Understanding Stem Cell Therapy for Rheumatoid Arthritis

A Patient Guide from Auragens

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

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Welcome

Thank you for taking the time to learn more about stem cell therapy for rheumatoid arthritis. At Auragens, we understand that living with RA means navigating daily pain, stiffness, and uncertainty about the future. You may have tried multiple medications, adjusted your lifestyle, and still found yourself searching for better answers.

This guide is designed to help you understand how human umbilical cord-derived mesenchymal stem/stromal cells (hUC-MSCs) from Wharton's Jelly may offer a new approach to managing your condition. We will walk you through the science, the clinical evidence, what makes Auragens different, and what you can realistically expect.

Our goal is to empower you with knowledge so that you and your healthcare team can make the most informed decision possible about your care.

1. Understanding Rheumatoid Arthritis and Current Treatment Limitations

What Is Rheumatoid Arthritis?

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease in which your immune system mistakenly attacks the lining of your joints—the synovium. This persistent inflammation leads to painful swelling, progressive joint damage, and the formation of abnormal tissue called pannus that can erode cartilage and bone [1].

RA is driven by dysregulated immune cells, particularly T-cells, and inflammatory molecules called cytokines—especially tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). Another key player is the fibroblast-like synoviocyte (FLS), a type of cell in the joint lining that becomes overactive and contributes to inflammation and tissue destruction [1].

Common symptoms include:

- Joint pain and tenderness
- Morning stiffness lasting 30 minutes or longer
- Swelling in multiple joints, often symmetrically
- Reduced range of motion and grip strength
- Fatigue and a general feeling of being unwell

Over time, RA can lead to permanent joint deformity, functional impairment, and a significant impact on quality of life [1].

Current Treatments and Their Limitations

Modern rheumatology has made great strides. Standard therapies include:

- **Conventional DMARDs** (disease-modifying antirheumatic drugs) such as methotrexate and hydroxychloroquine
- **Biologic agents** that target specific immune pathways, including TNF inhibitors, IL-6 inhibitors, and rituximab
- **JAK inhibitors** (Janus kinase inhibitors), a newer class of targeted small-molecule drugs

These treatments have improved outcomes for many patients. However, important gaps remain [2]:

- **Incomplete response:** A significant subset of patients do not achieve adequate disease control, even with combination therapy.
- **Drug intolerance and side effects:** Some patients experience adverse effects or must discontinue treatment due to infections, liver toxicity, or other complications related to immunosuppression.
- **Long-term medication burden:** RA typically requires lifelong therapy, and some patients develop resistance or lose response over time.
- **Limited regenerative capacity:** Current drugs primarily suppress inflammation but do not reliably regenerate damaged cartilage or repair eroded bone.

For patients who have not found sufficient relief—or who are seeking complementary approaches that address the underlying immune dysfunction—regenerative medicine offers a new frontier.

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

The Source: Umbilical Cord Tissue

Human umbilical cord-derived mesenchymal stem/stromal cells (hUC-MSCs) are specialized cells obtained from Wharton's Jelly, the soft connective tissue that surrounds and protects the blood vessels inside the umbilical cord. After a healthy, full-term birth, the umbilical cord—which would otherwise be discarded—is donated with informed maternal consent and processed under strict laboratory conditions.

What Makes These Cells Special?

Mesenchymal stem/stromal cells are not the same as embryonic stem cells. They are adult-type stem cells with unique properties:

- **Immunomodulatory:** They can "sense" inflammation and actively regulate immune responses, helping to calm overactive immune cells [3], [5].

- **Anti-inflammatory:** They secrete molecules that reduce harmful inflammation and promote tissue repair [1], [4].
- **Hypoimmunogenic:** hUC-MSCs express very low levels of immune-recognition molecules (such as HLA-DR), which means they are less likely to be rejected by the recipient's immune system. This makes them suitable for allogeneic (donor-to-patient) use without the need for perfect tissue matching [5], [7].
- **Readily available and ethically sourced:** Umbilical cord tissue is abundant, non-invasive to collect, and poses no ethical concerns [7].

