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# **Breaking the senescence-fibrosis loop: FAP-responsive inhaled molecular glues targeting IL-11/ERK PTM axis**

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## **Abstract**

1      Idiopathic pulmonary fibrosis (IPF) is a fatal degenerative disease characterized  
2      by repetitive alveolar epithelial damage and irreversible tissue stiffening. While  
3      existing therapies, including the recently approved Nerandomilast (October 2025),  
4      slow disease progression, they face challenges such as systemic toxicity and an in-  
5      ability to achieve fundamental fibrosis reversal. This study proposes an innovative  
6      de-modification strategy using fibroblast activation protein (FAP)-responsive in-  
7      haled molecular glues (MGs) to precisely target the IL-11/ERK axis, the key driver  
8      of the senescence-fibrosis cycle. We implemented a Z-Gly-Pro caging technology  
9      selectively activated by the FAP enzyme overexpressed on activated myofibro-  
10     blasts, eliminating off-target toxicity in normal tissues. Our approach utilizes a  
11     small-molecule inhaled formulation to maximize delivery to deep lung lesions.  
12     By hijacking SENP1 and USP15 to remove pathological RAS SUMOylation and  
13     ERK K63-linked ubiquitination, this dual-lock mechanism suppresses the entry  
14     of alveolar epithelial cells (AECs) into senescence and blocks the release of the  
15     senescence-associated secretory phenotype (SASP). Simultaneously, it normalizes  
16     the ERK-mTOR translational axis to halt excessive collagen accumulation. Con-  
17     sequently, this strategy collapses the senescence-fibrosis loop, reduces physical  
18     stiffness, and restores the regenerative microenvironment, representing a potent  
19     next-generation therapeutic option for the fundamental recovery of lung function.

20    **1 Introduction: current status and therapeutic limitations of IPF**

21    Idiopathic pulmonary fibrosis (IPF) is a fatal degenerative disease characterized by repetitive damage  
22    to lung epithelial cells and an abnormal wound-healing response, leading to progressive and irre-  
23    versible stiffening of the lung tissue. Driven by the global aging trend, its prevalence is increasing  
24    rapidly, yet the prognosis remains dismal, with a median survival period of only three to five years  
25    following diagnosis. Pathologically, it is defined by the destruction of alveolar structures, the ex-  
26    cessive proliferation of myofibroblasts, and the abnormal accumulation of the extracellular matrix  
27    (ECM) [1].

28    To date, the primary therapies approved by the FDA for the treatment of IPF include Pirfenidone [2],  
29    Nintedanib [3], and most recently, Nerandomilast [4], which received approval in October 2025 (Table  
30    1). While these agents utilize distinct mechanisms to slow the decline of lung function, significant  
31    limitations remain in their ability to completely halt the fundamental progression of the disease.

32    Pirfenidone, the first to be approved, works by inhibiting TGF- $\beta$  activity to suppress fibrotic cell  
33    proliferation, while Nintedanib acts as a multi-tyrosine kinase inhibitor, blocking various growth  
34    factor receptors such as FGFR, PDGFR, and VEGFR to disrupt fibrotic signaling. Although these

Table 1: Comparison of currently approved IPF therapies and their limitations

Drug	FDA approval	Primary mechanism	Limitations
Pirfenidone	2014	TGF- $\beta$ and cytokines inhibition	Photosensitivity, hepatotoxicity, and gastrointestinal distress
Nintedanib	2014	Multi-tyrosine kinase inhibition	Severe diarrhea, liver enzyme elevation, and bleeding risk
Nerandomilast	2025	PDE4B inhibition	Neurological side effects and potential immune suppression risks

35 two agents have clinically succeeded in reducing the rate of decline in forced vital capacity (FVC)  
 36 by approximately 50%, they possess a critical limitation in their inability to remove existing fibrotic  
 37 tissue or permanently arrest pathological progression. Furthermore, hepatotoxicity and severe  
 38 gastrointestinal disorders, such as vomiting and diarrhea, frequently force patients to discontinue  
 39 treatment or prevent them from maintaining recommended dosages.

40 In October 2025, nearly a decade after the initial approvals, the selective PDE4B inhibitor Nerandomi-  
 41 last obtained FDA approval, offering a new therapeutic option. Nerandomilast is characterized by its  
 42 high selectivity for the PDE4B isoform, which significantly improves the systemic gastrointestinal  
 43 side effects associated with previous PDE4 inhibitors. While this has enhanced patient compliance,  
 44 Nerandomilast shares the fundamental limitation of focusing on the "delay" rather than the "reversal"  
 45 of the fibrotic process. Additionally, concerns persist regarding potential neurological side effects,  
 46 such as depression, and immune suppression risks during long-term administration. Like existing  
 47 therapies, it also faces the challenge of failing to directly control core downstream signaling hubs,  
 48 such as the IL-11/ERK axis.

