To the editor:

Systemic dasatinib fails to prevent development of central nervous system progression in a patient with BCR-ABL unmutated Philadelphia chromosome–positive leukemia

Porkka et al demonstrated that dasatinib crosses the blood-brain barrier and exerts antitumor activity in a mouse model of intracranial chronic myelogenous leukemia (CML).[1] They reported that systemic dasatinib induced tumor cell clearance from cerebrospinal fluid (CSF) in patients with Philadelphia chromosome–positive (Ph^+) leukemias and central nervous system (CNS) involvement.[1] Mutational analysis of CSF leukemic cells suggested that progression was due to selection of drug-resistant clones within the CNS.[1]

We report on a 46-year-old man with Ph^+ chronic-phase (CP) CML without additional cytogenetic abnormalities. He received imatinib (400 mg/day) and achieved a complete hematologic response after 1 month, a complete cytogenetic response at 6 months, and a major molecular response at 12 months (Figure 1).[2] Bone marrow (BM) examination after 20 months of imatinib disclosed a 1-log rise of BCR-ABL transcripts. Imatinib was escalated (800 mg/day) but BCR-ABL levels showed a progressive increase leading to myeloid blast crisis (BC) 33 months after diagnosis. Dasatinib (140 mg/day) was started but discontinued after 4 weeks due to hematologic toxicity. A fludarabine (30 mg/m^2 per day on days 1-5), cytarabine (2 g/m^2 per day on days 1-5), and idarubicin (10 mg/m^2 per day on days 3-5) combination (FLAG-IDA)[3] course induced a second CP, which was consolidated by allogeneic bone marrow transplantation (allo-BMT). Because of the high relapse risk, dasatinib (100 mg per day) was administered between chemotherapy and allo-BMT, resulting in approximately 1-log reduction in BCR-ABL level, and resumed after transplantation with the patient in CP and stable BCR-ABL levels. After 2 months an isolated leukemic CNS relapse occurred, despite

