













progenitor cells by positive regulation of such genes as *CDK2*, *E2F1*, and *BIRC5* (33). The proposed function of *ASCL1* as an oncogenic transcription factor is, therefore, supported by its known function in upregulating growth promoting genes.

The characteristics of SCLC genomes include a high prevalence of mutations in the tumor suppressors *RB1* and *TP53*. More recently, whole-genome sequencing of SCLC specimens have uncovered potential driver mutations such as *PTEN* mutation or *FGFR1* amplification, both of which occur at relatively low frequency (28, 30). In one previous study, *SOX2* amplification was found in approximately 27% of SCLC samples, and *SOX2* knock-down by shRNA inhibited proliferation of SCLC cells with *SOX2* gene amplification (30). We analyzed the RNA-seq data published in that report, and found that *ASCL1* is expressed at high levels in 10 of 15 SCLC specimens, to a level greater than *SOX2*. These findings further underscore the importance of *ASCL1* as a potential driver oncogene in SCLC. More importantly, our results have demonstrated that inhibition of BET protein binding to chromatin is a feasible approach for pharmacologic inhibition of *ASCL1* expression and consequently SCLC cell growth. Our findings do not preclude a role for *SOX2* in SCLC, but a pharmacologic approach to inhibit *SOX2* expression remains to be demonstrated. Furthermore, the RNAseq data point to a higher prevalence of *ASCL1* deregulation in the disease and perhaps a greater therapeutic opportunity using BET antagonists. Inhibition of *CDK7* was recently shown to modulate the expression of genes associated with superenhancer features in SCLC (34). These highly expressed genes, including *ASCL1*, are enriched in those encoding transcription factors specific to a neuroendocrine lineage, and their modulation was proposed to mediate the sensitivity of SCLC cell lines to *CDK7* inhibition. These recent findings are consistent with our proposal that *ASCL1* has an important role in the survival of SCLC. BET and *CDK7* inhibitors are, therefore, two independent pharmacologic approaches for modulating the expression of putative oncogenic transcription factors, and their relative effectiveness will have to be further assessed in preclinical and clinical testing.

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SCLC is a disease with high unmet medical need, with chemotherapy being the only treatment option with a high rate of relapse. This study has provided the basis for evaluating BET inhibitors as a novel treatment option for SCLC. Furthermore, our data suggest that *ASCL1* expression may be used to select lung cancer patients who are likely to respond to BET inhibitor treatment.

## Disclosure of Potential Conflicts of Interest

C. Fairchild has ownership interest (including patents) in BMS stock. No potential conflicts of interest were disclosed by the other authors.

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