49 The pathogenesis of IPF is exceedingly complex, and recent studies have identified the interaction  
 50 between cellular senescence and the fibrotic network as a core driver, moving beyond simple inflam-  
 51 matory responses [5]. The senescence-associated secretory phenotype (SASP) released by senescent  
 52 lung epithelial cells induces a fibrotic state in surrounding cells, creating a vicious cycle that depletes  
 53 the regenerative capacity of the entire tissue [6]. Consequently, there is an urgent need to depart  
 54 from broad-spectrum inhibitory approaches and develop innovative therapeutics capable of precisely  
 55 targeting this senescence-fibrosis link.

## 56 2 IL-11 and IL-11 interactors as drivers of pulmonary fibrosis

57 Interleukin-11 (IL-11), a member of the IL-6 cytokine family discovered in the early 1990s, is a  
 58 protein of approximately 23 kDa composed of 191 amino acids. Classically, IL-11 was known for  
 59 biological functions such as enhancing hematopoiesis, regulating bone metabolism, and providing  
 60 neuroprotection. However, research over the past decade has revealed its identity as a fibrokinin,  
 61 showing that its expression is rapidly induced in damaged tissues, particularly in organs undergoing  
 62 fibrosis, to drive pathological changes [7].

63 In normal cells, IL-11 is transcribed at very low levels, but its expression increases explosively when  
 64 exposed to inflammatory cytokines or mechanical stress. IL-11 binds to its specific receptor, IL-11RA,  
 65 which then induces the dimerization of gp130, a common receptor shared by all IL-6 family members.  
 66 The resulting triple receptor complex transmits powerful signals into the cell. Interestingly, while  
 67 IL-6 primarily induces inflammation via the JAK/STAT pathway in immune cells, IL-11 prefers  
 68 non-canonical pathways in stromal cells.

69 The core interactors of the IL-11 signaling system begin with IL-11RA and gp130 at the recep-  
 70 tor level and extend to downstream signaling networks including Ras, Raf, MEK, ERK, and the  
 71 PI3K/AKT/mTOR axis. These interactors form a massive protein network that mutually activates its  
 72 components as fibrosis progresses. In particular, the cytoplasmic domain of gp130 recruits various  
 73 adapter proteins to diversify signaling, which further exacerbates the pathological complexity of  
 74 pulmonary fibrosis.

75 **2.1 The role of IL-11 in pulmonary fibrosis and senescence**

76 Within the mechanism of pulmonary fibrosis, IL-11 serves as a critical downstream effector of the  
 77 TGF- $\beta$ 1 signal. When TGF- $\beta$ 1 stimulates alveolar epithelial cells (AECs), IL-11 transcription is  
 78 induced through the Smad pathway. The secreted IL-11 then directly triggers AEC senescence via  
 79 autocrine signaling. Specifically, type II alveolar epithelial cells (ATII), which act as stem cells  
 80 responsible for lung regeneration, are driven into a permanent senescent state by sustained IL-11  
 81 stimulation, which activates cell cycle inhibitors such as *p21* and *p16* [8].

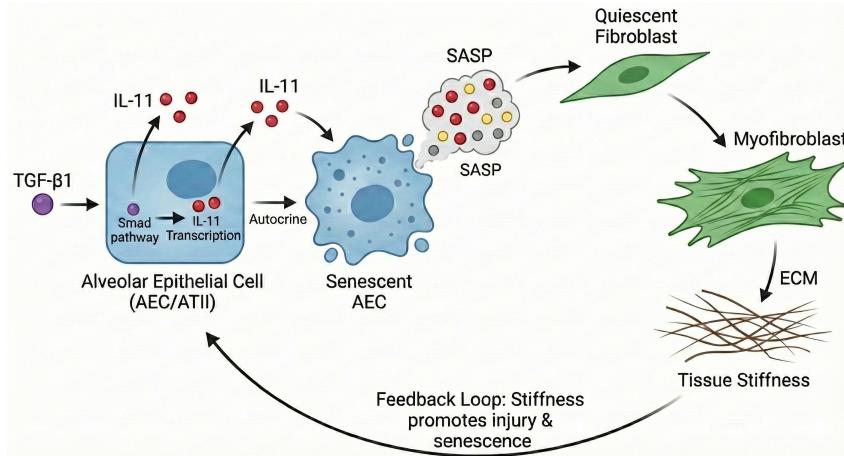


Figure 1: Positive feedback loop between IL-11-mediated alveolar epithelial senescence and myofibroblast-induced stiffness.