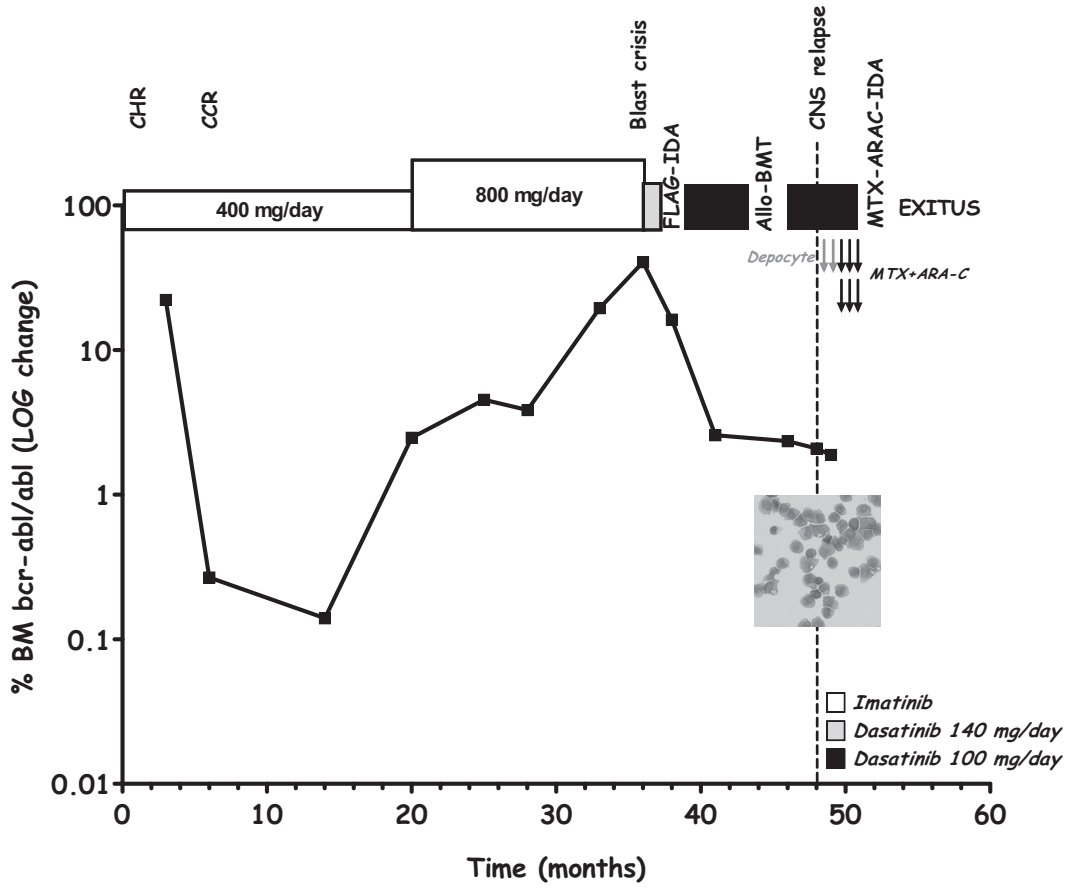

Figure 1. Clinical course of a patient with Philadelphia chromosome–positive chronic myelogenous leukemia developing isolated central nervous system relapse while under dasatinib therapy. At the time of blast crisis, morphologic and flow cytometry studies evidenced 55% of myeloid blasts in the bone marrow (BM) with a $CD33^+CD13^+CD10^-CD20^-CD45^+$ immunophenotype (not shown). BCR-ABL levels in BM were quantified by real-time polymerase chain reaction according to a described standard protocol.[2] Gray arrow indicates intrathecal therapy with liposomal cytarabine (Depocyte, 50 mg); black arrows indicate intrathecal therapy with methotrexate (MTX, 12 mg) and cytarabine (ARA-C, 50 mg). Inset displays a May-Grünvald-Giemsa–stained cytospin slide of cerebrospinal fluid (CSF) showing myeloid blasts with a $CD33^+CD13^+CD10^-CD20^-CD45^+$ at flow cytometry (not shown). At the time of documented leptomeningeal disease, the bone marrow examination was consistent with chronic-phase disease with a blast differential count of 4%. CHR indicates complete hematologic response; CCR, complete cytogenetic response; FLAG-IDA, fludarabine (30 mg/m^2 days 1-5), cytarabine (2 g/m^2 days 1-5), and idarubicin (10 mg/m^2 days 3-5) combination chemotherapy; Allo-BMT, allogeneic bone marrow transplantation; and MTX-ARA-C-IDA, systemic therapy with high-dose methotrexate (3.5 g/m^2 day 1) and cytarabine (2 g/m^2 days 2-3) plus idarubicin (8 mg/m^2 days 2-3).

further reduction of BCR-ABL levels and without BM blastosis. The patient succumbed to CNS disease 3 months afterward, despite CNS-directed chemotherapy. Sequencing of the BCR-ABL kinase domain from BM blasts, at the time of BC, and CSF tumor cells, at CNS relapse, did not show any mutation. The lack of BM blastosis, the reduced marrow BCR-ABL levels and the absence of a mutated clone, in BM and CSF, at the onset of meningeal leukemia, indicate that systemic dasatinib failed to prevent CSF disease while still controlling extra-CNS leukemia. Thus, relapse was most probably due to suboptimal penetrance/activity of the drug in CNS given the low dasatinib dose (100 mg per day) used being the patient in CP. In the 4 months preceding CNS progression, the patient was not given comedications known to decrease the plasma concentrations of dasatinib,[4,5] including CYP4503A4 inducers, but rather received the CYP4503A4 inhibitor itraconazole. Therefore, even though we did not assess plasma levels, it is reasonable to exclude a negative influence of comedications on dasatinib bioavailability.

Dasatinib achieves CSF concentrations of 5.0% to 28% of those found in the plasma and Authors speculated that the biologic potency of dasatinib and/or the lack of protein binding may explain antitumor activity at low CSF levels.[1] However, approximately 50% of patients received steroids and/or other intrathecal agents before, together with, or soon after dasatinib, suggesting that this agent alone is unable exert a proper control of CNS disease in all cases.[1,6] Factors other than tumor cell resistance might influence dasatinib activity in the CNS, including suboptimal systemic dosing. Further pharmacokinetic studies are needed to identify patients in whom dasatinib alone may effectively control CNS disease.

