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Title: ONX0912, a novel proteasome inhibitor for the treatment of lung fibrosis?

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Body: Background: Proteasome inhibition has been shown to prevent development of fibrosis in several organs. Effects of proteasome inhibitors (PI) on lung fibrosis are controversial and cytotoxic side effects of the inhibition of proteasomal protein degradation in the cell cannot be excluded. Hypothesis: Local administration of PI allows efficient drug delivery to the lung and prevents development of pulmonary fibrosis without systemic toxicity. Methods and results: ONX0912 (ONX), a new irreversible PI, was evaluated in comparison to bortezomib, the only FDA approved PI, with regard to cytotoxicity and proteasomal inhibition in the cell line A549. Primary lung fibroblasts were isolated from proteasome reporter mice (ODD-luc) and characterized using MTT survival, and proteasome activity assays. The ODD-luc reporter accumulates upon proteasome inhibition and can be quantified via bioluminescence reflecting the actual degree of proteasome inhibition in the cell. While bortezomib had strong cytotoxic effects, ONX only partially inhibited the proteasome at low doses but efficiently blocked fibroblast function without affecting cell viability of fibroblasts or epithelia cells. An optimal nontoxic dose of ONX was obtained after intratracheal instillation into ODD-luc mice. This dose then was applied locally into the lung of ODD-luc mice with bleomycin induced fibrosis and therapeutic effects were investigated by histochemical analysis of the lungs. Conclusion: ONX provides antifibrotic effects in murine lung fibroblasts in a non-toxic dose range. Local administration of ONX into the lungs partially inhibits the proteasome without toxic side effects and can be regarded as a promising approach to inhibit pulmonary fibrosis.