Idiopathic Pulmonary Fibrosis (IPF) afflicts five million people worldwide with a median survival rate of 3-5 years1,2,3. This fibrotic disease is considered a chronic inflammatory tissue-repair response and is characterized by an excessive deposition of connective tissues that leads to failure in organ structure and function4. Fibronectin (FN) fibrillogenesis, a cell-mediated process that converts soluble plasma FN into insoluble FN, plays a central role in the development of this disease5. FN is a glycoprotein secreted as a dimer connected by two C-terminal disulfide bonds. It is comprised of multiple functional domains including the N-terminal 70 kDa domain, the 120 kDa central binding domain, and the heparin-binding domain HepII4. These domains interact with cell-surface receptors in a stepwise process that initially involves binding to integrin and heparin sulfate proteoglycan (HSPG) cell-surface receptors (see Fig. 1)4. This binding triggers actin cytoskeleton reorganization which generates cell tension, leading to clustering and translocation of the FN-bound receptors which unfolds the compact FN dimer into an extended structure that exposes binding sites for FN-FN interactions4. Although fibrillogenesis can lead to misregulated fibrosis and has been linked to several diseases including IPF and malignant, unchecked tissue growth6,7, the insoluble cellular FN also plays a major role in cell adhesion, growth, migration, and differentiation which are important for restorative and developmental processes such as the deposition of connective tissue8, wound healing, and embryonic development9.

While there are no cures or direct treatments for IPF, there are several non-specific therapeutic options for IPF patients to help maintain their quality of life, including: the anti-inflammatory Pirfenidone, immune suppressors, corticosteroids and Azathioprine, antioxidant N-acetylcysteine, supplemental oxygen therapy, pulmonary rehabilitation, and surgery1. In addition, the anti-inflammatory agents Thalidomide and Macrolide have recently been suggested as a possible treatment for IPF3,4. Indeed, Macrolide antibiotic clinical trials have shown long term benefits for cystic fibrosis patients2. More direct treatment prospects include an anti-TGF-β compound or a FUD peptide4. Anti-TGF-β treatments in mice reduced skin and pulmonary fibrosis with sclerodermatous graft-versus-host disease3. However, anti-TGF-β treatments in human systemic sclerosis phase II/II trials were not successful. A residue sequence from the FUD domain of the F1 adhesin protein inhibits FN matrix assembly by binding to the N-terminal FN1-5 domain of FN. This domain is crucial for FN binding to cell receptors4 and demonstrates that FN binding domains could be promising drug targets for fibrosis disease treatments.
An increased understanding of the mechanisms that regulate FN matrix assembly may aid in the discovery of better treatments for fibrotic diseases. Enhancing or suppressing the effects of FN in vivo via specific modulators is of particular interest in fibrosis research. Recent advancements in high throughput screening (HTS) methods facilitated screening of small molecule libraries for their effects on FN fibrillogenesis. An assay, as described by Tomasini-Hohansson et al., utilizes fluorescent FN to provide a read-out of FN fibrillogenesis with Z' values of >0.5. Tomasini-Hohansson et al.'s pilot experiment screened 4160 known bioactive compounds. As a result of this study, 9 compounds were found to inhibit FN assembly, including four kinase inhibitors (ML-9, HA-100, tryphostin, and imatinib mesylate), two cancer cell apoptosis promoters (piperlongumine and cantharidin), and three modulators of biogenic amine signaling (maprotiline, CGS12066B, and aposcopolamine). By utilizing fluorescent FN along with HTS techniques, additional modulators of FN fibrillogenesis may aid in the development of therapeutics for fibrotic diseases. Cytoskeleton, Inc. offers rhodamine, HiLyte488™, and biotinylated ECM proteins to study FN fibrillogenesis (See next right for available products).

References


11. http://www.cytoskeleton.com