



Body Fluid-Derived Stem Cells: Myth, Mystery, or the Next Frontier in Regenerative Medicine?

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ABSTRACT

For decades, the prevailing paradigm of stem cell biology emphasized specialized tissue niches as the principal reservoirs of adult stem and progenitor cells, although clinically important hematopoietic stem cell populations from peripheral blood and umbilical cord blood have long been recognized and successfully utilized. Accumulating evidence now demonstrates that additional stem and progenitor cell populations can be isolated from a broad spectrum of human body fluids, such as urine, menstrual blood, peripheral blood, umbilical cord blood, amniotic fluid, synovial fluid, breast milk, and cerebrospinal fluid. The central question in regenerative medicine has consequently shifted from verifying the existence of these cells to deciphering their biological origins, physiological functions, and ultimate translational potential. Body fluid-derived stem cells (BFSCs) represent an extraordinarily accessible, non-invasively obtained source of regenerative biological material, yet significant questions remain regarding their cellular turnover dynamics, heterogeneity, and therapeutic scalability. Moreover, major challenges remain regarding standardization, lineage tracing, manufacturing reproducibility, and regulatory approval for clinical translation. This manuscript systematically reviews the origin, biological landscape, translational advantages, current preclinical applications, and future trajectories of BFSCs, framing them as a candidate paradigm shift in regenerative and precision medicine.

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Introduction & Biological Reality: Are BFSCs Real?

Beyond the well-established hematopoietic stem cell populations found in peripheral blood and umbilical cord blood, the concept of isolating functional non-hematopoietic stem/progenitor cells from other physiological fluids was initially met with substantial skepticism, often viewed as an artifact of cell debris or transient, terminally differentiated shedding. Today, independent studies from multiple laboratories have demonstrated that stem and progenitor cell populations can be reproducibly isolated from diverse human body fluids. Isolated BFSCs routinely display classical hallmarks of multipotent adult stem cells, including robust self-renewal capacity, single-cell colony formation, multilineage differentiation potential across mesodermal and non-mesodermal lineages, specific cell-surface marker signatures, immunomodulatory properties, and demonstrated tissue-repair potential in preclinical injury models.

Rather than constituting a singular, homogeneous cell class, BFSCs represent a highly heterogeneous spectrum of progenitor populations. Viewing BFSCs as a uniform therapeutic entity oversimplifies their complex biology; each fluid harbors unique sub-pop-

ulations with distinct functional behaviors and transcriptional profiles tailored to, or reflective of, their anatomical source.

Ontogeny and the Physiological Surveillance Hypothesis

A longstanding question surrounding BFSC biology concerns their precise developmental and anatomical origins. Current evidence points toward three non-mutually exclusive pathways:

- 1. Tissue-Shed Progenitors:** Cells detaching directly from the anatomical niches of surrounding organ systems. For example, urine-derived stem cells (USCs) predominantly originate from the nephron, urinary tract, and parietal/glomerular epithelial regions; menstrual blood-derived stem cells (MenSCs) stem from the functional layer of the endometrium; and breast milk-derived stem cells likely arise from the mammary epithelium during active lactation.
- 2. Circulating Systemic Progenitors:** Populations originating from distal systemic niches, such as the bone marrow or perivascular networks, that transit through the vascular

or lymphatic systems and enter body fluid compartments under baseline or pathological conditions.

3. The Physiological Surveillance Hypothesis:

Beyond passive shedding, a provocative but currently unproven hypothesis proposes that the continuous presence of stem/progenitor cells in physiological fluids may reflect broader biological processes involved in tissue surveillance, interorgan communication, or systemic maintenance of homeostasis. Indirect observations supporting further investigation include evidence of stem/progenitor cell trafficking, injury-associated mobilization of progenitor populations, and the potent paracrine activities of many body fluid-derived stem/progenitor cells. However, direct evidence demonstrating that these cells function as an organized systemic regenerative surveillance network remains limited. Despite its conceptual appeal, the physiological surveillance hypothesis remains largely speculative. Definitive validation will require lineage-tracing studies, single-cell multiomic profiling, and longitudinal analyses capable of determining whether BFSCs actively participate in tissue monitoring and repair or merely represent byproducts of normal cellular turnover.

