59.5% vs 50.4% for the controls. This should be compared with 47% on the nonmycophenolate arms of the preceding study 0302, which provided the lower boundary for estimating efficacy in this randomized comparison. Ultimately, the trial was stopped early because the futility rules were triggered after the first planned interim analysis.

Where do we go from here? Could high-risk patients be identified early using biomarkers, and referred for GVHD combination approaches, as suggested by Bolaños-Meade et al?[4,5] Roughly 70% of the patients enrolled in this trial had grade 1 or 2 acute GVHD, a group which historically has the highest response rates to standard therapy. It remains unknown whether the combination of mycophenolate and steroids would have proven superior had higher risk patients been targeted for this trial. Risk stratification of patients with newly diagnosed acute GVHD will form the cornerstone of acute GVHD studies in the next decade, wherein patients who are likely to fail with standard therapy are enrolled onto trials with novel and often organ-specific agents, whereas patients with favorable prognostic covariates are targeted for steroid-sparing strategies. It is quite frustrating that although steroids remain the backbone of GVHD treatment, ~35% to 50% of patients will have some degree of steroid refractoriness, with very poor outcomes. Undoubtedly, testing of novel GVHD prevention strategies with trial endpoints targeting not only a reduction in severe grade 3/4 acute GVHD but also chronic GVHD rates is needed. To this end, BMT CTN 1203 is set, this month, to open a prospective phase 2 evaluation of 3 novel GVHD prevention strategies (posttransplant cyclophosphamide with mycophenolate/tacrolimus, bortezomib and maraviroc). The primary endpoint of this trial will incorporate not only reduction in acute GVHD 3/4 rates, but also chronic GVHD, nonrelapse, and relapse mortality.

Merits and potential of novel agents and interventions[6] will have to be evaluated in a resource-limited environment, and will require newer statistical designs that will accommodate dynamic decision–making,[7] allowing for a reasonable triage of less promising strategies. The pitfalls of any "triage" design, however, are illustrated in the BMT CTN 0302 study, where mycophenolate looked like the "winner" that it never was…

The bar is indeed high: preserve the graft-versus-malignancy effect, do not jeopardize immune recovery, and abolish GVHD. As for Don Quixote, we do not want our pursuit to be associated with his name anyway. Rather, we should side with and imitate the author, who ushered in a new literary era. New paradigms for GVHD prevention and treatment, anyone?

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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● ● ● **HEMATOPOIESIS & STEM CELLS**

Not merely quiescent: telomeres in quiescent HSCs

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In this issue of *Blood*, Wang et al elegantly show that telomere shortening results in DNA damage that induces apoptosis and senescence in quiescent hematopoietic stem cells (HSCs).[1]

Altering the cell cycle and retaining a quiescent state protect cells from cell-intrinsic functional exhaustion and naturally produce extrinsic cellular insults.[2] HSCs are thus maintained in cell cycle quiescence, enabling lifelong hematopoietic cell production.[3,4] However, quiescence does not ensure that HSCs will be immortal. Organismal aging is reflected on the cellular level as stem cell potentials of HSCs decline with age. The mechanisms of how aged HSCs are functionally defective have recently started to be uncovered.

HSCs exhibit accumulation of DNA damage induced by intrinsic and extrinsic hazards.[5] Initially, it was postulated that acquisition of quiescence protected HSCs from genomic instability. Yet, recent studies indicate decreased expression of DNA damage repair pathway–associated genes in quiescent HSCs compared with cycling HSCs.[6] Attenuation of the DNA damage repair pathway leads to the accumulation of DNA damage in aged quiescent HSCs, and such damage is repaired upon cycling. Aged quiescent HSCs display a slower rate to enter the cell cycle to proliferate and display a persistent replication stress postcycling.[7] Mechanisms underlying HSC aging are thus linked to cell cycle status and cell cycle machinery. However, a quiescent state does not necessarily ensure protection from cellular insults and genetic instability.

