and other relevant tissues that could be applied in subsequent screening studies for populations at high risk of developing SCLC.
4. Issue a Program Announcement in the second half of 2015 to improve SCLC therapeutics focusing on understanding how the molecular vulnerabilities of this cancer could be used to develop targeted agent combinations as well as a better understanding of the rapid development of clinical resistance to drug and radiation therapy.

Oversight Timelines

1. Establish SCLC Action Planning Group (SCLCAPG) in 2014 to oversee implementation of recommendations.
2. Co-sponsor a joint workshop on SCLC with the International Association of the Study of Lung Cancer (IASLC) in early 2015.
3. Report implementation progress to the Clinical Trials and Translational Research Advisory Committee (CTAC) at least annually beginning in 2015.

Conclusion

The 2013 workshop, *Small Cell Lung Cancer: Seizing on Opportunities to Translate Recent Research into the Clinic*, provided the NCI with expert assistance in defining major research opportunities that could expand NCI's investigational program for SCLC. New research resources, technologies, and approaches with the potential to improve outcomes for patients with this disease include: 1) Building better research tools for the study of SCLC; 2) Expanding comprehensive genomic profiling of clinically-annotated SCLC specimens; 3) Investigating new diagnostic approaches for populations at high risk of developing SCLC; 4) Focusing therapeutic efforts on specific molecular vulnerabilities of SCLC; and 5) Examining the mechanism underlying both the high rate of initial rate of response to primary SCLC therapy and the rapid emergence of drug and radiation resistance. The NCI has developed an implementation plan with timelines to capitalize on these research opportunities. Reports to CTAC (the Clinical and Translational Research Advisory Committee) at regular intervals will inform the public of progress in this difficult disease and fulfill requirements of the Recalcitrant Cancer Research Act.

For several decades, SCLC patients treated with "state-of-the-art" therapy have experienced temporary remissions with rapid evolution of drug and radiation resistant disease. However, there is now an opportunity to expand understanding of SCLC at the genetic level and to use new technologies to generate GEMM and PDX mouse models and cell lines that reflect the clinical course of SCLC. Broader availability of these models and their incorporation into future drug development efforts could speed the elaboration of more effective, molecularly targeted interventions, improving the outlook for patients with SCLC.

Links and References

Links:

1. Report of the NCI Workshop: *Small Cell Lung Cancer: Seizing on Opportunities to Translate Recent Research into the Clinic* (July 2013) http://deainfo.nci.nih.gov/advisory/ctac/0614/SCLCworkshopReport.pdf
2. The Health Consequences of Smoking – 50 years of Progress: A Report of the Surgeon General, 2014 http://www.surgeongeneral.gov/library/reports/50-years-of-progress/50-years-of-progress-by-section.html

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13. Howlader N, et al., ed. SEER Cancer Statistics Review. National Cancer Institute, Bethesda (MD), Table 15.13; Small Cell Cancer of the Lung and Bronchus (Invasive), 5-Year Relative and Period Survival by Race, Sex, Diagnosis Year, Age and Stage at Diagnosis.
14. Ibid. Table 15.11: Small Cell Cancer of the Lung and Bronchus (Invasive) and Non-Small Cell Cancer of the Lung and Bronchus (Invasive), SEER Incidence Rates, Age-Adjusted and Age-Specific Rates, by Race and Sex.
15. Ibid. Table 15.4: Small Cell Cancer of the Lung and Bronchus (Invasive) and Non-Small Cell Cancer of the Lung and Bronchus (Invasive), Trends in SEER 9 Observed Incidence Using the Joinpoint Regression Program, 1975-2011 With up to Five Joinpoints, By Race and Sex.
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Addendum

Table 1. Genes of interest in SCLC

Gene	Role	Function
BCL2	proto-oncogene	apoptosis regulator
CCNE1	proto-oncogene	cell cycle, regulator of cyclin-dependent kinase
CDK14	proto-oncogene	serine/threonine protein kinase, cell cycle, Activation of Wnt signaling pathway, RB1 phosphorylation, Meiosis, neuron differentiation, regulator of insulin-responsive glucose transport
CDKN2A	tumor suppressor	Cyclin-dependent kinase, cell cycle, P53 stabilization, RB regulation
COBL	putative proto-oncogene	CNS development
CREBBP	tumor suppressor	epigenetic regulator, transcriptional co-activator, gene expression, cell growth, differentiation
DMBX1	tumor suppressor	transcriptional regulator, CNS development
EP300	tumor suppressor	histone acetyltransferase, transcriptional regulator, chromatin remodeling, hypoxia
EPHA7	putative proto-oncogene/ tumor suppressor	protein tyrosine kinase, axon guidance, retinotropic guidance, reverse signaling
FGFR1	proto-oncogene	receptor kinase, mitogenesis, differentiation
GPR113	putative proto-oncogene	G protein-coupled receptor
GPR133	putative proto-oncogene	G protein-coupled receptor
GPR55	proto-oncogene	G protein-coupled receptor
GRID1	putative proto-oncogene	ionotropic glutamate receptor, subunit of glutamate receptor ligand-gated ion channel, synaptic transmission
LRRK2	proto-oncogene	leucine-rich repeat kinase, apoptosis, autophagy,
MED12L	proto-oncogene	transcription regulator of RNA polymerase II-dependent genes
MLL	proto-oncogene/ tumor suppressor	histone methyltransferase, epigenetic regulator/ stem cell-related, gene transcription

Gene	Role	Function
MYCL1	proto-oncogene	transcription factor, cell proliferation, growth, apoptosis, stem cell renewal
NOTCH1-3	proto-oncogenes	receptors, cell development and differentiation
PIK3CA	proto-oncogene	lipid kinase, signal transducer, cell growth, proliferation, differentiation, motility, survival, intracellular trafficking
PPEF2	putative proto-oncogene	protein phosphatase, anti-apoptotic activity
PRKD3	putative proto-oncogene	serine/threonine-protein kinase
PTEN	tumor suppressor	phosphatase, cell cycle, apoptosis
PTPRD	tumor suppressor	protein phosphatase
RAB37	proto-oncogene	RAS-related pathway, GTPase, intracellular vesicle trafficking
RASGRF1	putative proto-oncogene	RAS-related pathway, guanine nucleotide exchange factor
RASGRF2	putative tumor suppressor	RAS-related pathway, guanine nucleotide exchange factor
RB1	tumor suppressor	cell cycle, chromatin remodeling
RUNX1T1	proto-oncogene	RAS-related pathway, zink finger transcription factor
SLIT2	tumor suppressor	axon guidance, cell migration, organogenesis, angiogenesis
SMO	proto-oncogene	G protein-coupled receptor
SOX2	proto-oncogene	stem cell-related transcription factor, ectoderm and mesoderm differentiation
STK38	proto-oncogene	serine-threonine protein kinase, centrosome duplication/mitosis
TP53	tumor suppressor	cell cycle, DNA repair, apoptosis
TRRAP	proto-oncogene	epigenetic regulator, adapter protein, histone acetyltransferase, MYC transcription