82 These senescent ATII cells not only lose their function as normal epithelial cells but also transform  
 83 into cells that release a potent SASP. This SASP contains high concentrations of IL-11, which  
 84 acts as a strong signal to convert quiescent fibroblasts into myofibroblasts [8]. During this process,  
 85 myofibroblasts produce vast quantities of ECM, leading to tissue stiffening. This physical stiffness,  
 86 in turn, promotes further epithelial damage and senescence, establishing a self-perpetuating vicious  
 87 cycle. Consequently, IL-11 functions as a bridge that physically connects epithelial senescence  
 88 with mesenchymal activation. This implies that IL-11 is at the center of a "senescence network"  
 89 that depletes the regenerative capacity of the entire lung tissue beyond mere fibrosis. Therefore,  
 90 controlling IL-11 is a fundamental strategy for blocking the secretion of toxic factors from senescent  
 91 cells and restoring the regenerative microenvironment (Fig. 1).

92 **2.2 IL-11 interactors and the fibrosis/senescence pathway**

93 In past studies of pulmonary fibrosis, research on the IL-6 family focused primarily on the JAK/STAT3  
 94 signaling pathway. While STAT3 is known to mediate early inflammatory responses by regulating  
 95 cell proliferation and the expression of inflammatory genes, recent high-resolution omics analyses  
 96 and molecular biology studies demonstrate that the SHP2-Ras-Raf-MEK-ERK1/2 pathway plays a  
 97 far more decisive role in IL-11-driven fibrosis [9]. This is because IL-11 binds to the gp130 receptor  
 98 to recruit SHP2 and powerfully activate the downstream MAPK cascade [10]. As a result, while  
 99 STAT3 is involved in the initial inflammatory response, ERK functions as the core driver of actual  
 100 collagen protein translation and the phenotypic transformation into myofibroblasts.

101 The non-canonical signals induced by IL-11, namely the ERK and PI3K/AKT/mTOR pathways,  
 102 are closely integrated to explosively increase the translation efficiency of collagen mRNA (Fig. 2).  
 103 This distinguishes IL-11 as a "translational effector" that practically synthesizes ECM proteins, a  
 104 point of differentiation from the TGF- $\beta$ /Smad pathway, which primarily increases the volume of  
 105 gene transcription. Furthermore, activated ERK simultaneously drives two pathological mechanisms:  
 106 first, it phosphorylates the linker region of Smad3 to further amplify Smad transcriptional activity,  
 107 thereby fixing the fibrotic response in a positive feedback loop; second, it mediates the activation of  
 108 *p21* and *p16* to promote AEC senescence. Ultimately, the axes of IL-11 to ERK/mTOR for collagen

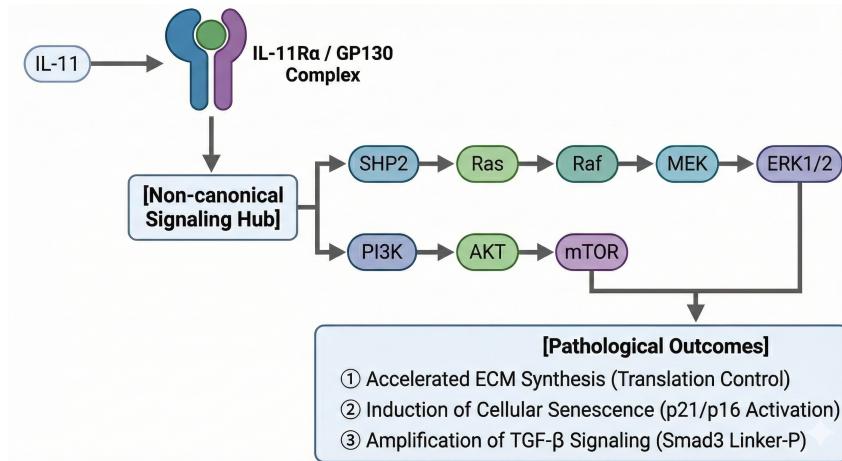


Figure 2: Non-canonical signaling hub and downstream pathological outcomes of the IL-11/IL-11RA receptor complex.

