

or the erasing of the m<sup>6</sup>A mark. Could there be a way to target mRNA readers like YTHDC1 in a way that would selectively affect leukemic cells and spare healthy hematopoietic cells?

YTHDC1 is a conductor that allows AML to expand and make a mess on the metaphorical train of the bone marrow. Studies like this from Sheng et al have demonstrated that we may be able invalidate its ticket by targeting RNA methylation.

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

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## THROMBOSIS AND HEMOSTASIS

Comment on Zwagemaker et al, page 2853

# Can we do something about ICH in hemophilia?

Guy Young | University of Southern California Keck School of Medicine

**Hemophilia is one of the diseases considered under the rubric of “benign hematology”; however, hematologists should never consider this severe bleeding disorder as anything but a life-threatening disease that, short of death, can result in debilitating and permanent sequelae. In this issue of *Blood*, the exceptionally well-done meta-analysis performed by Zwagemaker et al<sup>1</sup> clearly demonstrates that intracranial hemorrhage (ICH) is much more common in persons of any age with hemophilia than the general population, although the incidence rate is strikingly high in children, especially neonates. Among nonneonate children (ie, children >1 month of age), the highest rates of ICH occur in the first few years of life and often at ages before prophylactic therapy is typically initiated. Importantly, ICH was demonstrated to be associated with increased mortality. In my 20+ years of caring for many patients with hemophilia, I have cared for several dozen who suffered an ICH, many of whom suffered permanent neurologic damage.**

The strengths of the report are the number of studies reviewed and the sheer number of total patients included in those studies, which span many decades. Although period bias is sometimes an issue with studies that span such a long period of time, given that this study reports on an epidemiologic manifestation of hemophilia that should be static and for which specific (to ICH) preventive measures still do not exist, the fact that many decades of studies have been reviewed is a strength.

Thus, this confirmatory meta-analysis removes any question about the high incidence of ICH in persons with hemophilia and adds strength to the notion that this is largely a pediatric problem and moreover one that mostly occurs in the first few years of life. What is one to do with such important information regarding a potentially devastating complication? Of course, prevention of ICH would be ideal, but how could these data be used to alter the current paradigm of treatment? To be sure, prophylactic therapy with factor concentrates is the established standard of care for patients with severe hemophilia and many patients with moderate hemophilia; however, the current approach even in resource-rich countries is to start prophylaxis ~1 to 2 years of age before or shortly after the first joint bleed.

Although long-term studies have demonstrated this approach to be effective at preventing permanent joint damage,<sup>2</sup> more recent data suggest that this protection may not be as robust as we had thought.<sup>3</sup>

Although prophylaxis has been used for decades, it requires repeated IV infusions of factor concentrates, which carry with them a significant treatment burden especially in young children such that often the initiation of prophylaxis is delayed as much as possible. As such, the notion of using prophylaxis to prevent ICH has never taken hold despite the potentially devastating outcomes. Recently, emicizumab, a bispecific monoclonal antibody that mimics the function of factor VIII has become available and has been demonstrated to be very effective at bleed prevention.<sup>4,5</sup> Unlike factor concentrates, this medication is given subcutaneously and less frequently than factor therapy, easing the treatment burden. Importantly, it has also made it feasible to initiate prophylaxis at a much younger age, even in the neonatal period. The question is not whether one can administer emicizumab to neonates and young infants, but rather should this become the standard approach. To be clear, there are very limited data on the use of this agent in patients <2 years of age, and in particular,

