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prognostic information, in that 82% of patients with detectable *NPM1*-MRD relapsed. But so did one-third of patients without detectable *NPM1*-MRD. This raises the question as to whether gene mutations other than *NPM1* were present in those cells that survived chemotherapy, leading to relapse in the *NPM1*-MRD-negative cohort. In a comparison of flow-cytometric MRD with gene mutation status, only mutations of $DNMT3A^{R882}$, a gene mutation frequently found in *NPM1*-mutated AML, significantly predicted the presence of flow-cytometric MRD following induction chemotherapy.[8] In fact, *DNMT3A* gene mutations have been identified in preleukemic hematopoietic stem cells, whereas *NPM1* mutations arise later, beyond the preleukemic state, in leukemogenesis.[9] Is it clinically relevant to detect MRD at the level of preleukemic stem cells to account for the 30% of AML patients in whom conventional MRD is not informative? Monitoring mutational clearance after therapy by testing for as many combinations of mutations throughout the AML genome as is feasible has been suggested as a beginning to defining a genomic posttreatment risk stratification.[10] Does the heterogeneous make-up of any myeloid leukemia population, both at the genetic and the epigenetic levels, add a potentially insurmountable complexity to the monitoring of MRD? Without question, the clinically most useful MRD test and targets are yet to be determined, and both will most likely depend on the individual patient's characteristics and the therapy administered.

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

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DOI 10.1182/blood-2018-01-828145

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CLINICAL TRIALS AND OBSERVATIONS

Comment on Shapiro et al, page 1301

Woody eyes, be gone!

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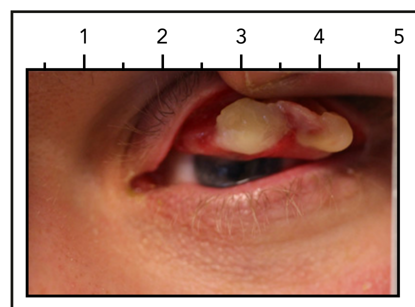
In this issue of *Blood*, Shapiro et al describe the first-in-class experience of infusing plasma-derived Glu-plasminogen to 14 patients with congenital deficiency of plasminogen as part of an ongoing, phase 2/3, open-label clinical trial, reporting encouraging results.[1] Congenital plasminogen deficiency is caused by homozygous or compound-heterozygous mutations in the plasminogen (*PLG*) gene, located on chromosome 6q26. It is, in the words of the authors, "ultra-rare," predicted to affect ~1 to 2 per million people.[2] Plasminogen is activated to plasmin and is critical for intravascular and extravascular fibrinolysis. Other functions include wound healing, cell migration, tissue remodeling, angiogenesis, and embryogenesis. Glu-plasminogen has a glutamic acid residue at its N-terminus, as opposed to Lys-plasminogen, which has a lysine. Glu-plasminogen is the predominant form found in circulation and has a half-life of 2 to 2.5 days, whereas the half-life of Lys-plasminogen is 0.8 days.[3]

Patients lacking plasminogen suffer from abnormal growth of fibrin-rich, woodlike ("ligneous") pseudomembranes on mucous membranes, such as conjunctiva, gingiva, airways, and the vaginal tract, typically within the first year of life.[4] Ligneous conjunctiva is the pathognomonic manifestation of congenital plasminogen deficiency (see figure). If left untreated, these woody growths over time severely affect quality of life and eventually lead to organ dysfunction, including blindness.



Ligneous conjunctiva. See Figure 3A in the article by Shapiro et al that begins on page 1301.

Historically, local therapy was the only available treatment. Topical eye drops containing plasminogen only treated conjunctival lesions, and surgery to remove the pseudomembranes predisposed to scar tissue and regrowth of lesions. The first publication reporting the successful use of IV infusions of unlicensed Lys-plasminogen to treat

widespread lesions in a toddler with homozygous plasminogen deficiency came out in 1998.[5] Because of the shorter half-life of Lys-plasminogen, this toddler was treated with a continuous infusion initially, followed by daily infusions. In comparison, based on individual pharmacokinetic studies, Glu-plasminogen used by Shapiro et al allowed for infusions every 2 to 4 days in these 14 patients. All evaluable lesions in these patients improved or resolved within the 12-week study window, and most improved after only 4 weeks of treatment.