Appendix 1: Investments in Small Cell Lung Cancer Research – NCI/NIH

Investments in Small Cell Lung Cancer Research

National Cancer Institute
National Institutes of Health

July 2013

Table of Contents

NCI Investments in Lung Cancer Research

In fiscal year 2012 (FY2012), the National Cancer Institute (NCI) invested $314 million in lung cancer research, a 39 percent increase over FY2007 (Figure 1).[1] As our knowledge about cancer biology has increased over the last several years, scientists have come to understand that there are at least three distinct forms of cancer that originate in the lung (adenocarcinoma, squamous cell, and small cell). NCI's FY2012 research portfolio included 745 projects that were at least 25 percent relevant to lung cancer.[2] A manual review of project abstracts was performed to identify projects focused on small cell lung cancer (SCLC). Of note, the vast majority of these abstracts did not specify a lung cancer type; moreover, a large number were focused on risk factors, such as tobacco, common to all forms of cancer originating in the lung.

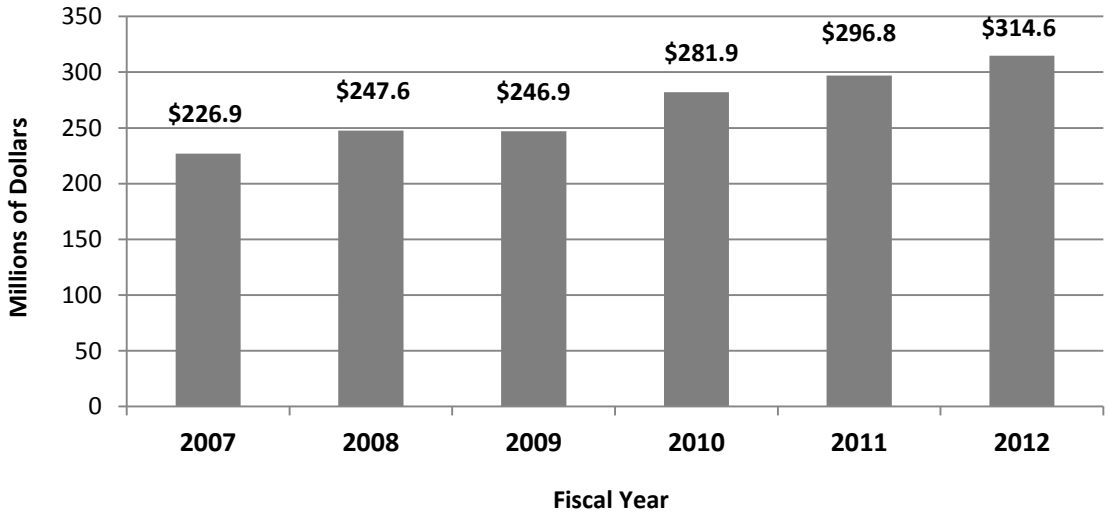

Figure 1. NCI Lung Cancer Research Investment

Investments in Small Cell Lung Cancer Research by NCI and Others

Research Projects

Analysis of the FY2012 NCI research portfolio identified 17 unique projects with a focus on SCLC (

Table **1**). One additional project funded by the National Institute of General Medical Sciences (NIGMS) also was identified as relevant to SCLC (Table 2). These projects include extramural research funded through grants and cooperative agreements (U awards); contracts; interagency agreements; and research being conducted within the NCI intramural program. Investigator-initiated clinical trials (e.g., funded through R01s) may be included among these projects. However, trials not funded by individual grants (e.g., Cooperative Group trials) are summarized separately in the Clinical Trials section (page 1-58). Figure 2 shows the distribution of these

[1] NCI Office of Budget and Finance.
[2] See Methods for additional details on percent relevance.

SCLC projects across scientific areas as defined by the Common Scientific Outline (CSO).[3] Note that projects may be relevant to more than one scientific area and, thus, be represented more than once in Figure 2. The largest number of projects focused on treatment, with several projects also studying the biology of SCLC. The distribution of SCLC projects across activity codes is shown in Figure 3.

The NCI research portfolio also includes several projects focused on neuroendocrine tumors, some of which may have relevance to SCLC. A list of neuroendocrine tumor projects that were not captured by the lung cancer portfolio analysis is included in **Addendum A.**

A number of other organizations fund SCLC research. A list of projects funded by members of the International Cancer Research Partnership is included in **Addendum B**.

