Fibrosis Disruption: SMITE Protocol for RT-Activated Anti-Fibrotic Nanoparticle

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Abstract

Pulmonary Fibrosis (PF) is a deadly progressive lung disease with no cure and very few effective treatments. Our dual-innovation therapy – SMITE radiotherapy protocol and a radiation-activated anti-fibrotic nanoparticles - targeting fibrosis at its core: the pathological extracellular matrix (ECM). SMITE protocol delivers low dose, high-dose rate, spatially fractionated radiation to selectively disrupt fibrotic tissue, while priming the lung for localized drug release. Inhaled nanoparticles respond to radiation-triggered Reactive Oxygen Species (ROS) burst to release taladegib, a Hedgehog pathway inhibitor, directly involved into scarred tissue. This precision approach transforms fibrosis from a managed condition to a treatable target. With scalable preclinical development and a US-focused commerical trajectory, our proposed innovation offers a paradigm shift for pulmonary fibrosis care.

Index Terms: Pulmonary fibrosis, SMITE Protocol, Radiation, Nanoparticle

1 Introduction

Pulmonary fibrosis is a progressive and ultimately fatal lung disease marked by relentless scarring of the alveolar architecture, resulting in impaired gas exchange, respiratory failure, and death. It affects an estimated 5-10 million people globally, with Idiopathic Pulmonary Fibrosis (IPF)—the most common subtype—impacting approximately 100k individuals in the United States alone and 30k–35k in the UK [1, 2]. Incidence continues to rise, particularly in aging populations, with up to 50% of cases misdiagnosed or diagnosed late due to nonspecific and overlap symptoms. Over 70% of patients are not diagnosed until moderate or advanced stages with a median diagnostic delay of 2.1 years, when irreversible architectural lung damage has already occurred [3]. Despite two FDA-approved antifibrotic drugs modestly slowing disease progression, they do not reverse existing fibrosis or significantly improve survival. The median time from diagnosis to death remains approximately 3 to 5 years [2]. With high symptom burden, limited therapeutic efficacy, & rising healthcare costs, fibrosis represents a substantial unmet clinical need.

2 Clinical Progression of Fibrosis

Following repetitive and sustained alveolar injury, dysfunctional repair leads to persistent activation of fibroblasts and accumulation of myofibroblasts within the interstitium [4]. These cells secrete dense networks of collagen and other extracellular matrix (ECM) components, which progressively thicken the alveolar walls and reduce their elasticity [5]. As fibrosis advances, normal lung parenchyma is replaced with stiff, non-functional scar tissue, impairing gas diffusion across the alveolar-capillary barrier. This tissue remodeling narrows airways, disrupts ventilation-perfusion matching, and increases the work of breathing—ultimately manifesting as reduced exercise tolerance, hypoxemia, & chronic dyspnea [4, 6]. The continued expansion of fibrotic foci compresses nearby healthy alveoli and vasculature, further exacerbating respiratory dysfunction [4].

2.1 Key Cellular Events

- **Alveoli epithelial cell injury** initiates fibrotic cascade by releasing damage-associated signals and profibrotic cytokines
- **Activation of fibroblasts & differentiation into myofibroblasts** promotes ECM remodeling
- **Excess ECM production**, accumulates in interstitial spaces, impairing lung mechanics
- **Apoptosis-resistant myofibroblast persistence** maintains fibrotic foci and prevents normal resolution of tissue repair

3 Innovation

SMITE the scar. Spare the lung. Leveraging accelerator technology, we have developed a dual-innovative solution aimed not just at managing fibrosis – but at dismantling it, precisely and at its source.

3.1 SMITE Protocol

Spatially-Modulated Intensity Therapy with Electron-LINAC (SMITE), is a novel radiation strategy that delivers low total dose, at a high dose rate, using spatial fractionation to maximize local tissue disruption while minimizing the collateral toxicity.

3.1.1 Core Principles: First,disrupt fibrotic ECM and diseased tissue using spatially focused energy.Second, exploit radiobiological weak points with low-dose, high dose-rate delivery while sparing healthy lung tissue [7]. Third, prime the tissue for follow-up therapies like drug-loaded nanoparticles.