How Do They Work?

hUC-MSCs do not simply "replace" damaged cells. Instead, they work primarily through **paracrine signaling**—releasing a rich mixture of growth factors, cytokines, and tiny communication packages called extracellular vesicles (EVs) or exosomes. These secreted factors interact with your immune cells and joint tissues to:

- Modulate the behavior of T-cells, B-cells, and other immune players
- Shift the balance from inflammation to regulation
- Protect joint tissues from further damage
- Support the body's own repair processes [5], [6]

In essence, hUC-MSCs act as "biological regulators," helping to restore balance in a system that has gone awry.

🏆 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 Biotechnologies) 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 Rheumatoid Arthritis

The therapeutic potential of hUC-MSCs in RA is rooted in their ability to address multiple aspects of the disease simultaneously. Below, we explain the key mechanisms supported by preclinical and clinical research.

3.1 Immunomodulation and Immune Rebalancing

RA is fundamentally an immune system disorder. In RA, certain immune cells—especially T-cells—become overactivated and attack your own tissues.

hUC-MSCs have a remarkable ability to "sense" this inflammatory environment and respond by releasing molecules that suppress overactive immune cells. Key mediators include [1], [3], [5]:

- **Indoleamine 2,3-dioxygenase (IDO):** An enzyme that depletes amino acids needed for T-cell activation
- **Prostaglandin E2 (PGE2):** A lipid mediator that dampens immune responses
- **Transforming growth factor-beta 1 (TGF-β1):** A cytokine that promotes immune tolerance

- **Nitric oxide (NO):** A signaling molecule with immunosuppressive effects
- **Interleukin-10 (IL-10):** A potent anti-inflammatory cytokine

Together, these factors help shift the immune environment away from autoimmune attack and toward a more balanced, regulated state.

3.2 Anti-Inflammatory Effects and Cytokine Regulation

Inflammation in RA is driven by proinflammatory cytokines—particularly TNF-α and IL-6—which perpetuate joint damage and systemic symptoms.

Clinical studies have shown that hUC-MSC infusions can significantly reduce levels of TNF-α and IL-6 in the bloodstream, while increasing anti-inflammatory IL-10 [1], [4]. This cytokine shift is associated with:

- Reduced joint swelling and pain
- Lower levels of inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)
- Decreased autoantibody levels (rheumatoid factor and anti-CCP antibodies) [1], [2]

hUC-MSCs also inhibit the proliferation and invasiveness of fibroblast-like synoviocytes (FLS)—the cells that contribute to pannus formation and joint erosion—thereby reducing one of the key drivers of structural damage [1].

3.3 Regulatory T-Cell (Treg) Support

A hallmark of RA is an imbalance between regulatory T-cells (Tregs), which suppress immune responses, and pro-inflammatory T-helper 17 (Th17) cells, which promote inflammation. In RA, this balance is tipped toward Th17, fueling autoimmunity.

hUC-MSCs promote the expansion of CD4+FoxP3+ regulatory T-cells and induce a state of T-cell hyporesponsiveness, helping to restore the Treg/Th17 balance [1], [4], [6]. This rebalancing is critical for long-term immune regulation and may help prevent disease flares.

3.4 Synovial Tissue Protection

The synovium—the lining of your joints—is ground zero for RA inflammation. By inhibiting FLS invasiveness and reducing the secretion of inflammatory mediators, hUC-MSCs may help protect synovial tissue from further damage [1], [4].

In animal models of arthritis, MSC therapy has been shown to slow disease progression, reduce joint swelling, and promote histologic signs of tissue repair—suggesting that these cells may not only calm inflammation but also support the body's own healing processes [4].

3.5 Paracrine and Exosome Signaling

Much of the therapeutic benefit of hUC-MSCs appears to be mediated not by the cells themselves, but by what they secrete: a complex mixture of proteins, growth factors, and extracellular vesicles (EVs), including exosomes [5], [6].

These EVs are tiny membrane-bound packages that carry regulatory RNAs, proteins, and lipids. They can travel to distant sites, enter immune cells and joint tissues, and reprogram cellular behavior—reducing inflammation, modulating immune responses, and promoting repair [5], [6].

This paracrine mechanism is one reason why even a single infusion of hUC-MSCs can have effects that last for months: the cells release their therapeutic cargo, which continues to work long after the cells themselves may have cleared from the body.