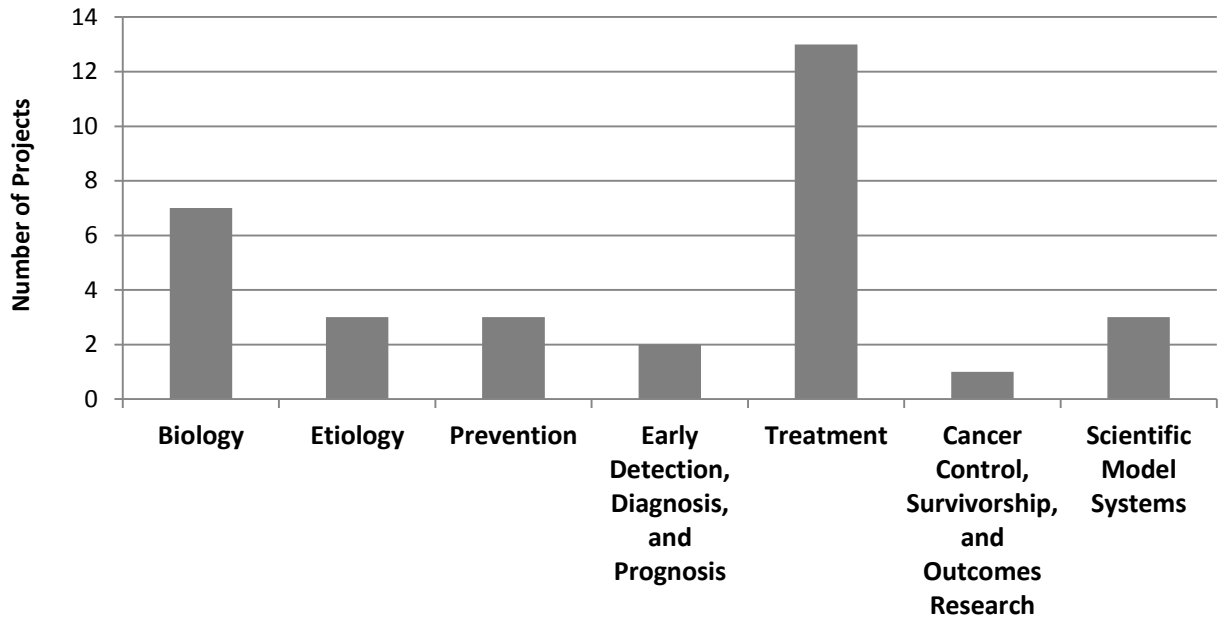

Figure 2. NIH-Funded Small Cell Lung Cancer Projects by Scientific Area

[3] The **Common Scientific Outline** is a classification scheme used by member of the **International Cancer Research Partnership (ICRP)**, including NCI, to classify cancer research. CSO includes seven broad area of scientific interest in cancer research. A project may be coded to more than one of the seven CSO areas.

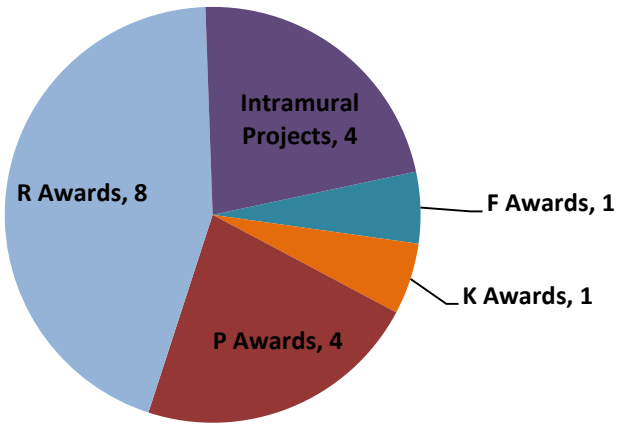

Figure 3. NIH-Funded Small Cell Lung Cancer Projects by Activity Code

Table 1. NCI-Funded Projects Related to Small Cell Lung Cancer

	Project Number	Title	PI	Institution
1.	1F32CA165856-01A1	Understanding the Role of SKP2 in small Cell Lung Cancer Progression	Nicolay, Brandon	Massachusetts General Hospital
2.	5K23CA164015-02	Novel Systemic Therapy to Improve Clinical Outcome in Small Cell Lung Cancer	Owonikoko, Taofeek	Emory University
3.	5P50CA058184-17	SPORE in Lung Cancer	Baylin, Stephen	Johns Hopkins University
4.	5P50CA058187-18	SPORE in Lung Cancer	Bunn, Paul	University of Colorado, Denver
5.	5P50CA070907-15	University of Texas SPORE in Lung Cancer	Minna, John	UT Southwestern Medical Center
6.	5P50CA119997-05	SPORE in Lung Cancer	Haura, Eric	H. Lee Moffitt Cancer Center & Research Institute
7.	3R01CA084354-10S1	Genetic Determinants of Lung Cancer Survival	Yang, Ping	Mayo Clinic
8.	5R01CA100750-09	Role of c-Met in SCLC and Potential for Novel Therapy	Salgia, Ravi	University of Chicago
9.	5R01CA131217-04	Nonpeptide Macrocyclic Histone Deacetylase (HDAC) Inhibitors for Targeted Lung Cancer Treatment	Oyelere, Adegboyega	Georgia Institute of Technology
10.	5R01CA136534-03	Structure-based Anti-cancer Drug Development	Deng, Xingming	Emory University

	Project Number	Title	PI	Institution
11.	7R01CA148867-04	Using Mouse Models to Understand Retinoblastoma Initiation and Progression	MacPherson, David	Fred Hutchinson Cancer Research Center
12.	1R15CA161491-01A1	Capsaicin and Small Cell Lung Cancer Therapy	Dasgupta, Piyali	Marshall University
13.	2R44CA162613-02	Targeted Treatment of Recurrent Small Cell Lung Cancer with Anti-AbnV2 Antibodies	Pang, Roy	Woomera Therapeutics, Inc.
14.	ZIABC010748	Clinical Investigation of Signal Transduction Inhibitors	Dennis, Phillip	National Cancer Institute
15.	ZIASC000167	Molecular Pathology of Pulmonary Carcinogenesis	Linnoila, Ilona	National Cancer Institute
16.	ZIASC010093	Targeting the Epigenome for Lung Cancer Therapy	Schrump, David	National Cancer Institute
17.	ZICBC011040	Molecular Profiling of Clinical Specimens	Edelman, Daniel	National Cancer Institute

Table 2. Non-NCI NIH-Funded Projects Related to Small Cell Lung Cancer

	Project Number	Title	PI	Institution
1.	2R01GM079719-06	Enabling New Translational Discoveries Using a Genomic Data-Driven Nosology	Butte, Atul	Stanford University

Specialized Programs of Research Excellence

The Specialized Programs of Research Excellence (SPOREs) are designed to facilitate the rapid and efficient movement of basic scientific findings into clinical settings by bringing together basic and applied researchers. Each SPORE is focused on a specific organ site. Of the seven NCI-supported SPOREs that focus on lung cancer, four include one or more subprojects relevant to SCLC (Table 3).

