

**Pharmacological Modulation of Platelet-derived Growth Factor Signalling with Imatinib Mesylate in a Murine Model**L. Costa<sup>a</sup>, N. Pasinetti<sup>a</sup>, P. Opolon<sup>b</sup>, D. Violot<sup>c</sup>, S.M. Magrini<sup>d</sup> and J. Bourhis<sup>c</sup>

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Objective : Evidence for the importance of platelet-derived growth factor (PDGF) signalling in the fibrotic process is provided by 1) the fact that PDGF elicits direct fibrogenic action stimulating production of ECM 2) reports showing that a number of fibrogenic mediators such as TGF $\beta$ , IL-1, TNF- $\alpha$ , bFGF and thrombin exhibit PDGF-dependent profibrotic activities. It has been suggested that the PDGF-PDGFR system might be a promising target for treating fibrotic diseases, thus we aimed at investigating whether the use of a tyrosin kinase inhibitor such as Imatinib mesylate (Glivec®) could reverse pulmonary fibrosis. Materials and methods: Lung fibrosis was induced in 15 pathogen-free 10-wk-old female C57/BL6 mice by IP injection of Bleomycin at 40 mg/kg body weight on Days 0, 2, 4, 6 and 8 and treated the mice with Glivec for 2 weeks with subcutaneous micro-osmotic pumps and sacrificed the 30th day. Mice were divided into 2 groups: controls treated with bleomycin alone and mice treated with bleomycin and Glivec at 50 mg/Kg. Mice follow-up was performed twice a week for the overall experimental period with check of weight. Tissue collection was performed at day 30. Fibrosis development was monitored by Hematoxylin Eosin Saffranin staining. Evolution of the molecular markers of fibrosis (CTGF,  $\alpha$ -sm Actin, TGF $\beta$ ) will be monitored by WB and Q-RT PCR. Results: In control mice treated with bleomycin alone, histopathological examination showed development of widespread fibrotic lesions with disruption of lung structure and accumulation of ECM in the sub-pleural areas. In mice treated with Glivec, lung fibrosis decreased. Inflammatory lesions persisted whereas fibrotic lesions became discontinuous and less dense. Conclusion: The present results showed that bleomycin-induced lung fibrosis can be improved by Glivec treatment. Experiments to quantify the reduction and the mechanism of reversion of fibrosis at the molecular level are currently ongoing. The next step it will be to combine Glivec with other anti-fibrotic agent (such as antioxidants or statins) to enhance the anti-fibrotic action.