Adverse events were largely limited to headache, nasopharyngitis, and gastrointestinal distress (abdominal pain, nausea, and/or diarrhea). Reassuringly, bleeding complications appear minimal, with only 2 patients each reporting epistaxis, hematuria, or dysmenorrhea during their treatment with Glu-plasminogen.

An astute reader or a scholar of congenital plasminogen deficiency will notice that thromboembolic disease is not a sequela of congenital plasminogen deficiency and that the disease manifests solely with extravascular deposition of fibrin. Despite initial reports implicating heterozygous hypoplasminogenemia as a risk factor for thromboembolic disease, more recent epidemiologic studies have not found an increase in thrombosis compared with those with normal levels of plasminogen.[2] Furthermore, thrombosis has not been described in patients with homozygous or compound-heterozygous plasminogen deficiency.[2] This suggests that other pathways, such as those involving cathepsins, elastases, or matrix metalloproteinases, can cleave intravascular, but not extravascular, fibrin and highlights how much more we need to learn about fibrinolysis.

Undoubtedly, many hematologists (cardiologists, stroke-ologists, and vascular surgeons too) are already daydreaming about all the indications that a widely available, licensed Glu-plasminogen product may serve for a myriad of acquired conditions. However, let us remember that (1) this is still an ongoing clinical trial that has shown preliminary efficacy in improving extravascular fibrin deposition and (2) other hemostatic products marketed for congenital conditions that were used off-label for acquired disease have demonstrated less than stellar outcomes.[6,7] Instead, let us celebrate that a potential treatment is one step closer to helping patients with this devastating orphan disease.

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

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DOI 10.1182/blood-2018-01-828194

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HEMATOPOIESIS AND STEM CELLS

Comment on Arndt et al, page 1311

Set(d1a)-ing novel links between HSC regulators

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In this issue of *Blood*, Arndt et al demonstrate the unique role of the histone methyltransferase *Setd1a* in regulating hematopoietic stem cells (HSCs) and provide a connection between 2 drivers of aberrant stem cell function, epigenetic dysregulation and DNA damage.[1]

HSCs are responsible for maintenance of the hematopoietic compartment and for the restoration of the system during conditions of stress or loss of homeostasis. Regulation of stem cell fidelity is considered paramount, as these self-renewing cells ensure the capacity for life-long hematopoietic function. To safeguard HSCs, cells are imbued with cytoprotective features to mitigate alterations to their functional potential and are regulated by the orchestration of both intrinsic and extrinsic signals. As we continue to piece together the molecular guardians of HSC potential (see figure), it is becoming more evident that this complex network is interconnected and that key regulators may play multiple roles in this maintenance.

Epigenetic regulation of HSC function and fate decisions has been a burgeoning topic in recent years. This literature has established that histone modifications, DNA methylation, and ncRNA are cornerstones of the HSC regulatory network.[2,3] The role the MLL/SET family of histone methyltransferases plays in hematopoiesis has been of particular interest because of the association of leukemias with chromosomal rearrangements of MLL1. The MLL/SET family is composed of 6 members (Mll1/KMT2A, MLL2/KMT2B, MLL3/KMT2C, MLL4/KMT2D, SETD1A/KMT2F, and SETD1B/KMT2G), and they methylate lysine 4 of histone H3 (H3K4). Previous work has demonstrated using constitutive knockouts of the MLL/SET family that loss of these methyltransferases results in embryonic death.[4] Although all MLL/SET proteins are critical for development, each factor appears to have specific roles in regulating adult hematopoiesis and stem cell function,[1,4] including playing a role in white blood cell output, B-cell development, and erythropoiesis (see figure).[5,6] Waskow's group uses a series of conditional knockout mice to elucidate the function of *Setd1a* in the primitive hematopoietic compartment.[1] Global loss of *Setd1a* led to significant

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