Ferdinando Frigeri, Manuela Arcamone, Luigia Luciano, Raffaele Di Francia, Fabrizio Pane, and Antonio Pinto

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To the editor:

Does the presence of anti-HIV miRNAs in monocytes explain their resistance to HIV-1 infection?

We read with interest the article by Wang et al[1] that concluded that the presence of higher levels of anti–HIV-1 microRNAs (miRNAs) in monocytes may be responsible for their relative resistance to HIV-1 infection compared with macrophages.

They rightly point out that differential expression of the CCR5 coreceptor has been postulated as a reason for the differential susceptibility of monocytes and macrophages to HIV-1 infection. In our experience, only a small subset of monocytes ($< 5\%$) express CCR5 and this is at low level, whereas CD4 expression is also uniformly low compared with $CD4^+$ T cells. It is unclear from the experiments presented whether the CCR5 tropic viruses tested bind to monocytes or are internalized. A defect in adhesion or internalization would occur prior to any opportunity for miRNA to directly affect viral replication. Figure 1A from Wang et al[1] clearly demonstrates the negligible reverse transcriptase (RT) activity detected in supernatants of monocyte cultures after viral inoculation. However, it is unclear from the data presented the stage of the viral life cycle at which inhibition occurs. Therefore, despite the higher levels of anti-HIV miRNAs in monocytes, it has not been demonstrated that low-level expression of both CCR5 and CD4 is not the more significant factor in explaining their relative resistance to infection.[2]

Furthermore, in preliminary work from our laboratory, we checked miRNA expression in $CD4^+$ T cells from 8 healthy, uninfected controls and from 7 patients with chronic HIV-1 infection using a microarray system. Analysis of expression levels of the 4 miRNAs examined by Wang and colleagues showed that healthy control $CD4^+$ T cells expressed significantly higher levels of miR-28-5p and miR-150 (Figure 1), whereas miR-223 and

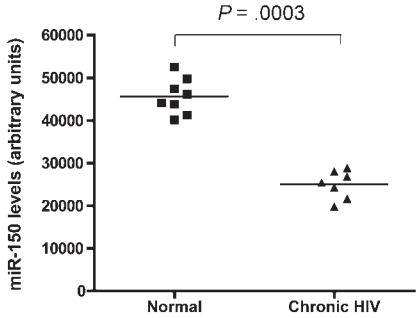

Figure 1. miR-150 levels in $CD4^+$ T cells. Shown are levels from 8 healthy volunteers (■) and 7 patients with chronic HIV-1 infection (▲) demonstrating a highly significant difference between the 2 groups. *P* value shown at top is by Mann-Whitney comparison of the 2 test groups.

miR-382 levels were not different between the 2 groups. It therefore appears that there is infection-related down-regulation of miR-150 and miR-28-5p in $CD4^+$ T cells during chronic HIV-1 infection. Using the same argument as the authors, we could conclude that because the uninfected controls had higher levels of miR-150 and miR-28-5p compared with the HIV-1–infected patients, $CD4^+$ T cells from healthy controls are relatively protected against HIV-1 infection. This conclusion is clearly incorrect with regard to $CD4^+$ T cells.

Our other concern is with the use of combined miRNA inhibitors to demonstrate changes in RT activity. Treatment of HIV-1–infected monocytes with miRNAs resulted in a rise in RT, but the effects were modest in comparison to RT levels achieved in HIV-1 infection of macrophages. It has been recently demonstrated that even inhibition of a single miRNA may modulate protein synthesis of thousands of genes.[3] The use of multiple inhibitors combined could lead to many unanticipated off-target effects. These may have unforeseen indirect effects on viral replication through changes in cellular phenotype or function. We contend that further studies confirming a lack of alteration in phenotype of monocytes after the use of these inhibitors is required before concluding that the change is a direct result of the actions of miRNAs on HIV protein synthesis.

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Conflict-of-interest disclosure: The authors declare no competing financial interests.