109 translation and IL-11 to ERK for *p21/p16*-mediated senescence constitute the pathological core of  
 110 pulmonary fibrosis [11]. Precisely controlling ERK, the central hub of this network, is a fundamental  
 111 therapeutic strategy to break the vicious cycle of fibrosis and senescence [12].

### 112 2.3 Precision control of IL-11-mediated ERK signaling: the role of PTMs

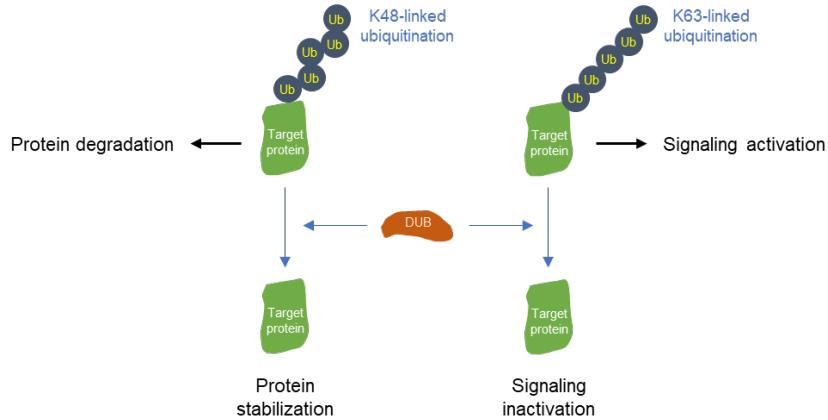


Figure 3: Functional differentiation of K48- and K63-linked ubiquitination and their regulatory reversal by deubiquitinases (DUBs).

113 Post-translational modification (PTM) is a critical molecular switch that regulates protein function,  
 114 activity, stability, and interactions by attaching chemical groups or proteins to specific residues  
 115 after protein synthesis [13]. To understand and precisely control the complex network of IL-11-  
 116 mediated ERK signaling, one must grasp the multifaceted modification processes involving not only  
 117 phosphorylation but also ubiquitination and ubiquitin-like proteins (UBLs). Phosphorylation, the most  
 118 common PTM, rapidly switches enzyme activity on or off by attaching phosphate groups to specific  
 119 *Ser*, *Thr*, and *Tyr* residues [14]. Ubiquitination is functionally differentiated by its linkage type;  
 120 while *K48*-linkage drives protein degradation, *K63*-linked ubiquitination acts as a non-canonical  
 121 activation signal that promotes protein scaffolding, intracellular trafficking, and the activation of  
 122 signaling molecules (Fig. 3) [15]. Additionally, UBLs such as SUMO, ISG15, and NEDD8 alter  
 123 target protein localization or mediate protein-protein interactions (PPIs) through processes like  
 124 SUMOylation, ISGylation, and NEDDylation to finely tune signaling intensity [16]. These PTMs

125 can be removed by deconjugation enzymes such as phosphatases, deubiquitinases (DUBs), and  
126 deSUMOylases [17].

Table 2: Major PTMs of IL-11/ERK signaling components and their functional impact

Protein	PTM Type	Influence	Functional impact and detailed results
SHP2	Phosphorylation	Activation	Links gp130 receptor to downstream signal sources
SHP2	SUMOylation	Activation	Increases Gab1 binding
RAS	SUMOylation	Activation	Promotes MEK/ERK activation, signal amplification
Raf	Phosphorylation	Activation	Induces MEK phosphorylation
MEK	Phosphorylation	Activation	Induces ERK phosphorylation
MEK	SUMOylation	Inhibition	Inhibits ERK binding
ERK1/2	Phosphorylation	Activation	Activates transcription factors
ERK1/2	K63-linked ubiquitination	Activation	Strengthens MEK interaction, promotes nuclear translocation

127 Each component of the IL-11 signaling pathway transmits signals downstream through the organic  
128 combination of these PTMs. Specifically, the phosphorylation and SUMOylation of SHP2 lay the  
129 foundation for RAS-ERK activation, while specific PTMs at the RAS and ERK1/2 stages serve as the  
130 core operational switches for the pathological mechanism of pulmonary fibrosis (Table 2) [18, 19].

