Understanding Stem Cell Therapy for Pulmonary Fibrosis

A Patient Guide from Auragens

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Advancing Regenerative Medicine:
Treatments & Empathy Amplified by Science and Technology

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Welcome

Receiving a diagnosis of pulmonary fibrosis — or watching a loved one navigate its daily challenges — can feel overwhelming. The relentless progression of breathlessness, the limitations it places on everyday life, and the uncertainty about what lies ahead are burdens that no one should carry alone.

At Auragens, we believe that every patient deserves access to the most current, honest, and compassionate information available — not just about what medicine can do today, but about what science is working toward tomorrow. This guide was created specifically for people living with pulmonary fibrosis and for the families who support them.

Inside, you will find a clear explanation of what pulmonary fibrosis is and how it affects your lungs; an honest discussion of current treatments and their limitations; a detailed look at human umbilical cord mesenchymal stem cells (hUC-MSCs) derived from Wharton's Jelly and the science behind how they may support lung health; a review of the current clinical evidence; and a transparent account of what a consultation and treatment experience at Auragens involves.

This guide is educational. It is not a promise of outcomes, a substitute for medical advice, or a recommendation to discontinue any current therapy. It is an invitation to become informed — so that you can ask better questions, have more productive conversations with your medical team, and make decisions that are right for you.

We are honored to be part of your journey.

1. Understanding Pulmonary Fibrosis and Current Treatment Limitations

What Is Pulmonary Fibrosis?

Pulmonary fibrosis is a chronic, progressive lung disease in which the delicate tissue of the lungs becomes scarred, thickened, and stiff over time. The word *pulmonary* refers to the lungs, and *fibrosis* means the formation of excess fibrous connective tissue — essentially, scar tissue. As this scarring accumulates, the lungs lose their ability to expand freely and to efficiently transfer oxygen from inhaled air into the bloodstream.

The most common and most studied form is **idiopathic pulmonary fibrosis (IPF)** — "idiopathic" meaning that no specific cause has been identified. Other forms of pulmonary fibrosis may arise from autoimmune conditions (such as systemic sclerosis or rheumatoid arthritis), prolonged exposure to environmental irritants (such as asbestos, silica, or certain molds), certain medications, or radiation therapy to the chest. While the triggers

differ, the underlying biology of progressive lung scarring shares many common features across these forms [1, 2].

What Happens Inside the Lungs

To understand pulmonary fibrosis, it helps to first understand how healthy lungs work. Your lungs contain hundreds of millions of tiny air sacs called **alveoli** — each one surrounded by a fine network of blood vessels. When you breathe in, oxygen crosses through the thin walls of the alveoli into the blood. When you breathe out, carbon dioxide moves in the opposite direction. This exchange happens continuously, and it depends entirely on the alveolar walls being thin, flexible, and intact.

In pulmonary fibrosis, this architecture is disrupted by a cascade of abnormal biological events:

1. **Repeated alveolar epithelial injury.** The cells lining the air sacs (alveolar epithelial cells, particularly Type II pneumocytes) are injured repeatedly — whether by microscopic environmental insults, oxidative stress, or other triggers. In a healthy lung, this injury heals cleanly. In susceptible individuals, something goes wrong in the repair process [1, 3].

2. **Aberrant wound healing and myofibroblast persistence.** The body recruits specialized repair cells called **fibroblasts**, which normally lay down temporary scaffolding to support healing. In IPF, these fibroblasts transform into hyperactive **myofibroblasts** that continue producing excessive amounts of collagen and other structural proteins long after the injury has passed. This creates the characteristic dense, stiff scar tissue of fibrosis [1, 4].

3. **Chronic inflammation and immune dysregulation.** Inflammatory immune cells accumulate in the lung, releasing cytokines — signaling proteins such as IL-1β, TGF-β, and TNF-α — that drive further fibroblast activation, collagen deposition, and ongoing tissue damage. Key inflammatory pathways including NF-κB and the NLRP3 inflammasome are persistently activated [5, 6].

4. **Oxidative stress.** An imbalance between harmful reactive oxygen species and the lung's antioxidant defenses compounds cellular injury and amplifies the fibrotic cycle [6].

5. **Loss of alveolar architecture.** As scarring progresses, the thin, gas-exchanging walls of the alveoli are replaced by thick fibrotic tissue. The lungs become stiff, their capacity shrinks, and their ability to deliver oxygen to the blood declines progressively [2, 3].

