



## Commentary

# Endotyping of progressive fibrotic interstitial lung diseases: It is the final destination that matters and not the journey



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In 1911, one of the most emblematic figures in poetry, Constantine Kavafis, published a poem named "*Ithaka*" which symbolizes the ultimate destination of a long journey. Kavafis suggests that, in life, the journey is more important than the destination because it gives you wisdom, experience and maturity. However, things are quite different in end-stage disease patterns.

Pulmonary fibrosis constitutes the end stage of a broad range of heterogeneous interstitial lung diseases (ILDs). It is characterized by the destruction of the pulmonary parenchyma, deposition of extracellular matrix and dramatic changes in the phenotype of both fibroblasts and alveolar epithelial cells [1]. It belongs to the group of fibroproliferative diseases that, collectively, account for many deaths in developed countries.

Since the introduction of two antifibrotic drugs (pirfenidone and nintedanib) in the treatment of idiopathic pulmonary fibrosis (IPF), there has been much interest in whether these drugs are effective in other progressive fibrotic interstitial lung diseases (PF-ILDs), including chronic (fibrosing) Hypersensitivity Pneumonitis (CHP), connective tissue disease-associated ILDs (CTD-ILDs) and unclassifiable forms of lung fibrosis (uILDs). Currently there are no guidelines for the diagnosis and treatment of CHP. Empirical therapy consists of a combination of immunomodulating agents with low doses of corticosteroids [2]. Similarly, there are only two randomized controlled trials (RCTs) for scleroderma lung disease supporting the use of cyclophosphamide (SLS-I) and mycophenolate mofetil (MMF) (SLS-II) as induction and maintenance treatment [3]; however, cyclophosphamide-related toxicity issues severely hamper its longitudinal use and the role of MMF as an anti-fibrotic agent is questionable.

Finally, uILDs still represent a major diagnostic and therapeutic uncertainty. Unfortunately, the progressive fibrotic phenotype in non-IPF disorders presents with a malignant IPF-like disease behavior,

especially when the Usual Interstitial Pneumonia (UIP) pattern is present on biopsy or high-resolution computed tomography (HRCT) imaging. To this end, three major RCTs, enrolling a total of 1492 patients with PF-ILDs, have been published this year. The INBUILD study investigated the potential of nintedanib in 663 patients with different forms of PF-ILDs including CHP, CTD-ILD and uILD. It showed similar safety and efficacy profiles to those observed in the INPULSIS trials with IPF patients (107 ml versus 109 ml in FVC decline, respectively) [4]. Similar therapeutic benefits (96 ml) were observed with pirfenidone in 256 patients with progressive fibrotic uILDs [5]. Finally, the SENSICIS trial of 576 patients with SSC-ILD treated with nintedanib [6] demonstrated significant reductions in disease progression with no major safety concerns. Strikingly, this was the first study that successfully combined in almost half of the patients (48%) an immunomodulating agent (MMF) with an anti-fibrotic agent (nintedanib). More importantly, in all RCTs, treatment response rates were more pronounced in patients with a UIP-like phenotype, extending previous prognostic observations [7,8]. Despite encouraging therapeutic data underlying the necessity to group PF-ILDs based on common disease behaviors and treatment responses, mechanistic insights that will help us link a specific endotype to a predictive or prognostic phenotype are still missing.

In this issue of *EBioMedicine*, Hoffmann-Vold AM et al. [9], performed an elegant series of experiments that provided us with valuable common pathogenic insights in different forms of PF-ILDs. The authors included a wide variety of lung samples derived from patients with both IPF and non-IPF fibrotic lung disorders at the time of lung transplantation and measured concentrations of different nintedanib-targeted tyrosine-kinase pathways (VEGF, FGF, PDGF, M-CSF). Interestingly, lung samples from patients with PF-ILDs, irrespective of disease etiology, exhibited similarly elevated levels of tyrosine-kinase pathways compared to controls. Though the study was not designed to scrutinize the entire spectrum of fibrotic lung pathways nor to provide in depth mechanistic data, it exhibits a number of significant attributes that should be highlighted accordingly. Firstly, this is the largest pathology study, so far, in the field of lung fibrosis and included 334 samples (134 whole lung explants from PF-ILD patients and 200 control samples derived from normal donor lungs). Secondly, the study enrolled a wide variety of different subsets of progressive fibrotic lung diseases (such as IPF, CTD-ILDs and sarcoidosis, as well as exposure-related ILDs; yet, all shared common clinical outcomes including end-stage lung disease and lung transplantation). Finally, this is the first study showing augmentation of nintedanib-targeted pathways across different types of lung fibrosis, setting up the

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mechanistic basis for lumping PF-ILDs into one entity (progressive phenotype) with regards to anti-fibrotic treatment.

While we strongly support the idea that the future lies in precision medicine approaches, including biological enrichment of clinical trials [10] and pathway-specific therapeutic regimens, splitting IPF from non-IPF progressive lung disease remains relatively premature. It may bring significant dangers to exclude a considerable number of non-IPF patients with similar disease behavior from beneficial anti-fibrotic agents. Rigid definition of the progressive fibrotic phenotype based on a combination of HRCT patterns, physiological indices and blood biomarkers may lead to early identification of at-risk individuals that could benefit from “lumping” therapeutic interventions. On the other hand, “splitting” may be a complementary approach that will require discovery of easy, reproducible and phenotype-specific biomarkers such as proteomic, genomic and cellular signatures to guide therapeutic decisions with major clinical purposes.

This work shows us that, regardless of the patient's journey to pulmonary fibrosis, the arrival to the same destination can inform clinical management.

#### **Declaration of Competing Interest**

All authors have no conflicts of interest to disclose

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