Table 3. SPORE Subprojects Relevant to SCLC

SPORE	Subproject	Project Leader(s)
University of Colorado	Inhibition of IGF and FGF Signaling Pathways in Lung Cancer	Bunn, Paul DeGregori, James
	SEMA3F and ZEBI in Lung Cancer: Therapy and Target Gene Discovery	Drabkin, Harry Gemill, Robert
Moffitt Cancer Center and Research Institute	p53-based Vaccine for Small Cell Lung Cancer	Gabrilovich, Dmitry Antonia, Scott
Johns Hopkins University	Epigenetic Therapy of Small Cell Lung Cancer*	Hann, Christine
The University of Texas Southwestern/MD Anderson Cancer Center	DHHC Protein Palmitoyltransferases as New Therapeutic Targets in Lung Cancer**	Hoffman, Sandra

* Career Development Project.
** Developmental Research Project.

Clinical Trials

As of May 2013, 19 NCI-supported interventional clinical trials on SCLC were actively accruing participants. These trials included 1 pilot trial; 5 phase I trials, 1 phase I/II trial, 11 phase II trials, and 1 phase III trial (Figure 5). A list of these clinical trials is included in Table 4.

In addition to trials focused on SCLC, NCI supports clinical trials for lung cancer (all types) and all types of solid tumors, which evaluate treatments that may be relevant to small cell lung cancer, as well as several studies evaluating tobacco cessation interventions.

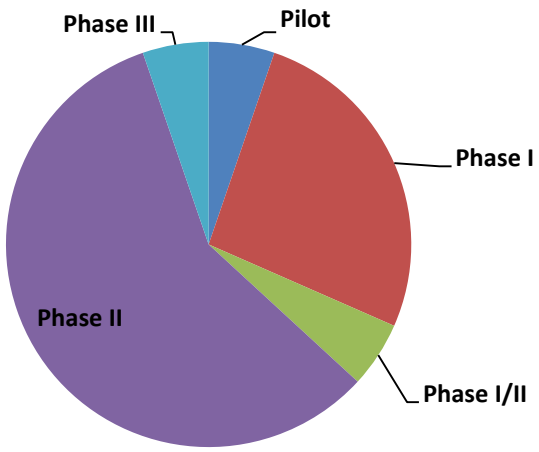

Figure 5. NCI-Sponsored Clinical Trials Related to SCLC, by Phase

Table 4. NCI-Supported Clinical Trials Related to SCLC*

	Trial Name	Clinical Trial ID number	Phase	Lead Organization	Focus
1.	Immunization of Small Cell Lung Cancer Patients with a Pentavalent Vaccine Composed of LH-conjugates of GD2L, GD3L, Globo H, Fucosyl GM1, and N-Propionylated Polysialic Acid	NCT01349647	Pilot	Memorial Sloan Kettering Cancer Center	Treatment
2.	A Phase I Study of ARQ 197 in Combination with IV Topotecan in Advanced Solid Tumors with an Expansion Cohort in Small Cell Lung Cancer	NCT01654965	I	City of Hope Medical Center	Treatment
3.	A Phase I Study of Dasatinib in Combination with Bevacizumab in Advanced Solid Tumors	NCT01445509	I	National Cancer Institute Medicine Branch	Treatment

	Trial Name	Clinical Trial ID number	Phase	Lead Organization	Focus
4.	An Early Phase 1 Study of ABT-888 in Combination with Carboplatin and Paclitaxel in Patients with Hepatic or Renal Dysfunction and Solid Tumors	NCT01366144	I	University of Pittsburgh Cancer Institute	Treatment
5.	A Phase I Study of Weekly Doxorubicin and Oral Topotecan for Patients with Relapsed or Refractory Small Cell Lung Cancer (SCLC)	NCT00856037	I	University of Nebraska Medical Center	Treatment
6.	A Phase I Trial of the Combination of the Hedgehog Inhibitor, LDE225, with Etoposide and Cisplatin in the First-Line Treatment of Patients with Extensive Stage Small Cell Lung Cancer (ES-SCLC)	NCT01579929	I	Memorial Sloan Kettering Cancer Center	Treatment
7.	Phase I and Randomized Phase II Double-Blind Clinical Trial of Cisplatin and Etoposide in Combination with Veliparib (ABT-888) or Placebo as Frontline Therapy for Extensive Stage Small Cell Lung Cancer	NCT01642251	I/II	Eastern Cooperative Oncology Group	Treatment
8.	A Multi-Center, Randomized, Double-Blind Phase II Study Comparing ABT-888, a PARP Inhibitor, Versus Placebo with Temozolomide in Patients with Relapsed Sensitive or Refractory Small Cell Lung Cancer	NCT04638546	II	Memorial Sloan-Kettering Cancer Center	Treatment
9.	Randomized Phase II Study Comparing Prophylactic Cranial Irradiation Alone to Prophylactic Cranial Irradiation and Consolidative Extra-Cranial Irradiation for Extensive Disease Small Cell Lung Cancer (ED-SCLC)	NCT01055197	II	Radiation Therapy Oncology Group	Treatment
10.	Randomized Phase II Study of Single Agent OSI-906, an Oral, Small Molecule, Tyrosine Kinase Inhibitor (TKI) of the Insulin Growth Factor-1 Receptor (IGF-1R) Versus Topotecan for the Treatment of Patients with Relapsed Small Cell Lung Cancer (SCLC)	NCT01387386	II	H. Lee Moffitt Cancer Center and Research Institute	Treatment
11.	Phase II Study Evaluating Safety and Efficacy of Stereotactic Body Radiotherapy and Radiofrequency Ablation for Medically Inoperable and Recurrent Lung Tumors Near Central Airways	NCT01051037	II	Jonsson Comprehensive Cancer Center	Treatment

