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EDITORIAL COMMENT

# Inhibiting Serotonin to Treat Pulmonary Arterial Hypertension

## An Exciting New Chapter in an Old Story*

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Pulmonary arterial hypertension (PAH) is a highly morbid disease characterized by fibroproliferative, plexogenic, and microthrombotic remodeling of distal pulmonary arterioles that increases pulmonary vascular resistance to promote right heart failure. Despite substantial recent progress contemporizing the criteria for disease diagnosis, prognosticating patients, and standardizing the approach to treatment, the longitudinal outcome in PAH remains unfavorable compared with that of other cardiovascular diseases.[1] For example, the median survival rate for patients with hereditary PAH due to a variant in the gene coding BMPR2 is approximately 6 years even though a substantial proportion of patients are young at the time of diagnosis (mean age 35 years).[2] However, the pathobiology of PAH is complex and involves interplay between genetic and other molecular disease drivers, suggesting that major opportunity exists to develop therapeutics that exert a clear and substantial benefit on survival and other hard clinical endpoints in affected patients.

In 1965, the catechol derivative aminorex fumarate (2-amino-5-phenyl-2-oxazoline) was sold in Europe as an anorexigenic drug to control weight. This coincided with an outbreak of PAH in users, prompting focus on potential causative links between the drug and pulmonary vascular injury, as well as subsequent discontinuation of drug sales. In the 1980s, fenfluramine and dexfenfluramine, which are structurally related to aminorex fumarate, were introduced to the U.S. market but, again, were ultimately discontinued due to epidemiologic and clinical reports suggesting causation between drug use and incident pulmonary hypertension. These observations were notable, since pharmacologic studies had long suggested that these drugs increase bioactive levels of the tryptophan derivative and vasoactive compound serotonin (5-hydroxytryptamine) by directly increasing serotonin release, re-uptake inhibition, and, possibly, functioning as an agonist at 5-$HT_2$ receptors.[3] Indeed, data in cellular and experimental animal models of PAH reinforced the pathogenetic effect of elevated serotonin through its effects on pulmonary artery smooth muscle constriction, proliferation, and migration; extracellular matrix expansion through fibroblast activation; and platelet aggregation among other events that underlie vascular remodeling in PAH.[4]

These collective observations make a compelling case in favor of pursuing antiserotonin therapies to treat PAH, particularly via the 5-$HT_{2B}$ receptor subtype which modulates signal transduction through the canonical $G_{q11}$ protein pathway that seems to drive the vascular pathophenotype. Notably, however, the distribution of 5-$HT_{2B}$ receptors includes numerous off-target tissue types, particularly the central nervous system (CNS), in which effects include processes of addiction, aggression, and delusions. Because patients with PAH who qualify for pharmacotherapy clinically are generally precarious with little reserve, a key barrier to advancing antiserotonin therapies in this patient population has to date been off-target effects. Nonetheless, technical

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advances in organic chemistry, the availability of small molecule screens, and information on the $5HT_{2B}$ crystal structure offer opportunity to engineer a strategy with enhanced selectivity to the $5HT_{2B}$ receptor but also, perhaps, limited blood-brain barrier penetration.

In this issue of *JACC: Basic to Translational Science*, Valentine et al[5] used a combination of classical and contemporary medicinal chemistry tactics to tackle this problem. They reviewed previously published data identifying a small series of indole (namely, aromatic, heterocyclic, and organic) urea compounds that emerged as high-affinity 5-$HT_{2B}$ receptor antagonists. The investigators then focused on introducing a polar modification to analogue compounds and, ultimately, coupled 5-isocyanato-1-methyl-1H-indole 1 and aminothiophene to a primary structure, which cyclized to the compound VU6047534 under basic hydrolysis conditions.

This compound was favored compared with 200 candidate compounds, presumably based on affinity and structural data, and experimentally exhibited high 5-$HT_{2B}$ potency with little evidence of off-target responses across 68 common membrane proteins, ion channels, and transporters.[5] In mice, minimal brain concentrations of VU6047534 were detected, which was consistent with a low total brain:total plasma partition coefficient. Interesting, a dichotomous activity pattern was observed for VU6047534 in a radioligand binding experiment in which partial agonist activity was observed at high concentrations while antagonist properties were observed at lower concentrations consistent with physiological conditions. Using a disease prevention protocol in the angioproliferative SU-5416/hypoxia-PAH mouse model, administration of VU6047534 caused a modest but significant decrease in right ventricular systolic pressure, which was consistent with a salutary benefit on vascular remodeling, defined by the number of muscularized pulmonary arterioles, as well as a substantial reduction in right ventricular mass as measured by using the Fulton index.

This study[5] marks an important advance in the field of translational science in PAH for several reasons. First, the work by Valentine et al[5] provides contemporary insights on a 50-year-old narrative suggesting that serotonin signaling is a pharmacologically modifiable contributor to PAH. Second, the investigators have integrated complex chemistry principles to address a key challenge in the field of serotonin signaling therapeutics: limiting CNS penetration of 5-$HT_{2B}$-targeting drugs. Their work marks an important step forward by proving that it is possible to modify a small molecule compound for reducing off-target tissue penetration without compromising target engagement. Third, this work naturally leads to exciting, additional avenues of investigation, including testing the effect of VU6047534 in BMPR2 genetic models of PAH as well as understanding potential synergy between VU6047534 and therapies that target orthogonal pathways; these include Src tyrosine signaling, which is already known to cause or attenuate PAH depending on the pharmacologic stimulus.[1]

The work by Valentine et al[5] also leaves several questions about VU6047534 unanswered. For example, it is not clear that polar modifications that are effective for limiting CNS uptake would also be effective for attenuating other potential off-target effects, as 5-$HT_{2B}$ is expressed in alternative tissues linked to important side effects in PAH such as gastrointestinal dysmotility. The hemodynamic data presented in this study were somewhat limited in scope, and understanding the effect of VU6047534 on numerous other parameters that are important to PAH clinically (eg, pulmonary vascular resistance, mean arterial pressure, left ventricular end-diastolic pressure, others) may yield important early insights on clinical translatability. Expanding on the mechanistic basis for 5-$HT_{2B}$ up-regulation in the hypoxia (only) model of pulmonary hypertension reported in this study may have unexpected insights into understanding opportunities to treat high-altitude syndromes that are associated with pulmonary vascular dysfunction. Finally, as the authors conclude, further *N-1* modification(s) to VU6047534 may be needed, as optimizing CNS penetration in humans could require greater P-glycoprotein efflux than is required to show a similar CNS uptake profile in rodents.

In summary, Valentine et al[5] are to be congratulated on an important accomplishment addressing the complex problem of drug development in PAH. Their work reinforces the importance of collaborative research that integrates medicinal chemistry, chemical assay design, and clinical context expertise to guide in vivo testing. Findings from their study highlight the promise of VU6047534 in PAH, and the study justifies further work that will rigorously profile off-target effects beyond the CNS and innovate potential analogues that optimize potency and maximize bioefficacy, perhaps through greater emphasis on structure-activity relationships. Overall, this work sets the stage for an exciting new

chapter in an old story, one in which serotonin may finally emerge as a truly modifiable driver of PAH pathobiology with pharmacotherapeutic potential.

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