Symptoms and Progression

Pulmonary fibrosis typically develops slowly, and symptoms may be subtle in the early stages. The most common include:

- **Progressive shortness of breath (dyspnea):** Initially noticeable only during exertion — climbing stairs, walking briskly — but advancing over time to breathlessness with minimal activity or at rest.
- **Persistent dry cough:** A chronic, non-productive cough that does not improve with standard cough remedies.
- **Fatigue and reduced exercise tolerance:** Resulting from chronically lower blood oxygen levels and the increased effort of breathing.
- **Chest tightness or discomfort.**
- **Finger clubbing:** A widening and rounding of the fingertips, seen in some patients with advanced disease.

Pulmonary function tests reveal a **restrictive ventilatory pattern** — reduced forced vital capacity (FVC) and reduced diffusing capacity for carbon monoxide (DLCO), reflecting both the loss of lung volume and the impaired ability to transfer oxygen. High-resolution CT (HRCT) of the chest typically shows characteristic patterns of peripheral, basilar-predominant reticulation and, in advanced cases, honeycombing [2, 3].

The course of IPF is variable. Some patients experience a slow, steady decline; others have periods of relative stability interrupted by acute exacerbations — sudden, severe worsening episodes that carry a high mortality risk. The disease is ultimately progressive, and prognosis remains serious, underscoring the urgent need for more effective therapies [2, 4].

Current Standard Treatments

The treatment landscape for pulmonary fibrosis has evolved meaningfully over the past decade, but important gaps remain.

Antifibrotic medications:

- **Pirfenidone** (Esbriet) — An oral medication with anti-inflammatory, antioxidant, and antifibrotic properties. Clinical trials have demonstrated that pirfenidone reduces the annual rate of FVC decline and may reduce mortality risk compared to placebo [4]. Side effects include gastrointestinal symptoms (nausea, diarrhea), photosensitivity, and fatigue, which can affect tolerability and adherence.

- **Nintedanib** (Ofev) — A tyrosine kinase inhibitor that blocks multiple growth factor signaling pathways involved in fibrosis, including PDGF, VEGF, and FGF receptors. Nintedanib has been shown to slow FVC decline and reduce the frequency of acute exacerbations in IPF and in some other progressive fibrosing interstitial lung diseases [4]. Common side effects include diarrhea and elevated liver enzymes.

Supportive care:

- Supplemental oxygen therapy to maintain adequate blood oxygen levels and reduce breathlessness.

- Pulmonary rehabilitation programs to improve functional capacity, breathing efficiency, and quality of life.
- Vaccination against influenza and pneumococcal pneumonia to reduce the risk of respiratory infections, which can trigger acute exacerbations.
- Management of gastroesophageal reflux disease (GERD), which may worsen IPF when present.

Lung transplantation:

For carefully selected patients — typically younger patients with advanced disease and no major comorbidities — bilateral lung transplantation offers the possibility of meaningfully improved survival and quality of life. However, transplantation is limited by donor organ availability, strict eligibility criteria, the risks of surgery and perioperative complications, and the burden of lifelong immunosuppression [4, 7].

The Limitations of Current Treatments

Despite the advances represented by pirfenidone and nintedanib, important limitations define the current treatment reality for patients with pulmonary fibrosis:

- **Neither antifibrotic drug reverses established fibrosis.** They slow the rate of lung function decline but do not restore damaged lung tissue or rebuild the alveolar architecture that has been lost [4].
- **Disease continues to progress** on both agents, albeit more slowly. Patients continue to lose lung function over time.
- **Side effect burden** can be significant, and some patients are unable to tolerate therapeutic doses.
- **Lung transplantation is not accessible to all patients** due to age restrictions, comorbidities, donor organ shortages, and the high demands of post-transplant care.
- **No approved therapy** currently addresses the underlying biology of fibrosis initiation or promotes meaningful lung tissue regeneration.

These unmet needs have motivated scientists and clinicians worldwide to explore regenerative medicine approaches — including mesenchymal stem cell therapy — as potentially complementary or investigational strategies that may target the disease from a different biological direction.

2. What Are hUC-MSCs from Wharton's Jelly?

Mesenchymal Stem Cells: A Brief Overview

Mesenchymal stem cells (MSCs) are a class of adult multipotent stem cells — meaning they have the capacity to give rise to several different cell types, including bone, cartilage, and fat cells. But what makes MSCs especially interesting for therapeutic applications is not primarily their ability to become new cells. It is their remarkable capacity to communicate with and influence the surrounding biological environment.