3.1.2 Accelerator Specifications SMITE uses 6 MV photon radiation delivered at high dose rates (>40 Gy/s) with low total doses—typically 2 Gy for fibrotic tissue degradation and 1 Gy for drug delivery [8]. These doses, 1-2 Gy, can be delivered within 25–50 ms, respectively, using only the initial beam pulses.

3.2 IR Activated Nanoparticle

To achieve targeted, radiation-activated disruption of fibrotic tissue & simultaneous delivery of anti-fibrotic therapy, we developed a multi-layered, inhalable nanoparticle system (see Figure 1) optimized for deep-lung delivery and responsive release.

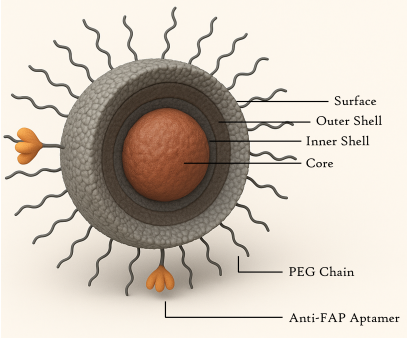

Figure 1. Schematic representation of radiation-activated nanoparticle designed for targeted disruption of fibrotic tissue (core=orange; inner shell=blue; outer shell=brown; surface=gray.

3.2.1 Core: Delivery of Anti-Fibrotic Payload & Anti-Fibrotic Drug: taladegib The innermost layer of the nanocarrier comprises a hydrophobic core of PLGA encapsulating taladegib—an anti-fibrotic drug that inhibits Hedgehog signaling, a pathway strongly implicated in fibroblast activation, myofibroblast persistence, and ECM deposition [9, 10]. This core serves as the primary therapeutic payload and remains shielded from enzymatic degradation or ROS oxidation until triggered. Taladegib was selected for its ability to suppress fibrotic gene expression and promote apoptosis in activated myofibroblasts while minimizing systemic toxicity due to localized delivery [11].

3.2.2 Inner Shell: Localized Disruption of fibrtotic ECM The MnO_2 inner shell is designed to amplify the oxidative damage at the fibrotic site. When exposed to radiation, the MnO_2 reacts with the local H_2O_2 to generate hydroxyl radicals, increasing ROS beyond baseline levels [12]. This localized ROS burst promotes degradation of the fibrotic ECM and compromises the cell's viability [12]. This inner shell design also contributes to destabilizing the outer thioketal-crosslinked PLGA shell, accelerating drug release in response to irradiation and oxidative stress. Its role is to enhance local damage without increase overall absorbed dose to the patient.

3.2.3 Outer Shell: Ensuring Stability Until IR Activation The outermost structural layer consists of a PLGA matrix crosslinked with thioketal linkers, forming a ROS-sensitive network [13, 14]. Thioketal bonds are cleaved specifically by ROS ($\geq$5–10 μM), ensuring minimal premature degradation under basal fibrotic ROS levels ($\approx$0.5–1 μM), while rapidly disassembling in response to radiation-induced bursts [15]. This shell acts as a protective barrier during circulation and pulmonary transit, while functioning as the primary gatekeeper for radiation-triggered release [16, 15].

3.2.4 Surface: Targeting and Immune-Evasion The surface of the nanoparticle includes PEG for circulation stability, a zwitterionic coating to reduce immune recognition, and an anti-Fibrotic Activation Protein (anti-FAP) aptamer. The PEGylation and the zwitterionic layer minimize protein absorption and improve lung retention [17, 18]. The anti-FAP aptamer ensures the particle binds selectively to only fibrotic tissue [19]. Together, the surface components enable precise delivery, limit off-target effects, and maintain the stability of the nanoparticle through the pulmonary transport.

4 Validation & Verification

After the initial development, synthesis, and characterization of the nanoparticle, the first step toward clinical viability will be to conduct in vitro studies based on evaluating the biocompatibility and toxicity of the nanoparticle (alone), the SMITE protocol (alone), and the combination of the two treatments. These spearheading experiments will focus on two key aspects: toxicity and cellular response of fibroblast to synthesized nanoparticles. We propose two of the following initial investigations. (See Section 5.4 for additional details)

- Utilizing 10-4A^{BFP}, a reporter fibroblast cell line commonly used to study the pathophysiological mechanism of fibrosis, will allow for initial in vitro studies to assess the cytotoxicity and anti-fibrotic effects on human lung fibroblasts in a 2D medium [20].
- To investigate the cellular response to the SMITE radiation protocol—specifically its ability to induce apoptosis in fibrotic fibroblasts, which are typically resistant even at high doses—an in vitro clonogenic survival assay will be conducted to assess whether SMITE effectively triggers cell death [21].