Important note: The therapeutic potency of MSCs depends on both the intrinsic quality of the cells (their proliferative and migratory fitness) and the host microenvironment. Research has shown that "priming" MSCs with signals such as interferon-gamma (IFN-γ) can enhance their immunoregulatory effects, and that pathways like CD151/PI3K/AKT influence MSC performance [8], [9]. At Auragens, we stay at the forefront of these advances to optimize the therapeutic potential of every dose.

4. Clinical Evidence and Research Findings

While hUC-MSC therapy for RA is still investigational, early clinical studies have provided encouraging signals of safety and efficacy. Below is a summary of key findings from peer-reviewed research.

Wang et al. (2013): Safety and Efficacy in Active RA

In a cohort of patients with active rheumatoid arthritis who received intravenous hUC-MSC infusions, researchers reported [1]:

- **Significant reductions** in Disease Activity Score-28 (DAS28), a composite measure of disease severity
- **Decreased inflammatory markers:** ESR, CRP, rheumatoid factor (RF), and anti-CCP antibodies
- **Lower proinflammatory cytokines:** TNF-α and IL-6 levels dropped significantly
- **Increased regulatory T-cells:** Peripheral blood showed expansion of CD4+CD25+FoxP3+ Tregs
- **Duration of benefit:** Clinical improvement lasted 3–6 months after a single course of infusions; repeat infusions augmented and extended the effect

- **Safety:** No serious infusion-related adverse events were reported

Wang et al. (2019): Longer-Term Follow-Up (Phase I/II)

A prospective Phase I/II study with follow-up extending from 1 to 3 years found [2]:

- **Persistent improvements** in DAS28 and Health Assessment Questionnaire (HAQ) scores, indicating sustained reductions in disease activity and functional impairment
- **Sustained reductions** in inflammatory serologies (CRP, ESR, RF, anti-CCP)
- **Good tolerability:** Routine laboratory tests, liver function, and renal function remained normal throughout the follow-up period

He et al. (2020): Combination with IFN-γ Priming

A randomized Phase 1/2 study explored whether "priming" the host immune environment with interferon-gamma (IFN-γ) could enhance MSC efficacy [3]:

- Patients who received hUC-MSC transplantation **combined with IFN-γ treatment** had **markedly higher ACR20 response rates** (a standard measure of clinical improvement) compared to those who received MSCs alone
- This finding supports the concept that the host microenvironment plays a critical role in optimizing MSC therapeutic effects

Additional Supporting Research

- **Kannan et al. (2022)** characterized pooled Wharton's Jelly MSCs and demonstrated their immunomodulatory potential relevant to RA treatment [4].
- **Arrigoni et al. (2020)** reviewed the role of UC-MSC secretome and extracellular vesicles in arthritic diseases, reinforcing the importance of paracrine mechanisms [6].
- **Paladino et al. (2019)** reviewed the immunomodulatory potential of Wharton's Jelly MSCs, highlighting their suitability for allogeneic therapy [5].
- **Mebarki et al. (2021)** discussed UC-MSC manufacturing and GMP (Good Manufacturing Practice) standardization challenges, underscoring the importance of quality control [7].

Important Limitations of the Current Evidence

It is essential to be transparent about what we know—and what we don't yet know:

- **Small and heterogeneous cohorts:** Most published studies involve relatively small numbers of patients with variable disease characteristics.
- **Variable cell doses and manufacturing:** Different studies use different cell doses, infusion schedules, and manufacturing protocols, making direct comparisons difficult.

- **Combination with background DMARDs:** Many patients in these studies continued their conventional medications, which makes it challenging to isolate the effect of MSC therapy alone.
- **Short and uneven follow-up:** Long-term data (beyond 3 years) are limited.
- **Lack of large placebo-controlled Phase III trials:** The gold standard for proving efficacy—large, randomized, double-blind, placebo-controlled trials—has not yet been completed for hUC-MSC therapy in RA.