MSCs are naturally found in many tissues throughout the body, including bone marrow, adipose (fat) tissue, dental pulp, and the placenta. They act as local regulators of tissue homeostasis — secreting growth factors, signaling molecules, and protective proteins that support cell survival, modulate inflammation, and coordinate repair processes. This paracrine activity (the ability to influence nearby cells without direct contact) is now understood to be central to the therapeutic potential of MSCs [8, 9].

Wharton's Jelly: A Uniquely Valuable Source

Among the various tissue sources of MSCs, the **umbilical cord** — and specifically a gelatinous connective tissue within it called **Wharton's Jelly** — has emerged as one of the most scientifically and clinically promising.

Wharton's Jelly is the soft, mucoid connective tissue that surrounds and protects the blood vessels of the umbilical cord. It is rich in MSCs that are biologically distinct from those derived from adult tissues in several important ways:

- **Younger biological age.** Wharton's Jelly MSCs (WJ-MSCs, also called hUC-MSCs — human umbilical cord mesenchymal stem cells) are derived from perinatal tissue, meaning they retain characteristics of younger, more primitive cells. They typically exhibit higher proliferative capacity and stronger secretory activity compared to bone marrow–derived MSCs from adult donors [8, 9].
- **Low immunogenicity.** One of the most clinically significant features of hUC-MSCs is their reduced expression of major histocompatibility complex (MHC) class II antigens — the surface proteins that trigger immune rejection. This means that hUC-MSCs can be administered to patients who are not genetically matched to the donor, with a lower risk of immune rejection. This property makes **allogeneic (donor-derived) therapy** feasible, allowing cells to be prepared in advance and made available when needed [8, 10].
- **Potent immunomodulatory capacity.** hUC-MSCs are strong modulators of the immune system. They can suppress overactive inflammatory responses, shift immune cell populations from pro-inflammatory to anti-inflammatory phenotypes,

and reduce the production of damaging cytokines — all properties highly relevant to fibrotic and inflammatory diseases [9, 10].

- **Rich trophic and paracrine secretome.** hUC-MSCs secrete a broad array of growth factors, cytokines, and extracellular vesicles (including exosomes) that support tissue repair, protect cells from programmed death (apoptosis), promote new blood vessel formation, and modulate the extracellular matrix [9, 11].
- **Ethically sourced.** The umbilical cord is a perinatal tissue that is routinely discarded after birth. Collection of Wharton's Jelly MSCs is non-invasive, carries no risk to the mother or newborn, and requires only appropriate informed consent from the donor family [8].

From Collection to Clinical Use

The journey of hUC-MSCs from donation to patient involves multiple carefully controlled steps:

Donor screening. All cord donors undergo rigorous medical history review and infectious disease screening — including testing for HIV, hepatitis B and C, cytomegalovirus, syphilis, and other relevant pathogens — in accordance with regulatory standards for human cellular products.

Cell isolation and expansion. Wharton's Jelly tissue is carefully isolated from the umbilical cord under sterile laboratory conditions. MSCs are then extracted, identified by their characteristic surface markers and biological properties, and expanded through controlled cell culture to produce therapeutically meaningful quantities.

Quality control and characterization. Each cell lot undergoes extensive testing to confirm cell identity (surface marker phenotyping), viability, sterility, absence of microbial contamination, and potency (functional activity). Only cell preparations that meet all quality specifications are advanced for clinical use.

Cryopreservation. Qualified cell lots are cryopreserved (frozen) in specialized media and stored under controlled conditions until needed. Prior to administration, cells are thawed and prepared according to standardized protocols to ensure viability and activity at the time of infusion.

This rigorous process — from ethical collection through quality-assured preparation — reflects Auragens' commitment to delivering cellular products that meet the highest standards of safety and scientific integrity.

🏆 Why Auragens: AABB Accreditation — The Gold Standard in Cellular Therapy

Auragens Stem Cell Center is proud to be AABB accredited — a critical distinction that sets us apart from unaccredited clinics.

What is AABB Accreditation?

AABB (Association for Advancement of Blood and Biotherapies) is the internationally recognized leader in setting quality and safety standards for cellular therapies. AABB is a deemed status organization by the FDA and AABB accreditation represents the gold standard in the field — the most rigorous, comprehensive certification available for facilities that process and administer cellular products.