patients <1 year of age, and although studies are underway in this younger age group, it will take years to accumulate these data. Thus, given the high risk for ICH early in life during ages at which prophylaxis is generally not begun, should clinicians consider prescribing emicizumab with the express purpose of preventing ICH? Clearly, emicizumab is only indicated in hemophilia A; however, novel therapies that are also given subcutaneously are in late stage clinical trials, which could be used for both hemophilia A and B. Although there are no data proving that emicizumab can prevent ICH, it will be very difficult, if not impossible, to prove this in a clinical study. For more discussion on this topic, the reader is referred to Mason and Young.<sup>6</sup> Of note, the Medical and Scientific Advisory Council of the National Hemophilia Foundation has made a recommendation that prophylaxis with emicizumab be considered in neonates because of the high risk for ICH.<sup>7</sup> Zwagemaker et al only further heighten the importance of this recommendation, and I would urge every hematologist who cares for infants with hemophilia to familiarize themselves with this important contribution to the knowledge of this potentially devastating and truly life-threatening complication of hemophilia and to use this information in their discussions with the parents of infants with hemophilia. Ultimately, the decision to start any form of prophylaxis and especially emicizumab in infants must be made on a case-by-case basis; however, that decision should be an informed one.

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## TRANSPLANTATION

Comment on Yeh et al, page 2874

# A CMV seronegative donor to avoid T-cell inflation?

Hermann Einsele<sup>1</sup> and Lars Dölken<sup>2</sup> | <sup>1</sup>University Hospital; <sup>2</sup>Institute for Virology and Immunobiology, Julius-Maximilians-University Würzburg

**In this issue of *Blood*, Yeh et al found that cytomegalovirus (CMV) drives the long-term expansion of donor CD4 cytotoxic T lymphocytes (CD57<sup>+</sup>/CD27<sup>-</sup>) after allogeneic stem cell transplant (SCT). This effect was associated with both a profound impairment in immune repertoire diversity and a loss of donor antigen-presenting cells (APCs) in grafts from seropositive donors. CMV may thus lead to a much broader defect in pathogen-specific immunity than previously thought, which would explain the higher transplant-related mortality in SCT recipients who have CMV-seropositive donors.<sup>1</sup>**

Despite advances in antiviral prophylaxis and treatment, positive donor CMV serological status remains an important risk factor for increased transplant-related complications and mortality.<sup>2</sup> The higher incidence of secondary bacterial and fungal infections in patients receiving their stem cell graft from a CMV-seropositive donor points to CMV-related defects in pathogen-specific immunity.<sup>3</sup>

CMV reactivation and the myelotoxic and lymphotoxic side effects of long-term antiviral chemotherapy with ganciclovir or valganciclovir are well documented to induce long-term immune deficiency. These side effects not only foster recurrent CMV infections and disease but also increase the incidence of secondary bacterial and fungal infections associated with increased transplant-related mortality.<sup>4,5</sup> In addition, CMV reactivation after allogeneic SCT skews the immune repertoire by a sizable expansion of effector memory T cells and a reduction in the overall T-cell receptor  $\beta$  (TCR- $\beta$ ) diversity, thus altering both CD4<sup>+</sup> and CD8<sup>+</sup> T-cell reconstitution.<sup>6,7</sup> Interestingly, the negative

association between donor CMV seropositivity and long-term clinical outcome after allogeneic SCT has been demonstrated to be independent of the extent of CMV reactivation and disease.<sup>2,8,9</sup>

As a likely cause, the results demonstrate that receiving a graft from a CMV-seropositive donor is associated with a significant expansion of a highly differentiated, cytotoxic effector memory T-cell subset characterized by the expression of CD57 (see figure). This expansion was found to be strongly dependent on the CMV serostatus of donor and recipient but independent of CMV reactivation and to persist over many years after allogeneic SCT. While this expanded fraction of CD57<sup>+</sup>/CD27<sup>-</sup> T-cells in both the CD4 and CD8 compartments comprised up to 15% of T cells in healthy CMV seropositive individuals, it increased beyond 70% or even 85% in CMV seronegative recipients of a CMV seropositive stem cell graft. This expanded CD57<sup>+</sup>/CD27<sup>-</sup> CD4<sup>+</sup> and, less impressively also a CD8<sup>+</sup> T-cell subset expressed an effector memory phenotype (TCR $\gamma$ <sup>-</sup>/CD45RA<sup>low</sup>