with refractory disease may be more debilitated and unable to tolerate aggressive combination treatments. In contrast, patients with refractory disease may stand to benefit the greatest from combination therapy. Thus, should we abandon the use of single-agent therapy in favor of combinations in all settings? The data from Larocca et al clearly demonstrate the benefits of triple drug combinations, combining the old with the new, and it appears that this regimen both is more active than pomalidomide/dexamethasone in lenalidomide-refractory patients and is well-tolerated. However, the patients, although lenalidomide-resistant, were less heavily pretreated overall (1-3 prior lines vs >5 for the Richardson study). This difference in inherent drug exposure limits the ability to extrapolate the pomalidomide/cyclophosphamide/prednisone data from Larocca to the generalized refractory myeloma patient population.

The unanswered question remaining for the clinician is, who is this regimen best suited for? It appears that the pomalidomide/cyclophosphamide/prednisone combination is effective and can be safely administered with very encouraging results. However, it remains unclear whether the benefits of combination therapy realized in early lines of therapy can be routinely applied to a sicker, less robust, refractory population after numerous lines of prior treatment. Until these types of trials are performed in the refractory relapse population, decisions regarding combination therapy, although they may be biologically appealing, need to be based on the physical and hematological reserve of the refractory patient in question. Thus, although the combination may be fortuitous, circumstances of an individual patient will dictate the ultimate utility and success of this approach.

Conflict-of-interest disclosure: S.L. is a consultant for Millennium, Celgene, Novartis, BMS, Onyx, and Sanofi. 

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LYMPHOID NEOPLASIA

Comment on Shukla et al, page 2848

IRF4<sup>−/−</sup>Vh11 mice: a novel mouse model of CLL

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In this issue of Blood, Shukla and colleagues identify IRF4<sup>−/−</sup>Vh11 mice, which develop spontaneous chronic lymphocytic leukemia (CLL) with 100% penetrance within 10 months as a novel mouse model of CLL, providing a new tool for investigating the pathogenesis of CLL and evaluating therapeutic agents.<sup>1</sup>

Genetically modified mice are essential tools for investigating the roles of genes in development and progression of diseases and for preclinical testing of new therapies. The absence of good mouse models of CLL, the most common leukemia in Western countries, has hindered research and the development of therapies to combat this incurable disease. Due to the nonproliferating nature of circulating CLL cells, xenograft models of human CLL are inaccurate models of disease. In the last decade, several mouse models representing different subtypes of CLL have been developed. For example, Eμ-TCL1 transgenic mice resemble aggressive CLL,<sup>2</sup> Dhu2/miR15a/16-1 deletion mice<sup>3</sup> and miR29b transgenic mice<sup>4</sup> are related to indolent CLL, and TRAF2DN/Bcl2 double transgenic mice<sup>5</sup> may be a model of refractory CLL. However, because of the complexity and heterogeneity of CLL and the limitations of current mouse models, the development of new mouse models of CLL is attractive. In this issue, Shukla and colleagues establish IRF4<sup>−/−</sup>Vh11 mice as a novel mouse model of CLL with 100% penetrance within 10 months.<sup>1</sup>

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Interferon-regulatory factor 4 (IRF4) is a critical transcription factor for hematopoietic development and the immune system. It has been identified as an oncogene in multiple myeloma but a tumor suppressor in CLL. In this study, Shukla and colleagues backcrossed Vh11 mice which have a dramatically expanded B1 cell population into IRF4-deficiency mice and found that 100% (n = 12) of IRF4−/−Vh11 mice developed CLL within 10 months (see figure). Among those IRF4−/−Vh11 mice, 70% resemble indolent CLL and 30% exhibit aggressive CLL. Even after just 5 months, 7 of 12 (58%) IRF4−/−Vh11 mice developed CLL and the rest developed monoclonal B-cell lymphocytosis (MBL). In contrast, no CLL or MBL was detected in the IRF4+/+Vh11 control mice within 12 months. The authors also reported that IgM CD35+ CLL cells started to increase in the blood of IRF4−/−Vh11 mice at 2 to 4 months of age and occupied ~69% of peripheral blood mononuclear cells at 8 months of age (see figure). IRF4−/−Vh11 mice exhibited splenomegaly and lymph node enlargement and those with aggressive CLL had enlarged livers. The authors then identified the surface phenotype of IRF4−/−Vh11 CLL cells as CD19+, B220low/+, CD23−, CD21−, IgDlow, and CD1dint, and demonstrated that IRF4−/−Vh11 CLL cells were transplantable into immunodeficient host mice.

To further characterize the IRF4−/−Vh11 CLL cells, Shukla and coworkers studied proliferation, survival, and molecular signatures of these cells and found that IRF4−/−Vh11 CLL cells mainly proliferated in spleen while not in blood nor in lymph node, and these cells were resistant to apoptosis. Consistent with these findings, reexpression of IRF4 in IRF4−/−Vh11 CLL cells in vitro promoted apoptosis. Very interestingly, the authors found that the expression of Mcl-1 which is a critical prosurvival factor for CLL cells was significantly increased in all 5 IRF4−/−Vh11 CLL samples compared with controls, while the expression of TCL1 and miR15a/16-1 was not deregulated.

Collectively, the findings in this study strongly indicate an important role of IRF4 in the initiation and progression of CLL and potential applications of this novel IRF4−/−Vh11 mouse model in understanding CLL etiology and testing preclinical drugs.

There are also several questions that need to be further addressed. First, in order to verify the role of IRF4 in the initiation of CLL, the transplantable ability of untransformed IRF4−/−Vh11 cells should be further investigated. Second, IRF4 deficiency affects other lymphocyte subsets; therefore, other potential abnormalities in IRF4−/−Vh11 mice need to be characterized. Third, as the authors discussed in the manuscript, more generations of backcrossing are preferred to get a pure genetic background in IRF4−/−Vh11 mice to further facilitate reproducibility of experiments. Overall, this study represents a significant step forward in our understanding of CLL, and the CLL field is looking forward to the applications of this new mouse model with respect to immunology, experimental therapeutics, and biology of this disease.

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Comment on Chaturvedi et al, page 2877

Targeting IDH: the next big thing in AML

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In this issue of Blood, Chaturvedi and coworkers use a small molecule inhibitor of mutant isocitrate dehydrogenase 1 (IDH1) to reverse the myeloproliferative effects induced by the “oncometabolite” 2-hydroxyglutarate (2-HG).1

Just occasionally, things in biomedical research actually work out the way they are supposed to. A few years back, groups of researchers all around the world began using next-generation sequencing techniques to sequence whole exomes and whole genomes from acute myeloid leukemia (AML) samples, a grand scheme that was supposed to identify new mutations that could be targeted with new therapeutics. One set of mutations emerging from these screens was found in genes encoding for the 2 isoforms IDH1 and IDH2. The mutations, first identified in gliomas, were noted to occur in 15% to 20% of newly diagnosed AML patients, particularly in those with normal cytogenetics.2,3 After dusting off our biochemistry textbooks and reviewing the intermediates in the Krebs cycle, many of us in the field immediately wondered how such mutations could promote malignant transformation.

Investigators who were not intimidated by a little biochemistry took up the challenge, and a clearer picture of how these new mutations promote transformation is now emerging.5,8 The IDH enzymes, as homodimers, convert isocitrate into α-ketoglutarate (α-KG), which turns out to be not only an intermediate in the

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