FOR IMMEDIATE RELEASE
Orthomolecular Medicine News Service, May 22, 2026

Why Cell Therapy Outcomes Vary: The Role of Host System Biology

by Richard Z. Cheng, MD, PhD
Editor-in-Chief, Orthomolecular Medicine News Service (OMNS)

Editor's Note:

This article is the first in a three-part series exploring a central question in regenerative medicine:

Why do patients receiving the same cell-based therapy often experience markedly different outcomes?

This series examines that question through a systems-level lens, focusing on the role of host biology, regulatory networks, and clinical context in shaping therapeutic response.

Subsequent articles will explore the underlying mechanisms-particularly the Insulin-Cortisol-Vitamin C (ICV) axis-and outline a practical framework for system-level optimization to improve clinical outcomes.

Introduction

Cell-based therapies-particularly stem cell interventions-are among the most promising frontiers in modern medicine. From metabolic diseases to reproductive disorders, they offer the potential not only to manage disease, but to restore function.

Yet in real-world clinical practice, one observation consistently emerges:

Outcomes vary significantly between patients.

Patients receiving similar cell products under comparable protocols often experience markedly different results. Some show meaningful improvement, while others achieve only modest benefit or none at all.

Clinical studies in both metabolic and reproductive medicine have reported heterogeneous outcomes following cell-based interventions, even under controlled conditions [1-5]. These observations suggest that factors beyond cell quality and delivery technique are at play.

A Missing Variable: The Host System

Across conditions such as Type 2 diabetes mellitus (T2DM) and premature ovarian insufficiency (POI), a consistent pattern emerges: cells do not function in isolation.

The same intervention may produce different outcomes in different biological environments.

This points to a critical-and likely dominant-determinant: the host system into which the therapy is introduced [6].

Cells do not function in isolation; their survival, integration, and activity are governed by the metabolic, endocrine, and biochemical state of the host.

From Cell-Centric to System-Centric Thinking

Modern regenerative medicine is largely **cell-centric**, focusing on:

- identifying dysfunctional or missing cell populations
- delivering replacement or stimulatory cells
- expecting functional restoration

Implicit in this model is the assumption that the host environment is sufficiently supportive.

However, chronic diseases are frequently characterized by:

- metabolic dysregulation
- chronic stress signaling
- micronutrient insufficiency
- impaired oxidative-reductive balance
- environmental and toxic burden

These factors define the **terrain** in which therapeutic cells must operate [7-10].

A key question, then, is how to conceptualize and measure this 'host system' in a clinically meaningful way.

The ICV Axis: A Regulatory Framework

A systems-level perspective can be conceptualized through the **Insulin-Cortisol-Vitamin C (ICV) axis** [11], integrating metabolic, endocrine, and redox regulation [6, 12].

- **Insulin** regulates metabolic signaling and nutrient utilization
- **Cortisol** coordinates stress responses and systemic adaptation
- **Vitamin C** plays essential roles in antioxidant defense, collagen synthesis, and steroid hormone biosynthesis

Vitamin C is particularly relevant in orthomolecular medicine. It is highly concentrated in endocrine tissues, including the adrenal glands and ovaries, where it supports hormone synthesis and protects against oxidative stress. In conditions of chronic disease, physiological demand for vitamin C may increase substantially, potentially leading to functional depletion.

Disturbances across this axis may result in a biological state that is:

- metabolically unstable
- hormonally dysregulated
- redox-compromised

Implications for Regenerative Therapies

The success of cell-based therapies depends on several system-dependent processes:

- cellular survival
- differentiation and signaling
- tissue integration
- sustained functional activity

In compromised systems, studies suggest that:

- cell survival may be reduced
- signaling pathways may be altered
- regenerative responses may be attenuated [13, 14]
- Conversely, optimization of the host environment has been associated with improved regenerative capacity in experimental and clinical contexts [15].

Two Diseases, One Principle

This systems-dependent variability can be observed across distinct clinical domains.

In Type 2 Diabetes:

- insulin resistance and hyperinsulinemia
- mitochondrial dysfunction
- chronic low-grade inflammation

create a metabolically unfavorable environment for beta-cell recovery and regeneration [6, 16].

In Premature Ovarian Insufficiency:

- disruption of the hypothalamic-pituitary-ovarian axis
- oxidative stress
- impaired follicular signaling

may limit the responsiveness of ovarian tissue to regenerative interventions.

Despite different clinical manifestations, both conditions reflect underlying disturbances in systemic regulation.

Reframing Regenerative Medicine

If therapeutic outcomes are influenced by system state, then regenerative medicine may benefit from a broader clinical model:

from "cell therapy" to "system-conditioned therapy [6]."

This approach may include:

Before intervention:

- metabolic stabilization
- stress regulation
- correction of micronutrient insufficiencies
- optimization of oxidative-reductive balance

After intervention:

- maintenance of metabolic and endocrine stability
- continued nutritional support
- reduction of environmental and toxic stressors

A Shift in Clinical Thinking

This perspective does not diminish the value of cell-based therapies. Rather, it provides a framework to better understand and potentially improve their outcomes.

Cell therapy introduces potential.
The biological system influences how that potential is expressed.

Conclusion

Variability in regenerative medicine outcomes is unlikely to be explained solely by technical factors [15, 17]. A systems perspective suggests that the host environment plays a central, and potentially modifiable, role.

Integrating metabolic, endocrine, and orthomolecular optimization into clinical protocols may help improve consistency and durability of outcomes.

The future of regenerative medicine may therefore depend not only on advancing cellular technologies, but on developing strategies to prepare-and maintain-the biological systems in which these therapies are applied.

