pneumonia, particularly among the vulnerable populations that bear a disproportionate share of the disease burden. ■

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Inhaled Treprostinil in Pulmonary Hypertension in the Context of Interstitial Lung Disease: A Success, Finally

Pulmonary hypertension in the context of interstitial lung disease (PH-ILD) is one of the most fatal medical conditions patients and doctors are faced with. The vascular component of advanced ILD is difficult to tackle and obviously differs from pulmonary arterial hypertension (PAH), as multiple high-quality clinical trials failed to convincingly demonstrate a clinical benefit of pulmonary vasoactive drugs in various PH-ILD populations, whereas those drugs are effective and approved in PAH (1–5). Some drugs like ambrisentan and riociguat even showed harmful effects in PH-ILD populations and were consequently banned from treatment in this indication (2, 4). One potential cause for this differential effect of pulmonary vasoactive drugs in PAH and PH-ILD might be the induction or aggravation of $\dot{V}/\dot{Q}$ mismatch in ILD lungs if vasodilators are

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administered systemically. Another reason might simply be the fact that vasoreagibility is fundamentally different in vessels located in otherwise normal lung tissue in idiopathic PAH or cemented in fibrotic tissue in PH-ILD (6). At least the $\dot{V}/\dot{Q}$ mismatch can be avoided by inhalative administration of vasodilating drugs, which will be distributed preferentially to the well-ventilated areas of the lungs, thus even reducing intrapulmonary mismatch and shunting. This concept has been successfully explored in single dose studies more than 20 years ago (7, 8). The recently published INCREASE study could show for the first time a significant positive effect of inhaled treprostinil, a stable prostacyclin analogon with potent vasodilative effects on pulmonary vasculature, in a population of patients with fibrotic ILD and PH confirmed with right heart catheter (9). The primary endpoint of the pivotal study—change in 6-minute-walking distance (6MWD) from baseline to Week 16—was significantly positive, showing improvement of 6MWD of 31 m ($P < 0.001$) in the active treatment group for the very first time in this population (9). The 6MWD can be regarded as a clinically meaningful endpoint *per se*, as it addresses reduced exercise tolerance, which is the cardinal clinical limitation of this patient population. Nonetheless, the question arises: how does this effect translate into other clinically meaningful endpoints? Time to clinical worsening has successfully been used as another clinical meaningful study endpoint in multiple PAH trials (10). In the INCREASE pivotal study, therefore, time to clinical worsening defined by hospitalization for a cardiopulmonary indication, a decrease in 6MWD greater than 15% from baseline, death from any cause, or lung transplantation was already a composite secondary endpoint and significantly favored the treprostinil-treated group (9).

Beyond the primary analysis, there remained urging questions to answer: does the observed effect apply equally to the different ILD subgroups included in this study? What happens after clinical worsening has occurred, obviously excluding death and transplantation? Does this mean that treatment is not efficacious and should be stopped, or could continuing treatment be beneficial, nonetheless? In this issue of the *Journal*, the INCREASE authors (pp. 198–207) set out to answer exactly these important questions in a *post hoc* analysis of the INCREASE data set focusing on ILD subgroups and consecutive clinical worsening events (11). The subgroup analysis revealed a very consistent favorable trend for all subgroups and for all the event categories investigated, which, however, reached statistical significance only for the overall number of events in the largest group of idiopathic interstitial pneumonias (11). This is not to blame, as statistical power was adjusted to the total study population and not to the subgroups. The clinical worsening events included a $\geq$15% decline in 6MWD, cardiopulmonary hospitalization, lung transplantation, or death during the study and a $\geq$10% decline in the FVC and exacerbations of underlying lung disease; the latter two criteria were collected as safety endpoints and were not included as part of the prespecified composite of clinical worsening. This elegant analysis demonstrated a huge imbalance of worsening events in favor of treprostinil therapy: in the inhaled treprostinil group, 11/163 patients had >1 event versus 26/163 patients in the placebo group; this also included a clearly lower mortality rate with inhaled treprostinil, suggesting that continuing treatment is the way to go (11). However, there are limitations that apply to this study and to *post hoc* analyses in general. Most importantly, the two subgroup cohorts of patients with >1 worsening event can no longer be regarded as a randomized subset, as the selection of these groups occurred not in a randomized fashion but following clinical events. Although the baseline characteristics show good matching, we do not know whether the functional status of the patients was still comparable at the time when the first event occurred (11). Moreover, two of the worsening categories, $\geq$10% decline in FVC and exacerbation of the pulmonary disease, were captured as safety variables and might therefore be less well standardized as variables that are captured for endpoint assessments. Because FVC decline and exacerbation accounted for almost 50% of all worsening events, this is a potential weakness of this analysis. Despite acknowledging these limitations, the current analysis provides a very consistent picture of the positive effects of continued inhaled treprostinil in PH-ILD and clearly further supports the primary analysis (9, 11). After a long and sometimes painful journey of negative and inconclusive clinical trials, inhaled treprostinil therapy is a success for the treatment of PH-ILD, finally. The question to be addressed now and in future trials will be is this impressive effect of inhaled treprostinil durable? ■

