Screening of new inhibitors against idiopathic pulmonary fibrosis by virtue of human myofibroblast dedifferentiation

Kenichi Suzuki¹,², Keita Ugai¹, Kento Yoshioka¹, Toshihiko Murayama³, Masahiko Hatano⁴, Koichiro Tatsumi², Yoshitoshi Kasuya¹

¹Department of Biochemistry and Molecular Pharmacology, Graduate School of Medicine, Chiba University, Chiba, Japan, ²Department of Respirology, Graduate School of Medicine, Japan, ³Laboratory of Chemical Pharmacology, Graduate School of Pharmaceutical Sciences, Japan, ⁴Department of Biomedical Science, Graduate School of Medicine, Japan

Idiopathic Pulmonary fibrosis (IPF) is a chronic lung disease that normal parenchyma is progressively replaced by fibrotic foci. Because IPF has an overall poor prognosis with median survival ranging from 2.5 to 3.5 years, discovery of drugs providing new therapeutic options for patients with IPF is waited for. In the development of IPF, an aberrant epithelial injury is thought to be the first step, followed by such events as innate immune activation, fibroblasts recruitment, proliferation and differentiation to myofibroblasts, and the abundant accumulation of extracellular matrix. Among these pathological steps, targeting myofibroblasts is one of practical and relevant strategies for IPF therapy as the following reasons: 1) Most IPF patients who present to clinicians for the first time with subjective symptoms show a reduced forced vital capacity, indicating that fibrosis is already present. 2) Fibrotic foci consist of myofibroblasts and their aberrant production of extracellular matrix proteins. 3) Agents promoting myofibroblastic dedifferentiation may ameliorate fibrosis. On basis of this notion, we have already reported that inhibition of hypoxia-inducible factor 1-α could dedifferentiate myofibroblast-like cells (MyoLC) derived from the patient with severe pleuroparenchymal fibroelastosis in vitro and attenuate bleomycin-induced lung fibrosis in mice. In the present study, we employed MyoLC as a screening system for drugs against IPF, and an inhibitor library for cancers was subjected to this screening with monitoring the downregulation of smooth muscle α-actin and ED-A-fibronectin (myofibroblast markers) and the upregulation of S100A4 (a fibroblast marker). We have already selected several candidate inhibitors promoting dedifferentiation of MyoLC. In conjunction with those beneficial effect on BLM-induced lung fibrosis in mice, we will discuss whether the selected inhibitors can be applied to IPF.