About the Author

Richard Z. Cheng, MD, PhD, is Editor-in-Chief of the *Orthomolecular Medicine News Service* and a physician-scientist specializing in integrative and orthomolecular approaches to chronic disease. His work focuses on systems-level frameworks for metabolic, inflammatory, and degenerative conditions.

He provides international consultations for complex cases requiring a systems-based approach. Additional writings are available at his Substack.

References (Selected)

1. Zarei, M. Mesenchymal Stem Cell Therapy for Type 2 Diabetes: Mechanisms, Clinical Evidence, and Future Directions. *Mol Biol Rep* 2025, 52, (1), 1046. DOI: 10.1007/s11033-025-11133-7.

2. Manikandan, S.; Hariprasad, R.; Bagepally, B.S. Efficacy and Safety of Stem Cell Therapy in Patients with Diabetes Mellitus - a Systematic Review and Meta-Analysis. *Syst Rev* 2026, 15, (1), 75. DOI: 10.1186/s13643-025-03054-0.

3. Waris, S.; Begam, H.H.; Kumar, M.P.; et al. Stem Cell-Derived Beta-Cell Therapies: Encapsulation Advances and Immunological Hurdles in Diabetes Treatment. *Cells* 2026, 15, (2), 191. DOI: 10.3390/cells15020191.

4. Lin, T.-M.; Lin, T.-C.; Lin, C.-H.; et al. Overview of the Major Clinical Trials Investigating Stem Cells-Based Therapies for Diabetes. *Diabetes & Metabolism* 2026, 52, (2), 101738. DOI: 10.1016/j.diabet.2026.101738; Available online: https://www.sciencedirect.com/science/article/pii/S1262363626000170.

5. Schwarz, K.A.; Leonard, J.N. Engineering Cell-Based Therapies to Interface Robustly with Host Physiology. *Adv Drug Deliv* Rev 2016, 105, (Pt A), 55-65. DOI: 10.1016/j.addr.2016.05.019.

6. Martins, A. Unifying Pharmacology, Systems Biology, and Regenerative Medicine to Advance Personalized Therapies. *Front. Pharmacol.* 2025, 16. DOI: 10.3389/fphar.2025.1729610; Available online: https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2025.1729610/full.

7. Lepp, H.-L.; Amrein, K.; Dizdar, O.S.; et al. LLL 44 - Module 3: Micronutrients in Chronic Disease. *Clinical Nutrition* ESPEN 2024, 62, 285-295. DOI: 10.1016/j.clnesp.2024.05.009; Available online: https://www.sciencedirect.com/science/article/pii/S2405457724001281.

8. Qin, Y.; Qian, C.; Li, W.; et al. Oxidative Stress: Molecular Mechanisms, Diseases, and Therapeutic Targets. *MedComm* (2020) 2026, 7, (2), e70600. DOI: 10.1002/mco2.70600.

9. Grant, W.B.; Wimalawansa, S.J.; Pludowski, P.; et al. Vitamin D: Evidence-Based Health Benefits and Recommendations for Population Guidelines. *Nutrients* 2025, 17, (2), 277. DOI: 10.3390/nu17020277.

10. Młynarska, E.; Lisińska, W.; Hossa, K.; et al. Vitamin D and Chronic Disorders: A Review of Metabolic and Cardiovascular Diseases. **Pharmaceuticals** 2025, 18, (10), 1467. DOI: 10.3390/ph18101467; Available online: https://www.mdpi.com/1424-8247/18/10/1467.

11. Cheng, R.Z.; Levy, T.E.; Hunninghake, R. The Insulin-Cortisol-Vitamin C Axis: A Missing Regulatory Framework in Metabolic and Hormonal Homeostasis A Narrative Review. 2025.

DOI: 10.20944/preprints202512.0217.v1; Available online: https://www.preprints.org/manuscript/202512.0217.

12. Pianko, M.J.; Golob, J.L. Host-Microbe Interactions and Outcomes in Multiple Myeloma and Hematopoietic Stem Cell Transplantation. *Cancer Metastasis Rev* 2022, 41, (2), 367-382. DOI: 10.1007/s10555-022-10033-7.

13. Terashvili, M.; Bosnjak, Z.J. Stem Cell Therapies in Cardiovascular Disease. *J Cardiothorac Vasc Anesth* 2019, 33, (1), 209-222. DOI: 10.1053/j.jvca.2018.04.048.

14. Gibson, D.; Leonforte, C.; Madrigal, A. Strategies for Dealing with Donor Variability. *Cell and Gene Therapy Insights* 2018. DOI: 10.18609/cgti.2018.087; Available online: https://www.insights.bio/cell-and-gene-therapy-insights/journal/article/278/strategies-for-dealing-with-donor-variability.

15. Petrus-Reurer, S.; Romano, M.; Howlett, S.; et al. Immunological Considerations and Challenges for Regenerative Cellular Therapies. *Commun Biol* 2021, 4, (1), 798. DOI: 10.1038/s42003-021-02237-4; Available online: https://www.nature.com/articles/s42003-021-02237-4.

16. Ahn, B. Advances in Insulin Resistance-Molecular Mechanisms, Therapeutic Targets, and Future Directions. *Int J Mol Sci* 2025, 26, (6), 2574. DOI: 10.3390/ijms26062574.

17. National Academies of Sciences, E.; Division, H. and M.; Policy, B. on H.S.; et al. Factors Contributing to Patient Variability. In *Exploring Sources of Variability Related to the Clinical Translation of Regenerative Engineering Products: Proceedings of a Workshop*, National Academies Press (US), 2019.; Available online: https://www.ncbi.nlm.nih.gov/books/NBK544024/.