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editorial

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Drug discovery in pulmonary arterial hypertension: attacking the enigmatic root of a deadly weed

As Spring flowers fade and Summer sets in, weed season begins. Tempting as it is to simply mow over them or even pull up the leaves and stems without a tool, those weeds will simply grow back and multiply – sometimes, it seems, even more vigorously than before. If you really want to remove a weed, you must use a tool and extract the root. The same could be true for the treatment of pulmonary arterial hypertension (PAH) (Fig. 1).

Although interest in PAH as an enigmatic and deadly clinical entity has always been high, progress toward understanding and treating PAH was slow in the first century after Romberg initially described the pathology of 'pulmonary vascular sclerosis' in 1891 [1]. In fact, the first hemodynamic description of PAH was not available until 50 years later when Swan and Ganz opened the door to cardiac catheterization, which enabled Dresdale to report the first direct measurements of right heart pressures [2]. Twenty years later, in 1976, Sir John Vane reported the initial preclinical work about prostacyclin and its pleiotropic physiologic effects [3]. Epoprostenol finally became the first therapy approved for USA marketing in 1995, after more than 15 years of human clinical experimentation [4].

Although it took 104 years from disease description until the first therapy, we have recently been attacking the weeds more vigorously. Since 2001, the unified effort of committed patients, collegial investigators and entrepreneurial companies has resulted in the FDA approval of a remarkable 11 additional drugs to treat this devastating disease, which restricts blood flow through the lungs, ultimately causing right heart failure and death. The rapid rate of drug development is all the more impressive when one considers the rare nature of PAH with an estimated prevalence of 15,000 patients in the USA. However, the 'root cause' of PAH remains a mystery and thus far only the symptoms have been attacked. Even with aggressive therapy at expert French centers, a recent analysis demonstrated 49% mortality within three years for newly diagnosed patients [5]. This is particularly sobering when one considers that PAH strikes at a median age of 50 – this is a disease that condemns the young. Far short of a cure, the approved drugs also leave much to be desired. Infusions of prostacyclin or its analogs, long valued as the most effective drugs, have cumbersome delivery systems, debilitating adverse effects and high costs. We have been grabbing at the leaves of this PAH weed and have yet to find and dig out the root. There remains a major unmet medical need.

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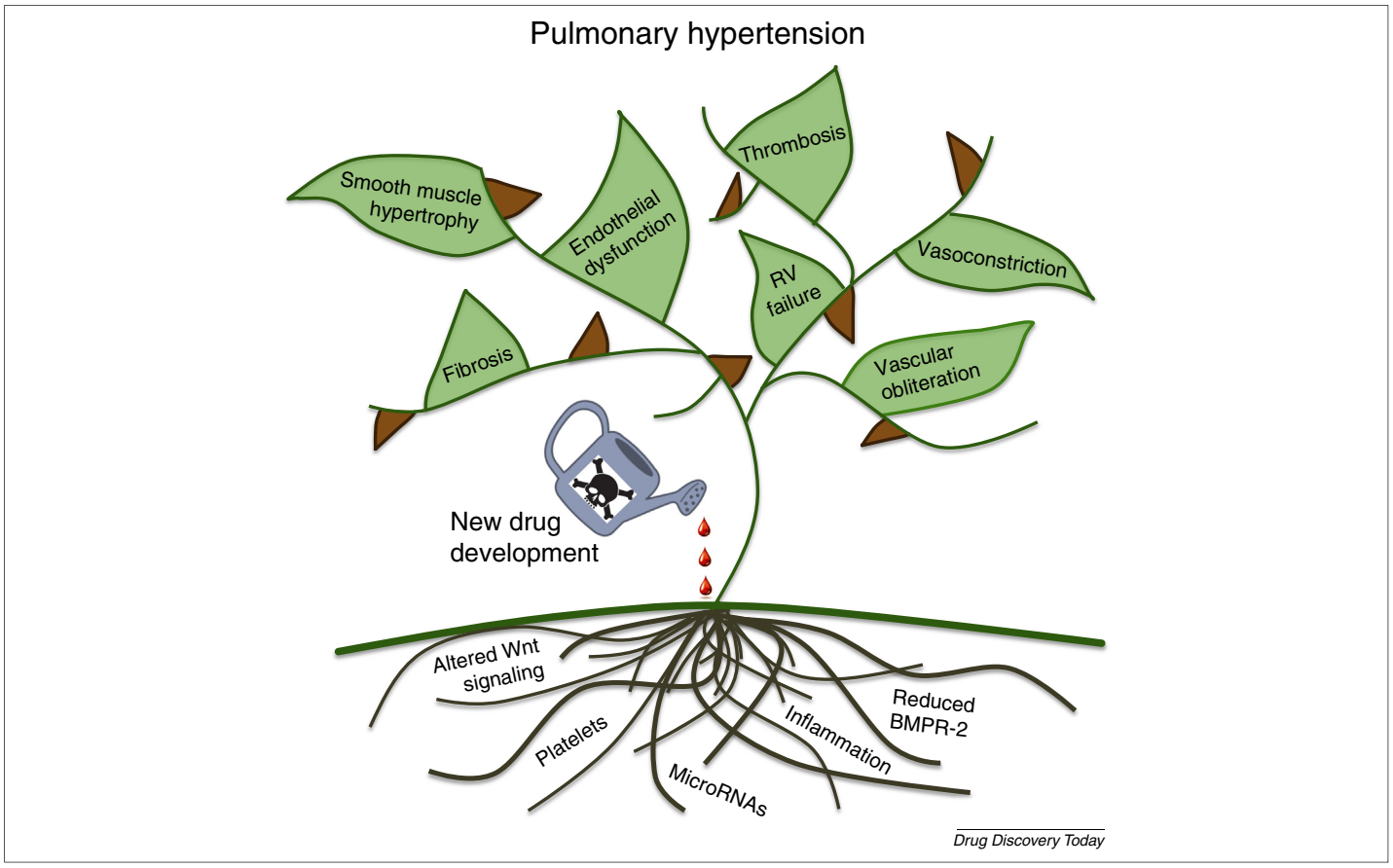