What Does AABB Accreditation Mean for You?

When you choose an AABB-accredited center like Auragens, you can trust that we meet the highest international standards in:

- **Cell Processing Excellence:** Our laboratory protocols follow strict, validated procedures ensuring every cell product meets pharmaceutical-grade quality specifications.
- **Donor Screening & Safety:** Comprehensive screening protocols ensure all donor tissue is thoroughly tested and meets stringent safety criteria.
- **Laboratory Practices:** Our facilities, equipment, and processes undergo regular inspection and must meet exacting standards for sterility, environmental control, and quality assurance.
- **Patient Safety:** From cell arrival through administration and follow-up, every step is designed and monitored to protect your safety.
- **Staff Expertise:** Our team maintains specialized training and competency requirements specific to cellular therapy.
- **Traceability & Documentation:** Complete tracking and documentation of every cell product ensures full accountability.
- **Continuous Quality Improvement:** Regular audits, proficiency testing, and quality reviews.

Why This Matters

The field of stem cell therapy is rapidly growing, but not all clinics meet the same standards. Many facilities operate without independent accreditation or oversight. AABB accreditation means an external, U.S., FDA, expert organization has thoroughly inspected and validated our practices — giving you independent verification, proven quality systems, and genuine peace of mind. When you choose Auragens, you're choosing a center that has been independently verified to meet the most stringent international standards for cellular therapy quality and safety.

AABB accreditation is not easy to achieve or maintain — it requires significant investment in infrastructure, training, quality systems, and ongoing compliance. We've made this commitment because you deserve nothing less than the highest standard of care.

3. How hUC-MSCs May Help with Pulmonary Fibrosis

Pulmonary fibrosis is driven by a complex interplay of chronic inflammation, aberrant immune activation, oxidative stress, and dysregulated tissue repair. The biological properties of hUC-MSCs position them as a potentially multi-pronged approach to addressing several of these interconnected pathological processes simultaneously. Below, we describe the key mechanisms that current research suggests may be relevant in the context of pulmonary fibrosis.

It is important to note that much of this mechanistic evidence comes from preclinical studies — primarily animal models of lung fibrosis — and early-phase human trials. These findings are promising but remain investigational. They provide the scientific rationale for ongoing clinical research rather than established clinical proof.

3.1 Anti-Inflammatory Effects

Chronic, dysregulated inflammation is a central driver of pulmonary fibrosis. Pro-inflammatory cytokines — including IL-1β, TNF-α, and IL-6 — fuel fibroblast activation, myofibroblast persistence, and ongoing tissue damage. Key inflammatory signaling cascades, particularly NF-κB and the NLRP3 inflammasome, sustain this inflammatory environment.

Research suggests that hUC-MSCs and their secreted products can significantly suppress this inflammatory milieu. Studies have shown that MSC-derived extracellular vesicles reduce IL-1β levels, downregulate NF-κB activity in lung epithelial cells, and inhibit NLRP3 inflammasome activation — collectively dampening the inflammatory drivers of fibrosis [6, 12]. By reducing the intensity and duration of inflammatory signaling, hUC-MSCs may help interrupt the cycle of injury and aberrant repair that perpetuates fibrosis.

3.2 Antifibrotic Signaling and Inhibition of EMT

A critical step in pulmonary fibrosis is **epithelial-to-mesenchymal transition (EMT)** — a process in which alveolar epithelial cells lose their normal identity and acquire fibroblast-like characteristics, contributing to the pool of myofibroblasts that drive scarring. Inhibiting EMT is therefore a meaningful antifibrotic strategy.

Preclinical studies have demonstrated that MSC-derived extracellular vesicles can inhibit EMT in lung epithelial cells, reducing the expression of fibrosis-associated proteins such as α-smooth muscle actin (α-SMA) and collagen [12, 13]. Additionally, MSCs may suppress the TGF-β signaling pathway — one of the most potent drivers of fibroblast activation and collagen production in IPF — through paracrine and direct cell-contact mechanisms.

3.3 Immunomodulation and Macrophage Reprogramming

Macrophages — immune cells that patrol the lung — play a dual role in pulmonary fibrosis. In their pro-inflammatory (M1) state, they amplify tissue damage; in their anti-inflammatory and repair-promoting (M2) state, they support resolution and healing. In IPF, this balance is dysregulated, with persistent pro-inflammatory macrophage activity contributing to ongoing fibrosis.

