participate in the telehealth intervention, as our traditional PR participation rate after discharge has been approximately 5% (4), a number reflected in the data for control subjects in this study. The videoconferencing sessions were performed using a Health Insurance Portability and Accountability Act–compliant app, and no video data were recorded. Although there are privacy concerns with conducting live monitoring at a patient's home, we believe these are no greater than those possible in supervised home PR sessions and perhaps group activities in traditional PR.

Dr. Moy suggests that the observed benefits of our video intervention were possibly due to individual counseling and monitoring that could have led to earlier detection of exacerbations and outpatient therapy. Although this is possible, we believe this is unlikely to explain the benefits, as patients who were not exposed to the telehealth intervention also received daily phone calls for 2 weeks and then weekly phone calls for 3 months (4).

Dr. Moy also calls for a randomized controlled trial with three arms comparing video PR, traditional PR, and no PR before video PR attains PR status. An important distinction to make in comparing our video telehealth PR program with other center-based and home-based programs is the indication for receipt of telehealth PR in our study (5). Our patients were enrolled during hospitalization and had extremely poor functional capacity at discharge. Their ability to participate in an optimal-intensity PR program was thus limited. We also believe we should not be too dogmatic about the notion that PR interventions can be called PR only if they involve attending sessions at a center with access to expensive equipment and a team of experts. Although this is ideal, this approach has clearly failed in the real world (6), and efforts should be made to test and invest in new and alternative methods for delivering PR (7). These approaches include alternative exercise strategies such as tai chi and yoga (8), interactive web-based PR (9), home-based supervised PR, and video telehealth PR (5). ■

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CD71^{-} Alveolar Macrophages in Idiopathic Pulmonary Fibrosis: A Look beyond the Borders of the Disease

To the Editor:

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrosing lung disorder characterized by an unavoidable decline in pulmonary function and poor clinical outcomes. Despite significant efforts in basic and translational research over the past two decades, many aspects of the pathobiology of IPF remain elusive. The recent introduction of two effective agents for the treatment of the disease has significantly changed the clinical management of patients with IPF; however, the behavior of the disease and response to therapy are highly variable among patients. The individuation of new therapeutic targets and the validation of diagnostic, prognostic, and therapeutic biomarkers are widely recognized as urgent clinical needs (1).

In a recent study published in the *Journal*, Allden and coworkers elegantly demonstrated by means of a modern flow-cytometry approach that in IPF airways there is a distinct subset of alveolar macrophages (AMs) that downregulate the expression of the surface transferrin receptor CD71 and are phenotypically distinct with regard to their expression of profibrotic genes and impaired ability to take up transferrin *in vitro* (2). This subset of AMs was not significantly present in any of the healthy subjects tested in the study as the control population, and interestingly, its presence was correlated with worse clinical outcomes for patients.