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Response:

Intracellular restriction factors contribute to susceptibility of monocytes/macrophages to HIV-1 infection

Swaminathan et al[1] stated that despite the higher levels of anti-HIV microRNAs (miRNAs) in monocytes, there is no demonstration in our paper that the low-level expression of both HIV-1 primary receptor CD4 and coreceptor CCR5 on monocytes is not the more significant factor contributing to monocytes' resistance to infection. They argued that in their experience only a small subset of monocytes ($< 5\%$) express CCR5. This argument, however, has its limitation, given the fact that there is tremendous variability in CCR5 expression on primary monocytes from different donors. Several studies have shown that monocytes express relative high levels of CCR5.[2,3] We pointed out in the paper that although the demonstration of differential expression of CCR5 receptor on monocytes and macrophages provides an explanation for the differential susceptibility of these cells to HIV-1 infection,[4-6] this observation does not account fully for differences in HIV-1 infectivity in monocytes and macrophages. Peng et al showed there was no substantial difference in the expression of CCR5 in donor-matched monocyte and macrophage populations; in contrast, they found that CD4 and/or CCR5 expression decreased during macrophage maturation, despite increasing susceptibility to HIV-1.[7] They demonstrated that the expression of intracellur APOBEC3 is linked to susceptibility of monocytes and macrophages to HIV-1 infection.[7] Their funding in conjunction with ours strongly support the notion that intracellular restriction factors indeed contribute to susceptibility of monocytes/macrophages to HIV-1 infection.

Swaminathan et al compared their preliminary work using $CD4^+$ T cells with ours. However, there are significant differences in the study designs between theirs and ours. First, in our study we used monocytes and macrophages isolated from the same donors. In contrast, Swaminathan et al used $CD4^+$ T cells from the subjects of 2 different groups. Second, we examined the levels of the anti–HIV-1 miRNAs in donor-matched monocytes and macrophages before HIV-1 infection, whereas Swaminathan et al compared HIV-1–infected $CD4^+$ T cells with uninfected cells. As they suggested, it is possible that HIV-1 infection may down-regulate the expression of the anti–HIV-1 miRNAs in $CD4^+$ T cells, which explains the difference in the miRNA expression in $CD4^+$ T cells from the subjects of 2 groups. Third, in our study we were able to establish the association between the expression of the anti–HIV-1 miRNAs and HIV-1 infectivity in monocytes and macrophages, as we demonstrated that the suppression of the anti–HIV-1 miRNAs in monocytes facilitates HIV-1 infectivity, whereas increase of the miRNA expression in macrophages resulted in the inhibition of HIV-1 replication.

Swaminathan et al also raised the concern about the use of the miRNA inhibitors and their modest effect on HIV-1 reverse transcription (RT) in monocytes. The difference in modulation of HIV-1 infectivity in monocytes and macrophages transfected with the miRNA inhibitors or the miRNAs could be due to the fact that the transfection efficiency differed in monocytes and macrophages. We agree with the suggestion that future studies are necessary to determine whether the miRNA inhibitors have indirect effects on HIV-1 replication through changes in function and phenotype of monocytes and macrophages. Nevertheless, our demonstration that the cellular miRNAs that have anti–HIV-1 ability in $CD4^+$ T cells[8] are also associated with the protection of monocytes and macrophages from HIV-1 infection not only provides an additional explanation to address the question that has puzzled us for almost 2 decades but also offers insight into development of intracellular innate immunity-mediated therapeutics for HIV-1 infection and AIDS.

Xu Wang and Wenzhe Ho

Acknowledgment: Approval was obtained from the University of Pennsylvania Institutional Review Board for these studies. Informed consent was obtained in accordance with the Declaration of Helsinki.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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To the editor:

Anticoagulants in portal vein thrombosis: don't be so shy!

We read with great interest the recent article in *Blood* by Martinelli et al on rare venous thromboses.[1] In the section on splanchnic vein thrombosis (SVT), it is speculated that the risk of bleeding might overweigh potential benefit from anticoagulants in patients with a high bleeding risk. We believe the definition of a "high bleeding risk" used by the authors may lead to an excessive limitation of the use of anticoagulation therapy (ACT) in these patients.

