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Pulmonary Arterial Hypertension Research Advancement through the Years

Department of Medicine, University of Auvergne, France

Pulmonary arterial hypertension (PAH) is a rare disease with a high mortality rate. Although treatment options have improved over the past two decades, patients still die prematurely from right heart failure. Although rare, they are heterogeneous at the genetic and molecular level, and understanding and exploiting this fact is key to developing

K **:** Pulmonary hypertension; BMPR2; Bone morphogenetic receptor type 2;New drug targets

I

In contrast to the systemic circulation, the normal adult pulmonary circulation is a low-pressure, low-resistance vascular bed. Pulmonary hypertension (PH) is diagnosed when the resting mean pulmonary artery pressure (mPAP) is at least 25 mmHg and is divided into ve major subgroups based on clinical and hemodynamic criteria. As a result, the workload of the right ventricle increases, which, if hypertrophied and uncoordinated, can lead to premature death.

PH is not uncommon in le ventricular failure where risk grading is increasingly recognized such that even borderline elevations in mPAP contribute to mortality. Pulmonary arterial hypertension (PAH) is less common. Incidence rates of 1.1 to 17.6 per million adults per year have been reported, and prevalence rates of 6.6 to 26.0 per million adults have been reported, suggesting that increased mPAP is due to precapillary resistance to lung perfusion [1]. In the absence of airway or parenchymal lung disease, or chronic thromboembolism. PAH is clinically heterogeneous, with PAH without a de nite cause (referred to as idiopathic PAH [IPAH]), hereditary PAH, drug-induced PAH, and related congenital heart disease, connective tissue disease, HIV, phyla. Hypertension or schistosomiasis [2] histology at postmortem or lung transplantation shows marked pulmonary artery remodeling with vascular cell proliferation invading the vessel lumen.

P A H

e current clinical classi cation of PAH is acknowledged to be inadequate from both diagnostic and drug development perspectives. Combining detailed analysis of genetics and molecular phenotypes is expected to de ne key drivers and novel drug targets of PAH, opening the possibility of more personalized medicine [3]. His associated national PAH cohort study has facilitated the collection of biological samples from his PAH patients across the UK, with deep representations such as metabolomics and proteomics that can be cross-checked with genetic data from the NIHRBR e ort [4]. We are starting to provide type data.

A subgroup of her PAH patients, less than 10%, responded well to calcium channel blockers, suggesting that this pharmacological phenotype should have distinct molecular signatures. is is supported by transcriptomic signatures reported in small patient populations that require further prospective validation 14 . It has been shown that the metabolic pro le of patients who respond to calcium channel blockers resembles that of healthy subjects more than those who do not respond to PAH [5].

High-throughput techniques such as aptamer-based assays, nuclear magnetic resonance, and mass spectrometry have been applied to plasma samples and used for patient risk strati cation. Prognostic panels developed from this approach can add valuable information to clinical assessments. For example, a panel of nine proteins has been shown to improve risk strati cation in combination with N-terminal pro-brain natriuretic peptide (NT-proBNP) or the registry risk equation REVEAL (Registry to Evaluate Early and Long-term PAH) [6]. It has been. Formula created from patient clinical assessment and comorbidities. An advantage of panels of circulating biomarkers is that they are more objective than functional class assessment and more accessible than imaging. Also, combinations of molecules reporting di erent disease states (proliferation, in ammation, coagulation, metabolic dysfunction, etc.) provide more detailed information than a single biomarker. (eg brain natriuretic peptide).

But the real power of these techniques lies in their potential to identify important and treatment-relevant subsets of patients in the clinic. An initiative funded by the US National Heart, Lung and Blood Institute wants to explore this. e PVDOMICS (Pulmonary Vascular Disease Phenomics Program) consortium aims to “rede ne pulmonary hypertension through the phenomenon of pulmonary vascular disease” [7]. e goal is to enroll his 1,500 participants with PH and healthy controls for comprehensive clinical and omics analysis. Recruitment was initiated and an analysis plan was outlined. Data integration challenges cannot be underestimated, but if successful, will provide the basis for molecular taxonomy and biologically relevant insights in pH.

