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].

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Radiomics of lung cancer

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Malignant cancers are characterized by microenvironmental heterogeneity, which is a leading cause of genomic heterogeneity. Microenvironmental heterogeneity can be viewed radiographically, wherein non-uniform patterns of enhancement or attenuation can be associated with poor outcome. In order to systematically investigate this, the process of "Radiomics" extracts quantitative first, second and higher order image feature data that can be statistically mined along with patient data for diagnostic, predictive and prognostic, models. The radiomics enterprise is divided into five processes with definable inputs and outputs: (i) image acquisition and reconstruction; (ii) image segmentation and rendering; (iii) feature extraction and qualification; (iv) databases and data sharing; and (v) informatics analyses. Each of these steps poses discrete challenges that have to be met. Even though this field is still emerging, translationally-directed classifier models have been generated in detecting and diagnosing a number of cancer subtypes.

To date, the radiomics effort has focused on computer-derived "agnostic" (e.g. texture) and radiologist-derived "semantic" image features, which quantify indescribable and describable features, respectively. These image features number in the hundreds and have been shown to have high prognostic value in both non-small cell lung cancer, NSCLC, and are being used to classify indeterminate lung nodules in lung cancer screening CTs. In NSCLC, prognostic models have been developed for patients treated with surgery, radiotherapy, or with targeted therapies. In each of these cases, binary classifiers have been used to predict response and/or survival with accuracies $>$ 80%. In addition, radiomic features have also been used to predict *EGFR* and *KRAS* mutation status in NSCLC, also with accuracies $>$ 80%. Current challenges for the nascent field of radiomics include development of a core lexicon of features, furthering the development and inter-institutional harmonization of computer-extracted features, and harmonization of image acquisition parameters for reduced variance.

In CT-based lung cancer screening and incidentally detected indeterminate pulmonary nodules, radiomics has shown value in improving diagnostic accuracy to discriminate cancer from benign pulmonary nodules. We have analyzed data from the National Lung Screening Trial, NLST, to identify subjects with cancerous and benign nodules, and have organized them into cohorts based on their screening history. Patients who are diagnosed with cancer following a prior nodule-negative screen have significantly worse outcome than patients who develop cancer following a prior nodule-positive/cancer-negative screen. In cohorts of patients with nodules not diagnosed as cancer in the first screen, we have identified significant radiomic features that can discriminate those who will subsequently develop cancer from those that remain benign with an accuracy of 80%, and this can be the basis for a "radiomics risk score" to predict subsequent cancer development. However, even the seemingly large "big data" NLST data set is underpowered once cohorts are assembled with similar histories, and co-variates are accounted for. Solutions to the problem of generating sufficiently powered data sets include capturing the radiomic data at the point of care (i.e. by the radiologists) and inter-institutional sharing of images, data, features and algorithms, which have yet to be reliably implemented.

From bench to bedside to beam: Hippocampal-sparing during cranial irradiation

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Whole-brain radiotherapy either therapeutically for brain metastases or prophylactically for small-cell lung cancer has been associated with cognitive toxicity, in the form of decline primarily in list-learning recall as well as patient-reported cognitive functioning. Emerging evidence suggests that the pathogenesis of radiotherapy-induced cognitive deficits may involve radiation-induced injury to proliferating neural stem cells in the subgranular zone of the hippocampus. Conformal avoidance of this hippocampal neural stem cell compartment during whole-brain radiotherapy using intensity-modulated radiotherapy has been proposed as an approach to preserving hippocampal neurogenesis and thus preventing or mitigating radiotherapy-related cognitive toxicity.

Promising results as compared to historical controls were observed in RTOG 0933, a phase II study of hippocampal avoidant WBRT for patients with brain metastases. Validation of these results in a phase III setting is being pursued through NRG CC001, a phase III trial of memantine plus whole-brain radiotherapy with or without hippocampal avoidance for brain metastases. Extrapolation of these results to the setting of prophylactic cranial irradiation for small cell lung cancer is being explored through NRG CC003, a randomized phase II/III trial of prophylactic cranial irradiation with or without hippocampal avoidance for small cell lung cancer. Both trials are currently activated and accruing patients.

This presentation will review the biology and radiosensitivity of the hippocampal neural stem cell compartment and prior and ongoing clinical studies to corroborate these preclinical observations using advanced radiotherapy techniques.

Primary and adaptive resistance to checkpoint blockade in lung cancer

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The incorporation of immunotherapies, and most notably immune checkpoint inhibitors, into the management of non-small cell lung cancer (NSCLC) has led to a paradigm shift in the management of patients with advanced disease. While PD1 antagonists have been shown to be superior to standard chemotherapy for subjects with progressive advanced disease many other immunomodulatory agents are currently under investigation as single agents or in combination with other therapies.

While the lung cancer community has made great strides in identifying genomic alterations in cancers which are associated with specific therapeutic vulnerabilities, our knowledge regarding predictive biomarkers for immunotherapies is limited. It remains the case that only a minority of patients respond to PD1:PDL1 antagonists, and for those who do, resistance to therapy develops over time.

Here, I will present data describing our efforts in profiling mouse models and patient specimens to describe two modes of resistance to PD1:PDL1 therapy. The first centers on primary non-response in patients with KRAS mutated lung cancers, tumors which typically display high rates of somatic mutations. I will present data demonstrating that within KRAS mutated lung adenocarcinoma tumors with concurrent loss of STK11/LKB1 display an adverse immune microenvironment for PD1:PDL1 therapy. I will discuss specific features of this immune microenvironment and suggest strategies to overcome primary resistance.