Recent studies evidence a high recanalization rate with ACT in acute portal vein thrombosis (PVT) in noncirrhotic patients. Indeed, in the study of Amitrano et al,[2] ACT was effective to obtain recanalization of acute SVT in 45.4% of patients. Similarly, in a recent multicentric study involving 105 patients,[3] early anticoagulation allowed a 44% recanalization rate of the portal vein at 1 year. In patients with cirrhosis, in the absence of hepatocellular carcinoma, the presence of PVT should stimulate rather than limit the use of ACT. Indeed, Francoz et al have shown that in patients with chronic liver diseases awaiting liver transplantation, the incidence of PVT reached 8.4% over a 6-year follow-up period.[4] The use of anticoagulants was associated with a 42% recanalization rate of the portal vein.

High risk of bleeding in the "flow diagram for treatment of portal vein thrombosis" in the article by Martinelli et al[1] is defined as the presence of esophageal varices or thrombocytopenia less than 50 000/mm^3. Esophageal varices are clearly a risk factor of bleeding, particularly when they are large. It is important to note that in absence of cirrhosis, esophageal varices may result from PVT itself.[5] Recanalization with ACT is the best therapy for varices, whereas thrombus extension is a recognized trigger of portal pressure increase and variceal bleeds. We believe that esophageal varices are accessible to effective therapy in the majority of cases. Ineffective medical treatment should lead to variceal band ligation, which is effective in 90% of cases.[5] In the exceptional situation where ligation is ineffective, transjugular intrahepatic portosystemic shunt (TIPS) can be considered. In our mind, only very few patients should temporarily be kept off anticoagulants because of uncontrollable varices. A large French cohort including 84 patients with both chronic and acute PVT who received ACT over a long follow-up period[6] showed no increased gastrointestinal bleeding risk and a similar severity of the hemorrhagic episodes (blood units transfused, duration of hospital stay) in patients who were treated with ACT compared with those who did not receive ACT. However, large esophageal varices were predictors of bleeding, justifying the use of a prophylactic approach (beta blockers [BBs] and endoscopic therapy). In the Francoz et al study,[4] only a minor risk of gastrointestinal bleeding was associated with ACT (1 patient with a postligation ulcer).

Concerning thrombocytopenia, few data are available about a "safe" platelet count. As for varices, thrombocytopenia may be secondary to PVT alone in noncirrhotic patients. Surprisingly, a low platelet count ($< 70\,000/mm^3$) was even an independent predictor of PVT.[4] In our experience, hemorrhagic episodes are infrequent in patients with PVT (with or without cirrhosis) and platelet counts greater than 30 000/mm^3.

As an alternative to the algorithm proposed by Martinelli et al, which limits the use of ACT in patients with esophageal varices and low platelets, we would like to propose the scheme shown in Figure 1

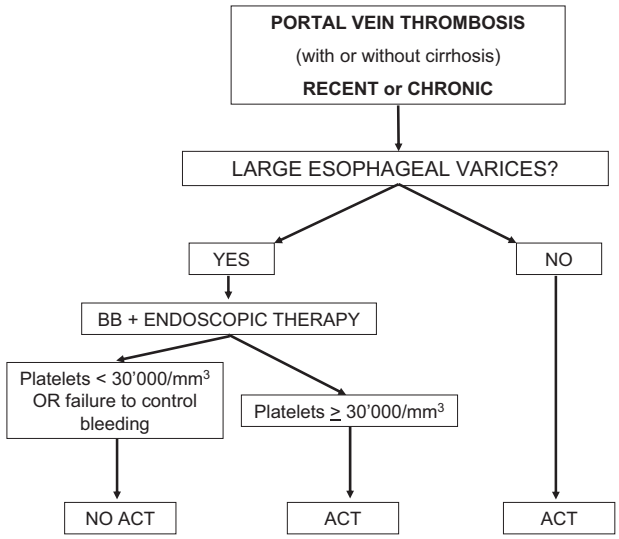

Figure 1. Algorithm for the use of ACT in portal vein thrombosis as followed in our institution. BB indicates beta blocker; and ACT, anticoagulation therapy.

that has been in use for several years in our institution for patients with PVT.