#### 131 2.4 Proposed final target candidates and rationale

132 The principles for identifying therapeutic targets are centrality and selectivity. In this signaling  
133 network, RAS SUMOylation determines the initiation of upstream signaling, and ERK1/2 K63-  
134 linked ubiquitination serves as the final gateway for the transmission of pathological signals to  
135 the nucleus (Fig. 4). Therefore, we have selected RAS and ERK1/2 as our final targets. Existing  
136 therapies often fail because they lack precision, inhibiting upstream signals entirely and thus activating  
137 compensatory pathways or causing systemic toxicity. We have chosen a fine-tuning approach that  
138 regulates PTMs instead of completely eliminating RAS and ERK. This strategy preserves the proteins'  
139 normal survival signals while selectively inhibiting pathological transcriptional processes, thereby  
140 providing a high therapeutic index that previous, more aggressive inhibitory methods could not  
141 achieve.

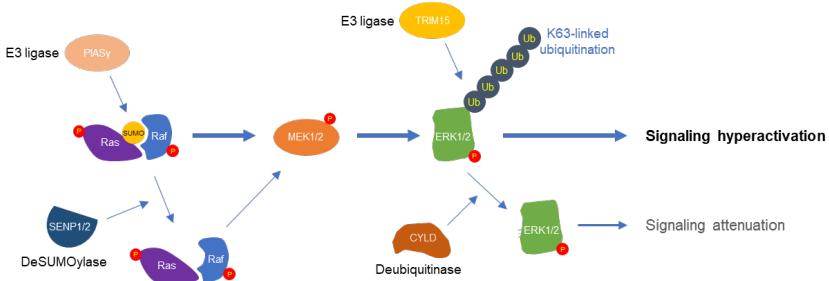


Figure 4: Molecular switches for pathological signal hyperactivation and therapeutic attenuation via PTM regulation.

### 142 3 Proposed drug candidates for the effective inhibition of IL-11 signaling

143 The rapid advancement of AI and structure-based drug design technologies has made it possible  
144 to precisely regulate target protein activity at the atomic level. Beyond simple enzyme inhibition,

145 new modalities are emerging that fundamentally re-engineer the fate and function of proteins. In  
146 this study, we propose innovative drug candidates that precisely regulate the core PTM nodes of  
147 IL-11 signaling to stop the progression of fibrosis and induce tissue regeneration. The most important  
148 considerations for IPF drug development are lung-specific delivery, ease of administration, and  
149 economic feasibility. Since IPF is a chronic progressive disease requiring frequent administration, a  
150 convenient self-administration method and a formulation suitable for mass production are essential.  
151 While existing antibody therapies offer high specificity, they are burdened by high costs and the  
152 inconvenience of injection. Technologies like antibody-drug conjugates (ADC) or lipid nanoparticles  
153 (LNP) can improve lung delivery but still face barriers in terms of complex processing, stability,  
154 and cost. To address these unmet needs, this study establishes a next-generation precision drug  
155 development strategy based on small molecules.

### 156 3.1 Drug modality

157 The modality we propose is an advanced form of targeted protein degradation (TPD) technology,  
158 which has recently gained significant attention [20]. Conventional PROTAC or molecular glue (MG)  
159 approaches focus on utilizing the ubiquitination process to entirely remove pathological proteins  
160 [21], however, since core IPF signaling proteins also perform essential roles in normal cell survival  
161 and proliferation, their complete removal carries a high risk of unexpected systemic toxicity or the  
162 inhibition of tissue regeneration [22]. Consequently, this study adopts a "de-modification" strategy  
163 that normalizes the pathologically activated state of proteins instead of destroying them. Specifically,  
164 the SUMOylation and K63-linked ubiquitination of our target proteins are the core switches that  
165 over-activate signaling. Instead of attaching an E3 ligase to the target to degrade it, we propose a  
166 method that directly removes the active PTM markers by bringing the target protein into proximity  
167 with deSUMOylases or deubiquitinases (DUBs) (Fig. 5).

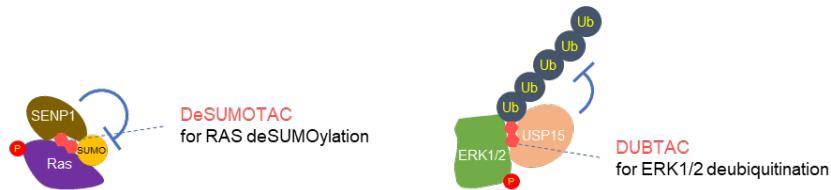


Figure 5: Action mechanism of RAS DeSUMOTAC and ERK DUBTAC.

