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Targeting NOTCH pathway in Glioblastoma
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Glioblastoma multiforme (GBM) is the most common malignant brain tumor in adults. The current standard of care includes surgery followed by radiotherapy (RT) and chemotherapy with temozolomide (TMZ). Treatment often fails due to the radiation and TMZ resistance of a small percentage of cells with stem cell-like behavior (CSC). The Notch signaling pathway is expressed and active in human glioblastoma and Notch inhibitors attenuate tumor growth *in vivo* in xenograft models. Here I will discuss the results of studies investigating combination treatments of RT Temozolomide and NOTCH inhibitors in an orthotopic model of Glioblastoma. Small Animal image guided preciscion Radiotherapy (SmART) treatment planning and delivery was used to achieve highly accurate dose prescriptions and treatment monitoring. Studies will be presented that investigate the role for NOTCH signaling in treatment response in different 2D and 3D culture systems.

Keywords: notch, glioblastoma, stem cell, radiotherapy, temozolomide, image guided radiotherapy, bioluminescence, resistance

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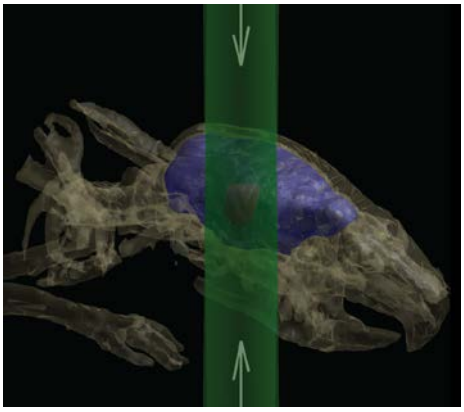

Figure Legend: SmART image-guided treatment plan for orthotopic GBM model. PTV (red), normal brain (blue) and parallel irradiation beams (green)

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Stroma mediated wound healing signals and cell response to radiation
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Stroma mediated wound healing signals induced by radiotherapy have been well characterized in normal tissue response and fibrosis. They are complex and involve the crosstalk between the various cellular type of the tissue including fibroblasts, endothelial, immune, epithelial cells as well as soluble paracrine factors including growth factors and proteases. In addition, recent studies suggest that these wound healing signals may share similarities with the ones produced by tumor's microenvironment. Therefore, their modulation may impact both normal tissue and tumor response to radiation therapy.
This lecture will illustrate the two important aspects of stroma mediated wound healing signals in normal tissue and tumour response to radiotherapy.
In a recent study (1), we investigated the role of macrophages in radiation-induced lung fibrosis, profiled alveolar (AM) and interstitial macrophages (IM) and show that both macrophage subtypes are playing specific and opposite role in fibrogenesis. Acute depletion of AM post-irradiation was shown and associated with cytokine secretion. This acute depletion was followed by a repopulation mediated via the recruitment and proliferation of monocytes/macrophages from the bone marrow. Interestingly, the newly recruited Alveolar macropahages exhibited hybrid polarization (M1/M2), associated with the up-regulation of both Th1 and Th2 cytokines. At delayed times points post-irradiation, interstitial macrophages were M2 polarized and simultaneously, a down-regulation of Th1 cytokines and up-regulation of Th2 cytokines was observed in irradiated lungs. The specific depletion of hybrid AM enhanced the severity of fibrosis whereas anti-fibrotic treatment based upon pravastatin administration decreased M2-IM levels. We also found that M2-IM were able to activate fibroblast into myofibroblasts when co-cultured.
In another study (2), we assessed the crosstalk between primary lung fibroblast and carcinoma cells (TC-1) in response to radiotherapy. We found that fibroblasts were not able to modulate intrinsic radiosensitivity of TC-1 but produce diffusible factors able to modify tumor cell fate. More specifically, RhoB deficient fibroblasts stimulated TC-1 migration through MMPs production whereas WT fibroblasts produce TGF-□.In addition RhoB deficiency stimulated pro-inflammatory signals (IL-6) that would impact on immune recruitment and favor antitumor immune response. In addition, co-irradiation of fibroblasts and TC-1 abrogated the pro-migratory phenotype by repression of TGF-ß and MMP secretion. This last result suggests that conversely to, the current view; irradiated stroma would not enhance

carcinoma migration and could be manipulated to promote anti-tumor immune response. The role of macrophages in this system is currently investigated.