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Conflict-of-interest disclosure: The authors declare no competing financial interests.

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Response:

Anticoagulation in splanchnic vein thrombosis

In response to Spahr et al,[1,2] we would like to point out that the "How I treat" *Blood* articles are meant to feature therapeutic aspects for which evidence from randomized trials is lacking. These articles are based on opinions of experts who have a large clinical experience in the specific fields.[3-5] With this as preamble, we believe that the main disagreement between Spahr et al[1] and us[2] is on whether or not indefinite anticoagulation should be always prescribed to patients with previous splanchnic vein thrombosis (SVT), because there is no disagreement—although data stem from studies with various limits—on the indication for anticoagulants in the acute phase of SVT.[6-8] In the acute phase, anticoagulants are meant to avoid the extension of thrombosis and thereby decrease the risk of portal hypertension and its related complications, mainly gastrointestinal bleeding from ruptured esophagogastric varices.

What about the use of these drugs beyond the acute phase, particularly when portal hypertension has developed despite anticoagulation? In this instance the risk of thrombosis recurrence must be carefully weighted against the risk of bleeding. Thrombosis recurrence, the prevention of which is the true goal of anticoagulation, is not frequent in SVT,[2] being the main reason for our "shyness" to recommend this therapy in these patients at high risk of bleeding. Barring a slightly higher cutoff in platelet count, the difference between our algorithm[2] and that promoted by Spahr et al[1] is that we do envisage the possibility that beta blockers and endoscopic therapies fail to prevent variceal bleeding. Because the latter is life-threatening, we find it important to avoid the additional risk that anticoagulants entail. Thrombocytopenia, so frequent in these patients, is a strong risk factor for bleeding, superimposed on that carried by anticoagulants themselves.

In conclusion, we are reluctant to recommend indefinite anticoagulation in the majority of patients with SVT. But of course, as in all clinical conditions where therapeutic evidence is lacking, each SVT case must be considered in itself, with an accurate balance of the pros for anticoagulation (thrombophilia abnormalities and inflammatory conditions) against the cons (severe thrombocytopenia and large gastroesophageal varices).

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Conflict-of-interest disclosure: The authors declare no competing financial interests.

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To the editor:

Scientific profiling

We regret to read that the editors at *Blood* would outright reject a review manuscript, regardless of its scientific merit, if someone employed by a pharmaceutical company had any role in the development of that manuscript.[1] This stance implies that all scientists employed by a pharmaceutical company do not have the ability to be unbiased while writing or contributing to a manuscript.

We have extensive experience working closely with many scientists from a variety of pharmaceutical companies (as well as with academic-based authors) in the development of scientific publications. We have found that these scientists are typically highly trained physicians and postdoctoral scientists who have been trained by or worked alongside their academic-based counterparts. They made a life decision to leave academia for any number of reasons—tired of the endless pursuit of grants from an ever-dwindling pool, underwhelmed by the unpredictable and uncertain career path—and now, having left the academic setting, find themselves the object of disparaging accusations.

The expertise of scientists employed by a pharmaceutical company is frequently recognized and called upon by academic physicians. These scientists have focused their careers on drug research and have extensive knowledge of the resulting clinical data as well as the therapeutic area. In addition, it would not be uncommon for an author preparing to write a review article to contact the medical information department of a pharmaceutical company and request relevant data. Either may be the case in the example cited in the "Ghostbusting" editorial, where the clinical investigator was provided several data sources from the pharmaceutical company. Apparently the author considered the data and wrote a manuscript that was deemed after the *Blood* peer review process to be "well-written, informative, and balanced." The fact that the manuscript, which reviewers found to be balanced, was rejected because of acknowledged pharmaceutical company involvement suggests that the editorial review process has fallen to "scientific profiling." Has the editorial review process become prejudiced against scientists from a different form of employment than their own?