The Landscape of Human Body Fluids: Permissiveness and Abundance

Stem cell density is not uniformly distributed across biological fluids. As a conceptual framework for discussion, human body fluids may be provisionally categorized into a three-tiered spectrum according to currently reported evidence, including reproducibility of stem/progenitor-cell isolation, relative abundance, expansion potential, and functional characterization. This classification is based on published reports describing reproducible isolation of progenitor populations from urine, menstrual blood, amniotic fluid, cord blood, peripheral blood, breast milk, cerebrospinal fluid, and synovial fluid [1-3].

Proposed classification criteria include: (1) reproducible isolation across independent studies and laboratories; (2) frequency or abundance of recoverable progenitor cells; (3) demonstrated self-renewal and differentiation capacity; and (4) availability of functional validation in preclinical models. These categories should be considered dynamic and subject to revision as additional quantitative and comparative studies become available.

- **BFSC-Enriched Fluids:** Consistently yield high concentrations of robust progenitor cells with reliable isolation rates. Key examples include urine, menstrual blood, amniotic fluid, and umbilical cord blood.

- **BFSC-Permissive Fluids:** Contain rare, transient progenitor populations primarily detectable during specific physiological states or following acute tissue injury, such as peripheral blood, synovial fluid, breast milk, and cerebrospinal fluid.

- **Stem Cell-Poor Fluids:** Liquids where compelling, reproducible evidence of functional stem cell isolation remains minimal or absent.

Despite established isolation protocols, fundamental quantitative metrics remain undefined. Key unknowns include the precise daily cell-shedding kinetics per individual, how biological age and underlying disease states alter shed cell viability, and the extent to which acute physiological stress accelerates progenitor release. Creating a comprehensive, quantitative atlas mapping BFSC abundance, molecular signatures, and dynamic shifts across the human lifespan remains an essential objective for the field.

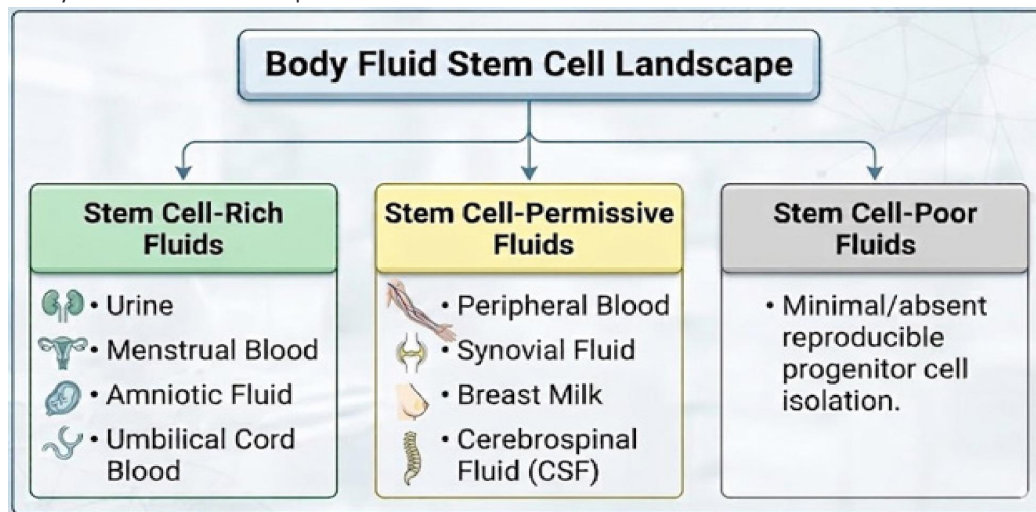
Biological Significance vs. Clinical Reality

The discovery of BFSCs carries profound biological significance, fundamentally expanding stem cell biology beyond the traditional concept of static, solid-tissue niches. It prompts renewed investigation into physiological cell trafficking, systemic homeostasis, and potential roles in tissue maintenance and repair. However, biological presence does not automatically equate to immediate clinical utility. Translating BFSCs into standardized cell therapies presents technical and regulatory challenges (Table 1):

Table 1. BFSC-based cell therapies

Operational Parameter	Traditional Tissue-derived Stem Cells (e.g., BM-MSCs)	Body Fluid-Derived Stem Cells (BFSCs)
Harvest Method	Invasive biopsy or aspiration; requires surgical suite	Non-invasive or minimally invasive; serial sampling feasible
Baseline Abundance	Moderate to high per tissue sample	Extremely low; highly variable per harvest
Phenotypic Uniformity	Moderately standardized across protocols	Heterogeneous; subject to donor hydration, age, and health status
Expansion Dynamics	Well-characterized baseline kinetics	Highly variable; risk of early senescence during scaling
Cost & Patient Burden	High operational overhead; elevated patient discomfort	Low harvest cost; exceptional patient compliance
Regulatory Readiness	Several established pathways	Emerging regulatory framework

Figure 1. Body fluid stem cell landscape.