	Trial Name	Clinical Trial ID number	Phase	Lead Organization	Focus
12.	A Phase II Study of the Hsp90 Inhibitor, STA-9090, in Patients with Relapsed or Refractory Small Cell Lung Cancer	NCT01173523	II	Dana-Farber Harvard Cancer Center	Treatment
13.	Randomized Phase II Trial Using Dendritic Cells Transduced with an Adenoviral Vector Containing the P53 Gene to Immunize Patients with Extensive Stage Small Cell Lung Cancer in Combination with Chemotherapy with or without All Trans Retinoic Acid	NCT00617409	II	H. Lee Moffitt Cancer Center and Research Institute	Treatment
14.	A Single Arm, Two-Stage Phase II Study of Arsenic Trioxide in Previously Treated Small Cell Lung Cancer	NCT01470248	II	Emory University	Treatment
15.	A Phase IIa Intrapatient Dose Escalation Study of Desipramine in Small Cell Lung Cancer and Other High-Grade Neuroendocrine Tumors	NCT01719861	II	Stanford University Hospitals and Clinics	Treatment
16.	A Randomized Double-Blind Phase II Trial of Platinum Therapy plus Etoposide with/without Concurrent ZD6474 in Patients with Previously Untreated Extensive Stage Small Cell Lung Cancer: Hoosier Oncology Group LUN06-113	NCT00613626	II	Hoosier Oncology Group	Treatment
17.	A Randomized Phase II Study of IV Topotecan versus CRLX101 in the Second Line Treatment of Recurrent Small Cell Lung Cancer	NCT01803269	II	University of Chicago Comprehensive Cancer Center	Treatment
18.	A Phase II Trial of Hippocampal-Sparing Prophylactic Cranial Irradiation (PCI) for Limited Stage Small Cell Lung Cancer (SCLC)	NCT01797159	II	Johns Hopkins University	Treatment
19.	Phase III Comparison of Thoracic Radiotherapy Regimens in Patients with Limited Small Cell Lung Cancer Also Receiving Cisplatin and Etoposide	NCT00632853	III	Cancer and Leukemia Group B	Treatment

* Clinical trial data were obtained from the NCI Clinical Trials Reporting Program in May 2013. Trial status was confirmed using ClinicalTrials.gov.

Workforce Development

NCI supports training and career development through a variety of activities. NCI-supported training and career development activities related to SCLC are listed in Table **5** (extramural support) and Table 6 (intramural support).

Table 5. NCI-Supported Small Cell Lung Cancer Workforce Development: Extramural

Grant Number	PI	PI Institution	# Trainees Supported
Undergraduate			
1R15CA161491-01A1	Dasgupta, Piyali	Marshall University	2
Graduate			
5R01CA131217-04	Oyelere, Adegboyega	Georgia Institute of Technology	7
Postdoctoral			
1F32CA165856-01A1	Nicolay, Brandon	Massachusetts General Hospital	1
5R01CA131217-04	Oyelere, Adegboyega	Georgia Institute of Technology	1
5R01CA136534-03	Deng, Xingming	Emory University	5
7R01CA148867-04	MacPherson, David	Fred Hutchinson Cancer Research Center	1
Career Development			
3K23CA164015-02	Owonikoko, Taofeek	Emory University	1
5P50CA058184-17	Baylin, Stephen / Hann, Christine	Johns Hopkins University	2

Table 6. NCI-Supported Small Cell Lung Cancer Workforce Development: Intramural

Intramural Number	PI	NCI Division	# Trainees Supported
Postdoctoral			
ZIA SC 000167	Linnoila, Ilona	Center for Cancer Research	3
ZIA SC 010093	Schrump, David	Center for Cancer Research	1

Research Resources

NCI has many resources available to researchers working on SCLC. The resource topics include: animals and animal models; drug and biological drug development, manufacturing, screening, and repositories; epidemiology and statistics; human and animal specimen collection and distribution; scientific computing; and family registries and cancer genetics (**https://resresources.nci.nih.gov**). Examples of some of these resources are highlighted below.

Tissue Banks

- Lung Cancer SPORE Tissue and Pathology Core Resources
- NCI National Clinical Trials Network (NCTN) Tissue Banks

Molecular Profiling

- The **NCI Center for Cancer Research Clinical Molecular Profiling Core** supports clinical trials and other studies within the Center for Cancer Research and NIH Clinical Center. Supported SCLC studies include:
  - Pilot Trial of Molecular Profiling and Targeted Therapy for Advanced Non-Small Cell Lung Cancer, Small Cell Lung Cancer, and Thymic Malignancies
  - Molecular Profiling of Small Cell Lung Cancer.
- The **Clinical Proteomic Tumor Analysis Consortium (CPTAC)** systematically identifies proteins that derive from alterations in cancer genomes and related biological processes, and provide these data with accompanying assays and protocols to the public.

Mouse Models of Human Cancers Consortium (MMHCC)

- A consortium which derives and characterizes mouse models, and generates resources, information and innovative approaches to the application of mouse models in cancer research.
- An intramural laboratory in the NCI Center for Cancer Research is producing a mouse model to investigate the role of the *ASH1* gene in SCLC.

Early Detection Research Network (EDRN)

- A network of laboratories and centers (Biomarker Developmental Laboratories; Biomarker Reference Laboratories; Clinical Validation Center; Data Management and Coordinating Center) whose goal is to accelerate the translation of biomarkers into clinical applications and to evaluate new ways of testing for cancer in its earliest stages.

The Cancer Intervention and Surveillance Modeling Network (CISNET)

- A consortium of NCI-sponsored investigators that use statistical modeling to improve the understanding of cancer control interventions in prevention, screening, and treatment and their effects on population trends in incidence and mortality.
- The CISNET lung group's interests include areas such as tobacco control policies, screening, and genetic susceptibility. Models incorporate the association between smoking and lung cancer in various ways, from epidemiologic models to more mechanistic models, including various versions of the two-stage clonal expansion model of carcinogenesis.

Methods

NCI Portfolio

Research Projects

The portfolio analysis focused on FY2012 projects. Project information on extramural grants was obtained from the Cancer Database System (CDBS, an internal Office of Science Planning and Assessment [OSPA] database). Information on intramural research and contract research projects was obtained from the NCI Funded Research Portfolio (NFRP) website. Both groups of projects were obtained by searching for projects at least 25 percent relevant to the cancer site "lung."[4] Through this method, 745 projects were identified. One additional relevant project was identified by searching for projects at least 25 percent relevant to the NIH Research, Condition, and Disease Categorization (RCDC)[5] term "small cell lung cancer" using the Query View Report (QVR) database. The abstract of each of these projects was reviewed and coded to the coding schema shown in Table 5.

Because SCLC is of neuroendocrine origin, research into neuroendocrine tumors at other anatomical sites may be of interest to SCLC researchers. A search was performed using the keyword "neuroendocrine" of all FY2012 extramural projects not coded to the "lung" cancer site in the CDBS, and an identical search was performed in the NFRP for intramural and contract research projects. Projects that did not include research on neuroendocrine tumors were excluded. Twenty projects were identified through this method.

