The Bleomycin Model: In Pursuit of Relevant Biomarkers

To the Editor:

In the February 2015 issue of the *Journal*, Bauer and colleagues (1) describe how they identified preclinical biomarkers in the rodent bleomycin-induced lung fibrosis model—biomarkers with the potential to predict pharmacological activity for novel therapeutic agents. Their effort should be applauded.

However, the authors proceed to assert the validity of their findings by maintaining that their 12-gene (biomarker) signature can discriminate patients with idiopathic pulmonary fibrosis from control subjects in an independent cohort, GSE24206. We are concerned about the analysis of this cohort. In this article, one cannot find a description of the population or a reference for the GSE24206 cohort. The label on Figure E17 in the online supplement to the article suggests the authors believe the GSE24206 population contains 17 patients with idiopathic pulmonary fibrosis and six control subjects; in fact, the GSE24206 population contains only 11 patients with idiopathic pulmonary fibrosis, with six additional samples (technical replicates) and six control subjects (2). If, in their analysis, the authors treated the six technical replicates as if they were unique patients with idiopathic pulmonary fibrosis, then this would skew the receiver operating characteristic curves and potentially inflate the area under the curve, which could inflate the evidence for biomarker validity. On this basis, the authors should consider recalculating the area under the curve for the GSE24206 cohort dataset, which may require modification of their interpretation of the results in their manuscript. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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References

1. Bauer Y, Tedrow J, de Bernard S, Birker-Robaczewska M, Gibson KF, Guardela BJ, Hess P, Klenk A, Lindell KO, Poirey S, *et al*. A novel genomic signature with translational significance for human idiopathic pulmonary fibrosis. *Am J Respir Cell Mol Biol* 2015;52:217–231.
2. Meltzer EB, Barry WT, D'Amico TA, Davis RD, Lin SS, Onaitis MW, Morrison LD, Sporn TA, Steele MP, Noble PW. Bayesian probit regression model for the diagnosis of pulmonary fibrosis: proof-of-principle. *BMC Med Genomics* 2011;4:70.

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Reply

From the Authors:

We thank Dr. Meltzer for pointing out a potential concern with our analysis of one of the confirmatory datasets mentioned in the supplement of our paper, titled “A Novel Genomic Signature with Translational Significance for Human Idiopathic Pulmonary Fibrosis” (1). In that analysis, we reported the ability of our 12-translational gene signature to segregate patients with idiopathic pulmonary fibrosis from controls by providing the receiver operating characteristic curves and calculating the area under the curve for three datasets: GSE47460, GSE24206, and GSE10667 (0.957, 0.882, and 0.919, respectively). In our analysis of GSE24206 (2), we handled samples from different lobes as unique samples, and thus had 17 disease samples (from 11 patients) and six controls. As Dr. Meltzer correctly points out, this analysis should be done for samples from unique patients with idiopathic pulmonary fibrosis. Taking this into consideration, we repeated the analysis including only one sample per patient. The area under the curve for patients with idiopathic pulmonary fibrosis versus

Figure 1. Receiver operating characteristic curves showing the ability of the 12 translational markers to segregate patients with idiopathic pulmonary fibrosis from control subjects in the Lung Tissue Research Consortium dataset (A: control subjects = 108, idiopathic pulmonary fibrosis = 100) and three publicly available and independent clinical idiopathic pulmonary fibrosis/control datasets (B: control subjects = 6, idiopathic pulmonary fibrosis = 11; C: control subjects = 15, idiopathic pulmonary fibrosis = 23; and D: control subjects = 8, idiopathic pulmonary fibrosis = 40). A perfect discrimination between control subjects and patients with idiopathic pulmonary fibrosis would result in an area under the curve (AUC) of 1, whereas the AUC of a random discrimination (as drawn by the diagonal line) would be 0.5.

controls, using our translational gene signature on the 11 unique idiopathic pulmonary fibrosis samples and six controls, was 0.864. In Figure 1, we provide the corrected receiver operating characteristic curve for GSE24206 and the two previous receiver operating characteristic curves (Figure 1A, GSE47460; Figure 1C, GSE10667), as well as a receiver operating characteristic curve from a recently published dataset (Figure 1D, GSE53845 [3]), with an area under the curve of 0.978. Thus, the reanalysis of GSE24206 and the addition of GSE53845 strongly reinforce the impressive ability of our translational signature to correctly segregate patients with idiopathic pulmonary fibrosis from control subjects. ■

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References

1. Bauer Y, Tedrow J, de Bernard S, Birker-Robaczewska M, Gibson KF, Guardela BJ, Hess P, Klenk A, Lindell KO, Poirey S, *et al.* A novel genomic signature with translational significance for human idiopathic pulmonary fibrosis. *Am J Respir Cell Mol Biol* 2015;52: 217–231.
2. Meltzer EB, Barry WT, D'Amico TA, Davis RD, Lin SS, Onaitis MW, Morrison LD, Sporn TA, Steele MP, Noble PW. Bayesian probit regression model for the diagnosis of pulmonary fibrosis: proof-of-principle. *BMC Med Genomics* 2011;4:70.
3. DePianto DJ, Chandriani S, Abbas AR, Jia G, N'Diaye EN, Caplazi P, Kauder SE, Biswas S, Karnik SK, Ha C, *et al.* Heterogeneous gene expression signatures correspond to distinct lung pathologies and biomarkers of disease severity in idiopathic pulmonary fibrosis. *Thorax* 2015;70:48–56.

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