

an heterogeneous cell population with a radio-resistant compartment. Evidence to support the use of particle therapy evolved in the past 25 years from level III (preclinical rationale) to level II (prospective non randomized trials). A hot debate has been on-going in the scientific community about the need of prospective RCT testing head to head particles versus modern X-ray radiotherapy. Those against the need of RCT argued that dose distribution was such a strong surrogate endpoint that RCT were not needed and that dose distribution had always guided the evolution of radiotherapy without the need of RCT. Those in favour argued that the only relevant endpoints were clinical outcome and measurable toxicity and that dose distributions of protontherapy despite its unquestionable advantage in terms of integral dose may be in some case less favourable than advanced x-ray dose distribution because of lateral scattering and shallower dose gradients in the high dose region. Historically only a single RCT of particle versus photons has been conducted, namely the UCSF-LBNL trial comparing helium ions radiotherapy versus Iodine-125 plaque brachytherapy for choroidal and ciliary body melanoma. Long terms result of the trial showed a clear advantage of charged particles over brachytherapy in terms of local control. However this result did not definitively solve the issue as helium is no longer used in clinical practice and extrapolation of this trial to protontherapy is maybe not straightforward; moreover the trial was criticized because of a supposed suboptimal technique in the brachytherapy arm. With the increased availability of proton facilities the amount of non-randomized evidence is rapidly increasing and several prospective non-randomized trial are being conducted. At present particle therapy has found its way in several guidelines. As an example in the last version of ESMO guidelines for bone sarcoma particle therapy is considered the first option for chordoma both in the post operative setting and for inoperable disease. In this framework also RCT are at present being conducted. A prospective phase II RCT in stage II-III NSCLC patients (NCT00915005) randomized to either photons or protons adaptive IGRT with two levels of dose (66 Gy [RBE] + vs. 74 Gy [RBE]) with primary endpoints local control and toxicity  $\geq 3$  has completed its accrual. Two other trials are testing protontherapy vs photons X-Ray in locally advanced NSCLC (RTOG 1308) or in centrally located stage I NSCLC (NCT01511081) and are expected to complete accrual in 2020 and 2016. Another prospective phase III RCT ongoing at MGH testing IMRT vs protontherapy for prostate cancer (NCT01617161) is expected to complete accrual in 2016. A prospective phase II/III RCT for stage III and IV oropharyngeal SCC (NCT01893307) is comparing 70 Gy [RBE] delivered with either IMRT or intensity modulated protontherapy. And is expected to complete accrual by 2023. Another trial is testing protons vs photons in GBM (NCT01854554) and should complete accrual by 2017. A RCT is recruiting patient with oesophageal cancer to test chemo radiation with photons vs. chemo radiation with protons (NCT01512589) and should be completed within 2018. Other RCT are ongoing comparing protons versus carbon ions in sacral chordoma (ISAC trial NCT01811394) in skull base chordoma (NCT01182779) and in skull base chondrosarcoma (NCT01182753). RCT are recruiting patient to test protontherapy vs RF ablation in HCC (NCT01963429) or protontherapy + sorafenib vs. sorafenib alone in HCC (NCT01141478). A RCT of particle therapy vs surgery for sacral chordoma (SACRO) is in its final design stage in Europe. Another phase III RCT of carbon ion radiotherapy versus photons or protons radiotherapy for head and neck soft tissue sarcoma and adenoid cystic carcinoma (PHRC ETOILE-ULICE) is going to start recruitment in the next year. In conclusion the present day clinical evidence for particle therapy is of level II (with the only exception of eye melanoma). A large effort to produce level I evidence is ongoing worldwide.

## Proffered Papers: Radiobiology 1: Radiation effects on normal tissues and the microenvironment

### OC-0044

#### Fingolimod mitigates radiation-induced cognitive deficits by restoring dentate gyrus neurogenesis

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**Purpose or Objective:** This study evaluates FTY720/Fingolimod as a potential mitigator of radiation-induced neurocognitive dysfunction.

**Material and Methods:** The effects of radiation and FTY720 on neural progenitor cells (NPCs) and brain tumor stem cells (BTSCs) were tested *in vitro*. To study radiation-induced neurocognitive deficits, 6 week-old C57/BL/6J mice received 0 or 7 Gy cranial irradiation and were treated with intraperitoneal FTY720 or vehicle for seven weeks. Fear conditioning and the Morris water maze were then employed to test learning and memory. Immunohistochemical staining for NPCs and mature neurons was used to assess changes in neurogenesis. To test effects on tumor growth, mice harboring BTSC xenografts were treated with intraperitoneal FTY720 or vehicle for six weeks.

**Results:** In NPCs, FTY720 induced ERK1/2 phosphorylation in the presence of radiation. In glioma cells, ERK1/2 phosphorylation was detected at baseline, and FTY720 did not elicit any further increase. Correspondingly, FTY720 increased the viability of NSCs but not glioma cells after radiation. Inhibiting S1P1/MAPK signaling in NPCs abolished the protective effects of FTY720. In irradiated mice, learning deficits were manifested by significantly longer latency times compared to non-irradiated controls ( $p = 0.001$ ). The deficits were fully restored by FTY720. In irradiated brains, FTY720 maintained a viable NPC pool and restored the cytoarchitecture of the DG granular cell layer. In mice harboring BTSC xenografts FTY720 delayed tumor growth and improved survival ( $p=0.012$ ).

**Conclusion:** FTY720 mitigates radiation-induced learning dysfunction by partially restoring DG neurogenesis. Furthermore, FTY720 appears to delay tumor growth and improve survival in a xenograft glioma mouse model.

### OC-0045

#### Dual pathway inhibition attenuates radiation-induced pulmonary inflammation and fibrosis

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**Purpose or Objective:** Radiation therapy is a mainstay for lung cancer therapy, but the effective dose is commonly limited by the onset of radiation-induced lung damage. Single pathway inhibitors against transforming growth factor  $\beta$  (TGF $\beta$ ), platelet-derived growth factor (PDGF) and others have been shown in experimental models to attenuate radiation-induced pulmonary injury. However, the effects of multiple pathway inhibition regarding the development of these diseases remain unknown.

**Material and Methods:** C57BL/6 mice were treated with a single dose of up to 20 Gy photons to their thorax to induce radiation induced lung toxicity. After Irradiation, small