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# Slipping out the Weibel-Palade body

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appropriate correlative studies will be performed to both validate the model systems and determine the degree to which the putative target is affected by the agent under evaluation.

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

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HEMOSTASIS

Comment on Babich et al, page 5282

# Slipping out the Weibel-Palade body

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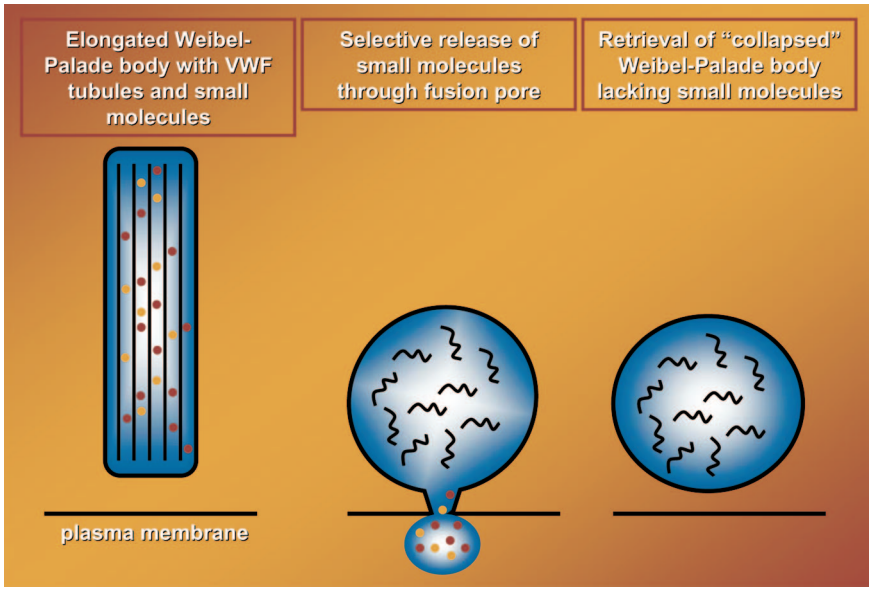
In this issue of Blood, Babich and colleagues disclose an elegant mechanism that serves to selectively release cargo from WPBs.

Weibel-Palade bodies (WPBs) are versatile storage organelles within endothelial cells that release their inflammatory and prothrombotic content into the circulation in response to a large number of agonists.[1] Using real-time analysis of fluorescently tagged von Willebrand factor (VWF) and VWF propolypeptide, Babich et al nicely show that a proportion of WPBs transiently fuse with the plasma membrane during a "lingering kiss." Fusion pores of approximately 12 nm in diameter are generated that facilitate the selective release of low-molecular-weight components like IL-8 from these organelles. An important physiological implication of these findings is that endothelial cells can selectively release proinflammatory cytokines like IL-8 and eotaxin-3 while retaining prothrombotic VWF. The selective release of small-core and membrane proteins comes at a cost, though; the elegantly shaped, cigarlike WPBs collapse into ordinary, circular vesicles.




**Selective release of small molecules (indicated in orange and red) during transient fusion of WPBs with the plasma membrane. During fusion elongated WPBs collapse into circular structures, designated collapsed WPBs. This most likely is due to the conversion of highly organized VWF tubules (thick black lines in left panel) into randomly organized VWF polymers (black curved lines in middle and right panels).**

In the original study by Weibel and Palade, the presence of tubular structures was noted.[2] It has recently been shown that the tubules present within these organelles are hollow cylinders that are created by propolypeptide-guided condensation of VWF.[3,4] The integrity of VWF-containing tubules that maintain the elongated form of WPBs is critically dependent on a low pH. The pH within WPBs during a lingering kiss increases considerably, and this most likely results in the so-called unfurling of tubules into long VWF filaments.[3] Although this has not been addressed, it is likely that the increase in intracellular pH results in the rapid disappearance of VWF tubules (see figure). The morphological characteristics of these collapsed WPBs have not been determined. Therefore, it is presently unknown whether this class of WPBs can reassemble into rod-shaped structures, fuse with newly formed organelles, or exocytose following application of a more rigorous stimulus.

In their visually appealing article, Babich and coworkers show that lingering kisses account for 10% to 25% of all fusion events following stimulation with histamine. A large number of agonists can provoke release of WPBs. Clinically, this is exploited by the administration of desmopressin (DDAVP) to patients with von Willebrand disease or mild hemophilia A. Under these conditions, the release of WPBs is induced by cAMP-dependent signaling pathways that result in only modest activation of signaling molecules involved in regulation of WPB exocytosis.[1] It will be interesting to determine whether, under these conditions, transient fusion of WPBs with the plasma membrane will occur at a higher frequency than observed following stimulation with histamine.

