Inhibitory antibody formation against infused therapeutic factor VIII (FVIII) concentrates remains an important and unresolved risk in treatment of hemophilia A (HA). Both severe and nonsevere HA have substantial risk of inhibitor occurrence. Inhibitor occurrence in severe HA has been a major focus of epidemiological, immunological, and genomic studies over past decades. Despite these major collaborative studies identifying candidate gene polymorphisms and epidemiological risk factors for inhibitor formation, this has not converted to meaningful interventions to avoid or risk-reduce inhibitor formation which typically happen early in the second year of life.

Emicizumab (Roche) has recently emerged as the first nonfactor prophylaxis molecule for severe hemophilia A. Although an ongoing phase 3b study of emicizumab is evaluating the efficacy, safety, pharmacokinetics, and pharmacodynamics in participants from birth to 12 months of age, it is already recognized, and approved by regulators, to offer a different early prophylaxis option for infants and young boys with severe HA, with the logistical advantage of infrequent, subcutaneous injection over the more challenging early commencement of more frequent, intravenous infusion of FVIII concentrate. So, does the emergence of emicizumab, as first-to-market nonfactor prophylaxis agent, represent the necessary paradigm shift for the hemophilia community to avoid FVIII inhibitor formation and the subsequent challenges of reestablishing tolerance to FVIII with immune tolerance induction? The answer is likely ‘no’. For those initiated on emicizumab as first-choice prophylaxis agent from a young age, the most likely scenario is that inhibitor risk will only be deferred to later in childhood or adolescence because of the unavoidable sporadic “on-demand” FVIII concentrate requirement for trauma, breakthrough bleeds, or procedures, as seen in nonsevere HA.

Might there be strategies to change the immunogenic risk of the FVIII molecule itself? Cell lineage of recombinant FVIII (rFVIII) manufacture and inhibitor risk has become a focus of interest in recent years. Despite compelling hypotheses that human cell line-derived rFVIII might have posttranslational modification immunological advantage, this has not converted to convincing reductions in inhibitor rates in previously untreated patients (PUPs) treated with human cell line products, when unselectively compared to a breadth of hamster-cell (CHO or BHK) derived rFVIII cohort studies. Data are awaited from the first PUP study of a pegylated, CHO-derived rFVIII molecule to gauge whether polyethylene glycol shrouds the immunogenic FVIII epitopes sufficiently to meaningfully reduce inhibitor rates (clinicaltrials.gov NCT02615691). This then focuses attention on what are the immunogenic epitopes of the FVIII molecule and are they modifiable to meaningfully reduce inhibitor risk? In this issue, Winterling et al. present preliminary preclinical data of their strategy to deimmunize the human FVIII molecule by in silico identification of predicted FVIII-peptide MHC-II binding motifs, altering
them to reduce this binding signal and thus hypothetically reduce T-cell help to any emerging reactive B-cell clones with inhibitory activity. Iterations of targeted deimmunized variants, not predicted to interfere with FVIII structure or activation, were taken forward into functional analysis, demonstrating appropriate structural and postactivation analyses and a T-cell proliferation model supportive of a less immunogenic molecule. The final molecule includes 19 amino acid sequence variations, predominantly in A1 and A2 domains. The inability to target all the predicted immunogenic sequences in the C1 or C2 domains because of potential functional interference reminds us of the challenges of this strategy and, at best, authors have only generated a "partially deimmunized" molecule. If/when this molecule proceeds into early-phase human trials, the design of the pivotal PUP studies will be crucial. Unless this "partial deimmunization" has such a profound reduction on inhibitor rates in PUPs to be convincing in isolation, it will need a head-to-head randomized controlled trial with a wild-type comparator rFVIII to truly answer the question of whether this deimmunization strategy has provided a meaningfully less-immunogenic rFVIII molecule.

The current prophylaxis algorithms for severe HA PUP management are in flux as we understand the relative benefits of current factor and nonfactor strategies. A truly less-immunogenic FVIII product, whether through pegylation, this deimmunization strategy, or other strategies in development, could provide the long-awaited impact in reducing the ever-present spectre of inhibitor formation in this patient group.

CONFLICT OF INTEREST
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AUTHOR CONTRIBUTION
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