



BET Signaling: A Novel Therapeutic Target for Pulmonary Hypertension?

To the Editor:

Pulmonary hypertension (PH) is a progressive clinical condition with poor prognosis if the patients do not receive adequate therapy. Recent clinical trials demonstrate that combined therapy with multiple drugs improves pulmonary arterial hypertension outcomes more significantly compared with monotherapy (1, 2). However, there are only three types of drugs targeting PH, including the nitric oxide–cyclic guanosine monophosphate pathway, prostacyclin pathway, and endothelin pathway, in current clinical practice. Thus, introduction of new drugs targeting novel pathways may provide more combination options, especially for patients with pulmonary arterial hypertension who are resistant to or show adverse effects from current drugs. In a recent issue of the *Journal*, Van der Feen and colleagues (3) report that a clinically available BET (bromodomain and extraterminal motif) inhibitor, RVX-208, shows therapeutic effects on three preclinical PH models, with reduced pulmonary vascular resistance, increased cardiac output, and decreased pulmonary vascular remodeling and inflammation through FoxM1 (forkhead box protein M1) and PLK1 (polo-like kinase) signaling pathways. In cultured cells from patients with PH, RVX-208 suppresses pulmonary artery smooth muscle cell proliferation and endothelial cell inflammation through FoxM1/PLK1 pathways also. Drugs targeting these novel pathways have not been used for patients with PH yet because RVX-208 is now clinically available only for coronary artery disease. The promising *in vivo* and *in vitro* data from Van der Feen and colleagues suggest that RVX-208 may bring new hope for patients with PH. It is of note that RVX-208 shows synergistic effects with current PH-target drugs such as tadalafil and macitentan in PH models, which is extremely important because combination therapy has been recommended for patients with PH according to recent guidelines for PH practice.

However, there are some pitfalls of this study; most of the PH-target drugs have the side effect of dilating blood vessels in systemic circulation. Given the fact that most patients with PH have relatively low blood pressure, it is very important to monitor the change of blood pressure after administration of PH-target drugs. In clinical practice, plasma level of BNP (B-type natriuretic peptide) and right atrial pressure are used to assess the severity and predict the prognosis of PH. It would be interesting to know the changes of

blood pressure, BNP, and right atrial pressure on the PH animals in this study. ■

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Reply to Chen *et al*.



From the Authors:

We thank Chen and colleagues for their interest in the BET (bromodomain and extraterminal motif) inhibitor as a promising therapeutic target for pulmonary arterial hypertension (PAH). As mentioned by Chen and colleagues, bringing a new compound into clinical practice stands on a solid scientific foundation not only with regard to potential drug efficacy but also with regard to anticipated side effects.

In the past two decades, we have witnessed the development of more than 10 drugs either enhancing pathways involved in vasodilation (nitric oxide–cyclic guanosine monophosphate and prostacyclin) or antagonizing vasoconstriction (endothelin) in addition to other pleiotropic effects. Because these processes are

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not unique for the pulmonary circulation, the use of these drugs may also be accompanied by increased systemic vasodilation, which at a certain level can be expected to reduce coronary to right ventricular (RV) perfusion gradient, increase neurohormonal activation, and diminish left ventricular end-diastolic pressures, ultimately promoting coronary and systemic hypoperfusion, increased right-to-left shunting (in case of intracardiac shunt), and further RV dysfunction through an enhanced septal shift in a setting of ventricular interdependence and pericardial constraints (1). Fortunately, except for the combination of sildenafil and riociguat (2), most studies confirmed that the limited effect of these vasodilators on systemic blood pressure was presumably offset by the pulmonary vasodilation resulting in increased cardiac output. Similarly, the detrimental effects of more recent therapeutic targets on the RV may easily be overlooked when the compound under investigation markedly improves the PAH pulmonary vasculature. Therefore, recent recommendations suggest that any new drug developed for PAH should be tested in preclinical models for its specific effects also on the pressure-overloaded RV (1, 3).

In humans, RV function is most commonly assessed using right heart catheterization, echocardiography, and cardiac magnetic resonance, whereas circulating biomarkers can serve as a noninvasive surrogate marker (4). In our recently published multicenter preclinical validation of BET inhibition for PAH (5), we documented that RVX208, a clinically available BET inhibitor, mitigates proproliferative, prosurvival, and proinflammatory pathways in cultured PAH vascular cells, leading to significant pulmonary histological and hemodynamic improvements in diverse rat models with experimentally induced PAH. Not surprisingly, BET inhibition was associated with significant hemodynamic improvements, confirming previous results documenting the beneficial effects of BRD4 inhibition on RV function (6) and coronary perfusion (7). More importantly, and as previously recommended (1, 3), we specifically studied the effects of RVX208 treatment in RV pressure load induced by pulmonary artery banding. Interestingly, RVX208 was associated with an increase in RV stroke volume, work, and power, suggesting some improvements in RV function independent of the afterload, confirming the safety of the drug during RV compromise in rats.

Although inhibition of BET impacts diverse cellular functions and interferes with proproliferative, prosurvival, procalcific, and proinflammatory pathways, to name a few, none of those were anticipated to result in changes in systemic blood pressure. Importantly, in the most recent cardiovascular outcomes study in 2,425 subjects over 2 years, apabetalone was not associated with any changes in blood pressure (8).

Therefore, the published data support the establishment of a clinical trial with RVX208 in patients with PAH specifically addressing the safety of BET inhibition in this specific study population. Based on extensive preclinical and human data, RVX-208 is not expected to negatively influence RV function or systemic hemodynamics in human PAH. ■

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