Overall, the findings of Babich et al highlight yet another fascinating aspect of the biology of the uniquely shaped WPB. Their study provides an excellent starting point to further explore the regulation and physiological significance of release of WPBs with different proinflammatory and vasoregulatory cargo.

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

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TRANSPLANTATION

Comment on Winston et al, page 5403

# Cytomegalovirus: time for a requiem?

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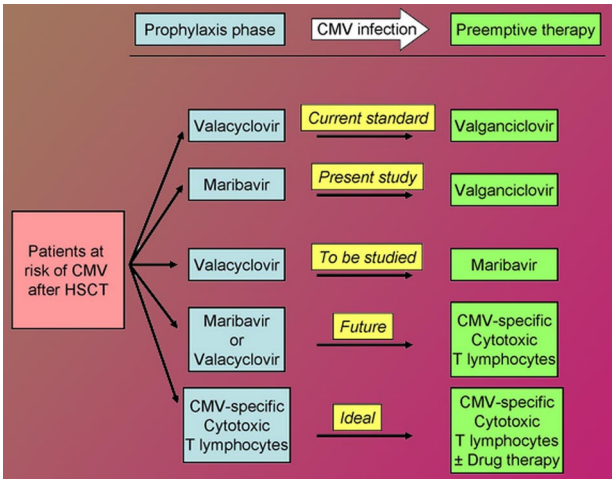
In this issue of *Blood*, Winston and colleagues show that the prophylactic administration of maribavir, an oral inhibitor of the CMV UL97 kinase, reduces CMV infection (reactivation or viremia) by more than 50% after allogeneic HSCT.

I remember cytomegalovirus (CMV) as a scourge that competed with relapse as the top cause of death after allogeneic bone marrow transplantation. Although ganciclovir eliminated CMV as a significant cause of mortality after hematopoietic stem cell transplantation (HSCT), neutropenia associated with its prolonged administration—whether prophylactic (before infection) or preemptive (after infection, but before the development of CMV disease)—increased bacterial and fungal infections, thereby blunting its beneficial impact on survival.[1-3] Prolonged ganciclovir administration also delayed reconstitution of CMV-specific cell-mediated immunity, contributing to late infections after therapy was discontinued. However, a short 3-week course of preemptive ganciclovir was found to be effective in treating cytomegaloviremia without increasing other infections or causing frequent episodes of repeat viremia.[4] Such preemptive short-course ganciclovir therapy (or its oral prodrug, valganciclovir) has become the gold-standard approach to CMV infection, and arguably is one of the few factors to have improved survival after allogeneic SCT over the last 15 years.[5]

The present study explores the prolonged use of maribavir to *prevent* CMV infection. However, because maribavir is also effective in *treating* CMV infection,[6] an approach worth exploring is the use of maribavir for preemptive treatment of CMV infection and the use of valacyclovir for prophylaxis. This approach is attractive because valacyclovir, while reducing CMV infection to some extent, effectively suppresses *H simplex* and *V zoster* reactivation, viruses against which maribavir is inactive.




**Approach to the allogeneic hematopoietic stem cell transplant recipient at risk of cytomegalovirus infection. This does not cover prophylaxis against *Herpes simplex* and *Varicella zoster* virus infections against which valacyclovir is active but maribavir is not.**

Although maribavir did not suppress marrow function or cause nephrotoxicity in this study, it did cause dysgeusia and nausea. These side effects may be of concern in a setting where adequate nutrition is a challenge, and poor compliance with other oral medications such as immunosuppressive and anti-microbial agents may affect outcome adversely. Will prolonged exposure to maribavir also prevent reconstitution of CMV-specific cell-mediated immunity? Will maribavir improve survival? What is the best way to use maribavir? These are important questions that need to be answered, in part by ongoing studies.

The mechanism of action of maribavir differs from the other drugs active against CMV available today (ganciclovir/valganciclovir, foscarnet, cidofovir, and fomivirsen—the last one for ophthalmic use only). Despite similar mechanisms of action, there is evidence to suggest that each of these drugs is effective in some instances of failure of one or more of the others. Additionally, CMV-specific cytotoxic T lymphocytes have been used to reconstitute immunity after HSCT to prevent and treat CMV infection.[7]

As the figure shows, the availability of maribavir will increase options for the management of the allogeneic hematopoietic stem cell transplant recipient at risk of CMV infection, today and in the future. Nearly 17 years after I helplessly saw my first patient die of CMV, the multiple drugs and adoptive cell therapy active against CMV have practically "rid me of this turbulent" pest as a major concern after HSCT.

*Conflict-of-interest disclosure: Northwestern University is a participant in the ongoing randomized, double-blind study of maribavir in allogeneic HSCT with the author as the local principal investigator.* ■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