Telomeres cap the ends of linear chromosomes, protecting chromosomes from degradation or fusion.[8] Telomeres shorten with cell division and aging but are repaired by telomerase ribonucleoprotein complex and the shelterin complex.[8] Telomerase is expressed in HSCs, and telomerase activity is essential for the maintenance of HSC potentials.[9] Yet details of the mechanism underlying the effect are largely unknown. Wang et al profiled the gene expressions
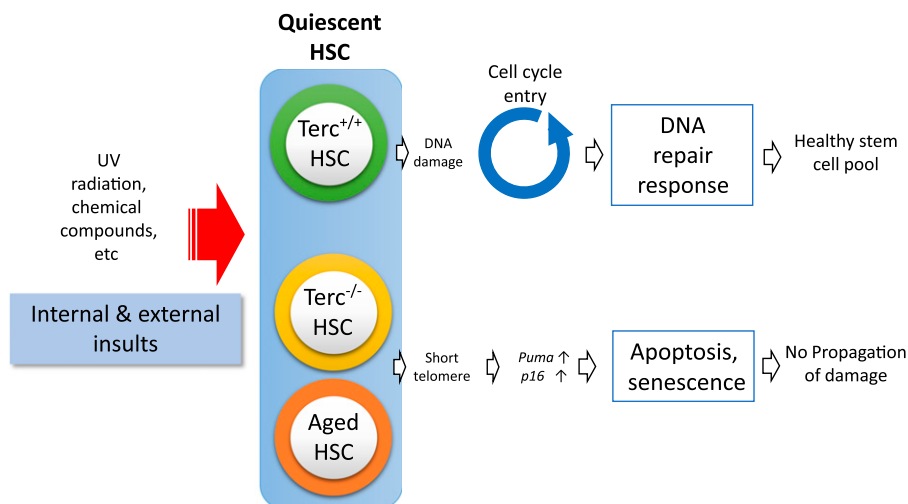
Quiescent HSC

Schematic representation showing quiescent HSC response to cellular insults. Terc$^{-/-}$ HSCs and aged HSCs are inhibited from entering the cell cycle because of induction of senescence and apoptosis related to short telomeres.

of HSCs and progenitor cells from third-generation *Terc*-deficient mice (G3mTerc$^{-/-}$). They revealed that gene expression changes were confined to HSCs. More excitingly, the gene expression changes were further prominent in quiescent G3mTerc$^{-/-}$ HSCs rather than actively cycling HSCs. When G3mTerc$^{-/-}$ HSCs were stimulated to cycle, HSCs that remained quiescent significantly expressed elevated levels of senescence-associated (*p16*) and apoptosis-associated (*Puma*) genes. These data indicate that telomere shortening in quiescent HSCs activates a genetic program prior to cell cycle checkpoints, which eliminates damaged HSCs through senescence or apoptosis (see figure).

The current study indicates that genomic machinery regarding telomeres actively participates in determining the cell fate of HSCs even before they confront cell cycle checkpoints upon proliferation. Although it has been shown that DNA damage repair responses are attenuated in quiescent HSCs,[6] it is still too early to conclude that quiescence is a detrimental state for the preservation of HSC functions. In fact, with regard to telomere-mediated responses, quiescent HSCs integrate a surveillance program so that damage is not propagated to HSC progeny. The current paper provokes the question of how telomere shortening and telomerase modulate effects on cell cycle entry. This will provide greater insight into the biology of HSC aging.

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● ● ● **IMMUNOBIOLOGY**

Fc-optimized antibodies quickly pull the trigger

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In this issue of *Blood*, Romain et al demonstrate that natural killer (NK) cell–mediated killing of tumor cells coated with the Fc-optimized CD33 antibody DLE-HuM195 reveals a distinct kinetic profile.[1] The presented work gives important novel insights into the mechanism of effector cell–mediated target cell killing triggered by Fc-engineered antibodies and explains how they achieve a higher antibody-dependent cell-mediated cytotoxicity (ADCC) potency than native immunoglobulin G1 (IgG1) antibodies. Using time-lapse imaging microscopy in nanowell grids (TIMING), the authors were able to demonstrate at the single-cell level that antibody Fc engineering improves frequency and promotes kinetic boosting of serial killing mediated by NK cells.

Today, antibody therapy is an established treatment option in cancer therapy. Monoclonal antibodies such as rituximab, which targets the CD20 antigen on various B-cell malignancies, have significantly improved the clinical outcome of tumor patients. Unfortunately, not all patients can benefit from a generally well-tolerated antibody therapy. For example, antibody-based therapeutic approaches in acute myeloid leukemia (AML) using unconjugated monoclonal antibodies have not been clinically approved at the moment. CD33, a candidate antigen in targeting AML, is significantly expressed in about 85% to 90% of cases and is considered a promising target structure for developing effective antibody-based AML therapies. Lintuzumab (HuM195), a humanized CD33 antibody, had observable efficacy in patients with advanced AML, but