occur across the genome and need to be further explored in the context of pulmonary function and disease. Extensive research into the epigenomic changes observed in cancer cells has led to the discovery of a wide array of specific pharmacologic inhibitors and CRISPR-Cas9–based epigenome technologies as therapeutics. The current study by Morrow and colleagues provides a template for discovering new epigenetic biomarkers and points the way for targeted basic studies, with the eventual goal of discovering new classes of treatments for pulmonary disease. ■

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Treatment of Acute Exacerbation of Idiopathic Pulmonary Fibrosis
A Call to Arms

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrosing interstitial lung disease with an unfavorable prognosis (1). Different from many other chronic lung diseases, deaths of individuals with IPF are primarily related to progression of lung fibrosis rather than occurring due to comorbidities (2). Acute exacerbations (AEs) of IPF (AE-IPF), characterized by the development of widespread acute lung injury, are an important cause of IPF-related disease progression and mortality, which may even occur in individuals with limited fibrosis and well-preserved lung function (3). When it comes to AE-IPF, there are important lacunae in knowledge, including understanding of pathogenesis and triggers, optimal strategies for prevention, and best approaches to (early) diagnosis. Although considerable progress has been made in the management of IPF, optimal treatment of AEs has yet to be defined, and varies considerably across the globe (4). Despite current international guidelines giving a (weak) positive recommendation for the use of glucocorticoids to treat AE-IPF, there are no proven, effective therapies for this devastating complication of IPF (1, 3). Currently used therapeutic approaches, usually glucocorticoids or immunosuppressants, are based on expert consensus and small, uncontrolled, or retrospective studies (3, 4). Before now, with the exception of a trial examining a procalcitonin-guided antibiotic treatment approach, prospective, clinical randomized placebo-controlled trials (RCTs) have been nonexistent in AE-IPF (3, 5).

Given the uncertainty around best management of AE-IPF, in this issue of the *Journal*, the article by Kondoh and colleagues (pp. 1110–1119) is very timely (6). Kondoh and colleagues report the outcomes of a multicenter RCT of recombinant thrombomodulin alfa in AE-IPF. This drug has been

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used in Japan for a number of years on the strength of several small, uncontrolled, observational, and retrospective clinical studies, all of which were conducted in Asia, which suggested efficacy of thrombomodulin alfa in improving outcomes for patients hospitalized with AE-IPF (7–13). Thrombomodulin alfa is a recombinant and soluble protein, which inhibits thrombin, high-mobility group box 1 protein, and the complement system, while also stimulating protein C. As such, in preclinical experiments, thrombomodulin alfa is associated with anticoagulant, antiinflammatory, and cytoprotective properties (14). The coagulation cascade has been shown to be involved in lung inflammation and fibrosis; thus, inhibition of key clotting pathways combined with the other effects of thrombomodulin provides a strong rationale for assessing its use in the treatment of AE-IPF (15). Kondoh and colleagues (6) are to be highly commended, as they have made strenuous efforts to conduct a rigorous trial on a lethal complication of an already deadly disease. This reflects the major strength of their study, demonstrating that it is possible to perform a multicenter RCT studying a relatively infrequent complication of a rare disease. Furthermore, they overcame the not-inconsiderable obstacle of studying a therapy that was already established in Japan for treatment of AE-IPF. In reporting a negative outcome, Kondoh and colleagues provide an important reminder of the need for establishing the efficacy of expensive and/or potentially harmful therapies before adopting them into routine clinical practice. This underscores the fact that retrospective, observational, and open-label trials, while providing information on safety and tolerability, should be treated as hypothesis generating at best when it comes to assessing efficacy. Appropriately designed and conducted RCTs remain the gold standard for assessing drug efficacy.

A number of limitations relating to the trial should, however, be kept in mind. Thrombomodulin was tested on the background of high-dose corticosteroid pulse therapy. Although corticosteroids are (weakly) recommended by international guidelines (1), they also lack evidence of efficacy, and may potentially be associated with detrimental outcomes. In addition, there was a clinically important imbalance with regard to disease severity between groups (a consequence, in part, of stratification by site, but not by disease severity), which favored the placebo group. A further weakness of the study design was the exclusion of patients who, in the opinion of the investigator, had significantly impaired survival probability. Furthermore, acute exacerbations were not classified into "triggered" and "idiopathic" (3); it is therefore unknown whether such a distinction might have altered study outcomes. Finally, it should be acknowledged that this trial was conducted in Japan, where, when compared with non-Asian countries, acute exacerbations are diagnosed more frequently in patients with IPF, and are treated differently compared with many other countries, including the United States (3, 4). Thus, the results might not be entirely generalizable.

In conclusion, Kondoh and colleagues provide us with the first blinded, randomized, prospective, and placebo-controlled trial on AE-IPF. In itself, this undertaking is of huge importance, given the need to develop evidence-based therapies for this life-threatening complication of IPF. However, the negative outcome of this trial demonstrates clearly that the management of AE-IPF still represents an area of major unmet medical need. Fundamentally, this can only be improved through the delivery of further large-scale, well-designed clinical trials. This should be seen as a call to arms for all health care professional caring for patients with IPF! ■

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rhIGF-1 Therapy: A Silver Bullet for Bronchopulmonary Dysplasia Prevention?