A landmark study by Mansouri et al. (2019), published in *JCI Insight*, demonstrated that MSC-derived exosomes (MEx) could reprogram monocytes and macrophages toward an immunoregulatory phenotype, preventing and even reversing bleomycin-induced pulmonary fibrosis in a mouse model [14]. This finding highlights the potential of MSC exosomes to reset the immune microenvironment of the fibrotic lung — shifting it from a state of destructive inflammation toward one that supports repair.

3.4 Exosome and Paracrine Signaling

A growing body of evidence suggests that many of the beneficial effects of MSCs are mediated not by the cells themselves taking up permanent residence in the lung, but by the bioactive molecules they secrete — a phenomenon known as **paracrine signaling**. Among the most important of these secreted products are **exosomes**: nanoscale vesicles that carry proteins, lipids, growth factors, and small regulatory RNA molecules (microRNAs) to recipient cells.

MSC-derived exosomes can deliver antifibrotic microRNAs that silence profibrotic gene expression in fibroblasts, carry anti-apoptotic signals that protect injured alveolar epithelial cells, and transfer molecular cargo that modulates immune cell behavior [11, 15]. Importantly, a recent clinical investigation published in 2025 explored nebulized human umbilical cord MSC-derived extracellular vesicles specifically for pulmonary fibrosis treatment, reflecting the growing interest in harnessing exosome biology as a potentially cell-free complement or alternative to whole-cell therapy [16].

3.5 Oxidative Stress Reduction

Oxidative stress — the excess production of reactive oxygen species (ROS) relative to the lung's antioxidant capacity — is both a consequence and an amplifier of lung injury in pulmonary fibrosis. ROS damage alveolar epithelial cells, activate fibroblasts, and accelerate ECM deposition.

Research has shown that MSC-derived extracellular vesicles can upregulate key antioxidant defense systems in lung tissue, including the **Nrf2/HO-1 pathway** — a master regulator of the cellular antioxidant response. By enhancing antioxidant capacity and reducing oxidative injury, hUC-MSCs may help protect residual functional lung tissue from further damage [6].

3.6 Matrix Remodeling and Tissue Repair

The dense, collagen-rich extracellular matrix of fibrotic lung tissue is not merely a passive scar — it is a biologically active environment that sustains fibroblast activation and impairs alveolar regeneration. Remodeling this matrix is an important component of any potential therapeutic reversal of fibrosis.

Preclinical studies with Wharton's Jelly–derived MSCs have demonstrated that these cells can increase the expression of **matrix metalloproteinase-9 (MMP-9)** — an enzyme that degrades excess collagen — in macrophages within the lung. Simultaneously, HUMSC transplantation was associated with increased hyaluronan production and upregulation of TLR-4 in alveolar epithelial cells, supporting a regenerative microenvironment conducive to alveolar repair [17, 18].

3.7 Hepatocyte Growth Factor Secretion

Hepatocyte growth factor (HGF) is a multifunctional protein with anti-apoptotic, anti-inflammatory, and antifibrotic properties. MSCs naturally secrete HGF, and research has shown that augmenting HGF delivery to the fibrotic lung may enhance the antifibrotic effects of MSC therapy. Studies using umbilical cord MSCs engineered to overexpress HGF demonstrated significantly greater reductions in fibrosis scores, lung collagen content, and inflammatory markers — including modulation of IL-17 signaling in the lung — compared to unmodified MSCs [19]. While HGF overexpression strategies remain experimental, this research underscores the importance of MSC-secreted trophic factors in mediating antifibrotic effects.

4. Clinical Evidence and Research Findings

Section 4: Clinical Evidence and Research Findings

The Current State of the Evidence

Research into stem cell therapy for pulmonary fibrosis is genuinely advancing — but it is important to be transparent about where the evidence currently stands. The majority of published human studies are early-phase trials or case reports designed primarily to establish safety and feasibility, with secondary observations of potential functional benefit. Large, definitive randomized controlled trials have not yet been completed. What we have is a growing and scientifically coherent body of evidence that supports continued investigation and provides a credible rationale for clinical exploration.

Key Human Studies

Averyanov et al. (2020) — Stem Cells Translational Medicine

The most rigorously designed human clinical trial to date was conducted by Averyanov and colleagues in Russia and published in *Stem Cells Translational Medicine* in 2020 [20]. This was a randomized, placebo-controlled Phase I/II study enrolling 20 patients with rapidly progressive IPF. Patients were assigned to receive either high-cumulative-dose allogeneic bone marrow–derived MSCs (delivered intravenously in multiple infusions over 26 weeks) or matched placebo.