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Data from the EORTC Cancer Survivorship Task Force

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During the past decades, important progress has been made in the treatment of cancer. With early detection and more effective treatments, cancer has become a curable disease for many patients, while for others it could now be considered a chronic disease. As a consequence, the number of long-term cancer survivors is rapidly increasing, in particular among patients treated for Hodgkin's lymphoma, testicular, prostate, colo-rectal, breast cancer or children's leukemia.
Most of these patients, however, face immediate (mostly transient) and long term (mostly irreversible) physical and mental side effects: hair loss, changes in body image, fatigue, depression, cognitive dysfunction, as well as increased risk of cardiovascular disease, bone loss, infertility and secondary malignancies. Cancer survivors are also confronted with socio-economical consequences of their disease, including too often exclusion from insurances, mortgages and loss of jobs.
Most of the current knowledge regarding the long-term side effects of cancer and its treatment is based on registry data that is missing important treatment details. Clinical trial databases on the other hand include treatment and outcome data, but often fail to produce very long-term follow-up of outcome and late effects because of the high costs of conducting such long-term follow-up.
The European Organisation for Research and Treatment of Cancer (EORTC) Survivorship Task Force aims to use and, if needed, to complete the impressive EORTC databases accumulated over 50 years of conducting cancer clinical trials. The goal is to document and analyse how long-term outcomes and side effects are associated with cancer treatment. With experience in updates of lymphoma and leukemia trials, early breast cancer trials are now being assessed as well. These studies provide large patient numbers (over 6000 patients for the lymphoma studies and over 10,000 patients for the early breast cancer cohort). For the lymphoma trials, the first results on cardiovascular disease and secondary malignancies (incidence and mortality) have recently been published. The effects of the different treatment components on these endpoints have been quantified. Additional information will be gathered through a number of questionnaires sent to survivors, asking them about the impact of cancer diagnosis and treatment on relationships (social situation, parenthood), education, work and insurance, fatigue, emotional well-being and quality of life. To estimate the relative risks compared to the general population, a linkage with data of registries from several geographic areas is needed. Establishing such a network will enable us to quantify the impact of cancer treatment on late side effects in absolute terms.
The information that the EORTC will gather through this series of projects is expected to help and guide future patients in trading off treatment efficacy and late side effects, seen as important costs in surviving cancer.

Keywords:
Long-term outcome, treatment side-effects, survivorship

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RTQA platform of the EORTC

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Radiotherapy (RT) planning and delivery for cancer management has substantially evolved over the last three decades with lately the introduction of intensity modulated RT, image-guided RT and stereotactic ablative RT to name a few techniques. The evaluation of these ehigh precision delivery techniques in routine care and in clinical trials alike requires optimal RT quality (RTQA) assurance programs which aim at defining the range of acceptable variations and importantly developing mechanisms of action for correction and prevention of potential variations[1, 2]. RTQA outside a clinical trial is defined by all processes that ensure consistency of the dose prescription and the safe delivery of that prescription with regard to dose to the target and critical structures, minimization of the exposure of the RT personnel, particularly so the radiation technologists[3]. In the framework of clinical trials assessing the efficacy of RT with or without a combined modality, RTQA is also necessary to avoid the corruption of the study-endpoint[4], as RT variations from study protocol decrease the therapeutic effectiveness and/or increase the likelihood of radiation-induced toxicities[5]. Prospective trials have shown that RTQA variations have a significant impact on the primary study end-point and could bias the analysis of the trial results[6]. Other specific consideration for RTQA in trials includes, but is not limited to, education of the accruing sites in RT-trial guidelines, promotion of consistency between centers and estimation of inter-patient and inter-institutional variations. Additionally, global cooperation is essential in the environment of common and rare cancers alike, in order to be able to create sufficiently large patient data sets within a reasonable recruitment period. This cooperation is not without issues and recently the need to have harmonized