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Anti–Vascular Endothelial Growth Factor Antagonists: A Potential Primary Prevention for Bronchopulmonary Dysplasia?

Despite being the focus of a large amount of clinical, translational, and molecular research, the incidence of bronchopulmonary dysplasia (BPD) has remained basically unchanged for the last 30 years (1). This is due largely to the increased survival of extremely preterm infants born prematurely (<28 wk of gestation) as a result of multifactorial etiologies and distinct biological pathways. BPD has a broad operational definition that does not indicate the pulmonary pathophysiology of disease in an individual patient, particularly in relation to potential *in utero* exposures for preterm delivery (2). Although there is scientific support for a relationship between *in utero* exposures/etiologies for preterm delivery, such as preeclampsia (PE) (3) and chorioamnionitis (CA) (4), and the subsequent development of BPD, most interventions for BPD have been done postnatally.

In this issue of the *Journal* (pp. 776–787), Wallace and colleagues (5) present the results of a novel study demonstrating the potential importance of increased expression of sFlt-1 (soluble fms-like tyrosine kinase 1), an endogenous antagonist to VEGF (vascular endothelial growth factor), as a mediator of the important antenatal factors of PE and CA for BPD. Pregnancies complicated by PE have increased sFlt-1; therefore, Wallace and colleagues modeled PE in a rat model by injecting intraamniotic sFlt-1. This caused abnormal lung structure as assessed by radial alveolar counts, abnormal lung function via pulmonary function tests, abnormal vessel density, and indicators of right ventricular hypertrophy (RVH). These investigators also studied a CA model with intraamniotic endotoxin injections. These rats demonstrated increased sFlt-1 in blood and BAL, and they also demonstrated abnormal lung structure and function as well as indicators of RVH, similar to those of the PE model. Wallace and colleagues then evaluated the potential of a selective anti–sFlt-1 monoclonal antibody (mAb) given either antenatally or postnatally in the scenario of either the PE or CA model. The anti–sFlt-1 mAb improved lung structure, function, and vessel density and decreased indicators of RVH.

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The paper by Wallace and colleagues has a number of strengths. Importantly, it adds to the growing body of evidence that an imbalance of pro- and antiangiogenic factors and disruption of lung vascular growth are likely important to the development of BPD (6). It also emphasizes that preterm birth is not a single process, because the authors have modeled/focused on important antenatal conditions (PE and CA)/delivery phenotypes for the development of BPD. They have identified sFlt-1 as a potential biomarker/mediator for the development of BPD in these context-specific situations, and the model of decreased radial alveolar counts and altered pulmonary function appeared reproducible when either endotoxin or sFlt-1 was given by intraamniotic injection. The authors have employed well-established techniques to quantify radial alveolar counts and pulmonary function tests and have evaluated both structure and function. In addition, their paper presents a "contemporary" model of BPD, which is characterized by alveolar simplification. This is contrasted with "older" BPD models, which were induced via inflammation, fibrosis, and abnormal vascular remodeling (7). Most importantly, the authors focus on primary prevention through the administration of a novel anti–sFlt-1 mAb given antenatally or early postnatally to attenuate many of the structural and functional changes associated with current BPD (1).

Although the paper by Wallace and colleagues presents important proof-of-concept data pointing toward potential primary prevention of BPD, it also has several limitations. As always, it is difficult to extrapolate the results of controlled and desired reproducible animal studies to the complex and multifactorial biological variability that occurs with human experiences. BPD has been studied extensively in the rat model; however, the heterogeneity of lung pathology seen in human BPD is not seen in the rat or in small animal models (8). The rat model is also not one of premature delivery and does not allow the study of the important genetic predisposition to BPD (9). Genetic factors may account for between 53% of variance in susceptibility to BPD and 79% of variance in susceptibility for moderate to severe BPD (8). Although animal models may simulate the histology of human BPD, the genetic basis of BPD and resulting abnormalities in signaling

pathways may be dissimilar. Although largely unstudied, epigenetic changes may also be important in the development of BPD.

As mentioned by the authors, there are likely multiple interactive pathways beyond VEGF signaling in the pathogenesis of PE and CA that need further study. Several important questions and challenges remain: How translatable will this therapy be to prevention of BPD in extremely preterm infants (10)? At what gestational age would treatment need to occur? What would the effect of sFlt-1 mAb be on other organ systems, including the brain and retina? How was the mAb protective, by protecting the placenta or the fetus? Understandably, in this study, the authors examined very short-term outcomes, and as treatment development progresses, it will be essential for longer-term outcomes to be detailed.

In conclusion, the paper by Wallace and colleagues is an important beginning step in moving interventions for BPD toward primary prevention, which will require better elucidation of placental function in lung development (11, 12); increased knowledge of normal lung/vascular growth and development, healing, and repair; genetics and epigenetics; and effects of nutrition (13). A recent paper (14) illustrated the importance of environmental factors, demonstrating that maternal smoking during pregnancy was associated with a twofold increase in the odds of the child having BPD. These data reemphasize that one of the most effective measures for decreasing both preterm deliveries and BPD in infants born preterm is attenuating the effects of *in utero* smoke exposure on lung development (15) through smoking cessation and nutritional and pharmacological interventions. Preterm delivery alters lung development, decreases lung function, and increases subsequent respiratory morbidity with increased wheeze even in initially asymptomatic neonates (16). Would sFlt-1 mAb also enhance lung development in these circumstances? ■

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Amphetamine Derivatives and the Risk of Pulmonary Arterial Hypertension

A New Chapter of the Story

In this issue of the *Journal*, Zamanian and colleagues (pp. 788–800) present the results from a prospective cohort study of patients with pulmonary arterial hypertension (PAH) associated with the use of methamphetamine (Meth-APAH) (1).

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In the classification of drug-associated PAH (2), anorexic amphetamine derivatives (aminorex and fenfluramine) are considered as "definite" risk factors for PAH because of the occurrence of an epidemic and/or the results of a multicenter epidemiologic study. Between 1967 and 1971, an epidemic of idiopathic PAH (IPAH) occurred in Switzerland, Germany, and Austria, with a 20-fold increase in the incidence of IPAH. Among 582 patients with a new diagnosis of PAH, 70% had used aminorex.