of noncoding SNVs and their interactions with enhancers and repressors, as well as to test how polymorphisms in SNVs relate to chronic diseases. Second, the results support previous in vitro and in vivo studies indicating that browning of white adipose tissue has physiological relevance and that disorders of mitochondrial function and brown fat may play a role in pathophysiological aspects of obesity. Finally, shifting adipocytes from energy storage to energy expenditure with pharmacologic and nonpharmacologic measures may become more feasible as the ARID5B–FTO–IRX3/IRX5 regulatory network becomes fully defined. Future studies are certain to focus on how FTO, which is highly expressed in several tissues, can affect other organs.7 The creation of a knock-in mouse with high-risk FTO alleles should facilitate the determination of the contribution of these gene variants to obesity. As yet, there is still no simple path to an anti-obesity drug that can be derived from this research.

Importantly, the present work demonstrates new ways to use data from genomewide association studies. The study thus provides a strategy for translating information from genomewide association studies and ultimately for identifying new pathways in conditions beyond obesity.

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Treating Myeloproliferation — On Target or Off?

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The classic myeloproliferative neoplasms — essential thrombocythemia, polycythemia vera, and primary myelofibrosis — are clonal disorders marked by overproduction of mature blood cells.1 Disease often evolves over many decades, and affected patients have symptoms related to extramedullary hematopoiesis, a thrombotic tendency, and, rarely, leukemic transformation.1 Hematopoietic stem-cell transplantation is the only curative therapy, and treatments usually focus on controlling symptoms.

In this issue of the Journal, two groups of investigators present the results of studies of imetelstat, an antisense oligonucleotide, in phase 2 trials involving patients with essential thrombocythemia and primary myelofibrosis. Baerlocher et al.,2 who conducted a multi-institutional trial of imetelstat involving 18 patients with essential thrombocythemia in whom first-line therapies had failed, report a complete hematologic response rate of 89%. Ten of the 18 patients received therapy for a median of 17 months. Tefferi et al.3 describe the results of a single-institution trial involving 33 patients with myelofibrosis, and they report a partial or complete response rate of 21%. The duration of response ranged from 10 to 18 months.

The studies used slightly different dosing schedules, but both documented side effects that included hepatotoxicity, myelosuppression, and bleeding tendencies. Given the limited treatment options in myeloproliferative neoplasms, these results are compelling and warrant further study, especially as to whether imetelstat can change the natural history of these disorders.

Imetelstat was designed as a telomerase en-
zyme inhibitor; it is an antisense phosphorothioate oligonucleotide that targets the telomerase RNA template. Cell-culture and xenograft studies have shown that imetelstat can block telomerase and shorten telomeres; however, telomere shortening in animal tissues or in humans has not been demonstrated. Imetelstat has been previously studied in two telomerase-positive cancers — non–small-cell lung cancer and breast cancer (ClinicalTrials.gov number, NCT01256762) — and there was no clinical benefit.

Short telomeres trigger a DNA-damage response that induces cell death or senescence, which is the primary effect that limits tumor growth; telomerase inhibition itself is not sufficient. Thus, an effective telomerase inhibitor would be expected to shorten telomeres in malignant cells to exert its therapeutic effect.

In the studies reported here, the initial telomere length did not predict the clinical responses, and there was no change in telomere length over the course of treatment in the myelofibrosis cohort. Both groups of investigators examined telomere length with the use of a quantitative polymerase-chain-reaction method that has high variability, rather than with the use of the flow cytometry–based assay that has emerged as the clinical standard for diagnosing telomere syndromes. Precise measurement of telomere length will be critical for testing the biologic efficacy of a drug that targets telomerase.

If telomere shortening is not the primary mechanism underlying the clinical effects of imetelstat, what might be the mechanism? Myelosuppression, especially thrombocytopenia, is a common side effect of phosphorothioate antisense oligonucleotides. In fact, in previous trials of imetelstat, these toxic effects were dose-limiting. These side effects are independent of the antisense sequence and are thought to be mediated through mechanisms that include binding to cell-surface receptors such as TLR9. If such an off-target effect is the primary mechanism of imetelstat action in myeloproliferative neoplasms, this knowledge will be critical for patient selection, for understanding mechanisms of resistance, and for future drug development in myeloproliferative neoplasms.

Telomerase is up-regulated in most cancers, and the concept of inhibiting telomerase to treat cancer was proposed more than 25 years ago. The recent evidence of frequent somatic mutations that up-regulate telomerase levels in many cancers lends further support to the idea that telomerase inhibition is an important target in cancer. However, if the mechanism of action of imetelstat in myeloproliferative neoplasms is through off-target effects, the generalizability of imetelstat for treatment of other cancers is drawn into question.

Whether the mechanism is on target or off, the results of the clinical studies published here spark new possibilities for the treatment of myeloproliferative neoplasms. Further analysis of both the mechanism and, more importantly, the long-term side-effect profile of imetelstat may provide a new approach to treat these debilitating disorders.

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