Clinical Trials

The NCI Clinical Trials Reporting Program (CTRP) database was searched for interventional clinical trials for small cell lung cancer (conducted May 2013). Trials were limited to those currently accruing patients. ClinicalTrials.gov was consulted to verify trial status. Trials were excluded if they were addressing lung cancer in general; focused on tobacco cessation; or enrolling patients with several types of unrelated tumors (e.g., all solid tumors). Noninterventional trials, including ancillary-correlative trials, were not included in this analysis.

Non-NCI NIH Portfolio

Lung cancer projects funded by NIH Institutes and Centers other than NCI were identified by searching the NIH Research Portfolio Online Reporting Tools (RePORT) for projects relevant to the NIH spending category "lung cancer." NCI was excluded from this search. Each of these projects was subject to abstract review to determine lung cancer relevance and coded to the schema in Table 5. One grant relevant to small cell lung cancer was identified using this approach.

ICRP Portfolio

Small cell lung cancer research being supported by members of the International Cancer Research Partnership was identified using the ICRP web site. Potentially relevant projects were

[4] NCI grants are indexed for a variety of research categories and organ sites. Each category is assigned a 'percent relevance' based on the portion of the grant relevant to the category that is used to prorate the total amount of the grant. Percent relevance values are assigned by professional staff based on review of complete grant applications. A grant may be 100 percent relevant to multiple categories, and the sum of the percent relevance assignments may exceed 100 percent.

[5] More information on the RCDC coding process can be found at http://report.nih.gov/rcdc/index.aspx.

identified by performing a search using the key term "SCLC" for projects of all organizations (excluding NCI) that were active anytime between 2008 and 2012. ICRP partners submit data on a volunteer basis, and 2012 may not be the most current year for each organization. The abstract for each project was screened for relevance to SCLC. Note that this search identified only those projects with the keyword "SCLC"; SCLC grants not using the SCLC acronym were not included in this analysis.

Table 5. Coding Schema

Type of Lung Cancer
1. Small cell lung cancer
1.1. Small cell carcinoma (oat cell cancer)
1.2. Combined small cell carcinoma
2. Non-small cell lung cancer
2.1. Adenocarcinoma
2.2. Large cell carcinoma
2.3. Adenosquamous carcinoma
2.4. Sarcomatiod carcinoma
2.5. Carcinoid carcinoma
2.6. Salivary gland carcinoma
2.7. Squamous cell carcinoma
3. Benign epithelial tumors
4. Preinvasive lesions
5. No type mentioned
Research Resources
1. Biobank/specimen
2. Patient registries
3. Genetic registries
4. Model development
4.1. Animal
4.2. Other
Imaging
1. Detection/early detection
2. Image-guided therapy
Stem cells
Epidemiology

Addendum A: NCI-Funded Research on Neuroendocrine Tumors

	Project Number	Title	PI	Institution
1.	1F32CA168330-01	Role of Ascl1 in Glioma	Vue, Tou Yia	UT Southwestern Medical Center
2.	1K01CA160602-01A1	Cytoprotective Autophagy in Bone Metastatic Prostate Cancer	Delk, Nikki	Rice University
3.	5K99CA154888-02	Role of Jmjd1a in Hypoxia-induced EMT and Prostate Cancer Stem Cells	Qi, Jianfei	Sanford-Burnham Medical Research Institute
4.	1R01CA163907-01A1	Interactions of the Angiopoietin and PD-ECGF Pathways in Tumor Angiogenesis	Schwartz, Edward	Albert Einstein College of Medicine Yeshiva University
5.	2R01CA116337-06A1	Molecular Signatures of Lethal and Indolent Prostate Cancer	Rubin, Mark	Weill Medical College of Cornell University
6.	3R01CA116477-07S1	Dose-Response in Radionuclide Therapy	Sgouros, George	Johns Hopkins University
7.	3R01CA121115-04S1	GSK3-beta Signaling in Medullary Thyroid Cancer	Chen, Herbert	University of Wisconsin, Madison
8.	5R01CA096823-10	Determinants of Metastatic Progression	Nikitin, Alexander	Cornell University
9.	5R01CA099948-10	Mechanism and Therapeutic Targeting of Evasive Resistance to Antiangiogenic Drugs	Bergers, Gabriele	University of California, San Francisco
10.	5R01CA107263-09	Integrins and Caspase 8 in Tumor Progression	Stupack, Dwayne	University of California, San Diego
11.	5R01CA111515-08	Novel Insights in the Regulation of HIF1alpha Stability	Ronai, Ze'Ev	Sanford-Burnham Medical Research Institute
12.	5R01CA116477-07	Dose-Response in Radionuclide Therapy	Sgouros, George	Johns Hopkins University
13.	5R01CA121115-04	GSK3-beta Signaling in Medullary Thyroid Cancer	Chen, Herbert	University of Wisconsin, Madison
14.	5R01CA140468-03	Interleukin-6 and Castration-resistant Prostate Cancer	Gao, Allen	University of California, Davis
15.	5R01CA148814-02	Identifying Mechanisms Linking Stress Biology to Human Breast Cancer	Conzen, Suzanne	University of Chicago
16.	5R01CA154383-02	Multipotential Mesenchymal Stem-cell-like Cells in Pancreatic Tumorigenesis	Bergers, Gabriele	University of California, San Francisco
17.	1R43CA174132-01	Development of Transporter Targeted Platinum Drugs for Neuroblastoma	Mamelok, Richard	Apricity Therapeutics, Inc.
18.	ZIABC011012	Study of Hepatic Arterial Infusion of Melphalan for Malignancy in the Liver	Hughes, Marybeth	National Cancer Institute

	Project Number	Title	PI	Institution
19.	ZIABC011275	Gene Expression and Regulation in Endocrine Cancers	Kebebew, Electron	National Cancer Institute
20.	ZIASC010437	Molecular Pathology of Cancer	Emmert-Buck, Michael	National Cancer Institute

Addendum B: International Cancer Research Partnership Investment in Small Cell Lung Cancer

ICRP is an alliance of cancer organizations working together to enhance global collaboration and strategic coordination of research. ICRP partners include organizations from Canada, France, the Netherlands, the United Kingdom, and the United States. ICRP maintains a web-based database of research projects funded by partner organizations, which can be accessed at www.icrpartnership.org. Researchers can use the database to identify potential collaborators and avoid duplication of efforts.