In no way do we advocate ghosts of any sort, and by the same token we should recognize that there has been a positive shift during the last 4 to 5 years within the pharmaceutical and biotech environment to improve transparency of roles involved in the preparation of manuscripts. There is now widespread endorsement by these companies of Good Publication Practice (GPP) guidelines[2] and increasing development of rigorous company-specific publication policies that recognize new and evolving regulations and guidance from the government (eg, the Food and Drug Administration Amendments Act of 2007 [FDAAA]) and various professional societies (eg, the International Society for Medical Publication Professionals [ISMPP]).

The peer review process—an assessment of the scientific content by qualified experts—remains the best method to evaluate the scientific merit of a publication; we urge editors of journals such as *Blood* to continue to use this method without profiling. The true measure of progress in medical publishing will be when the finger-pointing stops and we judge a submission based on content, strength of science, and methodology first and foremost, not on an inherent anti-industry bias.

Daniel Donovan, Sue Sutch, Neil Baker, and Jeanette Cook

Conflict-of-interest disclosure: D.D. is the founder of Envision Pharma, a medical publications specialty agency, and is currently a senior vice president at United BioSource Corporation. He also spent over a decade in the pharmaceutical industry. S.S., PharmD, is a senior manager at Envision Pharma. She has worked for 13 years in the medical communications arena, prior to which she was employed in the pharmaceutical industry and in academia as a researcher and teacher. N.B., PhD, MRPharmS, is a senior manager at Envision Pharma. He has worked for 15 years in the medical communications arena, prior to which he was employed in both academia as a researcher and the pharmaceutical industry in research and commercial roles. J.C., PhD, is a senior manager at Envision Pharma. She has worked for 12 years in the medical communications arena, prior to which she was an academic researcher in both the United Kingdom and United States.

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Response

More on ghostbusting

We appreciate the comments made by Dr Donovan and colleagues[1] at Envision Pharma (a medical communications company) responding to our recent editorial entitled, "Ghostbusting at *Blood*." We want to clarify several points in response. First, we did not suggest that a review article (or any other manuscript) would be summarily rejected because of any involvement by an employee of a pharmaceutical company, but rather that a manuscript should be rejected because of undisclosed involvement. This is particularly pertinent if a drug discussed in the manuscript is a product associated with the company paying for the editorial, writing, or research assistance, because of real or perceived conflict of interest. *Blood* editors have a responsibility as part of the review process to identify these conflicts so that the readers can evaluate the merits of the scientific contribution without such confounding undisclosed factors. Transparency should be in place whether an author is from industry or academia. Second, no one disputes the important contributions made by talented scientists in industry. Indeed, we emphasized this point in our editorial. Productive collaborations between the two will only become more important in the future as the elucidation of the mechanism(s) of action and determination of clinical efficacy of new therapeutic agents are jointly studied. In our editorial, we distinguished between primary research articles carried out collaboratively between academia and industry, or by industry scientists, which are treated no differently from those without industry involvement, versus Review Articles or How I Treat pieces, which are designed to give readers broad and hopefully unbiased summaries and interpretations of the state of our understanding of a particular disease or therapeutic approach. Avoiding real or perceived bias in these articles is particularly important because they involve more subjective choices regarding which primary sources to discuss and synthesize. It is possible that a pharmaceutical company author would be appropriate for such an article based on his or her general experience, but it is unlikely that *Blood* would solicit or publish a review article from such an author or allow involvement of a company-sponsored medical communciations company on a topic that encompasses the use of a product marketed by that company. Third, we believe that requesting new data from industry or a university or any other source for an author to incorporate and interpret in a review article is one thing, but the provision of complete tables of compiled data is another. *Blood*

editors continue to welcome manuscripts from qualified authors that make novel and definitive contributions to the field with full disclosure of all people involved in the preparation. Our submission screens now include specific questions for disclosure of nonauthor involvement with manuscripts, and instructions for obtaining presubmission screening in any situations that could be problematic. By discussion and negotiation before submission and full review, we believe we can better ensure high-quality and unbiased articles for our readers.

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Reference

1. Donovan D, Sutch S, Baker N, Cook J. Scientific profiling. [letter]. Blood. 2009;113:5032-5033.