Accurate diagnosis of type 1 von Willebrand disease (VWD) remains a clinical challenge. In many instances, there is great overlap between VWD patients and normal individuals in both clinical and laboratory outcomes. To address these difficulties, provisional diagnostic criteria established by experts focus on 3 components of disease: (1) presence of bleeding symptoms, (2) reduced von Willebrand factor (VWF) levels, and (3) autosomal inheritance of the phenotype. In this issue of Blood, Tosetto and colleagues have developed a novel method that allows for a more rigorous, quantitative analysis of the relative contribution of these 3 components to the odds of having VWD.

In the general population, prevalence estimates of VWD range from 0.1% to 1%, meaning that a random person would have a 0.1% to 1% chance of having VWD. Intuitively, gathering more information about the person (such as bleeding score) changes one’s estimation of his or her probability of having VWD. In their study, Tosetto and colleagues have translated this intuitive concept into a mathematical model. Based on the Bayes theorem, their algorithm utilizes clinical and laboratory phenotypes to update individual odds of having VWD. Statistically speaking, population prevalence serves as the prior estimate of disease that is multiplied by likelihood ratios (LRs) for specific outcomes to obtain a person’s final odds of having the disease.

Corresponding to the clinical definition of disease and to the 3 components of the provisional diagnostic criteria, Tosetto and colleagues have defined 3 informative LRs for assessing disease odds: an LR based on bleeding score, an LR based on VWF level, and an LR based on family history of disease. Assessing disease odds: an LR based on bleeding score changes one’s estimation of his or her probability of having VWD.

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Corresponding to the clinical definition of disease and to the 3 components of the provisional diagnostic criteria, Tosetto and colleagues have defined 3 informative LRs for assessing disease odds: an LR based on bleeding score, an LR based on VWF level, and an LR based on family history of disease. Although their methods are theoretically sound, the strength of their results hinges on the appropriateness of the populations used to derive these likelihood ratios. To retain multiplicative properties of the method, the 3 populations must be independent from each other (for example, platelet function analyzer [PFA-100TM; Dade Behring, Deerfield, IL] values cannot determine an independent LR because they are directly correlated with VWF levels). Tosetto and colleagues provide good arguments for the use of their populations, but also recognize the need for verifying LR estimates with other populations.

Results reported by Tosetto and colleagues offer important insights into VWD diagnostic

Clinical Observations

Comment on Tosetto et al, page 3998

VWD type 1: a calculated diagnosis

Diana Abbott and Jorge Di Paola

Tosetto and colleagues have developed a mathematical method to quantify the odds of having type 1 von Willebrand Disease based on a person’s family history, bleeding score, and VWF level.
Comment on Abdel-Azim et al, page 4064

Cell expansion and maintenance of stemness

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Manipulation of hematopoietic cells to expand output while maintaining stem-cell potential has been an elusive goal of experimental hematology. The development of a system using a chemically induced dimerizer and modified thrombopoietin receptor has now allowed the expansion of primitive hematopoiesis without sacrificing stem cells.

Hematopoietic-cell expansion represents a much-sought-after therapeutic goal of the biomedical sciences. With the cloning and characterization of a large and growing number of hematopoietic growth factors, a mechanism for hematopoietic expansion seemed to be at hand. However, ex vivo expansion strategies using cocktails of cytokines have failed to expand transplantable hematopoietic stem cells (HSCs). In contrast, most such approaches lead to the differentiation and extinction of the most primitive cells in the cultures. The explanation for these results is the requisite coupling of cell proliferation and differentiation that results when hematopoietic growth factors bind their cognate receptors.

The work of Abdel-Azim and colleagues in this issue of Blood has used a previously described cell-expansion strategy in a new target-cell population to massively expand hematopoietic cells of multiple lineages, including, apparently, the HSC. The approach involves chemically inducing dimerization of the cytoplasmic domain of the thrombopoietin receptor (c-Mpl) in highly purified, primitive human marrow cells. The rationale for this approach began with the discovery that c-Mpl and its ligand, thrombopoietin, provide important and nonredundant support for HSC survival and proliferation.1

Hematopoietic growth factors act by binding to their cognate receptors, altering the conformation of the latter, resulting in cross-phosphorylation of 2 tethered Jak signaling kinases. Once phosphorylated, Jak kinases phosphorylate the receptors themselves as well as several secondary survival and proliferation signals, including signal transduction and activator of transcription 3 (STAT3) and STAT5, phosphoinositide-3-kinase (PI3K), and mitogen-activated protein kinases (MAPKs). Ultimately, some of these same signals lead to signal extinction, by inducing receptor internalization and STAT-induced expression of suppressors of cytokine signaling (SOCS) molecules, which block further Jak signaling.2

Identification of the FK506 binding protein (FKBP), the target of the commonly used immunosuppressant drug FK506, and the demonstration by Spencer et al that a chemically synthesized dimeric form of FK506, FK1012, could artificially dimerize 2 molecules of FK506,3 led to the first chemical inducer of dimerization (CID) strategy. Following a minor modification in FKBP (F36V) to render it responsive to the nonimmunosuppressive AP20187 compound, the stage was set to use this CID to mimic cytokine-induced cellular signaling. By transducing marrow cells with an FKBP (F36V)–c-Mpl fusion protein, Jin et al first established the ability of the CID approach to influence hematopoietic-cell proliferation.4 These efforts expanded mature blood cell production both in vitro and

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<th>Number of family members with reduced VWF</th>
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<td>Number of sibs in the family / Family structure</td>
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Likelihood ratios for VWD in a nuclear family, based on the number of siblings in the family and on the number of family members with reduced VWF levels (below the 25th percentile). Including propositus. See the complete figure in the article beginning on page 3998.
VWD type 1: a calculated diagnosis

Diana Abbott and Jorge Di Paola