care with chronic IV IgG supplementation, surveillance for EBV exposure and reactivation, and treatment of autoimmune manifestations have been mainstays of management.

The development of HLH or lymphoma has often prompted allogeneic hematopoietic cell transplantation (HCT). A recently published international survey of transplant outcomes in the current era showed that 81.4% of patients with genetically defined XLP are surviving after allogeneic HCT with evidence of immunologic improvement in most. However, post-HCT survival in patients who had developed HLH was shown to be substantially worse at 50%, while all patients without prior HLH survived the HCT procedures. What’s more, not surprisingly all but 1 of the deceased patients had received HCT from mismatched donors. A number of deceased patients reported by Booth et al who only received HCT donors, had received allogeneic HCT with evidence of immunologic improvement in most. However, post-HCT survival in patients who had developed HLH was shown to be substantially worse at 50%, while all patients without prior HLH survived the HCT procedures. What’s more, not surprisingly all but 1 of the deceased patients had received HCT from mismatched donors. A number of deceased patients reported by Booth et al who only recovered with partial sustained donor chimerism (as low as 5%) were noted to develop clinical symptoms.

Thus the time has come to develop clinical vector(s) and plan future clinical trials for XLP in patients lacking suitably matched HCT donors. Lentiviral vector constructs, as used in the current report, have been shown to be highly effective in terms of transduction because of their ability to infect both replicating and nonreplicating cells, including hematopoietic stem cells. Current data from experimental systems indicate that lentiviruses have significantly lower genotoxicity compared with the long terminal repeat–driven γ-retroviral retroviruses used in earlier trials of gene therapy in other immunodeficiencies that resulted in cases of leukemogenesis directly linked to the therapy: X-linked severe combined immunodeficiency (SCID), 3 Wiskott Aldrich syndrome, 4 and X-linked chronic granulomatous disease. 5

In addition to selection of the safest effective vector, the time frame and intensity of patient conditioning after stem cell harvest but before infusion of gene-corrected autologous stem cells requires thoughtful planning and discussion.

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might be altering CLL cell biology. By testing the expression of several homolog isomers of UGTs in CLL patient samples and in the CLL cell line MEC-1, UGT2B17 mRNA expression was the only isoform expressed to any significant level. UGT2B17 mRNA expression was also shown to directly correlate with its enzymatic activity. Extending the biology further, UGT2B17 RNA silencing in the MEC-1 cell line was pursued followed by analysis of comparative microarray that identified several important activation markers including CD38 and CD86. Further phenotype associated with UGT2B17 knockdown as related to proliferation, spontaneous apoptosis, or resistance to fludarabine or the active metabolite of cyclophosphamide (4-HC) was not reported.

The current study is provocative and identifies something entirely new and leaves several questions to be addressed. First, is the UGT2B17 protein expressed in CLL and what does its knockdown do to proliferation and cell survival? The expression of UGT2B17 is investigated only at mRNA level in this article and the MEC-1 cell phenotype after knockdown is not described. Second, what factors induce UGT2B17 overexpression in CLL and what are the direct versus indirect consequences of UGT2B17 overexpression? Although gene-expression profile in the UGT2B17 knockdown MEC-1 cells is described in the article that identify several important genes modified including CD38 and CD86, it is uncertain if this is a direct or indirect consequence of UGT2B17 expression. Finally, how do we translate these findings to clinical applications relevant to CLL patients? UGT2B17 expression may be used as a prognostic marker in CLL; however, therapeutic drugs targeting UGT2B17 have not been investigated. Cathchins in green and white tea and flavonoids from red wine have been shown to inhibit UGT2B17. These findings may help to design drugs targeting UGT2B17 for CLL therapy. Furthermore, efforts to eliminate induction of UGT2B17 with treatment once the mechanism of this is understood might be a relevant strategy. Gruber and colleagues are commended for this fine study that provides new leads to pursue progression of CLL and potential drug resistance associated with its treatment.

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Comment on Schmidt et al, page 1200

Inhibiting the hepcidin inhibitor for treatment of iron overload

Laura Silvestri1,2 1VITA-SALUTE UNIVERSITY; 2SAN RAFFAELE SCIENTIFIC INSTITUTE

In this issue of Blood, Schmidt et al report a lipid nanoparticle (LNP)–based pharmacologic treatment to induce liver–specific Tmprss6 silencing and modulate hepcidin, the main regulator of iron homeostasis, in murine models of primary and secondary iron overload.1

Liver iron transcriptionally activates BMP6, which recruits BMP receptors (BMPRs) and HJV for SMAD1/5/8 pathway activation. The SMAD complex translocates to the nucleus to bind the BMP Responsive Elements (BREs) in hepcidin promoter. Binding of HFE to TFR2 positively modulates BMP expression through a still unclear, likely SMAD-related, mechanism. Tmprss6 inhibits hepcidin through the cleavage of HJV that reduces the BMP-SMAD pathway signaling. Ineffective erythropoiesis down-regulates hepcidin expression through activation of hepatic inhibitors (iron deficiency and hypoxia and/or Tmprss6, not shown). High hepcidin/low iron improves ineffective erythropoiesis, likely decreasing iron supply to single erythroid cells. Professional illustration by Marie Dauenheimer.

In genetic hemochromatosis and in β-thalassemia, iron overload is the primary cause of liver cirrhosis, diabetes, heart failure, and other clinical complications, including liver cancer. In both conditions iron overload is due to inappropriately low levels of the iron regulatory hormone hepcidin, which controls iron absorption from the diet and iron release from macrophages through the degradation of the sole cell iron exporter ferroportin.2 Hepcidin is up-regulated by iron through Bone Morphogenetic Protein (BMP) 6, which activates the BMP–Son of Mothers Against Decapentaplegic (SMAD) signaling pathway upon interaction with BMP receptors and their co-receptor hemuovulin (HJV). This pathway can be modulated by the hemochromatosis gene HFE through a still unclear mechanism (see figure).3 Hepcidin inhibition occurs in iron deficiency, hypoxia, and erythropoiesis expansion to meet the increased iron requests. Tmprss6 is the only hepcidin inhibitor whose role has been clearly demonstrated in vivo. Tmprss6 encodes for the hepatocyte–specific
UGT2B17 as a disease accelerator in CLL

Yiming Zhong and John C. Byrd