Key findings included: - **No significant adverse events** attributable to MSC therapy were observed, supporting an acceptable safety profile. - At **13 weeks**, the MSC group showed improved **six-minute walk distance (6MWD)** — a measure of functional exercise capacity — compared to placebo. - At **26 weeks**, the MSC group demonstrated improved **DLCO** (diffusing capacity), reflecting better oxygen transfer efficiency. - At **39 weeks**, the MSC group showed improvements in **FVC** (forced vital capacity). By 12 months, the MSC group had a mean FVC *increase* of approximately 7.8%, while the placebo group experienced a mean FVC *decline* of approximately 5.9% — a clinically meaningful difference.

These results are encouraging, but the study was small (20 patients), conducted at a single center, and used bone marrow–derived rather than umbilical cord–derived MSCs. The findings require replication in larger, multicenter trials before firm conclusions can be drawn.

Zhang et al. (2017) — Experimental and Therapeutic Medicine

Zhang and colleagues published a case report of a single patient with severe IPF treated with intravenous human umbilical cord MSC (hUC-MSC) infusions [21]. Over a 12-month follow-up period, the patient demonstrated: - Reduced dependence on long-term oxygen therapy. - Improvements in physical performance and respiratory parameters. - No serious adverse events related to the infusions.

While a single case report cannot establish efficacy, this publication represents one of the earliest direct clinical observations of hUC-MSC administration in an IPF patient and provides important initial safety and feasibility data specifically for umbilical cord–derived cells.

Glassberg and Toonkel (2014) — Respirology

This important early commentary and safety review, published in *Respirology*, assessed the emerging evidence for MSC therapy in IPF and concluded that MSC infusions appeared safe and well-tolerated in early-phase human studies [22]. The authors called for further clinical investigation, noting that the biological rationale was scientifically sound and that safety data from early trials were encouraging. This paper helped establish the foundation for subsequent clinical trial development in this field.

Wharton's Jelly–Specific Preclinical Evidence

While the human clinical trial data for hUC-MSCs in pulmonary fibrosis specifically remains limited to early-phase studies and case reports, the preclinical evidence for Wharton's Jelly–derived MSCs is notably robust:

- **Chu et al. (2019), *Theranostics*:** Demonstrated that human umbilical mesenchymal stem cells (HUMSCs) from Wharton's Jelly, when administered to rats with established bleomycin-induced pulmonary fibrosis, could *reverse* established fibrosis — improving lung architecture, oxygenation, and respiratory parameters, with increased MMP-9 and hyaluronan expression associated with collagen degradation and alveolar regeneration [17].
- **Chu et al. (2020), *Stem Cell Research & Therapy*:** In a direct head-to-head comparison in a rat model, HUMSC transplantation produced significantly better recovery of lung volume, lung pathology scores, oxygenation, and respiratory rates than treatment with either nintedanib or pirfenidone alone [18].
- **Chu et al. (2023), *International Journal of Molecular Sciences*:** Reported that Wharton's Jelly–derived MSCs were more effective than adipose-derived MSCs for functional and histologic recovery in a bleomycin model, and identified specific molecular mechanisms — including MMP-9 upregulation and TLR-4 expression in alveolar epithelium — associated with their superior efficacy [23].

These preclinical findings provide a mechanistically coherent scientific rationale for the clinical investigation of hUC-MSCs in pulmonary fibrosis and support the translational potential of Wharton's Jelly–derived cells specifically.

Ongoing Clinical Trials

Several clinical trials are actively investigating MSC-based therapies for pulmonary fibrosis. Key registered studies include:

- **NCT05468502 (Phase I, Shanghai Life Science & Technology):** A completed Phase I trial of human umbilical cord MSC injection in patients with idiopathic pulmonary fibrosis (17 patients enrolled). Results from this trial are anticipated and will contribute important safety and preliminary efficacy data for hUC-MSCs specifically.
- **NCT05016817 (Phase I, The Foundation for Orthopaedics and Regenerative Medicine):** A currently recruiting Phase I trial evaluating the safety of allogeneic adult umbilical cord–derived MSC intravenous infusion (AlloRx) in patients with IPF (target enrollment: 20 patients).
- **NCT07515066 (Phase I):** A planned trial of nebulized 3D-cultured human placental MSC-derived extracellular vesicles for IPF — reflecting growing interest in exosome-based approaches.