168 This de-PTM strategy offers clear advantages over conventional TPD technology. First, because the  
169 target protein is not physically removed, severe side effects resulting from the loss of the protein's  
170 native function can be minimized. Furthermore, by fine-tuning the signaling rather than blocking  
171 it entirely, the activation of compensatory signaling—which the system normally triggers when  
172 it perceives a signal deficiency—can be effectively suppressed [23]. As a result, pathological  
173 over-activation can be selectively removed while maintaining the basal signaling necessary for cell  
174 proliferation, thereby dramatically increasing the therapeutic index. To implement this mechanism,  
175 we favor the molecular glue format, which offers more pharmacological advantages than PROTACs.  
176 PROTACs require a long linker to connect two ligands, which often results in a larger molecular  
177 weight and lower lung tissue penetration. In contrast, molecular glues are compact small molecules  
178 that induce binding by fitting into the gaps between two protein surfaces, possessing excellent drug-  
179 like properties and high tissue penetration suitable for inhaled formulation development. Although  
180 developing molecular glues is challenging because it requires finding a compound that binds to both  
181 proteins, optimal adhesive molecules can be quickly derived using modern AI-based protein structure  
182 and ligand binding prediction technologies.

### 183 3.2 Drug design strategy: FAP-triggered proximity induction

184 This study ultimately proposes an "inhaled FAP-responsive small-molecule molecular glue (Inhaled  
185 Pro-Molecular Glue)." This drug combines three engineering designs to achieve a level of precision  
186 and safety that existing therapies have not reached.

187 **3.2.1 Inhaled small-molecule compound**

188 Molecular glues (MG) possess a smaller molecular weight and more compact structure than typical  
189 PROTACs, resulting in superior bioavailability and drug-like properties. We adopt an inhaled  
190 administration route to maximize lung delivery efficiency. Small-molecule-based MGs can effectively  
191 cross the alveolar epithelial barrier to reach deep into the stroma where fibrosis is occurring, providing  
192 a foundation for dramatically increasing drug concentration at the lesion site while reducing systemic  
193 exposure.

194 **3.2.2 Eliminating toxicity at the source via FAP-responsive strategy**

195 While inhaled formulations have the advantage of delivering drugs directly to lung tissue, the risk of  
196 non-specific exposure affecting essential signaling systems in normal lung tissue remains. To address  
197 this, we introduce a reactive caging strategy utilizing the fibroblast activation protein (FAP), an  
198 enzyme specifically overexpressed only on the surface of activated myofibroblasts. Specifically, we  
199 construct a "dual-lock" system by attaching the Z-Gly-Pro sequence, a substrate for the FAP enzyme,  
200 to the protein-binding site of the molecular glue, creating an inactive pro-drug form [24]. This design  
201 ensures that the drug remains inactive when it resides in normal epithelial cells or other organs,  
202 thereby fundamentally excluding the possibility of cytotoxicity caused by ERK signal inhibition. The  
203 masking group is only removed to transform into an active molecular glue in fibrotic lesions where  
204 FAP is densely concentrated, thereby maximizing safety.

205 **3.2.3 Targets of the molecular glue**

206 We utilize a hijacking strategy that reverses the pathological equilibrium of signaling by exploiting  
207 enzymes that have changed in the disease environment. For the first core axis, the RAS DeSUMOTAC,  
208 we target the mechanism in which MAPK signaling is abnormally amplified due to a surge in E3 ligase  
209 activity that promotes RAS SUMOylation in the fibrotic environment [18]. Although the natural  
210 deSUMOylase SENP1 is present in the cell, its action is highly restricted in pathophysiological  
211 conditions due to the excessive SUMO modifications or spatial constraints between the nucleus  
212 and the cell membrane. By using a molecular glue to forcibly induce the proximity of SENP1 to  
213 RAS at the cell membrane, we can dramatically increase local enzyme concentration and push the  
214 natural reversible equilibrium toward deSUMOylation, thereby effectively blocking RAS-driven  
215 signal amplification at its source.