	Project #	Title	PI	Institution	Award Type	Funding Organization
1.	CRU2233	CONVERT: A 2-arm Randomised Controlled Trial of Concurrent Chemo-radiotherapy Comparing Twice-daily and High-dose Once-daily Radiotherapy in Patients with Limited Disease Small Cell Lung Cancer	Faivre-Finn, Corinne	The Christie NHS Foundation Trust	Clinical Trial	Cancer Research UK
2.	CRU3581	CRUKE/10/019: ICE: A Phase II Trial of the Addition of Ipilimumab to Carboplatin and Etoposide Chemotherapy for the First-line Treatment of Extensive Stage Small Cell Lung Cancer	Ottensmeier, Christian	University of Southampton	Clinical Trial	Cancer Research UK
3.	CRU1933	LungStar: A Multicentre Phase III Randomised Double-blind Placebo-controlled Trial of Pravastatin Added to First-line Standard Chemotherapy in Patients with Small Cell Lung Cancer (SCLC)	Seckl, Michael	Charing Cross Hospital	Clinical Trial	Cancer Research UK
4.	CRU3879	CRUK/06/009: LungStar - A Multicentre Phase III Randomised Double-blind Placebo-controlled Trial of Pravastatin Added to First-line Standard Chemotherapy in Patients with Small Cell Lung Cancer (SCLC)	Seckl, Michael	University College London	Clinical Trial	Cancer Research UK
5.	CRU3671	POMC as an Exploratory Circulating Biomarker for Small Cell Lung Cancer	White, Anne	University of Manchester	Clinical Trial	Cancer Research UK
6.	CRU3792	CRUK/10/037: STOMP (previously OPIUM-SCLC): A Randomised Phase II Study of Olaparib Maintenance Treatment in Patients with Chemosensitive Small Cell Lung Cancer	Woll, Penella	University of Sheffield	Clinical Trial	Cancer Research UK

	Project #	Title	PI	Institution	Award Type	Funding Organization
7.	DGOS_0387	Prospective Multicentric Optimization and Phase I/II Study of Pretargeted Radioimmunotherapy (PRAIT) Using Anti-CEA x Anti-HSG TF2 Bispecific Antibody (bsMAb) and 177Lu-IMP-288 Peptide in Patients with CEA-expressing Small Cell Lung Carcinoma (SCLC)	Bodere, Fran Kraeber	Centre Hospitalier Universitaire de Nantes	Clinical Trial	DGOS-Ministère de la Santé
8.	IKZ 2007-3865	Treatment and Outcome for Cancer Patients aged 75 or Older: A National Population-based Study	Janssen-Heijnen, M.L.G.	Integraal Kankercentrum Zuid	Clinical Trial	KWF Kankerbestrijding/Dutch Cancer Society
9.	VU 2008-4290	Randomized Trial on Chest Irradiation in Extensive Disease Small Cell Lung Cancer. (CREST Study)	Slotman, B.J.	Vrije Universiteit	Clinical Trial	KWF Kankerbestrijding/Dutch Cancer Society
10.	BUIT 2009-4451	Antibodies and Paraneoplastic Syndromes Related to Neuro-endocrine Tumours	Titulaer, M.J.	University of Pennsylvania	Clinical Trial	KWF Kankerbestrijding/Dutch Cancer Society
11.	SCO179	The Role of CD45 as a Novel Prognostic Marker of Survival and Treatment Response in Patients with Small Cell Lung Cancer	Sethi, Tariq	University of Edinburgh	Clinical Trial	Scottish Government Health Directorates, Chief Scientist Office
12.	RSG-10-071-01	Mechanisms of Small Cell Lung Carcinoma Initiation and Maintenance	Sage, Julien	Stanford University	Research	American Cancer Society
13.	CRU2742	Research Bursary: MicroRNA Expression in Small Cell Lung Carcinoma—A Novel Means of Classification, Predicting Prognosis and Identification of Therapeutic Targets?	Andrews, Timothy	NHS Lothian	Research	Cancer Research UK

	Project #	Title	PI	Institution	Award Type	Funding Organization
14.	CRU2999	Clinical Research Training Fellowship: Chemoresistance and Progression of Small Cell Lung Cancer—The Effects of Tumour Cell Fibroblast and Extracellular Matrix Interactions	Lawson, Malcolm	University of Cambridge	Research	Cancer Research UK
15.	NKI 2008-4253	Designing and Testing New Intervention Therapies for Lung Cancer and Mesotheliomas	Berns, A.J.M.	NKI-AVL	Research	KWF Kankerbestrijding/Dutch Cancer Society
16.	NKI 2006-3566	Mechanisms of Chemotherapy Resistance in Spontaneous Tumors of Genetically Modified Mice	Borst, P.	NKI-AVL	Research	KWF Kankerbestrijding/Dutch Cancer Society
17.	KUN 2006-3575	Pan-cholecystokinin (CCK) Receptor Binding Ligands for Radionuclide Targeting of CCK-receptor-positive Tumors	Laverman, P.	UMC Nijmegen St. Radboud	Research	KWF Kankerbestrijding/Dutch Cancer Society
18.	SCO198	Characterisation of Fam38A, A Novel Integrin Activator, in Lung Cancer	Sethi, Tariq	University of Edinburgh	Research	Scottish Government Health Directorates, Chief Scientist Office
19.	LC090436	Elucidation of the Mechanisms of Immune Reactivity in Small Cell Lung Cancer to Identify Targets for Detection, Imaging, and Treatment	Laird-Offringa, Ite	University of Southern California	Research	U. S. Department of Defense Congressionally Directed Medical Research Program
20.	DOH421	Topotecan for the Second-line Treatment of Small Cell Lung Cancer	Clegg, A	University of Southampton	Research	UK Department of Health

