modulators are being actively pursued.[9] Once novel modulators with a better therapeutic index are discovered, their cardioprotective effects can be tested by using the animal model presented by Efentakis et al.

Overall, the study by Efentakis et al provides new insights into the mechanism of Cfz-induced cardiotoxicity by establishing a relevant animal model and demonstrates the protective effects of Met. But a few questions remain to be answered. In addition to those raised by the authors in the "Discussion," there are other questions of interest. Because all proteasome inhibitors are reported to cause some cardiotoxicity but less cardiotoxicity than Cfz, what is the mechanism for the other proteasome inhibitor–induced cardiotoxicities and how can the higher incidence of cardiotoxicity with Cfz be explained? Are the animal data from this study or any other animal model going to be clinically applicable to human patients? Clinical trials in humans are needed to answer this question. And last, will the recently approved dose and dosing schedule for Cfz be less or more cardiotoxic?

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LYMPHOID NEOPLASIA

Comment on Qian et al, page 724

Yet another susceptibility variant for ALL: what's next?

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In this issue of *Blood*, Qian and colleagues[1] add *ERG* variants to a growing list of common host DNA polymorphisms that have been associated with an increased risk of childhood acute lymphoblastic leukemia (ALL). It has long been known that Hispanics more frequently develop childhood ALL. In addition to *GATA3*, *PIP4K2A*, and *ARID5B*, this increased risk is now also accounted for by *ERG* variants with the frequency of risk variants being positively related to the proportion of Native American Ancestry.

Susceptibility for ALL covers a wide continuum that ranges from rare, but highly penetrant, cancer prone syndromes with a 10- to 100-fold (or even more) increased risk of ALL to common germline DNA variants that mediate only a modest (1.2- to 3.0-fold) increased odds ratio.[2] The former group includes both syndromes dominated by their nonmalignant phenotype, such as Down syndrome and ataxia telangiectasia, as well as pure cancer syndromes, such as Li-Fraumeni syndrome. At the other end of the spectrum, the risk genes include *ARID5B*, *PIP4K2A*, *IKZF1*, *CDKN2A*, *CEBPE*, *GATA3*, and now also *ERG*. Many of the risk genes associated with ALL are transcription factors involved in hematopoietic development. Several of these are frequently affected by somatic mutations in ALL, such as *IKZF1*, *CDKN2A*, and *ERG*, but the common variants that associate with ALL risk in most cases reside in noncoding regions.

Adding to this, the susceptibility variants and cancer-prone syndromes are often strongly associated with certain subsets of ALL, such as *ARID5B* variants being associated with high-hyperdiploid ALL, *GATA3* variants with Philadelphia-like ALL, and Li-Fraumeni syndrome with hypodiploid ALL. Of interest, the gap between the common susceptibility variants and the rare cancer-prone syndromes is slowly closing with the demonstration that 1% to 3% of ALL patients harbor deleterious coding variants in genes previously only linked to rare cancer-prone syndromes, such as *ETV6*[3] and *TP53*.[4]

Whereas some of the common variants, like those residing in *ARID5B*, have been associated with an increased risk of ALL across multiple ethnicities, others like *ERG* seem to be more race restricted. However, it remains uncertain whether this reflects the broader, yet undefined, ethnicity-dependent genomic context within which they mediate their biological effect, or whether it reflects interactions with environmental risk factors for ALL that are influenced by certain behavioral profiles.[5]

The mapping of the natural history of ALL has mostly used the *ETV6/RUNX1* and high-hyperdiploid ALL subsets as prototypes as they are the most common ALL subsets and furthermore frequently initiated prenatally. Thus, clone-specific markers representing preleukemic cells can be detected in neonatal blood spot samples or Guthrie cards.[6] The preleukemic cell burden at birth can then taper off, or the preleukemic cells can persist and acquire the additional somatic mutations necessary for development of

overt ALL, and likely mediated by activation-induced cytidine deaminase and recombination-activating genes.[7] Models of these dynamics have been based on epidemiological and animal research that links ALL risk with reduced microbial exposure in early life.[8] Thus, one of the most consistent epidemiological findings is the association of daycare center attendance with a 20% to 25% reduced risk of childhood ALL.[9] Importantly, immune system maturation in early postnatal life may not just reflect infectious exposures because abnormal profiles of inflammatory markers can already be detected in neonatal blood spot samples.[10]

Although traditional genome-wide association study analyses have granted us some insight into the biological pathways involved in leukemogenesis, a deeper understanding of childhood leukemia development will require integration of large-scale screening of cord blood samples,[6,10] mapping the infectious burden in early life through population-based registers that provide data on known risk factors for ALL, such as birth weight, birth order, sibship size, and daycare center attendance, as well as hospital admissions and antibiotic use, and linkage of these data with genomic profiling of both host and tumor DNA.

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PLATELETS AND THROMBOPOIESIS

Comment on Zhao et al, page 730

More than one pathway: novel treatment for ITP

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In this issue of *Blood*, Zhao et al explored the role of low doses of the histone deacetylase inhibitor (HDACi) chidamide in restoring immune tolerance in patients with immune thrombocytopenia (ITP).[1]

For their investigation, the authors used both an animal model and a translational model with patient samples. Their work adds to the knowledge about the pathophysiology of ITP and explores a novel therapeutic avenue for patients with refractory disease who need alternative therapies. The authors recognized that $CD4^+CD25^+Foxp3^+$ regulatory T (Treg) cells are reduced in ITP. That, combined with the knowledge that use of low-dose HDACi's restores Treg cell populations in patients with graft-versus-host disease and other autoimmune conditions, led them to hypothesize that these agents may be useful as therapy for ITP.[2,3] The Zhao et al study was a proof-of-concept study that investigated this novel approach to treating ITP.

By starting treatment at the time of antiplatelet antibody exposure in a passive ITP murine model, the authors were able to ameliorate thrombocytopenia at 72 and 120 hours. In this model, ITP is induced in mice by giving animals antiplatelet antibodies, which simulates some, but not all, of the characteristics of patients with ITP. Therefore, the authors used a second animal model of ITP, in which mice that lacked certain platelet antigens were used as donor mice to cause an immune response, which could then be transferred by harvesting spleen cells and infusing these splenocytes. This active ITP model more accurately simulated a severe chronic ITP scenario and showed development of durable thrombocytopenia (lasting ~28-35 days) with associated bleeding mortality. By using this model, the authors were again able to ameliorate thrombocytopenia by administering chidamide beginning with the infusion of splenocytes. This therapy increased the number of Treg cells in the splenocytes and effectively improved the thrombocytopenia. Even more relevant to clinical use, mortality from bleeding rates was reduced in mice treated with chidamide. In a translational experiment, the authors used peripheral blood mononuclear cells from 8 patients and 8 healthy controls and cultured these cells with low-dose chidamide, thus demonstrating that cells from patients with ITP responded by increasing the number of Treg cells in culture.

The authors then explored additional mechanisms by which HDACi's might ameliorate thrombocytopenia in ITP. They demonstrated ex vivo that chidamide treatment of macrophages decreased macrophage phagocytosis of antibody-coated platelets, which supports a role of HDACi's in modulating macrophage activity and