Jean Perriot, Department of Medicine, University of Auvergne, France, E-mail: perriot.jean.@hotmail.com

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N D

Current therapy for PAH consists of four classes of drugs (prostanoid analogues, endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and soluble guanylate cyclase) that treat endothelial dysfunction and reduce vasomotor tone stimulant) [9]. Although they relieve symptoms and improve function, there is limited evidence that these drugs slow the progression of his PAH and prolong the patient's survival. To do this, the drug must at least support right ventricular function and, even better, reverse pulmonary artery remodeling. ere is no shortage of potential new drug targets for PAH.

F G

Impaired BMPR2 signaling causes an imbalance of TGFβ/BMP signaling in favor of TGFβ and may underlie vascular remodeling in PAH patients with and without BMPR2 mutations. Beyond the pursuit of gene therapy, many therapeutic strategies have been proposed, including pharmacological approaches such as chloroquine (to prevent lysosomal degradation of BMPR2), atallen (to detect missense mutations), and increasing BMP9 levels. I'm here [10]. To date, tacrolimus is the only treatment used in clinical trials that targets his BMPR2 signaling. e drug binds to all three her BMP type 1 receptors and removes FKBP12, activating BMPR2-mediated signaling in the absence of exogenous ligand and her BMPR2. Although some patients showed marked increases in her BMPR2 expression, improvement in 6-minute walking distance (6MWD) and heart failure serological and echocardiographic parameters, changes were not observed in all patients [11]. ere is none. An alternative approach is to inhibit TGFβ activity using a novel activin receptor fusion protein (Sotatercept) that competitively binds to and neutralizes TGFβ superfamily ligands. Although this approach is developing into clinical trials, the e ects of increased hematocrit associated with this treatment need to be carefully monitored and understood.

G F

Much has been said about the similarities between dysregulated growth of vascular cells and tumor cell growth, leading to interest in repurposing oncology drugs. Research on the tyrosine kinase

without anemia is common in PAH and associated with poor survival. e cause is unknown. It cannot be explained by in ammation [21]. Orally administered iron is poorly absorbed by patients with PAH. His two open-label studies of intravenous iron supplementation in PAH reported improvements in athletic performance measures. A randomized, double-blind trial is nearing completion.

e 5-HT1B receptor is highly expressed in human pulmonary arteries, is upregulated in PAH patients, and mediates serotonin-induced vasoconstriction and remodeling. 5-HT1B e ects are speci c to the lung, as 5-HT2A receptors mediate these e ects systemically. Both the 5-HT1B receptor and the serotonin transporter (SERT) are critical for her Nox1-derived ROS production and serotonin-mediated vascular e ects in PAH. However, so far, clinical studies evaluating pharmacological manipulation of serotonergic activity in PAH have been disappointing. Current interest is in the inhibition of tryptophan hydroxylase 1 (TPH1), the rate-limiting enzyme of serotonin biosynthesis. KAR5585, a prodrug of KAR5417, is a function-selective inhibitor of TPH1. Dose-dependent inhibition of serum serotonin and its plasma and urinary degradation product 5-hydroxyindoleacetic acid (5-HIAA) has been demonstrated in healthy volunteers. In preclinical models of PAH, KAR5585 dose-dependently reduced serum, intestinal, and pulmonary levels of serotonin and 5-HIAA, and signi cantly reduced pulmonary artery pressure and pulmonary vessel wall thickness and occlusion.

DNA D

Dysregulation of DNA damage and repair mechanisms has been identi ed as a trigger for disease progression in PAH, and inhibition of poly (ADP-ribose) polymerase (PARP) reverses PAH in several animal models. A safety study has been proposed to repurpose olaparib, an orally available PARP inhibitor approved for the treatment of BRCA-associated breast cancer, for PAH.

C

ese opportunities come with challenges. Animal models do not faithfully mimic the human condition and have a poor track record in predicting e cacy. Not suitable for development of drugs targeting vascular remodeling. Clinical trials must compete for relatively small patient pools.

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