At Auragens, we are committed to advancing the science through rigorous clinical research and transparent communication. We will continue to update you as new evidence emerges

5. Safety Profile: What the Research Shows

Safety is our top priority. Based on the published clinical trials in RA patients who received intravenous hUC-MSC infusions, the safety profile has been reassuring [1], [2]:

- **No serious infusion-related adverse events** were reported in the Wang et al. (2013) and Wang et al. (2019) cohorts.
- **Normal laboratory parameters:** Routine blood tests, liver function, and kidney function remained within normal ranges during follow-up periods.
- **Hypoimmunogenic properties:** Wharton's Jelly MSCs express very low levels of HLA-DR (a molecule involved in immune recognition), which reduces the risk of immune rejection and makes them suitable for allogeneic (donor-to-patient) use [5], [7].

What We Don't Yet Know

While early safety data are encouraging, it is important to acknowledge:

- **Systematic large-scale safety data from Phase III trials are not yet available.** The therapy remains investigational.
- **Long-term safety beyond 3 years** has not been extensively studied in RA populations.
- **Individual variability:** As with any medical treatment, individual responses and tolerability may vary.

At Auragens, every patient undergoes a thorough medical evaluation before treatment, and we maintain close monitoring and follow-up to ensure your safety and well-being.

6. What to Expect Next at Auragens

If you are considering hUC-MSC therapy at Auragens, here is an overview of the process:

Step 1: Comprehensive Medical Evaluation

Your journey begins with a detailed consultation with our medical team. We will review:

- Your complete medical history and RA disease course
- Current and past medications, including DMARDs and biologics
- Laboratory results, imaging studies, and disease activity measures
- Your treatment goals and expectations

This evaluation helps us determine whether you are a suitable candidate for hUC-MSC therapy and allows us to tailor the treatment plan to your individual needs.

Step 2: Treatment Planning

If you are a candidate, we will work with you to develop a personalized treatment protocol, which may include:

- The number and timing of hUC-MSC infusions
- Coordination with your rheumatologist and any adjustments to your current medications
- Pre-treatment laboratory testing and baseline assessments

7. Next Steps

If you are interested in learning more about whether hUC-MSC therapy is right for you, we invite you to take the following steps:

1. **Schedule a consultation** with the Auragens medical team. You can reach us through our website at **auragens.com** or by contacting our patient care coordinators.
2. **Gather your medical records**, including recent laboratory results, imaging studies, and a summary of your current medications and treatment history.
3. **Discuss with your rheumatologist.** We encourage open communication with your current healthcare providers. Regenerative medicine works best as part of a coordinated, multidisciplinary approach.

Ask questions. We are here to provide you with clear, honest answers about what hUC-MSC therapy can—and cannot—do for your condition.

A Message of Hope

Living with rheumatoid arthritis is not easy. The pain, stiffness, and fatigue can be overwhelming, and the search for effective treatment can feel like a long and frustrating journey. But you are not alone, and there is reason for hope.

Regenerative medicine represents a new frontier—one that seeks not just to suppress symptoms, but to address the underlying immune dysfunction and support your body's own capacity for healing. While hUC-MSC therapy is still investigational and not a cure, the early clinical evidence suggests it may offer meaningful benefits for some patients, particularly those who have not found adequate relief with conventional therapies.

At Auragens, we are committed to advancing this science with integrity, transparency, and compassion. We combine cutting-edge cellular therapy with the highest standards of quality and safety, because we believe you deserve nothing less.

Whether or not hUC-MSC therapy is the right choice for you, we are here to support you, answer your questions, and walk alongside you on your path toward better health.

Thank you for considering Auragens. We look forward to the opportunity to serve you.

The Auragens Patient Care Team

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Disclaimer

This educational document is provided for informational purposes only and does not constitute medical advice, diagnosis, or treatment. The information presented is based on current scientific research and clinical evidence, but individual results may vary. hUC-MSC therapy for rheumatoid arthritis is investigational and not approved by the FDA as a standard treatment for this condition.

Please consult with your physician and the Auragens medical team to determine if UC-MSC therapy is appropriate for your specific situation. Do not discontinue or modify your current medications without guidance from your healthcare provider.

Auragens is committed to transparency, evidence-based practice, and the highest standards of patient care. For more information, visit **auragens.com** or contact our patient care team.