To transition BFSCs from experimental biological phenomena into scalable cell therapies, standard operating procedures must be established to address population heterogeneity, overcome finite donor-to-donor expansion limits, and ensure long-term genetic stability post-expansion.

Translational Advantages and Current Clinical Applications

One of the most compelling advantages of BFSCs is their exceptional accessibility and translational flexibility. Harvesting cells from fluids like urine or menstrual blood eliminates invasive surgical procedures, drastically reducing patient discomfort, clinical overhead, and operative risks. Furthermore, non-invasive collection enables painless serial sampling over time, providing a scalable source of autologous cells for personalized medicine and patient-specific disease modeling without the ethical complexities associated with embryonic tissues. Additionally, many BFSC populations exhibit

potent paracrine and immunomodulatory profiles, secreting rich secretomes and extracellular vesicles packed with proangiogenic, anti-inflammatory, and neuroprotective factors. Preclinical and early-phase clinical investigations demonstrate therapeutic potential across several medical domains:

- **Genitourinary Regeneration:** Application of USCs in lower urinary tract reconstruction, stress urinary incontinence, erectile dysfunction, and acute/chronic kidney damage models.
- **Ocular Surface Repair:** Utilization of progenitor populations for corneal epithelial reconstruction and limbal stem cell deficiency management.
- **Musculoskeletal and Neurological Disorders:** Cartilage and bone lesion repair using synovial or menstrual blood stem cells, alongside neuroprotective secretome therapies targeting central nervous system injuries.

- **Disease Modeling & Exosome Therapeutics:** Development of patient-specific cell platforms for high-throughput drug screening and the deployment of BFSC-derived extracellular vesicles as cell-free biologics.

Importantly, for many BFSC populations, their *in vivo* physiological function, cellular origin, and long-term therapeutic value remain incompletely understood.

Future Trajectories and Strategic Priorities

To fully leverage body fluids as a novel class of therapeutic biological materials over the coming decade, scientific efforts should align around five overarching goals:

1. **The Human BFSC Atlas:** Establishing a high-resolution, multiomic atlas mapping every progenitor population isolated across human biological fluids in healthy and diseased states.
2. **Single-Cell Lineage Tracing:** Utilizing advanced lineage tracking and spatial genomics to pinpoint the exact physiological niches and anatomical origins of each fluid-derived population.
3. **Cell-Free Biologics:** Accelerating the development of standardized, fluid-derived exosome and secretome formulations to achieve therapeutic paracrine effects without live-cell transplantation risks.
4. **Precision Regenerative Therapeutics:** Engineering autologous, patient-derived cell formulations harvested on demand from routinely shed body fluids.
5. **Living Cellular Biomarkers for Precision Diagnostics:** Developing diagnostic assays that utilize the quantity, molecular state, and secretome changes of BFSCs as dynamic biomarkers for early-stage oncogenesis, renal dysfunction, neurodegeneration, and systemic aging.
6. **Artificial Intelligence–Driven BFSC Analytics:** Integrating machine learning and multiomic datasets to identify BFSC signatures predictive of disease progression, therapeutic responsiveness, and regenerative capacity.

Conclusion

The discovery of body fluid-derived stem cells expands the boundaries of stem cell biology from

solid tissue niches to accessible physiological fluids. The central question is no longer whether BFSCs exist, but rather how these cells contribute to physiology, disease, and tissue regeneration, and whether they can be reliably translated into safe and effective therapies.

Their exceptional accessibility, autologous nature, and strong paracrine profiles position them as a flexible platform for regenerative and precision medicine.

As standardized isolation protocols, lineage-tracing studies, and advanced molecular analyses mature over the coming decade, research will help determine whether body fluid-derived stem/progenitor cells play meaningful physiological roles and whether these accessible biological fluids represent a clinically useful reservoir of regenerative cells. Much like hematopoietic stem cells transformed transplantation medicine following their discovery in blood, BFSCs may ultimately redefine how regenerative cells are identified, collected, and deployed for personalized medicine.

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