Breakthrough points to cure for debilitating heart and lung disease

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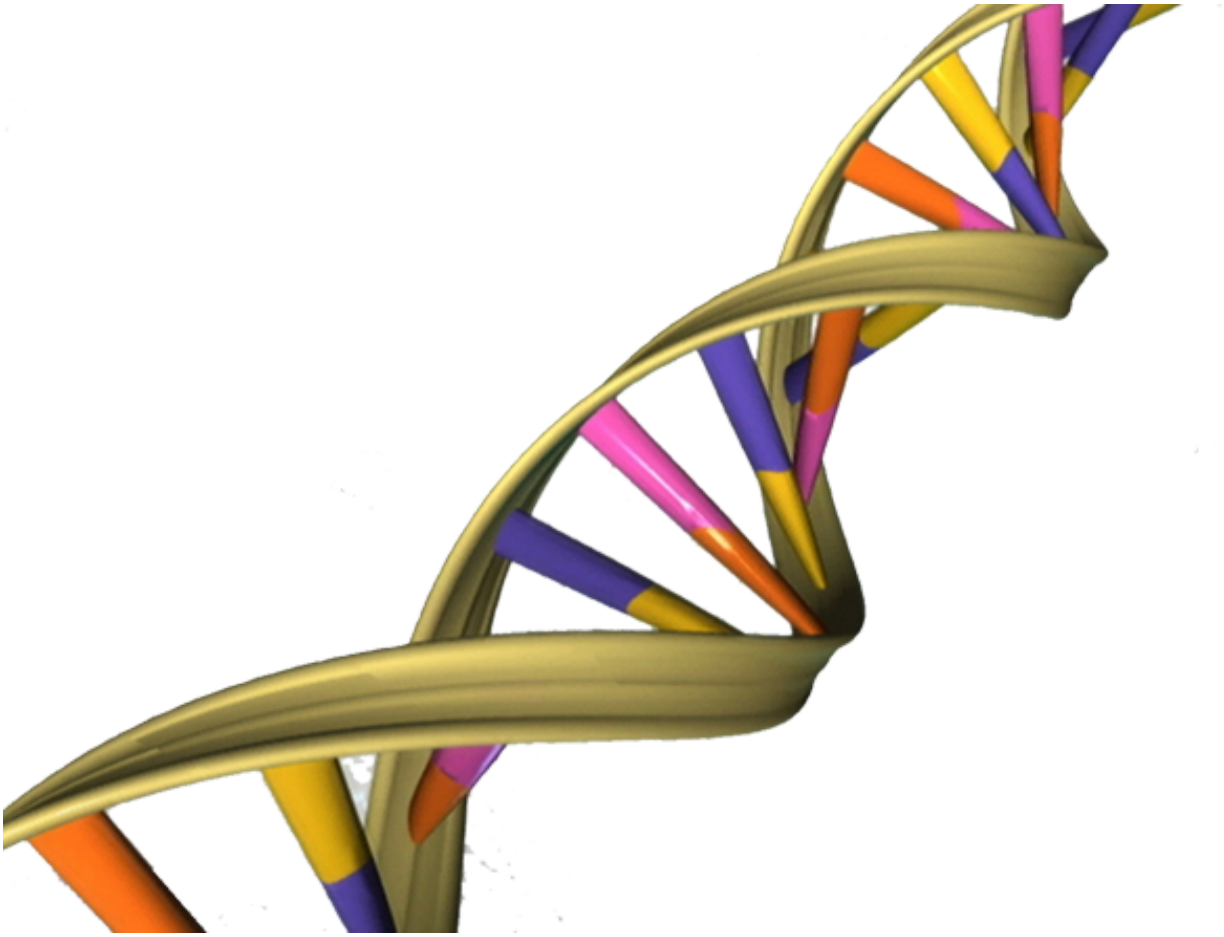

A depiction of the double helical structure of DNA. Its four coding units (A, T, C, G) are color-coded in pink, orange, purple and yellow. Credit: NHGRI

A protein that targets the effects of a faulty gene could offer the first treatment targeting the major genetic cause of Pulmonary Arterial Hypertension (PAH), according to research funded by the British Heart Foundation (BHF).

Genetic evidence dating back to 2000, from research the BHF helped to fund, indicated that the absence or reduced activity of a particular protein, bone morophogenetic protein type II receptor (BMPR-II), leads to PAH. BMPR-II is important to the normal function of the blood vessels of the lungs. PAH is thought to affect around 6,500 people in the UK.

This new study led by BHF Professor of Cardiopulmonary Medicine Nick Morrell and including expertise from Dr Rajiv Machado from the School of Life Sciences at the University of Lincoln, UK, is the first to use a protein, called BMP9, to reverse the effects of reduced activity of BMPR-II and to reverse the disease itself. The study was conducted in mice and rats, but also using cells from patients with PAH. It is published today in *Nature Medicine*.

PAH is a chronic and debilitating disease that affects the blood vessels in the lungs, leading to heart failure, and leaves sufferers feeling breathless and exhausted. Current treatments only target the symptoms and prognosis remains poor. The only effective cure is a lung, or heart and lung, transplant, which has associated risks and complications.

Once diagnosed with PAH, a person has a 30 per cent chance of dying within three years and the condition affects more women than men. Researchers speculate that this gender disparity is caused by pregnancy triggering the disease in genetically susceptible women or that oestrogen can affect the function of BMPR-II.

A team at the University of Cambridge, with contributions from

researchers at the University of Lincoln, Switzerland and the US, searched for a BMP protein that could enhance the function of BMPR-II to target the condition. The researchers firstly trialled different BMP proteins on lung blood vessel cells grown in a dish. This process showed BMP9 to be most selective, and therefore less likely to have negative effects on other cells.

This study used the first animal model, a mouse, which closely mimics the human genetic form of the disease. The University of Lincoln's Dr Machado was instrumental in designing the strategy for development of this experimental model employed in the study.

Using a specific set of molecular tools, Dr Machado replicated a mutation frequently observed in human PAH patients which, subsequently, was introduced into the mouse genome. This facilitated the generation of a mouse model that naturally mirrored the human disease state critical for the assessment of therapeutic options.

Ultimately, the team showed that BMP9 treatment reversed PAH in three separate mouse and rat models. They found that the treatment works in mice with both the genetic from of the disease, and in acquired forms of PAH, where the cause is unknown.

BHF Professor Nick Morrell, who led the research, from the Department of Medicine at the University of Cambridge School of Clinical Medicine, and Director of the BHF Cambridge Centre for Cardiovascular Research Excellence, said: "The next step for our research is studies in people with pulmonary arterial hypertension – first, safety testing to ensure the compound can be given to people. But we're confident of passing this phase because BMP9 exists naturally in the body. We're just giving patients more of it."

Professor Jeremy Pearson, Associated Medical Director of the British

Heart Foundation, which funded the research, said: "We're very excited by these results. This condition is horrible and an effective treatment that prevents the need for a transplant would be a game-changer. Clinical trials of the treatment in patients are still needed but these findings, from years of research supported by the BHF, offer real promise of a cure."

More information: "Selective enhancement of endothelial BMPR-II with BMP9 reverses pulmonary arterial hypertension." *Nature Medicine* (2015) DOI: 10.1038/nm.3877

Provided by University of Lincoln