5 Developmental Plan

This project proposes a dual-innovative strategy targeting fibrosis. The core of this hypothesis is that SMITE can selectively disrupt fibrotic tissue architecture, enhance vascular and ECM permeability, and create a transient therapeutic window for localized nanoparticle activation. The nanoparticle, in turn, releases anti-fibrotic agents in response to ROS exposure from the radiotherapy of the SMITE protocol, providing targeted biochemical intervention precisely where pathological remodeling occurs.

5.1 Rational and Preliminary Support

While still in the conceptual stage, the SMITE-nanoparticle combination is built on a solid foundation of mechanistic plausibility and precedents from the literature review. Fibrotic fibroblasts, though not malignant, adopt many traits that mirror cancer cells. They share several key microenvironmental and cellular features that make them similarly targetable with nanoparticle-based and radiation-activated therapies [22]. Each aspect of the SMITE protocol (low dose, high dose rate, and spatial fractionation) has been shown to modulate the immune and microenvironment without causing widespread toxicity to localized healthy tissue [23, 24]. Similarly, several preclinical models have demonstrated that inhaled nanoparticle-mediated drug delivery can improve pharmacokinetics and reduce off-target effects to fibrotic tissue [16]. Importantly, there is a growing body of clinical and translational research supporting the role of radiotherapy in modulating fibrotic microenvironments – including in pulmonary fibrosis [25, 16, 23].

5.2 Target Population and Market Focus

The initial target indication is pulmonary fibrosis – a chronic progressive lung disease with poor prognosis and limited therapeutic options. Despite FDA approved drugs (e.g. pirfenidone and nintedanib), there is significant unmet need, particularly for therapies that reverse or halt structural fibrosis. Given the high cost burden of PF management in the United States and

the limitations of subsidized reimbursement in many European system, the primary commercial focus will begin with the U.S. market. A secondary application may target post-COVID pulmonary fibrosis, where incidence and public interest still remain high.

5.3 Estimated Cost Per Treatment

Our projected cost per patient is 9.2 k€, based on detailed calculations using IAEA staffing recommendations and average salaries for oncologists, medical physicists, radiation therapists, and oncology nurses. This estimate includes two radiotherapy sessions (4 k€ each), one follow-up appointment (442 €), and a ≈30 mg nanoparticle/drug treatment (798 €) [26, 27]. Compared to the current alternative—lung transplantation, this represents a substantial reduction in cost. A single lung transplant often exceeds 846 k€, while a double lung transplant can cost more than 1.2 M€ [28]. This cost-effective approach could expand access to care, reduce financial strain on healthcare systems, and offer a viable treatment option for patients who are not eligible or can not afford a transplant.

5.4 Development Roadmap

The development trajectory is structured with conservative, staged milestones with emphasis on proof-of-concept and validation prior to focusing on translational work. Anticipated phases include:

Phase I: In Vitro Validation (Months 0-18)

- **Nanoparticle Development:** Synthesis and physiochemical characterization (size, charge, payload capacity, radiation-responsiveness, release kinetics)
- **Cellular Studies:** Cytotoxicity assessment, uptake, and release in fibrotic cell lines under radiation exposure
- **SMITE Protocol Optimization:** Dosimetry modeling and cell-level assay to determine the therapeutic window and ECM remodeling effects.

Phase II: In Vivo Proof of Concept (Months 18-48)

- **Murine Pulmonary Fibrosis Models:** Testing SMITE Protocol (alone), nanoparticle (alone), and combination therapy
- **Biodistribution and Pharmacodynamics:** Imaging and histopathology to assess nanoparticle localization in tissue and overall therapeutic efficacy
- **Safety and Toxicology:** Preliminary profiling of off-target effects and tolerability

Phase III: Translation (Months 18-36)

- **Regulatory Strategy & Pre-IND Engagement:** Initiate communication with regulatory authorities to clarify classification & define data requirements for clinical entry
- **Clinical Trial Protocol Development:** Define patient population, inclusion and exclusion criteria, dose escalation plan, and endpoints

5.5 Projected Development Cost

The cost estimates presented for the preclinical development of the SMITE protocol and radiation-activated anti-fibrotic nanoparticle are grounded in current industry standards, historical data from comparable nanomedicine programs, and early-stage biotechnology development models.

