Pioneering Research Driving Progress toward a Cure for Interstitial Lung Disease (ILD): Introduction to the *AJRCCM* Special Issue on ILD (Part 2)

Welcome to the second *American Journal of Respiratory and Critical Care Medicine* (*AJRCCM*) special issue of 2024 dedicated to interstitial lung disease (ILD). Because of the exceptional volume of high-quality submissions from the global ILD community, we are excited to publish two issues this year that focus on these complex conditions. The articles included in this edition highlight new therapeutic strategies, innovative diagnostic tools, and emerging biomarkers that promise to reshape our clinical management of ILD. Additionally, we gain new mechanistic insights that provide a deeper understanding of disease processes and their implications for patient care. We hope that these studies will inspire further research and collaborations in our ongoing effort to improve outcomes for those affected by these challenging diseases.

The Spectrum of ILD

ILD encompasses a large and heterogenous group of diagnoses, ranging from more inflammatory disorders such as connective tissue disease–associated ILD (CTD-ILD) to intrinsically more fibrotic disease such as idiopathic pulmonary fibrosis (IPF), as described in the Pulmonary Perspective by Behr and colleagues (pp. 392–400). The authors detail existing tools to guide clinical decision-making and persistent knowledge gaps in distinguishing each disease process. Adegunsoye and colleagues (pp. 401–423) present a state-of-the-art update on recent genetic and genomics advancements in fibrotic ILD and their application to patient care. It is clear from both review articles that better molecular characterization of ILD—including integration of genetic testing, novel biomarkers, advanced imaging algorithms and deeper immune cell profiling—is essential and will allow for more personalized approaches to patient care.

Therapeutic Advances

It has been a decade since the approval of the two existing drugs for the treatment of IPF in the United States. There is an urgent need for more effective therapeutic targeting of fibrotic pathways to not only slow disease progression but also fully stabilize or reverse it. In this issue of the *Journal*, we highlight two clinical trials of novel treatments for IPF. Lancaster and colleagues (pp. 424–434) present the results of INTEGRIS-IPF, a Phase-2a trial of bexotegrast, an investigational drug that interferes with transforming growth factor β binding to αvβ6 and αvβ1 integrins, thereby inhibiting transforming growth factor β signaling. Bexotegrast was well tolerated both when taken alone and in combination with existing antifibrotic therapy. Exploratory analyses support efficacy at 3 months, as measured by lung function, quantitative imaging, and blood biomarkers. Mattos and colleagues (pp. 435–443) report on the findings from a Phase-2 trial of c-Jun N-terminal kinase inhibitor for the treatment of IPF. This investigational drug had a reasonable safety profile, and treated patients had a numerically smaller decline in FVC and a reduction in fibrotic biomarkers at 24 weeks. Finally, in a secondary analysis of data from two prior IPF clinical trials, Whalen and colleagues (pp. 508–511) identify a pharmacogenomic interaction between a SNP in the *TOLLIP* gene and treatment with doxycycline. Taken together, these and other ongoing studies inspire optimism that novel therapeutic approaches for IPF are on the horizon.

Precision-Based Diagnostics

The current diagnostic approach to classifying ILD requires integrating clinical data with visually identified imaging and histopathologic patterns during multidisciplinary discussion. This can often be challenging and result in suboptimal management. Molecular classification of ILD promises to significantly enhance diagnostic accuracy and facilitate precision-based treatments. However, valid tools for molecular classification have been elusive. In this issue of the *Journal*, Huang and colleagues (pp. 444–454) identify a blood-based proteomic classifier that differentiates IPF from CTD-ILD with high accuracy. Maddali and colleagues (pp. 455–464) leverage proteomic biomarkers to identify two endotypes of IPF using latent class analysis. These two endotypes had distinct outcomes and treatment responses. Marges and colleagues (pp. 512–514) analyze exhaled breath volatile organic compounds using an electronic nose sensor to detect ILD among patients with systemic sclerosis. As proteomic platforms and other machine learning–enabled tools become more affordable and clinically accessible, we look forward to a future where these biomarkers are used for earlier detection and improved diagnosis of patients with ILD.

Next-Generation Imaging

Imaging is the cornerstone of ILD diagnosis, and advancements in computed tomography (CT) technique and interpretation have reduced the need for invasive histopathologic sampling. Further developments in imaging have the potential to better inform prognosis and provide deeper mechanistic insights into human fibrosis at the microscopic level. Here, Thillai and colleagues

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(pp. 465–472) leverage a deep-learning CT algorithm to develop imaging biomarkers that predict IPF progression and mortality. The study demonstrates the feasibility of rapid automated segmentation of a diverse set of CT data to quantify imaging features that could complement clinical radiology reads. Berigei *et al.* (pp. 473–483) use endobronchial optical coherence tomography to reveal a marked loss of small airways in patients with early IPF, even in areas minimally involved by fibrosis. Finally, Munchel and colleagues (pp. 514–517) use fibrin–positron emission tomograpy scanning to show *in vivo* activation of the coagulation cascade in lungs of patients with IPF. These next-generation imaging tools expand the armamentarium available for ILD research, driving future progress in understanding and treating the disease.

Novel Mechanistic Insights

Future advancements in treatments require a deeper grasp of the mechanisms underlying fibrotic and inflammatory ILD. The contribution of immune cells to the pathogenesis of IPF has been particularly underestimated. Here, Unterman and colleagues (pp. 484–496) use single-cell transcriptomics of peripheral blood mononuclear cells to identify immune aberrations in IPF. Calamita and colleagues (pp. 521–523) identify a key role for natural killer T cells in promoting lung fibrosis. Also, in sarcoidosis, an inflammatory disease that has been gravely understudied, Crouser and colleagues (pp. 497–507) perform elegant experiments to address the long-standing question of the role of angiotensin-converting enzyme. Using an *ex vivo* granuloma model, they demonstrate that the renin-angiotensin-aldosterone system promotes early sarcoidosis granuloma formation and that pretreatment with angiotensin-converting enzyme inhibitors significantly inhibited sarcoidosis granuloma formation. These key studies pave the way for novel therapeutic targeting of immune pathways in IPF and the renin-angiotensin-aldosterone system in sarcoidosis.

We hope that the breadth of ILD research included in this issue highlights the significant progress that has been made and provides a glimpse into a future where patients living with ILD experience improved outcomes and quality of life. We thank the American Thoracic Society community for supporting the *AJRCCM* as we witness and contribute to this ransformation. ■

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INTEGRIS-IPF: A New Hope for Tomorrow

Transforming growth factor-β (TGF-β) is a well-known and key mediator in the pathogenesis of idiopathic pulmonary fibrosis (IPF).

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Integrins are heterodimeric transmembrane proteins crucial to a wide range of biological functions and consist of α- and β-subunits (1). $\alpha_v\beta_1$, $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, and $\alpha_v\beta_8$ can bind the arginine-glycine-aspartic acid motif and activate latent TGF-β (2, 3). $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins, particularly, are involved in the activation of TGF-β (4): $\alpha_v\beta_6$ drives TGF-β activation in alveolar epithelial cells, whereas $\alpha_v\beta_1$ mirrors this in myofibroblasts (1). $\alpha_v\beta_1/\beta_6$ are upregulated in patients with IPF, and $\alpha_v\beta_6$ is correlated with poorer prognosis (4, 5). Given the crucial role of $\alpha_v\beta_1/\beta_6$ in IPF pathogenesis, a specific