FIGURE 1

The therapeutic challenge in pulmonary arterial hypertension (PAH). At this time, our drugs attack thrombosis, endothelial dysfunction, vasoconstriction and right ventricular (RV) failure, which are visible manifestations of a much deeper problem. The 'root' of PAH is enigmatic and complicated, but in this issue we identify five promising avenues of drug discovery that could address the disease at its very source. The final article addresses the complex problem of endpoints and clinical trial design–a task almost as complex as the aberrant signaling in PAH. Abbreviation: BMPR, bone morphogenetic protein receptor.

We have therefore organized this issue of *Drug Discovery Today* on PAH to serve as a lightning rod and attract provocative ideas that should re-energize the drug discovery process. In the first manuscript, Rubin Tuder briefly describes the normal pulmonary vasculature and then reviews pathology data derived from the modern treatment era. His work demonstrates that severe pathologic changes remain widespread in the lungs of advanced patients, even when there was at least a partial therapeutic response. He offers a novel approach to histologic analysis of the right ventricle (RV) and the lung, and these more sophisticated and quantitative techniques should certainly be considered by those of us analyzing tissue from animal models of the disease. Harm Bogaard and colleagues from Amsterdam then provide us with an overview of the methods to study RV function and dysfunction in patients with PAH. They list in tabular form the many measurements that describe RV function and then provide context about the relationship between intrinsic RV function and RV afterload (the pulmonary circulation). Clinicians have traditionally measured 'load-dependent' parameters of RV function (like stroke volume), and our Dutch colleagues sensibly advocate for 'load-independent' assessments, which are crucial if we are to understand and treat severe RV dysfunction in PAH patients. They provide an accessible and graphic description of the load-independent parameter, end-systolic elastance (Ees), which is most easily obtained in animals, but can also be derived in humans when pulmonary hemodynamic measurements are combined with either invasive or noninvasive measures of RV volume.

These first two articles provide the foundation for describing and measuring the disease as a prelude to the subsequent articles, which advocate for drug development to: reduce vascular inflammation; modify bone morphogenetic protein receptor (BMPR) signaling; alter microRNA expression; reduce thrombosis and platelet dysfunction; and correct Wnt-signaling. Frederic Perros and colleagues from Paris provide a rich description of the cellular and humoral inflammation known to be more active in PAH patients. Of particular interest is the recent observation that patients with so called 'idiopathic' PAH (those not known to have a systemic inflammatory disease like lupus) have circulating autoantibodies and tertiary lymphoid structures surrounding the small pulmonary arteries. Although an increase in circulating chemokines such as macrophage chemoattractant protein-1 (MCP-1) has long been recognized in patients with systemic and pulmonary vascular disease, these more recent findings strongly suggest that inflammatory cells in idiopathic PAH patients are specifically attacking components of the pulmonary vasculature. Whether this is an important initiator of disease or rather a key factor in PAH progression remains to be determined, but this increasing evidence for autoimmune destruction of the pulmonary arterioles

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