trials, standard therapies and outcomes for patients have changed very little over the past 30 years.

Immunotherapy represents a new treatment paradigm that may have clinical activity in SCLC. Multiple lines of evidence suggest that SCLC tumors may be immunogenic. First, a subset of SCLCs are associated with production of auto-antibodies or paraneoplastic syndromes, and production of auto-antibodies predicts a higher likelihood of complete response to first-line chemotherapy and prolonged survival (Graus et al., 1997). Second, higher ratios of circulating T effector cells to T regulatory cells have been observed in patients with earlier stage disease and correlate with prolonged response to therapy (Koyama et al., 2008). Third, although expression of programmed death ligand-1 (PD-L1) is low on SCLC tumor cells, PD-L1 expression is observed on tumor-infiltrating macrophages and is correlated with the presence of tumor-infiltrating lymphocytes (Schultheis et al., 2015).

Clinically, SCLCs are associated with a history of significant tobacco exposure. In patients with non-small cell lung cancer (NSCLC), response rates to inhibitors of the immune checkpoint programmed death 1 (PD-1) receptor are higher in current or former smokers compared to never or minimal smokers. This increased response rate is attributed to a higher mutational burden of these carcinogen-associated tumors, leading to expression of immunogenic neoantigens (Rizvi et al., 2015). Indeed, SCLCs are characterized by a high somatic mutation burden (George et al., 2015). This is likely largely attributable to the carcinogenic effects of tobacco exposure, though genomic instability may also be potentiated by the universal loss of the tumor suppressor gene Tp53.

On the basis of these preclinical observations, several clinical trials are now underway to assess role of immunotherapy in SCLC. Emerging data suggest that immune checkpoint inhibitors may have meaningful clinical activity in this disease. CheckMate 032 (NCT01928394) is a phase 1/2 trial of nivolumab either alone or in combination with ipilimumab in various tumors. Calvo et al. (ESMO, 2015) recently presented preliminary findings from this study, including an overall response rate of 12.7% with nivolumab and 31.1% with nivolumab plus ipilimumab. In a separate phase 1b study, Keynote-028 (NCT02054806), Ott et al. (ASCO, 2015) reported an overall response rate of 35% among PD-L1 positive SCLC patients treated with the PD-1 inhibitor pembrolizumab. Other inhibitors of PD-1, PD-L1 and CTLA-4 are also in clinical development. The durability of responses to immune checkpoint inhibitors is not yet well established, and close monitoring for signs/symptoms of paraneoplastic syndromes and autoimmune disease is necessary. Current and future trials utilizing immune checkpoint inhibitors and other modulators of the immune response will further explore clinical activity, biomarkers, toxicities, and the role of combination strategies in SCLC.

Using stem cell biology to design precision medicine for non-small cell lung cancer

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Stem cell biology is integral to understanding the development and treatment responses of lung cancers. Our laboratories used ideas from stem cell biology to explore one of the first genetic mouse models of the lung squamous cell carcinoma, driven by conditional biallelic inactivation of Stk11 (Lkb1) and Pten in the murine lung. Cells that could serially transplant disease (i.e. cancer stem cells) expressed markers of basal cells, the upper airway stem cells, and highly expressed the immune evasion molecule PD-L1. This was in contrast to the lung adenocarcinoma stem cells from the Kras/p53 mouse model that rely upon other pathways and share characteristics of distal lung stem cells. Since anti-PD1 blockade has shown promise in treating lung squamous cell carcinomas, we are now exploring if anti-PD1 targets cancer stem cells, and if so, in what genotypes and contexts. We have also used ideas from stem cell biology to build a rationale for combining epigenetic therapies with common chemotherapies. It is often found that cancer stem cells are resistant to chemotherapy, and combination of chemotherapies with targeted therapies could improve treatment outcomes. Expression of the histone methyltransferase EZH2 in lung tumors is correlated with a poor survival of lung cancer patients, and is therefore an attractive targeted therapy candidate. Because EZH2 is highly co-expressed with the Topoisomerase II (Topoll) gene TOP2A in lung cancers, we examined whether EZH2 inhibition synergized with the common chemotherapy etoposide, which targets Topoll. We found that lung cancers with activating mutations in EGFR, or with inactivating mutations in the BAF complex member BRG1, were both sensitized to etoposide by EZH2 inhibition. We are now exploring the mechanism through which BRG1 loss of function lung cancers, which represent up to 40% of lung adenocarcinomas, are specifically sensitized to etoposide by EZH2 inhibition.
Together these studies exemplify how stem cell biology concepts can help to design precision medicine opportunities for the genetically complex disease of non-small cell lung cancer.

Potential of FLASH irradiation to minimize the incidence of radio-induced damage and fibrosis to normal lung in a mouse model

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Submillisecond pulses of radiation have been shown to generate less exchange chromosomal aberrations [1, 2] and a smaller extent of delayed cell death [3, 4] than continuous irradiation delivered at conventional dose-rate. This prompted us to determine whether and how pulsed irradiation affects the response of normal lung tissue in vivo. For this purpose, C57BL/6j mice were given a single dose of 17 Gy of 4.5 MeV electrons in bilateral thorax exposure either at a high (> 60 Gy/s, beam-on time < 0.5 s, FLASH) or conventional dose-rate (0.03 Gy/s, beam-on time 8 min, CONV) using an experimental linear electron accelerator established in the Research Division of Institut Curie at Orsay (France). DNA damage response, apoptosis and fibrosis development were subsequently analyzed at suitable times in the two modes of irradiation. The anti-tumor efficiency was also evaluated in vivo with two xenografts (HBCx-12A, HEP-2) and one syngeneic, orthotopic carcinoma (TC1-Luc). The results indicate that, in the hours following irradiation, FLASH-irradiated lungs present less DNA damages and less apoptosis than lungs irradiated at a conventional dose-rate. Furthermore, compared to the classical radiation-induced lung fibrosis observed past 16-weeks after CONV irradiation, analysis of FLASH-treated lungs did not show any histological sign of fibrosis nor activation of the TGF-beta pathway. However, FLASH irradiation was as efficient as CONV treatment in controlling tumor growth. Taken together, these results show that FLASH irradiation selectively spares normal lung tissue without any loss of the anti-tumor activity [5].

References