216 The second axis, the ERK DUBTAC strategy, focuses on blocking the process where K63-linked  
217 ubiquitination of ERK1/2 is induced by E3 ligases like TRIM15, which fixes ERK's nuclear entry and  
218 pathological transcription [19]. In healthy lung tissue, the natural deubiquitinase CYLD appropriately  
219 removes K63-ubiquitin from ERK to prevent signal overload. However, in the lesions of IPF patients,  
220 the expression of CYLD is significantly decreased, resulting in a loss of fibrotic control, while  
221 another DUB, USP15, is very highly expressed in myofibroblasts and acts as a "disease resource"  
222 that promotes fibrotic progression [25, 26]. We hijack the abundantly present USP15 to replace  
223 the missing function of CYLD by bringing it close to ERK1/2. By re-engineering USP15, which  
224 originally contributed to fibrosis, into a tool for removing K63-ubiquitin from ERK, we implement  
225 an innovative reversal strategy that converts pathological resources into therapeutic resources. This  
226 serves as a core rationale for selective therapy, as the drug's efficacy is even more powerfully exerted  
227 in lesion areas where USP15 is abundant.

228 **3.2.4 Derived drug candidate and virtual screening strategy**

229 This study combines structure-based drug design and AI simulation to derive an actual drug that  
230 implements the RAS DeSUMOTAC and ERK DUBTAC mechanisms. First, we sophisticatedly  
231 construct models for SUMOylated RAS (*K42*) and K63-ubiquitinated ERK2 (*K302*) based on  
232 high-resolution structural data like PDB 4NIF and 2IY1 using AlphaFold-Multimer [27]. We set  
233 core pockets for substrate binding, such as the CD docking site of ERK2, as key interface hotspots to  
234 ensure an optimal orientation where the target PTM molecule is precisely positioned within 3~5Å of  
235 the enzyme's active site. This induced proximity design is the core mechanism that forcibly triggers  
236 the de-modification reaction that could not occur in nature due to spatial constraints.

237 To identify the optimal molecular glue from millions of compounds in a library, we apply physical  
238 property filtering favorable for inhaled formulations and then select candidates that maximize binding

239 cooperativity through ternary complex docking simulations. A caged structure design is applied  
 240 by introducing the Z-Gly-Pro masking group, which is cleaved by the FAP enzyme, into the active  
 241 functional groups of the selected candidates to grant disease-specific activity. This design blocks  
 242 binding when the cage is present, but upon activation in the fibrotic areas where FAP is overexpressed,  
 243 it forms a powerful ternary complex, fundamentally excluding systemic side effects. This strategy  
 244 is chemically simpler than PROTACs, which require large and complex linkers, and effectively  
 245 preserves the superior tissue penetration inherent to small molecules.

246 Finally, we perform molecular dynamics (MD) simulations of over 100ns on the top selected can-  
 247 didates to precisely verify binding stability in a biological environment. During the simulation, we  
 248 monitor the RMSD changes of the ternary complex to ensure it remains structurally robust and track  
 249 whether the distance between the target PTM site and the enzyme's active center remains stable  
 250 within the reaction range. Finally, we confirm the final drug candidate with high therapeutic index by  
 251 precisely predicting the actual binding affinity through MMPBSA calculations, which prove that the  
 252 de-modification reaction efficiency increases dramatically in the simulation [28].

### 253 3.2.5 Integrated predictive data and efficacy validation of the derived drug

254 The derived drug will be used to prove efficacy and safety through multifaceted experimental  
 255 approaches, including fluorescence resonance energy transfer (FRET) for biochemical binding,  
 256 western blotting for protein modification changes, immunofluorescence for intracellular localization,  
 257 and validation in disease animal models. In particular, we intend to secure comprehensive predictive  
 258 data where molecular-level regulation leads to the improvement of the pathological phenotype of the  
 259 entire tissue by analyzing the correlation between the PTM status changes of RAS and ERK induced  
 260 by the molecular glue and the actual intensity of downstream signaling and the expression of cellular  
 261 senescence markers (Fig. 6).

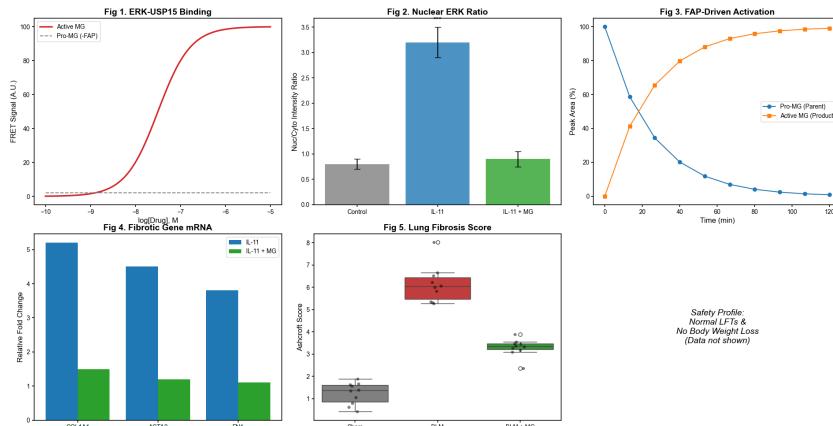


Figure 6: Computational prediction of molecular glue efficacy, signaling normalization, and therapeutic safety.

