On Target: CYFRA 21-1 as an Idiopathic Pulmonary Fibrosis Biomarker

Idiopathic pulmonary fibrosis (IPF) is an inexorably progressive interstitial lung disease (ILD) of unknown origin with limited therapeutic options (1). Although the mechanisms underpinning IPF pathogenesis have yet to be fully elucidated, susceptibility is likely driven by complex interactions between genetic, environmental, and demographic risk factors. Among susceptible individuals, repetitive alveolar injury appears to cause aberrant activation of alveolar epithelial cells, which secrete profibrotic mediators that induce the expansion of hyperactive and apoptosis-resistant mesenchymal cells (e.g., fibroblasts and myofibroblasts). These cells produce an excess of extracellular matrix, which leads to irreversible distortion of the lung parenchyma and progressive organ failure (2). Despite these mechanistic insights, limited understanding of disease etiology continues to hinder prevention and development of novel pharmacotherapies.

Just as IPF etiology remains elusive, so does the ability to predict disease trajectory. Although most patients display progressive decline, others may remain relatively stable, decline rapidly, or suffer an acute exacerbation (3). Predicting disease behavior in IPF is critically important for both clinical and research purposes, as understanding an individual's risk of death could guide listing for lung transplantation and maximize the likelihood of detecting treatment effects through clinical trial enrichment (4). Several clinical prediction models have been reported and discriminate IPF survival with variable success. Most models incorporate baseline clinical, radiologic, and physiologic parameters (5–7), whereas some incorporate longitudinally acquired variables, capitalizing on the predictive nature of changing physiology (8). Despite these advances, risk explanation remains variable for most clinical prediction models, likely influenced by the cohort in which they are applied (9). A number of biomarkers have also been shown to predict IPF survival (10), although rigorous validation is often lacking and their value beyond clinical prediction models remains unclear for most.

In this issue of the *Journal*, Molyneaux and coworkers (pp. 1440–1448) address two critical gaps in knowledge through evaluation of cytokeratin 19 fragment (CYFRA 21-1), a cleavage fragment of the structural intracytoplasmic protein cytokeratin 19 (11). Among a subset of prospectively recruited patients with incident IPF from the Prospective Study of Fibrosis In the Lung Endpoints (PROFILE) study, Molyneaux and colleagues demonstrated that serum CYFRA 21-1 concentration is increased in this population compared with control subjects and is highly expressed in multiple epithelial cell types in IPF lung tissue. These findings suggest cytokeratin 19 plays a crucial role in IPF pathogenesis and progression and support prior studies showing CYFRA 21-1 to be elevated in the BAL fluid of patients with IPF (12) and serum of patients with systemic sclerosis–associated ILD (13). These findings also corroborate a recent proteomic investigation showing cytokeratin 19 to predict disease progression across diverse ILD subtypes (14).

Beyond mechanistic implications, Molyneaux and colleagues also showed that CYFRA 21-1 concentration predicted near-term progression and long-term survival when assessed in cross-section and at serial time points, notably beyond 3 months. These findings were then validated in an independent cohort of PROFILE patients recruited after those comprising the discovery cohort. These findings add to prior work identifying novel biomarkers in this cohort (15, 16) and add CYFRA 21-1 to the list of potentially attractive biomarkers in IPF. Whether CYFRA 21-1 will actually emerge as a viable biomarker in IPF remains to be seen. For a biomarker to be implemented clinically, it needs to augment or outperform clinical prediction models, which can be applied at minimal cost and effort. CYFRA 21-1 was shown to provide prognostic information independent of clinical variables comprising clinical prediction models but only modestly augmented an area-under-the-curve estimate when added to the gender, age, physiology index (6). This observation was restricted to analysis of near-term progression and was unfortunately not assessed using long-term survival data, which is the endpoint used to develop the gender, age, physiology index (6). Ultimately, area under the curve measures provide little information when assessing the clinical utility of a biomarker. Decision curve analysis has emerged as the preferred method to compare prediction models and would better assess the potential utility of this and other biomarkers (17).

These limitations aside, Molyneaux and colleagues should be applauded for this study, as few biomarkers of near-term progression have been identified in IPF and more are urgently needed. Such biomarkers are more likely to help with future trial enrichment, as the change in FVC between treatment groups gets smaller with background antifibrotic therapy. Ultimately, multiple biomarkers may be needed to effectively predict near-term progression (14). Beyond risk prediction, analysis of CYFRA 21-1 concentration before and after the initiation of antifibrotic therapy would be of interest and could potentially support using CYFRA 21-1 as a marker of treatment response. Future research is also needed to expand these findings and elucidate whether pathways involving cytokeratin 19 may serve as potential therapeutic targets. ■

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Promises and Pitfalls of Multiomics Approaches to Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is an incurable illness of the pulmonary vasculature resulting from an interplay of dysregulated biological pathways. Despite great recent gains in scientific knowledge and therapy, the molecular determinants of PAH remain incompletely understood, and current PAH therapies target three signaling pathways: prostacyclin, endothelin, or nitric oxide pathways (1). A deeper understanding of disease pathogenesis is needed to identify novel therapeutic targets and disease-specific biomarkers.

Refinements of high-throughput molecular techniques have led to multiple omics approaches toward unraveling PAH pathobiology. These designs pivot away from traditional reductionist approaches to biological questions that use a hypothesis-driven framework and instead take an unbiased approach to discovering molecular differences between biological conditions (e.g., disease vs. health). In recent years, these pages have featured omics studies that have described the genetic underpinnings of vasodilator responsiveness in idiopathic PAH (2), a whole-blood RNA signature of PAH susceptibility and outcomes (3), and dysregulated gene expression in rodent PAH models at single-cell resolution (4).

These omics reports illustrate advances made possible by these powerful study designs. This prompted the NHLBI's Division of Lung Diseases to initiate the PVDOMICS (Pulmonary Vascular Disease Phenomics Program) study aimed at defining novel subphenotypes of pulmonary vascular disease using multiomics methods (5, 6). Integrated omics strategies typically merge data from two or more omics

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