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Dynamism of the Human Lung Proteome during Alveolarization
Moving beyond the Transcriptome

Human lung development extends throughout pregnancy and continues at least through the first decade of postnatal life (1). During alveolarization, the final stage of lung development, division of the primitive alveolar ducts into terminal saccules and marked expansion of the capillary bed significantly increases gas exchange surface area (2). However, completion of lung development after birth heightens the susceptibility of the lung to injuries that disrupt development. This is frequently observed in the context of premature birth, when impaired alveolarization leads to bronchopulmonary dysplasia, a chronic lung disease associated with significant morbidity and mortality. Thus, a comprehensive understanding of the molecular mechanisms that promote postnatal lung development might motivate the development of novel therapies to enhance lung growth and repair in infants and young children (3).

Over the past two decades, significant advances have been made relative to the molecular control of alveolarization. These include the identification of essential signaling pathways (4), transcription factors (5, 6), and key cell types that drive alveolarization (7, 8). Recently, the development and application of multiomic methodologies, including single-cell transcriptomics, have provided novel insight into the heterogeneity and maturation of the lung at single-cell resolution, providing comprehensive atlases of cell abundance and phenotype across development (9–11). However, many of these prior studies used experimental murine models, and there are key differences between human and murine lung development, including differences in timing, with alveolarization beginning before birth in humans but after birth in mice. Furthermore, the majority of these invaluable cell and expression maps were constructed using only gene expression data. Thus, there remains an absence of similar, comprehensive data sets defining how the lung proteome evolves during postnatal development, particularly in humans.

In this issue of the *Journal*, Clair and colleagues (pp. 208–218) performed deep proteomic profiling on postmortem human lung samples obtained from donors ranging from 1 day old to 8 years of age (12). The authors used two-dimensional liquid chromatography–mass spectrometry to identify almost 9,000 proteins, representing an almost fourfold increase in proteome coverage compared with a prior proteomic analysis of human lung development (13). Of the proteins identified, ∼50% changed across development, with the majority decreasing linearly over time, consistent with a gradual transition to quiescence as the lung reaches maturity. Further analyses of these dynamic proteins identified that proteins related to telomerase activity, the proteasome, RNA splicing, and post-translational modifications decreased with age, suggesting a gradual differentiation of lung cell progenitors and a significant contribution of post-transcriptional mechanisms to postnatal lung development. In contrast, proteins associated with immunity and inflammation, lipid metabolism, and extracellular matrix increased with age. Using principal component analysis, the authors identified four molecularly distinct substages that are present during alveolarization, consistent with the four substages previously identified in the murine lung using bulk RNA sequencing (14). The authors also demonstrate that the developmentally regulated proteome profiles they identified accurately predicted donor age in a separate validation cohort, indicating high consistency and reliability of these temporal changes in the lung proteome. Interestingly, when proteomic and transcriptomic analyses were performed on the same donor, the dynamic protein/transcript pairs only exhibit the same trend (e.g., linear decreasing or increasing, etc.) ∼50% of the time, highlighting the importance of validating potentially relevant transcriptomic changes with methodologies that assess protein expression rather than relying on gene expression alone.

Although this study represents a great resource for clinicians and scientists studying normal and aberrant lung development at the molecular and cellular level, there are some limitations, and a number of questions remain. The authors make the important point in the introduction that a key difference in human versus murine lung development is the onset of alveolarizations at 36 weeks in humans. However, in this study, the earliest time point included was 1 day after birth, precluding an elucidation of the molecular mechanisms driving early alveolarization in humans. Furthermore, it is important to note that the authors identified substages of alveolarization that were similar to those identified in the murine lung using transcriptomics, suggesting significant conservation of key regulatory mechanisms promoting alveolarization in both mice and humans.

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