- Published benchmarks from biotechnology and pharmaceutical development reports, including estimates for R&D and preclinical expenditures
- Fee structures from preclinical Contract Research Organizations (CROs)
- First-principles budgeting based on personnel, material, & facility requirements for nanoparticle development and radiation-based therapeutic validation, guided by current regulatory frameworks.

Table 1
Estimated Cost of Preclinical Development

Category	Estimated Cost
Nanoparticle Design and Optimization	273 000 € – 546 000 €
In Vitro Validation Studies	228 000 € – 455 000 €
SMITE Protocol Modeling & Dosimetry	182 000 € – 364 000 €
Small Animal In Vivo Studies	683 000 € – 1 365 000 €
Regulatory Preparation	137 000 € – 273 000 €
Total Estimated Cost	**1.5 M€ – 3.0 M€**

While not inclusive of downstream Phase I clinical trial costs, this budget, shown in Table 1, represents a realistic and phased investment plan required to scientifically de-risk the therapeutic strategy and prepare for translational advancement.

5.6 Feasibility and Risk

While the SMITE-nanoparticle system is in the early-development stage, feasibility is supported by prior evidence and literature for each component individually. Nonetheless, several key risks must be acknowledged.

Limitation of Accelerator: Despite growing interest in FLASH radiotherapy (high dose rate), the translation of photon-based FLASH to clinical practice remains technically constrained. Although modified LINACs can produce electron dose rates exceeding 300 Gy/s, photon conversion efficiencies remain low, and resultant dose rates (~3 Gy/s) fall short of FLASH thresholds. Techniques such as reducing the source-to-surface distance (SSD) to 80 cm can modestly increase photon dose rates [29, 30], but these improvements remain insufficient [31]. For SMITE, which delivers only 1–2 Gy total dose per field, thermal damage to the Bremsstrahlung converter is likely avoidable. However, the key limitation remains the achievable photon dose rate, which currently falls short by roughly an order of magnitude.

Technical Risk: Engineering a nanoparticle that reliably responds to radiation within clinically relevant dose parameters is challenging. Precise control over radiation-triggered drug release of our nanoparticle, especially under the low-dose of the SMITE conditions, has not yet been demonstrated. Synchronizing the nanoparticle activation with spatial dose heterogeneity also introduces complexity in dosimetry & treatment planning.

Biological Risk: The nanoparticle clearance by alveolar macrophages or unwanted immunogenic response could undermine efficacy. Additionally, the heterogeneity of fibrosis progression across patients further complicates treatment standardization and response prediction.

Regulatory Risk: The combined use of novel radiotherapy protocol and a drug-loaded nanoparticle is likely to be classified as a combination product, necessitating a more complex regula-

tory pathway. Furthermore, radiation is currently not a recognized therapeutic modality for treating fibrosis, so the burden of proof for safety and efficacy will be high.

5.7 Mitigation Strategies

To address these risks, we propose a stepwise development process beginning with in vitro proof-of-concept studies. Nanoparticle formulations will be screened for radiaiton-responsiveness and biocompatability, while SMITE parameters will be refined for safety and localized ECM Modulation. SMITE feasibility will be supported by ongoing efforts to adapt current LINAC infrastructure for reliable high-dose-rate photon delivery. Early engagement with regulatory authorities will help define an appropriate translation path.

6 Conclusion

The SMITE protocol, combined with a radiation-activated anti-fibrotic nanoparticle, offers a fundamentally new way to treat fibrosis – not by slowing progression, but by physically disrupting pathological tissue and enabling localized therapeutic delivery. This is a precision approach to a disease long treated with blunt instruments. The science is sound. The mechanism is plausible. The unmet need is undeniable.

We're entering a phase where fibrosis is no longer untouchable. *SMITE the scar. Spare the lung.* With early validation studies, we aim to prove that this platform can be safely and effectively translated. What's needed now is the support to take it from concept to clinic.

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