News Release

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ATS Press Room: 504-670-6926 (May 15 to 20)

Poster session time: 8:15-4:00 p.m. May 19
Location: CC-Area D, Hall G (First Level), Morial Convention Center

Gene Therapy May Be Effective in Treating PAH

ATS 2010, NEW ORLEANS— Gene therapy has been shown to have positive effects in rat models of pulmonary arterial hypertension (PAH), according to researchers at the University of Adelaide in Australia.

PAH is a life-threatening disease in which pressure in the blood vessels of the lungs increases, causing a back-pressure strain on the heart. In inherited forms of the disease, PAH is caused by a mutation in a receptor called bone morphogenetic protein receptor, type II (BMPR2). Even in some non-inherited forms of the disease, BMPR2 levels are low.

There have been many improvements to outcomes in PAH in recent years with new drug therapies, but many patients still ultimately die of the disease and thus new treatments are still needed.

“We investigated whether increasing BMPR2 levels might improve pulmonary hypertension. We used two rat models of pulmonary hypertension, and increased BMPR2 levels in the lungs using a gene therapy approach,” said Paul Reynolds, M.D., Ph.D, FRACP, principal investigator. “We found in both models that BMPR2 gene delivery significantly reduced pulmonary hypertension and the strain it causes on the heart.”

The results will be reported at the ATS 2010 International Conference in New Orleans.

Dr. Reynolds and colleagues induced PAH in Sprague-Dawley rats by keeping them in a hypoxic (10 percent oxygen) chamber for three weeks. Half of the rats were then treated with a viral vector bearing a pulmonary endothelial targeting conjugate designed to boost BMPR2; half were treated with a placebo vector. Then all rats were subjected to a further three weeks of hypoxia at which time PAH was assessed. In a separate model, the researchers induced PAH by injecting the chemical monocrotaline (MCT), which causes inflammation in the pulmonary blood vessels. Rats were first injected with MCT to induce PAH, then half were given the BMPR2 vector or a placebo vector and PAH was assessed 10 days later.

The researchers found in both models that the rats that were treated with the BMPR2 vector compared to placebo had significantly reduced right ventricular hypertrophy, reduced pulmonary vascular resistance, and improved cardiac output.

“These findings were based on the knowledge that low BMPR2 levels are associated with pulmonary hypertension, but it has not previously been shown that increasing BMPR2 levels might be used as a therapy,” said Dr. Reynolds. “This research strongly suggests that increasing BMPR2 levels might offer a new therapeutic target in pulmonary hypertension.”

Further research is need to better understand how and why increasing BMPR2 signalling in the lungs leads to improvements in PAH, and improvements to the gene delivery vectors would be needed for application to human patients.

“We feel encouraged to see such strong therapeutic results from increasing BMPR2 in the rat model,” said Dr. Reynolds. “To apply the gene therapy approach to human patients will require more refinement of the gene therapy vector system, which is something we are working on. However, the principal established here also identifies BMPR2 upregulation as a target for the development of more conventional pharmaceuticals. Either way, there is hope that this approach will ultimately lead to more effective therapies for this potentially deadly condition.”

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“Gene Delivery of Bone Morphogenetic Protein Receptor Type-2 Attenuates Established Hypoxic and Monocrotaline-Induced Pulmonary Hypertension” (Session D61, Wednesday, May 19, 8:15-4:00 p.m., CC-Area D, Hall G (First Level), Morial Convention Center; Abstract 4268)

**Please note that numbers in this release may differ slightly from those in the abstract. Many of these investigations are ongoing; the release represents the most up-to-date data available at press time.*

Gene Delivery of Bone Morphogenetic Protein Receptor Type-2 Attenuates Established Hypoxic and Monocrotaline-Induced Pulmonary Hypertension

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Idiopathic pulmonary arterial hypertension (PAH) is a fatal disease characterised by abnormal proliferation of pulmonary vascular endothelial and smooth muscle cells. Mutations in the gene for bone morphogenetic protein receptor type 2 (BMPR2) have been identified as a cause of PAH, and reduced BMPR2 expression has also been implicated in secondary PAH. Thus, gene therapy using a normal BMPR2 gene could be therapeutic.We previously developed a system for the upregulation of pulmonary endothelial BMPR2 gene expression in rats using adenoviral (Ad) vectors linked to a pulmonary endothelial targeting conjugate (Fab-9B9, directed to angiotensin converting enzyme, ACE), and showed that pre-hypoxia treatment could ameliorate hypoxia-induced PAH. We now investigated whether targeted BMPR2 gene delivery modulates established hypoxia-induced PAH and monocrotaline-induced (MCT; inflammatory model) PAH.

Methods: Hypoxia: Sprague-Dawley rats were exposed to hypoxia (10% oxygen) for 3 weeks, and then assigned to two treatment hypoxic groups. Rats were a given tail vein injection of AdTracLuc (irrelevant viral control) or AdBMPR2, each with Fabâ€‘9B9. Rats were then returned to the hypoxic chamber for a further 3 weeks then PAH assessed by cardiac catheterisation. MCT: Rats were assigned to 3 groups (2 MCT injected and 1 saline control). 10 days after MCT, rats were injected with AdTracLuc+Fab-9B9 or AdBMPR2+Fab-9B9. After a further 8-10 days, PAH was assessed.

Results: Numbers in parenthesis indicate % difference. Hypoxia: Compared to animals that received control vector, AdBMPR2 treatment significantly reduced right ventricular hypertrophy (28%), reduced pulmonary vascular resistance (34%), and improved cardiac output (24%) and cardiac index (22%). BMPR2 therapy partially attenuated right ventricular systolic pressures (16%). MCT: Compared to MCT treated rats that received control vector, those receiving BMPR2 had significantly lower right ventricular systolic pressures (36%), lower pulmonary vascular resistance (47%), less right ventricular hypertrophy (21%) and improved cardiac output (21%) and cardiac index (25%) ($P<0.05$, ANOVA & Holm-Sidak multiple comparison test).

Conclusion: Upregulation of BMPR2 expression may be a therapeutic strategy for pulmonary hypertension, including that related to inflammatory processes.