- **NCT02277145 (Completed, Jianwu Dai):** A completed Phase I trial of clinical-grade umbilical cord MSCs in patients with radiation-induced pulmonary fibrosis (10 patients enrolled), providing safety data in a fibrosis population.
- **NCT02013700 (AETHER Trial, Joshua M. Hare, University of Miami):** A Phase I trial of allogeneic human MSCs in IPF patients, which was terminated early after enrolling 9 patients. Lessons from this trial have informed subsequent study designs.

The overall clinical trial landscape reflects an active and growing field, with early-phase safety studies now giving way to larger efficacy-focused trials. The field is at an important inflection point.

Interpreting the Evidence: What It Means for Patients

It is important to approach this evidence with both optimism and appropriate scientific caution:

- **The safety signal is encouraging.** Across multiple early-phase trials and case reports, MSC infusions — including hUC-MSC infusions — have generally been well tolerated, with no consistent signals of serious MSC-related adverse events in pulmonary fibrosis populations.
- **The functional signals are promising but preliminary.** The improvements in FVC, DLCO, and 6MWD observed in the Averyanov trial are meaningful, but replication in larger studies is essential before these findings can be considered established.
- **The preclinical evidence for Wharton's Jelly MSCs is particularly strong.** The consistent demonstration of antifibrotic, pro-regenerative effects in multiple independent animal studies — including direct comparisons with approved antifibrotic drugs — provides a credible biological foundation for clinical investigation.
- **More research is needed.** Larger, multicenter, randomized controlled trials with longer follow-up are needed to determine the magnitude, durability, and predictors of clinical benefit. Response variability between individuals is expected and not fully understood.

5. Safety Profile: What the Research Shows

General Safety Observations in MSC Therapy

Across the broader MSC clinical trial literature — spanning multiple diseases and thousands of patients worldwide — MSC infusions have generally demonstrated a favorable short-term safety profile. Serious adverse events directly attributable to MSC administration are uncommon, and no consistent pattern of MSC-driven tumor formation, ectopic tissue growth, or immune-mediated toxicity has emerged in well-conducted studies [22, 24].

Safety in Pulmonary Fibrosis–Specific Studies

In the context of pulmonary fibrosis specifically:

- The **Averyanov et al. (2020)** randomized controlled trial reported no significant adverse events attributable to MSC therapy across 20 patients receiving high-cumulative-dose intravenous MSC infusions over 26 weeks [20].
- The **Zhang et al. (2017)** case report of hUC-MSC administration in a severe IPF patient reported no infusion-related serious adverse events over 12 months of follow-up [21].
- Early-phase safety reviews and small cohort studies have consistently reported acceptable tolerability, with the most commonly noted effects being mild and transient infusion-related reactions (such as low-grade fever or mild chills) that resolved without intervention [22].
- Importantly, no studies to date have reported evidence of MSC therapy *worsening* pulmonary fibrosis or accelerating disease progression.

Route-Specific Considerations

The predominant route of administration in pulmonary fibrosis trials has been **intravenous (IV) infusion**, which allows systemic delivery and potential homing of cells to sites of active lung inflammation and injury. IV administration is generally well tolerated, though as with any IV infusion, standard monitoring for infusion reactions is maintained throughout the procedure.

Emerging research is also exploring **nebulized delivery of MSC-derived extracellular vesicles** — a potentially advantageous route that delivers bioactive cargo directly to the lung parenchyma. Early data on this approach are being generated in ongoing trials.

Honest Acknowledgment of Uncertainty

While the available safety data are reassuring, it is important to be transparent about the limitations of the current evidence base:

- **Studies are small and follow-up periods are relatively short.** Long-term safety data (beyond 12–24 months) in pulmonary fibrosis populations are limited.
- **Standardization of cell preparations varies** across studies, making direct comparisons difficult.
- **Individual patient factors** — including disease severity, comorbidities, and concurrent medications — may influence both safety and tolerability.

At Auragens, patient safety is the foundational priority of every treatment we offer. Our AABB-accredited processes, rigorous donor screening, standardized cell preparation, and comprehensive clinical monitoring are all designed to minimize risk and maximize the integrity of the cellular product you receive. Every patient is individually evaluated, and treatment decisions are made transparently and collaboratively.

