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The role of platelet derived growth factor (PDGF) in radiation induced lung fibrosis *in vitro* and *in vivo*.

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Radiotherapy is an important therapy regimen in the management of malignant diseases, in particular for lung cancer. However, radiation therapy is particularly toxic to the lung, potentially inducing pneumonitis and fibrosis, thus limiting the dose necessary to achieve higher rates of cured patients. Moreover, fibrosis may reduce the patient's quality of life and potentially overall survival. The development of effective new drugs protecting from fibrosis formation is therefore an imminent issue in the clinical application of radiotherapy. Although the mechanism of radiation induced fibrosis is still not fully understood, the role of platelet derived growth factor (PDGF) isoforms

and their receptors has been suggested to be implicated in this process.

Expression of PDGF has been shown to be increased after radiotherapy following both *in vivo* and *in vitro*. Thus we proposed that inhibition of PDGF receptor down-stream signaling would attenuate the development of radiation induced lung toxicity.

Recently, small molecule tyrosine kinase inhibitors (TKIs) potentially have a broad range of applications because they are cell permeable, can be administered orally and can be rationally designed to target individual tyrosine kinases or groups of related kinases. Most synthetic TKIs produced to date target the adenosine triphosphate (ATP) binding site and have proved remarkably specific, given the high degree of conservation of this domain. To our knowledge this is the first study to elucidate the effect of a PDGF receptor tyrosine kinase inhibitor on lung fibrosis after radiation.

The purpose of this study was to investigate whether PDGF is a mediator of radiation induced lung fibrotic response and whether SU9518, a novel synthetic indolinone that potently and selectively inhibits the cellular PDGF receptor tyrosine kinase, can protect against radiation induced lung fibrosis.

Here we show *in vitro* that, SU9518 inhibits PDGF receptor phosphorylation, PDGF-dependent cell proliferative response, clonogenic survival of endothelial cell and fibroblast cells and radiation induced cell proliferation.

To investigate the effect of SU9518 that can repress receptor kinase activity in radiation induced lung injury. *In vivo*, in a radiation induced lung fibrosis mouse model, C57BL/6 mice were studied untreated, treated with SU9518 alone, with 20 Gy alone, or 20 Gy combined with SU9518. The lung tissues exposed to 20 Gy (including SU9518 treated and untreated groups) from different time points were analyzed by immunohistochemistry and H&E and Goldner`s staining. We found that cells and architecture of the lung tissue were grossly distorted by radiation and that SU9518 treatment could dramatically reduce this pathological change as evidenced by a limited influx of inflammatory cells, minimal collagen deposition, and minimal septal thickening. It is demonstrated that SU9518 could selectively inhibit the cellular PDGF receptor kinase and reduce radiation induced lung fibrosis in vivo. The results from computed tomography scans indicated that radiation increased lung density and that

SU9518 could reduce this radiation induced increase of lung density.

The data provide evidence that PDGF receptor ligand may be a potent mitogen for collagen-producing mesenchymal cells in radiation induced pulmonary fibrosis. It is suggested that targeting PDGF tyrosine kinase receptors by SU9518 can attenuate the fibrotic process thus offering a strategy for the prevention of radiation induced fibrosis, or fibrosis of other origin.