

## Small cell lung cancer: updates and new concepts

The standard of care for both limited stage and extensive stage SCLC has seen little change since the introduction of platinum/etoposide doublet therapy in the mid-1980s (1,2). There have been advances in the clinic since then, including the approval of topotecan for recurrent SCLC and the application of new radiation therapy strategies, but despite these advances the outlook for patients afflicted with SCLC remains dismal (3-8). The frequent and rapid incidence of acquired resistance to these therapies (6) and the inability to detect early-stage disease by radiographic approaches (9-11) has bedeviled progress in this deadly disease.

It was precisely this situation that led the U.S. National Cancer Institute (NCI) to designate SCLC as a “recalcitrant cancer” according to the definition mandated by the Recalcitrant Cancer Research Act (RCRA) (12-14). This statute, passed by the U.S. Congress in 2012, required the NCI to designate at least two such recalcitrant cancers (the other was pancreatic ductal adenocarcinoma), with a 5-year relative survival of less than 20% and that result in 30,000 or more deaths in the U.S. per year, and to develop a set of initiatives aimed at advancing research in those cancers. In implementing its response to the RCRA, the NCI assembled a working group of international experts in SCLC to identify research opportunities and new research initiatives. The working group assessed the state of the science (circa mid-2013) and identified research advances that were ripe for expanded investigation and represented translational opportunities. These findings are summarized in the report of the SCLC working group to Congress (11) and an updated picture of the research landscape can be found in more recent reviews (15-21).

The report to Congress defined a set of recommended initiatives including the development of new research models for SCLC, the expansion of genomic and other ‘omic’ profiling, the development of novel therapies, research into mechanisms of resistance, and new approaches to diagnosis and early detection. Working upon these recommendations, the NCI has designated funds to the newly established SCLC Consortium, consisting of a coordinating center and a series of hub sites, each funded by cooperative agreements with the NCI. The coordinating center is also actively partnering with other NCI grantees to provide central services for biobanking and informatics. In addition to these new research initiatives and funding opportunities, the recent gathering of SCLC researchers at two workshops organized by the International Association for the Study of Lung Cancer (IASLC) in 2015 (22) and 2017 are an encouraging and welcome sign that the burgeoning opportunities for research advances in SCLC are attracting scientists to the field.

Two years ago, Translational Lung Cancer Research in its February 2016 issue devoted a series of articles to SCLC. Since then more than 800 scientific papers on SCLC have been published and thus it is appropriate to revisit at least some aspects of research in this disease.

The collection of articles following this preface was written by members of the NCI SCLC Consortium. Rather than covering all most recent advances, the authors focus on some overarching themes giving a historical perspective in light of current data. One of these topics is the intra- and intertumoral heterogeneity that is observed in other cancers, but has specific and interesting features in SCLC. Given the neuroendocrine background of SCLC, there are some similarities but also differences with neuroendocrine cancers in other organ sites, such as prostate and bladder (23,24). Two articles in our series cover SCLC heterogeneity: Adi Gazdar and his team created a 40-gene expression score which allowed them to divide SCLCs into low neuroendocrine and high neuroendocrine subtypes (low NE/high NE) and to further characterize them. The loss or decrease of NE characteristics seems to be quite frequent and signals an epithelial-mesenchymal transition. One of the activated oncogenes in this subtype, *MYC*, was recently shown to have a critical role in the generation of an aggressive and highly metastatic form of SCLC that, in turn, may respond to Aurora kinase inhibitors (25). The second paper by Julian Sage and his team deals with the complexity of SCLC heterogeneity through the prism of animal models. The extreme plasticity of SCLC is a result of various subpopulations of SCLC cells and their functional interactions. The understanding of these mechanisms will ultimately lead to a more refined and diversified therapeutic approaches in SCLC. For example, some newer attempts to take advantage of SCLC vulnerabilities have yielded promising signals and this is documented in the paper by Lauren Byers that focuses on targeting the DNA damage repair. This paper is paired with a broader review of the status of SCLC therapies by Ana Farago. However, many gaps remain in our knowledge of this disease and Kwon-Sik Park’s article

on the role of transcription factors and co-factors in SCLC pathogenesis reviews our current, rapidly growing understanding of SCLC biology. A model of transcriptional network for SCLC is described and its validation could possibly lead to better interventions in SCLC.

As stated above, this series does not attempt to completely list all the recent progress in SCLC research that has been well covered elsewhere in recent reviews (22,26). Rather it focuses more in depth on a few critical developments that may lead to improved diagnosis and interventions for SCLC patients. The field is rapidly moving forward and we will hopefully see translation of these new discoveries into clinical practice soon.

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