6. What to Expect Next at Auragens

A Personalized, Evidence-Based Consultation

If you are considering exploring hUC-MSC therapy at Auragens, your journey begins with a comprehensive, individualized consultation with our medical team. We believe that informed patients make better decisions — and that the consultation process is as important as any treatment.

Medical history and records review. Our team will carefully review your complete medical history, including your pulmonary fibrosis diagnosis, current medications, pulmonary function test results, imaging reports, and any prior treatments. Understanding where you are in your disease course is essential to any meaningful discussion of therapeutic options.

Goals and expectations discussion. We will take time to understand what matters most to you — whether that is preserving current function, reducing breathlessness, improving exercise tolerance, or simply understanding what options exist. We will be transparent about what the current evidence does and does not support, and we will not overstate the likelihood or magnitude of benefit.

Treatment plan review. Based on your individual profile and goals, our team will outline a proposed treatment approach — including the number and timing of infusions, the administration route, monitoring protocols, and any recommended adjunctive measures. We will explain the scientific rationale for each element of the plan.

Realistic expectations. We are committed to honesty. We will clearly communicate that hUC-MSC therapy for pulmonary fibrosis is investigational, that responses vary between individuals, and that we cannot guarantee specific outcomes. We will also discuss how we will monitor your response over time.

Logistics and support. Our team will walk you through all practical aspects of the treatment experience — including travel arrangements (for patients coming to our Panama or US facilities), accommodation, the treatment schedule, and follow-up communication. We want the process to be as smooth and supported as possible.

Ongoing communication. Our relationship with patients does not end when treatment is completed. We maintain follow-up communication, track outcomes, and remain available to answer questions as they arise.

7. Next Steps

Who May Want to Explore a Consultation

A consultation with the Auragens medical team may be appropriate if you:

- Have a confirmed diagnosis of idiopathic pulmonary fibrosis or another form of progressive pulmonary fibrosis.
- Are currently on antifibrotic therapy (pirfenidone or nintedanib) but are experiencing ongoing decline or significant side effects.
- Are seeking to understand all available options, including investigational approaches, as part of an informed decision-making process.
- Have been evaluated for lung transplantation but are not currently eligible, or are seeking complementary approaches while awaiting transplantation.
- Are a caregiver or family member seeking information on behalf of a patient with pulmonary fibrosis.

Questions to Consider Before Your Consultation

Taking time to reflect on the following questions can help you get the most from a consultation:

- What are my most significant symptoms, and how are they affecting my daily life?
- What are my current pulmonary function test results, and how have they changed over the past year?
- What medications am I currently taking, and how well am I tolerating them?
- What are my primary goals for any new therapy — symptom relief, slowing progression, improving function, or another priority?
- What questions do I most want answered about stem cell therapy?
- Have I discussed this option with my pulmonologist or specialist, and what is their perspective?

The Importance of Your Specialist Team

We strongly encourage all patients considering any new or investigational therapy to discuss it openly with their current pulmonologist or specialist. hUC-MSC therapy at Auragens is not intended to replace standard-of-care treatment. We work collaboratively with referring physicians and encourage transparent communication between all members of your care team. Your specialist's knowledge of your complete medical history is invaluable and should inform any decision about additional therapies.

To learn more or to schedule a consultation, please visit auragens.com or contact our patient care team directly.

A Message of Hope

Living with pulmonary fibrosis requires courage — the courage to face an uncertain prognosis, to adapt to changing physical limitations, and to continue seeking answers even when the path forward is not always clear.

Science is not standing still. The research into mesenchymal stem cell therapy for pulmonary fibrosis reflects a genuine and growing scientific commitment to finding better answers for patients who need them. The early clinical data are encouraging. The preclinical evidence for Wharton's Jelly–derived MSCs is among the most compelling in the regenerative medicine field. And the biological rationale — addressing inflammation, fibrosis, oxidative stress, and tissue repair simultaneously — is scientifically coherent and increasingly well-supported.

We do not promise miracles. We do not claim to have all the answers. What we do offer is a commitment to rigorous science, honest communication, the highest standards of cellular quality and safety, and genuine care for every patient who walks through our doors.

Regenerative medicine is still writing its story in pulmonary fibrosis. You may be part of that story — not as a passive recipient of care, but as an informed, empowered participant in your own health journey and, in some ways, in the advancement of science itself.

There is reason for hope. And at Auragens, we are honored to walk alongside you.

The Auragens Patient Care Team

References

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