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Letter to the Editor

Reply to "Bone morphogenetic protein's contribution to pulmonary artery hypertension"

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Sir,

We appreciate Dr. Epstein's raising awareness of potential complications related to the usage of recombinant Bone Morphogenetic Protein (BMP).[5] Certainly, the list of potential adverse events are concerning to numerous audiences, including dentists, oral surgeons, orthopedists, and the biomedical science community.[6] However, in addition to the well-documented complications such as marked dysphagia, acute upper airway inflammation, and respiratory distress, Dr Epstein raises the suspicion of a possible connection between BMP usage for spine fusion and the development of pulmonary arterial hypertension (PAH). We respectfully disagree with this point of view, and wish to highlight evidence that PAH likely develops from aberrant loss-of-function of the BMP pathway rather than over-activation of the BMP pathway, as would be expected if recombinant BMP were to diffuse away from a local delivery site.

In 2000, two independent groups provided the first connection between PAH pathogenesis and the BMP pathway by identifying heterozygous mutations in the gene encoding the BMP Receptor Type 2 (BMPR2) underlie a rare, familial form of PAH.[4,8] Since then, hundreds of distinct mutations in *BMPR2* have been identified, and numerous genetic studies in mouse models have demonstrated that loss of or impairment of BMPR2-dependent signalling predisposes animals to developing pulmonary hypertension (PH), which is consistent with the fact that BMP signal transduction and pathway components are generally down-regulated in the lungs of PH patients.[10] Animal models also suggest that various strategies aimed at increasing BMP signaling in the pulmonary vasculature – such as increasing BMPR2 expression,[2,7,11,12] inhibiting a BMP antagonist that sequesters BMP ligands,[3] alleviating BMP pathway repression at the receptor-level using the Food and Drug Association (FDA)-approved drug tacrolimus,[13] or potentiating BMP pathway signal transduction using the FDA-approved phosphodiesterase-5 inhibitor sildenafil[14] – may be beneficial in treating PAH. Furthermore, systemic delivery of the BMP ligand BMP9 reverses established disease in mouse and rat models of PH[9] rather than promoting its development. While it might be argued that BMP2 and BMP9 ligands may have different, even opposing effects, because of differences in their receptor selectivity,[10] mice with heterozygous null *Bmp2* mutations develop more severe PH than their wild type littermates,[1] suggesting that BMP2 also has protective effects against the development of PH.

For these reasons, we contend that the experimental evidence indicates that BMP signalling serves a protective role against the development of PAH. While we agree there are important side effects associated with the use of recombinant BMP in spine fusion, and these must be taken into consideration, it is unlikely that development of PAH is one of them.

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