

Stress and Aging in Hematopoietic Stem Cell Transplantation and Cellular Therapy

**March 9, 2026, 1:00–2:00 p.m. ET
Webinar Q&A**

Mechanistic Aging and Biological Processes

1. To what extent are biological processes reversible?

Cellular senescence is a permanent state of cell growth arrest; however, research has identified that senescent cells can be cleared from the body through the use of pharmacologic agents (e.g., senolytics) and behavioral interventions (e.g., exercise).¹ Researchers have also suggested that epigenetic aging processes (e.g., DNA methylation-based measures) are modifiable through interventions such as caloric restriction. This is an area of great interest in the field.

2. Can stress-induced (or any other kinds of mouse/human) aging involve different CpN (Cytosine–phosphate–Nucleotide) modifications that include formyl-cytosine and 5-carboxy-cytosine, in addition to the primary 5-methyl-cytosine in CpG (Cytosine–phosphate–Guanine) contexts?

This is an interesting question, and we would think that stress-induced aging can involve different modifications. However, the measures that we examined are based on 5-methyl-cytosine modifications, and we're not aware of studies that have examined other types of epigenetic modifications in relation to stress.

3. Do you consider unusual animal models of extreme longevity, such as naked mole rats?

We have not conducted any studies with naked mole rats.

Transplantation Biology and Cellular Therapy

4. In chimeric antigen receptor (CAR) T-cell therapy or mesenchymal stem cell (MSC) therapy, does donor- or manufacturing-related stress influence cellular aging and therapeutic efficacy?

We have not conducted research on MSC therapy; however, as Jennifer Knight, M.D., M.S., presented, donor socioeconomic status was associated with worse clinical outcomes among allogeneic hematopoietic cell transplant recipients.² With respect to CAR T-cell therapy, recent research conducted by our colleagues suggests that T cells that have been cryopreserved and thawed show up-regulation of senescence-related genes compared to fresh cells.³

5. In mouse models, aging phenotypes can be transferred through the hematopoietic system, and young stem cells can partially rejuvenate immune function. Do these findings suggest that stem cell transplantation in humans might also influence the trajectory of immune aging in recipients, depending on the biological state of the donor cells?

This is a great question. Although donor (chronological) age has been recognized as a factor that influences recipient outcomes following allogeneic hematopoietic cell transplantation (HCT), we aren't aware of research with humans that has tested whether the biological state of donors can influence the trajectory of immune aging in recipients, but this is an active area of investigation in our labs.

Epigenetic Clocks and Immune Profiling

6. Did you control for cancer stage when analyzing epigenetic clocks?

Analyses with the epigenetic clock measures did not adjust for cancer stage because the sample involved patients with relapsed, refractory disease; however, we did adjust for lactate dehydrogenase (LDH) levels at apheresis as a marker of disease burden that predicts response to CAR. Analyses also adjusted for previous autologous HCT.

7. Were immune cell proportions accounted for in the analysis of the epigenetic clock measures, and do you think CAR T cells could affect the pre- vs. post-treatment effects of epigenetic age?

Immune cell proportions were not accounted for in the epigenetic clock measures. However, we think that CAR T cells could contribute to some of the changes in epigenetic aging that we observed before and after CAR T-cell therapy, and we are planning to examine this further as a next step.

- 8. One potential challenge with biological aging clocks (particularly in immune-modulation settings like transplant) is the known residual confounding of clocks by immune cell subsets. Has this been considered, or has the cellular immune profile of the participants been assessed using cell-type deconvolution with methylation data or measured with flow cytometry?**

We agree, and this is an important question. As we mentioned in response to the previous question, these preliminary analyses did not adjust for immune cell subsets, but we plan to examine this further by using both methylation-based and flow cytometry data as a next step.

Clinical Translation and Patient Considerations

- 9. As this work moves into the clinical space, any thoughts on how to overcome patient biases with mental health concerns?**

One important way to overcome patient bias or stigma is to frame mental health concerns as not separate from cancer care but as part of the same biobehavioral processes that influence inflammation, immune recovery, symptom burden, and outcomes. With our and others' work demonstrating that stress, social adversity, symptoms, and cancer outcomes track with stress-responsive transcriptional pathways and markers of biological aging in cancer, research findings help position these concerns as biologically relevant and clinically meaningful rather than as a personal weakness. In practice, this means normalizing distress screening and supportive care as a routine part of cancer therapy, and using language around stress, sleep, coping, and functioning, which patients often find more acceptable than psychiatric labels alone. It also means embedding interventions into oncology care whenever possible, because our data suggest that both behavioral and pharmacologic approaches may favorably influence stress-related biology, making this feel like whole-person cancer care rather than a separate mental health referral.

References

1. Mandelblatt JS, Antoni MH, Bethea TN, et al. Gerotherapeutics: aging mechanism-based pharmaceutical and behavioral interventions to reduce cancer racial and ethnic disparities. *J Natl Cancer Inst.* 2025;117(3):406-422. doi:10.1093/jnci/djae211.
2. Turcotte LM, Wang T, Beyer KM, et al. The health risk of social disadvantage is transplantable into a new host. *Proc Natl Acad Sci U S A.* 2024;121(30):e2404108121. doi:10.1073/pnas.2404108121.

3. Shah S, Li M, Lee M, et al. Sasp-driven immune evasion defines a novel African ancestry-associated DLBCL subtype with distinctive molecular and immune vulnerabilities. *Blood*. 2025;146(suppl 1):3. doi:10.1182/blood-2025-553642.