3. Ball MK, Hillman NH, Kallapur SG, Polglase GR, Jobe AH, Pillow JJ. Body temperature effects on lung injury in ventilated preterm lambs. *Resuscitation* 2010;81:749–754.
4. De Luca D, Vázquez-Sánchez S, Minucci A, Echaide M, Piastra M, Conti G, Capoluongo ED, Pérez-Gil J. Effect of whole body hypothermia on inflammation and surfactant function in asphyxiated neonates. *Eur Respir J* 2014;44:1708–1710.
5. Duan M, Berra L, Kumar A, Wilcox S, Safford S, Goulet R, Lander M, Schmidt U. Use of hypothermia to allow low-tidal-volume ventilation in a patient with ARDS. *Respir Care* 2011;56:1956–1958.
6. Pietrini D, Pennisi M, Vitale F, Pulitanò SM, Conti G, Mancino A, Piastra M, De Luca D. Rescue hypothermia for refractory hypercapnia. *Eur J Pediatr* 2012;171:1855–1857.
7. Azzopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E, Kapellou O, Levene M, Marlow N, Porter E, *et al.*; TOBY Study Group. Moderate hypothermia to treat perinatal asphyxial encephalopathy. *N Engl J Med* 2009;361:1349–1358.
8. Kattwinkel J, Perlman JM, Aziz K, Colby C, Fairchild K, Gallagher J, Hazinski MF, Halamek LP, Kumar P, Little G, *et al.*; American Heart Association. Neonatal resuscitation: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Pediatrics* 2010;126:e1400–e1413.
9. Karnatovskaia LV, Festic E, Freeman WD, Lee AS. Effect of therapeutic hypothermia on gas exchange and respiratory mechanics: a retrospective cohort study. *Ther Hypothermia Temp Manag* 2014;4:88–95.
10. Villar J, Slutsky AS. Effects of induced hypothermia in patients with septic adult respiratory distress syndrome. *Resuscitation* 1993;26:183–192.
11. Dassios T, Austin T. Respiratory function parameters in ventilated newborn infants undergoing whole body hypothermia. *Acta Paediatr* 2014;103:157–161.

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Myeloid Targets for Pulmonary Arterial Hypertension: Time for Another Look

To the Editor:

We commend Yan and colleagues (1) on their elegant studies, which add to the accumulating evidence of a myeloid/bone marrow origin of pulmonary arterial hypertension (PAH). Using reciprocal bone marrow chimeras in immunocompetent *Bmpr2* mutant and wild-type mouse models, the authors identify bone marrow-dependent mechanisms in the muscularization of pulmonary arterioles and right ventricular systolic pressure elevation, without right ventricular hypertrophy. The findings are complementary to our previous xenograft study (2), in which hematopoietic stem cells derived from patients with PAH were transplanted into immunocompromised mice. Similar to the work by Yan and colleagues (1), hematopoietic stem cells from patients had fivefold higher engraftment, and transplant of stem cells from patients with *Bmpr2* mutations resulted in greater vascular smooth muscle cell hypertrophy than animals engrafted with mutation-negative PAH bone marrow stem cells. Just as important, prior study has shown that transplantation of serotonin 2B receptor-deficient bone marrow is protective against development of hypoxia-induced PAH (3), which indicates that myeloid stem cells can promote or block development of pulmonary vascular disease. Patients with PAH uniformly have an increase of hematopoietic progenitor and stem cell pools in the bone marrow compartment, even when there are no apparent blood abnormalities (2, 4). Intriguingly, patients with myeloproliferative malignancies, which are defined by

clonal stem cell expansion, have a high incidence of elevated right ventricular systolic pressure, providing complementary evidence that proliferative hematopoietic stem cells are closely related to pulmonary vascular disease (5). Altogether, these studies point to an abnormal hematopoietic progenitor/stem cell population that is an early step in the pathophysiology of PAH. Future studies are needed to define mechanisms via which hematopoietic progenitor/stem cells lead to PAH and whether this holds true for all subgroups of the disease. However, the anti-*c-Kit* drug imatinib, which targets stem cells, was effective in PAH (6), although complications limited its use. The recent work by Yan and colleagues (1), together with prior studies, provides a strong rationale to reconsider approaches that target hematopoietic progenitor/stem cells in the treatment of PAH. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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References

1. Yan L, Chen X, Talati M, Nunley BW, Gladson S, Blackwell T, Cogan J, Austin E, Wheeler F, Loyd J, *et al.* Bone marrow-derived cells contribute to the pathogenesis of pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2016;193:898–909.
2. Asosingh K, Farha S, Lichtin A, Graham B, George D, Aldred M, Hazen SL, Loyd J, Tudor R, Erzurum SC. Pulmonary vascular disease in mice xenografted with human BM progenitors from patients with pulmonary arterial hypertension. *Blood* 2012;120:1218–1227.
3. Launay JM, Hervé P, Callebort J, Mallat Z, Collet C, Doly S, Belmer A, Diaz SL, Hatia S, Côté F, *et al.* Serotonin 5-HT_{2B} receptors are required for bone-marrow contribution to pulmonary arterial hypertension. *Blood* 2012;119:1772–1780.
4. Farha S, Asosingh K, Xu W, Sharp J, George D, Comhair S, Park M, Tang WH, Loyd JE, Theil K, *et al.* Hypoxia-inducible factors in human pulmonary arterial hypertension: a link to the intrinsic myeloid abnormalities. *Blood* 2011;117:3485–3493.
5. Roach EC, Park MM, Tang WH, Thomas JD, Asosingh K, Kalaycio M, Erzurum SC, Farha S. Impaired right ventricular-pulmonary vascular function in myeloproliferative neoplasms. *J Heart Lung Transplant* 2015;34:390–394.
6. Farha S, Dweik R, Rahaghi F, Benza R, Hassoun P, Frantz R, Torres F, Quinn DA, Comhair S, Erzurum S, *et al.* Imatinib in pulmonary arterial hypertension: *c-Kit* inhibition. *Pulm Circ* 2014;4:452–455.

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Reply: Expanded Role for Bone Marrow-derived Hematopoietic Stem and Progenitor Cells in Pulmonary Arterial Hypertension

From the Authors:

We agree with Asosingh and colleagues that there are now considerable data to indicate that the hematopoietic compartment of bone marrow contributes to the pathophysiology of pulmonary arterial hypertension (PAH). Initial direct evidence of this was provided by their seminal work, and our data further expanded and clarified their findings