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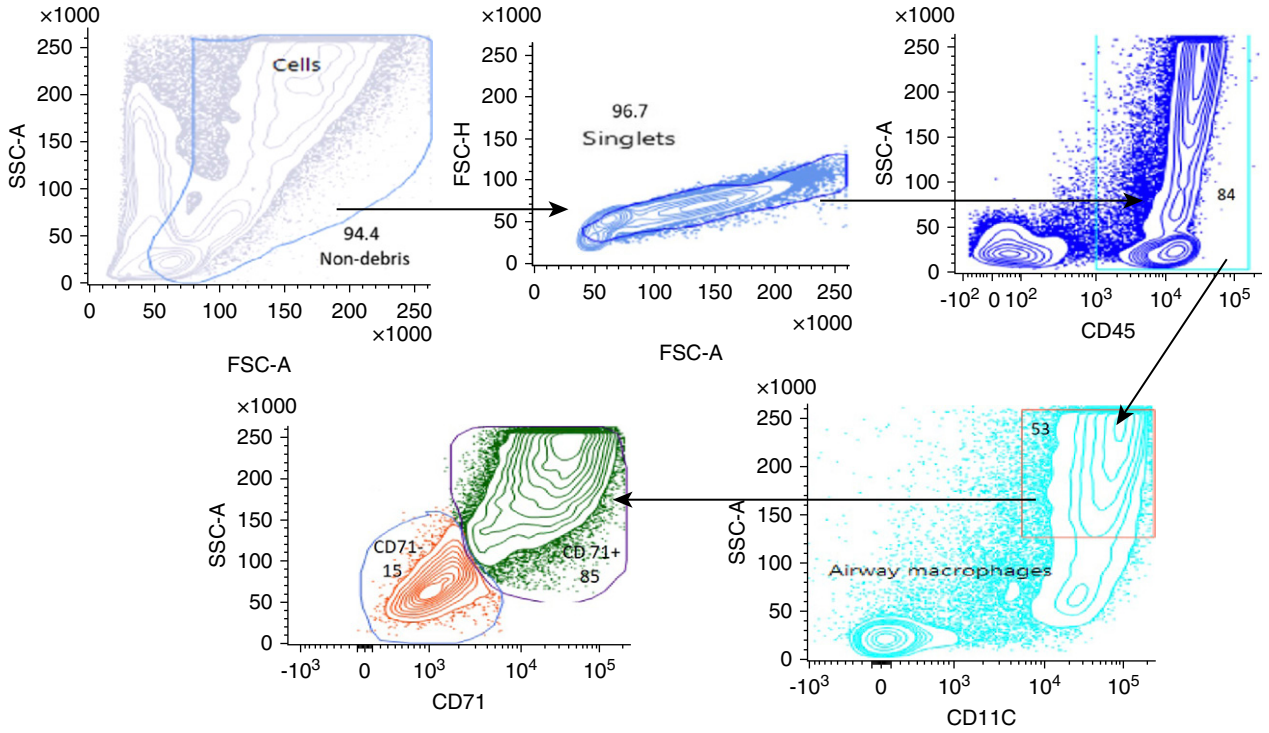

Figure 1. Gating strategy applied for flow-cytometry analysis and individuation of BAL CD71-expressing alveolar macrophages.

In recent years, our group has proposed disruption of lung iron homeostasis as a possible key mechanism in IPF pathogenesis and progression. We demonstrated an increased iron burden in the IPF lung, both in the alveolar epithelial lining fluid and in AMs (3). Furthermore, we demonstrated that AMs produce an increased amount of reactive oxygen species via an iron-dependent mechanism (4) and display at the transcriptomic level a proinflammatory, prorepair, and proangiogenic activation pattern likely induced by iron accumulation (5).

With that as a background, we learned with great interest the results reported by Allden and coworkers, which again put iron metabolism under the spotlight in the pathobiology of IPF. In particular, the presence of an AM population lacking one of the fundamental mechanisms of intracellular iron uptake is intriguing and appears to be, at least in part, in line with our previous results. However, we believe that it would be of great interest to understand whether the presence of $CD71^{-}$ AMs represents a unique characteristic of the IPF lung or if they can also be detected in other chronic degenerative lung diseases. To address this issue, we performed a retrospective flow-cytometry analysis on BAL cell samples that were collected during our previous studies on iron metabolism and pulmonary fibrosis (4, 5). In particular, BAL cell samples from 21 patients with IPF and 18 patients without IPF (six with hypersensitivity pneumonitis, six with connective tissue disease–interstitial lung disease [ILD], three with nonspecific interstitial pneumonia, two with sarcoidosis, and one with Churg-Strauss syndrome) were tested for a panel of cell-surface markers that included CD45, CD11c, and CD71.

Applying the same gating strategy reported by Allden and coworkers to the above-mentioned flow-cytometry data, we were able to confirm the presence of two populations of AMs based on CD71 expression not only in patients with IPF but also in patients without IPF (Figure 1). In particular, the proportions of $CD71^{-}$ cells were similar between the two populations (10.90% ± 5.88% vs. 8.95% ± 5.75%; $P = 0.46$; Figure 2), although they appeared to be slightly lower than those reported by Allden and coworkers. Interestingly, among patients without IPF, the highest proportions of $CD71^{-}$ AMs were found in patients with a final diagnosis of Churg-Strauss syndrome and patients with stage II sarcoidosis.

