Moreover, current knowledge with regard to major immune subsets in different human and mouse tissue sites has not been well elucidated. It remains unknown if humans have similar immune subsets in different tissues compared with mouse tissue sites. It may be possible that tumor-reactive T cells to CLL antigens are present in Tc1−tg mouse spleen but may not be present in human lymph nodes or other tissues. Taken together, it may not be surprising that the immunotherapy results observed in this relevant CLL mouse model do not recapitulate the human disease.

Despite the promise of PD-1 blockade in RT patients, this approach did not prevent the progression of underlying clonally related CLL, suggesting that these interesting anti–PD-1 findings might be best translated to combination therapies for RT/CLL patients. To this end, early work in a pilot study from the MD Anderson Cancer Center using BTKi therapy with PD-1 blockade has been ongoing and may add to these results. Nonetheless, to establish further advances for RT therapy, there remains a great need for a better understanding of the mechanisms involved in the development of RT. The important work described by Ding et al may be the initial step by demonstrating single-agent PD-1 blockade can benefit RT patients with modest improvements of survival. While other early-phase trials are ongoing, these results clearly must be confirmed in a larger phase 3 study testing the efficacy of checkpoint inhibition in RT patients. Overall PD-1 blockade may finally be the next move toward significant progress in the treatment of RT since conventional chemoimmunotherapy.

Conflict-of-interest disclosure: J.M.P. is a consultant for Pharmacyclics and Gilead Pharmaceuticals.

REFERENCES
the Tc1 model. By using adoptive transfer approaches, the team also demonstrated that CD1d expression by CLL cells was not required for initial tumor control, implicating a third player in CD1d-dependent tumor surveillance by NKT cells.

Gorini et al then explored these findings with a series of experiments using samples from patients with stable and progressive CLL, confirming previous reports that high CD1d expression was more evident in the group with progressive CLL. NKT cell function was impaired in patients with progressive CLL, with poor responsiveness to stimulation with strong agonists, such as CD3/CD28 or phorbol myristic acid/ionomycin. This indicated that strong CD1d stimulation rendered NKT cells unresponsive to additional stimulation. Interestingly, these effects were observed in the absence of any exogenous CD1d ligand, demonstrating that a CLl self-ligand could be driving NKT cell exhaustion. Although the nuances of NKT cell anergy versus exhaustion were not explored due to a lack of material, these observations suggest that additional studies could be done to functionally characterize the “exhausted” NKT cells. Such characterization might also involve sublineage determination and whether there is any skewing away from an antitumor Th1 phenotype.

The authors then tested the hypothesis that NKT cells could suppress the CLl-supporting functions of monocye-derived CD1d

The study by Gorini et al therefore sheds important new light on the mechanisms underlying the progression of CLL and may impact other areas of study. Arguably, new therapeutics for CLL may involve breaking the cycle between CD1d

leads to NKT cell exhaustion, such that they are unable to suppress NLC differentiation and subsequently support NLCs (see figure).

Although investigators and clinicians will await independent confirmation of these findings, this intriguing new model may have far-reaching implications for CLl diagnosis and treatment and may also impact research outside this immediate field. Firstl, CLl may remain a very useful diagnostic marker for early-stage and stable CLl. Furthermore, the use of exogenous CD1d-binding glycolipids to boost NKT cell control of CLl, as suggested in previous studies,

Under certain conditions, CD1d-binding glycolipids, such as α-galactosylceramide, render NKT cells anergic.

If such glycolipids are used for therapy, they could lead to desuppression of NLCs and have the unintended consequence of leading to more aggressive CLl.

A functional link between CD1d expression by B-lineage cells and NKT cells is also contributory to the humoral immune response to vaccination,

to blood-group antigen alloreactivity,

and to NKT cell–regulated autoreactive B cells in systemic lupus erythematosus.

Investigators in these other fields may wish to consider the consequences of low versus high CD1d expression by B-lineage cells and indirect mechanisms involving other CD1d

cells types.

The study by Gorini et al therefore sheds important new light on the mechanisms underlying the progression of CLl and may impact other areas of study. Arguably, new therapeutics for CLl may involve breaking the cycle between CD1d

cells, NKT cells, and NLCs.

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PLATELETS AND THROMBOPOIESIS

Comment on Vo et al, page 3486

Singling out FLI1 in Paris-Trousseau syndrome

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In this issue of Blood, using induced pluripotent stem cell (iPSC)–derived human megakaryocytes (iMega), Vo et al find that the megakaryocyte/platelet defects observed in patients with Paris-Trousseau syndrome (PTS) are due solely to hemizygous deletion of the transcription factor (TF) FLI1.

TFs bind to specific DNA sequences adjacent to the genes they regulate to promote or block the recruitment of RNA polymerase, thereby controlling the transcription of genetic information from DNA to RNA. Hematopoiesis critically depends on
CD1d-dependent CLL progression?

Mark L. Lang