	Project #	Title	PI	Institution	Award Type	Funding Organization
21.	CRU2251	Defining the Clinical Importance of mTOR and S6 Kinases in Small Cell (SCLC) and Non-small Cell Lung Cancer (NSCLC).	Dhillon, Tony	Imperial College of Science, Technology and Medicine	Training	Cancer Research UK
22.	CRU2931	PhD Studentship: Molecular Mechanisms by Which FGF-2 Blocks Chemotherapy-induced Apoptosis in Small Cell Lung Cancer Cells	Seckl, Michael	Imperial College of Science, Technology and Medicine	Training	Cancer Research UK
23.	1656_1	The Role of Specific Genomic Alterations in the Aggressive Nature of Small Cell Lung Cancer	Coe, Bradley	BC Cancer Agency, Vancouver Centre	Training	Michael Smith Foundation for Health Research

Appendix 2: Report from Small Cell Lung Cancer Workshop 2013

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

June 18, 2014

Organization of the Report

A. The Workshop

(1) Origin of the Workshop
(2) Overview of the Workshop Program

B. Current Approaches to SCLC

(1) Risk Assessment and Screening
(2) Diagnosis, Staging, and Monitoring
(3) Therapy and Resistance

C. Recent Scientific Advances and Emerging Research Questions

(1) Characterization of the SCLC Genome, Transcriptome, and Epigenome
(2) Analysis of Acquired Chemotherapy Resistance in SCLC
(3) *TP53* and *RB* as Gatekeeper Mutations in SCLC
(4) *MYC* Family Members in SCLC
(5) Developmental and Stem Cell Signaling Pathways in SCLC

D. Attracting Investigators to the Field of SCLC

E. Recommended Initiatives

(1) Develop Better Research Tools for the Study of SCLC
(A) Optimize Collection of Tumor Tissues
(B) Develop New SCLC Models
(2) Assemble Comprehensive Genomic Profiling for SCLC
(3) Develop New Diagnostic Approaches
(4) Facilitate Therapeutic Development Efforts
(5) Understand Mechanisms Underlying Both the High Initial Rate of Response and the Rapid Emergence of Drug and Radiation Resistance

F. Summary

G. References

H. List of Abbreviations

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[5]; recent and ongoing genomic studies of genetically engineered mouse models (GEMMs) of SCLC[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[9]; and recent clinical data using temozolomide both as a single agent[10] and with a poly-(ADP-ribose)-polymerase (PARP) inhibitor[11]. Finally, promising opportunities for targeting Bcl-2 in SCLC[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[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, ^{18}Fluoro-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[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[16]. PET staging now approaches a 100% level of sensitivity and greater than 90% specificity[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[21, 22] with concomitant radiation that can be encompassed in a single radiation port[23, 24]. Treatment for ED includes the same chemotherapy options, without concomitant radiation[22]. In some instances, particularly for small peripheral lung nodules, surgery can also be considered[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[23, 26-28]. An alternative first-line chemotherapy regimen, cisplatin and irinotecan, appeared to be superior in a Phase III study conducted in Japan[29], but these results could not be confirmed in subsequent US comparative trials[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[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[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[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.

(1) 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[22]. 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[6]. 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[6, 43, 44]. 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[8]. 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[45]. It was confirmed and further refined in recent genomic sequencing studies of SCLC[1, 2]. New observations included identification of a recurrent in-frame fusion involving *RLF* and *MYCL1* in a primary SCLC tumor and four SCLC cell lines, and that siRNA targeting *MYCL1* in such lines inhibited proliferation[2]. In contrast to the tumor suppressors *TP53* and *RB*, *MYC* family members are activated oncogenes in SCLC and other cancers[46]. Previous efforts to design specific inhibitors of MYC signaling have been, broadly speaking, disappointing, but many new research tools and approaches are emerging[47].

Questions regarding the role of MYC signaling in SCLC: Could a reinvigorated effort focused on inhibition of MYC family members create novel MYC-directed therapeutics? Are there common dependencies among MYC-driven tumors? Could 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. ASCL1-dependent embryonic developmental signaling and Hedgehog stem cell signaling pathways in particular have been implicated in SCLC clonogenic potential[48, 49]. Despite disappointing results of a randomized clinical trial of a Hedgehog pathway inhibitor in extensive stage SCLC[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 Collection 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 of 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[51]. 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[52]. 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 for SCLC

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[53]. Further, the failure of spiral CT screening to detect SCLC early enough for successful 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[54, 55] suggest that more sensitive screening tests for SCLC, perhaps incorporating assessments of mutant *RB* and *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[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[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[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 regulate[57, 58], potentially restoring control of cancer cell growth. An additional experimental approach involves local delivery of tumor suppressor genes via gene therapy[59]. 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 screening[47].

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[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[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[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.

(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[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*)[64]; 2) the expression of certain cancer stem cell markers (CD133) that are associated with the overexpression of mitogenic neuropeptide receptors[65, 66]; 3) elevated levels of DNA repair proteins and/or activation of the PI3K/mTOR pathway[67]; and 4) overexpression of ATP-binding cassette transporters[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.

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H. List of Abbreviations

ADP	adenosine diphosphate
ATP	adenosine triphosphate
CT	computed tomography
CTAC	Clinical Trials and Translational Research Advisory Committee
CTC	circulating tumor cell
DCE	dynamic contrast-enhanced
DNA	deoxyribonucleic acid
ED	extensive-stage disease
FDA	Food and Drug Administration
GEMM	genetically engineered mouse model
IASLC	International Association to Study Lung Cancer
LD	limited-stage disease
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NK cells	natural killer cells
PDX	patient-derived xenograft
PET	positron emission tomography
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	ribonucleic acid
RNASeq	RNA sequencing
SCLC	small cell lung cancer
shRNA	short hairpin RNA
siRNA	small interfering RNA
SNP	single nucleotide polymorphism
SPORE	Specialized Programs of Research Excellence
TCGA	The Cancer Genome Atlas

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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

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

Roundtable: Denise Aberle, M.D., Ramaswamy Govindan, M.D., David Harpole, M.D, John Heymach, M.D., Ph.D., Paul Hwang, M.D., Ph.D., Matthew Meyerson, M.D., Ph.D., Deborah Morosini, M.D, Rich Simon, D.Sc., Ming Tsao, M.D.

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 **<u>Session 3</u>: 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 **<u>Special Session</u>: 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 **<u>Breakout sessions on each of the 3 topics above</u>** 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**