### 262 3.3 Hypothesis: fibrosis and senescence inhibition and safety strategy

263 The combination strategy of RAS DeSUMOTAC and ERK DUBTAC proposed in this study is  
 264 expected to achieve a fundamental reversal effect that existing treatments have not reached by  
 265 precisely striking the "senescence-fibrosis vicious cycle," the core driver of pulmonary fibrosis, at  
 266 the molecular level. Hypothetically, the dual-lock mechanism—which inhibits the initial signal  
 267 amplification of the MAPK cascade by removing RAS SUMOylation and blocks the nuclear entry  
 268 of pathological transcriptional programs by removing the K63-linked ubiquitin of ERK1/2—will  
 269 induce two core pathological changes within the lung tissue.

270 First, it will prevent cells from entering a permanent senescent state by stopping the activation of  
 271 cell cycle inhibitors such as *p21* and *p16* in type II alveolar epithelial cells (ATII). This results in  
 272 the suppression of fibrotic spread to surrounding tissues by fundamentally blocking the release of

273 the senescence-associated secretory phenotype (SASP), a potent toxic substance. Simultaneously,  
274 it will contribute to halting the excessive accumulation of collagen and restoring the regenerative  
275 microenvironment inherent to lung tissue by normalizing the pathological over-activation of the  
276 ERK-mTOR translation axis, which drives practical matrix synthesis.

277 These therapeutic effects are likely to lead to the structural recovery of the tissue rather than a  
278 mere delay of the disease. As the positive feedback loop fixed by IL-11 signaling collapses, cells  
279 already converted into myofibroblasts lose their additional ECM production drive, resulting in a direct  
280 lowering of tissue stiffness. Lowered physical stiffness, in turn, reduces mechanical stress on the  
281 epithelial cells, forming a virtuous cycle that supports their spontaneous survival and proliferation.  
282 Consequently, this drug possesses the powerful potential to return hardening lung tissue to a flexible  
283 state and significantly improve forced vital capacity, leading to clinical outcomes directly linked to  
284 the patient's quality of life.

285 Regarding safety, this design presents a new alternative that completely overcomes the limitations of  
286 existing broad-spectrum kinase inhibitors. The FAP-responsive activation system ensures that the drug  
287 remains inactive in normal lung tissue or other organs, thereby selectively fine-tuning only the over-  
288 activated signals in lesion areas while preserving the basal levels of RAS and ERK signaling essential  
289 for cell survival. This localized mechanism of action will fundamentally exclude systemic side effects  
290 such as hepatotoxicity or gastrointestinal disorders, dramatically increasing the therapeutic index.  
291 Furthermore, the small-molecule-based inhaled formulation maximizes administration convenience  
292 while directly reaching fibrotic lesions located deep within the lung tissue, confirming its potential  
293 as the safest and most effective next-generation standard treatment option for IPF patients requiring  
294 long-term management.

## 295 4 Closing remarks

296 In conclusion, this study introduces a transformative therapeutic paradigm for idiopathic pulmonary  
297 fibrosis by integrating AI-driven structural modeling with the precise regulation of post-translational  
298 modifications. The proposed de-modification strategy using FAP-responsive molecular glues repre-  
299 senters a significant departure from conventional inhibitory approaches, enabling the fine-tuning of  
300 pathological signals while preserving the essential cellular functions required for homeostasis. By  
301 hijacking disease-specific resources and utilizing a targeted lung-delivery system, our dual-lock mech-  
302 anism offers a safer and more effective path toward reversing fibrotic degeneration. We anticipate  
303 that this research will serve as a foundational cornerstone for developing high-precision therapies  
304 for intractable degenerative diseases, ultimately providing a definitive clinical solution for patients  
305 suffering from IPF.

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357 **AI Co-Scientist Challenge Korea Paper Checklist**

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361 Answer: [Yes]

362 Justification: The abstract and introduction clearly state our primary contribution: an  
363 innovative de-modification strategy using FAP-responsive inhaled molecular glues targeting  
364 the IL-11/ERK axis to reverse lung fibrosis.

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498 Justification: The mathematical assumptions and Python-based modeling parameters used  
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