Advancements in neonatal care over the past two decades have improved survival of extremely premature infants, yet bronchopulmonary dysplasia (BPD) continues to be a vexing problem that plagues these infants. Initially described in the presurfactant era as a disorder associated with lung injury and fibrosis, the "new" BPD is characterized by reduced alveolarization and impaired microvascular development in the immature lung (1). Although it is considered a disease of the neonatal period, infants with BPD continue to suffer from its consequences well into adulthood (2). Both prenatal insults, such as exposure to chorioamnionitis and maternal smoking, and postnatal injury from mechanical ventilation and hyperoxia increase the risk of BPD (3). The multifactorial etiology of BPD has made the development of therapies a unique challenge, and currently no effective treatment exists to prevent or cure this debilitating disease.

IGF-1 (insulin-like growth factor-1) is a peptide hormone with structural homology to proinsulin that is expressed in various tissues in the body, including the lung (4). IGF-1 binds to its receptor, IGFR-1 (IGF receptor-1) and promotes cellular growth and differentiation (4). Circulating IGF-1 is bound to one of seven IGFBPs (IGF-binding proteins), of which IGFBP-3 is the most abundant (5). IGF-1 levels are high in the fetus and increase rapidly in the third trimester of pregnancy, a period of rapid growth and development (6, 7). Serum levels of IGF-1 then decrease after birth, in the early neonatal period. The decrease in IGF-1 levels is especially pronounced after preterm birth, which leaves prematurely born infants relatively IGF-1 deficient (5). As in other tissues, IGF-1 regulates numerous functions in the fetal lung that are critical for morphogenesis, including VEGF-dependent endothelial cell proliferation, epithelial cell proliferation and differentiation, and mesenchymal production of extracellular matrix components. IGFR-1–null mice develop pulmonary hypoplasia and diaphragmatic defects and die of respiratory failure (8). In addition, blocking IGF-1 signaling prevents *ex vivo* branching in human fetal lung explants (9). Thus, IGF-1 is indispensable for normal lung development and its deficiency could contribute to lung disease in preterm infants. Indeed, reduced serum IGF-1 levels in the early postnatal period are associated with later development of BPD in preterm infants (5, 10, 11). Given its critical importance in lung development, and the established link between lower serum IGF-1 levels and BPD, replenishment of IGF-1 after preterm birth represents a viable strategy to prevent BPD that requires further investigation.

In a study reported in this issue of the *Journal*, Seedorf and colleagues (pp. 1120–1134) tested the efficacy of rhIGF-1/BP3 (recombinant human IGF-1/IGFBP-3) in preserving normal lung growth in three well-described murine models of BPD (12). Two antenatal models (intraamniotic administration of sFlt1 or endotoxin to model preeclampsia and chorioamnionitis, respectively) and a postnatal hyperoxia model were used to test the hypothesis that IGF-1 therapy would preserve lung growth and function in BPD. Postnatal administration of rhIGF-1/BP3 intraperitoneally to rat pups improved alveolarization and microvascular density in the distal lung in all three models and prevented the development of right ventricular hypertrophy, a sign of pulmonary hypertension. Furthermore, rhIGF-1/BP3 increased *in vitro* proliferation of fetal type II alveolar epithelial cells and endothelial cells, suggesting that IGF-1 may act as a mitogen and proangiogenic factor and promote normal lung growth.

Different inciting insults can activate distinct signaling pathways, thereby leading to the abnormal lung development seen with BPD. Thus, a major strength of this study is the use of three distinct yet clinically relevant models of BPD to test the efficacy of rhIGF-1/BP3 in preserving normal lung growth. The finding that rhIGF-1/BP3 was effective in all three models suggests that reduced lung IGF-1 expression and/or disruption of signaling pathways activated by IGF-1 may be important in BPD pathogenesis. These findings bear relevance when we consider the results of a recent phase 2, multicenter randomized control trial (RCT) that evaluated the efficacy and safety of rhIGF-1/IGFBP-3 in decreasing the severity of retinopathy of prematurity in preterm infants (13). Although the study did not find any difference in retinopathy of prematurity occurrence, there was a substantial (53%) decrease in the incidence of severe BPD (a secondary outcome in the RCT) in rhIGF-1/IGFBP-3–treated infants compared with placebo-treated infants. Although further studies are clearly needed, these data indicate that augmenting IGF-1/BP3 levels may be an effective therapeutic approach to treat BPD.

Although the study by Seedorf and colleagues has many strengths, we need to consider some additional points when interpreting its results. The molecular mechanisms involved in IGF-1–dependent cellular growth and differentiation remain poorly defined; however, IGF-1 has been shown to increase proliferation in lung epithelial cells through stimulation of the PI3K/AKT pathway (14). IGF-1–mediated

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