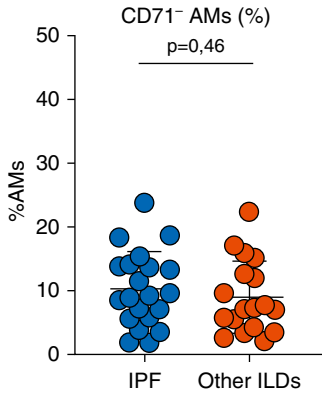

Figure 2. Proportions of $CD71^{-}$ alveolar macrophages (AMs) in idiopathic pulmonary fibrosis (IPF) and non-IPF BAL. ILD = interstitial lung disease.

As discussed by Allden and coworkers in their article, among other hypotheses, CD71$^-$ AMs could be an expression of a subpopulation of immature monocytes recruited into the alveolar space from the bloodstream during active inflammation/tissue injury, as was previously shown in a preclinical animal model of lung fibrosis (6). We believe that the lack of specificity about the presence of CD71$^-$ AMs in IPF that we show in this brief report supports the latter interpretation. Furthermore, the reported association between the proportion of CD71$^-$ cells and the clinical course of patients with IPF may reflect the ongoing fibrotic process that characterizes the rapidly progressive form of the disease and may also characterize other, non-IPF ILDs that in some cases display an accelerated pathological/clinical evolution. Although further studies on large populations of patients with ILD will be needed to confirm these preliminary observations, we believe that the study by Allden and coworkers is very promising and reinforces the role of BAL as a potential source of fundamental information in the field of translational medicine in respiratory diseases. ■

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Reply to Puxeddu *et al.*

From the Authors:

We thank Puxeddu and colleagues for their interest in our paper and for opening a dialogue regarding the role of CD71-expressing airway macrophages (AMs) in interstitial lung disease (ILD) (1). Indeed, it is interesting that the authors found a similar population of CD71$^-$ AMs in a second cohort of patients with idiopathic pulmonary fibrosis (IPF), further validating our findings. The authors describe a level of CD71$^-$AMs in a group of patients with non-IPF ILD comparable to that observed in patients with IPF. These data raise the question of whether CD71$^-$ AMs may be an important pathogenic component of IPF as well as other fibrotic lung diseases.

To determine whether the proportions of CD71-expressing AMs were altered during non-IPF ILD, we examined BAL samples from a cohort of patients with hypersensitivity pneumonitis ($n = 18$), respiratory bronchiolitis–associated ILD ($n = 2$), sarcoidosis ($n = 2$), or undifferentiated connective tissue disease ($n = 5$), and used a multicolor flow-cytometry gating strategy identical to that described in our initial publication (1). We found that in patients with non-IPF ILD, there was an increase in the proportion of CD71$^-$ AMs compared with healthy control subjects, and furthermore, the proportions of these populations were similar to those found in patients with IPF (Figure 1). One of the key findings of our original study is that CD71$^-$ AM status was an independent predictor of survival in patients

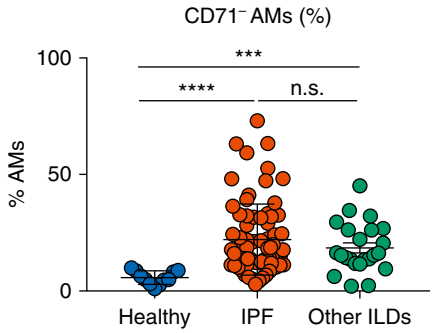

Figure 1. Proportions of CD71$^-$ airway macrophages (AMs) in BAL from healthy subjects ($n = 11$), patients with idiopathic pulmonary fibrosis (IPF) ($n = 75$), and patients with non-IPF interstitial lung disease (ILD) ($n = 23$). ***$P < 0.001$ and ****$P < 0.0001$, Mann-Whitney U test. n.s. = not significant.

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