Breakthrough could help sufferers of fatal lung disease

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Pioneering research conducted by the University of Sheffield is paving the way for new treatments which could benefit patients suffering from the fatal lung disease pulmonary arterial hypertension (PAH).

For the first time scientists have found an antibody treatment that not only stops PAH getting worse, but also reverses the condition in mice and rats. The research was funded by the British Heart Foundation and the Medical Research Council (MRC) and is published in the Journal of Experimental Medicine.

PAH – high pressure in the blood vessels supplying the lungs – is a devastating condition that affects almost 2,200 adults in England and Wales. It is caused by changes in the cells lining the arteries that take blood from the heart to the lungs (a process called vascular remodelling).

Vascular remodelling causes the walls of the vessels to become stiff and thickened making it harder for blood to flow through them, which in turn causes an elevation in blood pressure. This increased pressure places significant strain on the right side of the heart, which can lead to fatal heart failure if left untreated. PAH often affects young people, and more commonly women.

Current treatments for PAH target the constriction of the arteries, but fail to fully reverse the underlying vascular remodelling. The researchers demonstrated that a protein called TRAIL (tumour necrosis factor-related apoptosis-inducing ligand) worsened the progression of PAH in

animal models, but blocking TRAIL with an antibody improved the disease.

Dr Allan Lawrie, a MRC Career Development Fellow from the University of Sheffield's Department of Cardiovascular Science, who led the study, said: "This research opens up a new insight into the mechanisms of PAH and suggests that TRAIL is critical to this process. If we can interrupt this process by blocking the TRAIL pathway, we have the potential to stop the disease in its tracks and even reverse the damage already done."

Since the discovery of TRAIL and its network of receptors, the majority of attention has focused on the clinical potential of manipulating this pathway in cancer therapy. However new research suggests that TRAIL plays broader roles in regulating immune processes, with this latest study suggesting it is critical to PAH.

"These data, from animal models, provide validation and we are now actively pursuing a route to develop human antibodies as a potential new treatment for PAH, though this is likely to be several years from the clinic," said Dr Lawrie.

Dr Shannon Amoils, Research Advisor at the British Heart Foundation (BHF), which co-funded the study, said:

"We urgently need to find new treatments for people with pulmonary arterial hypertension, a condition which can have a devastating effect on people's quality of life and is often fatal. This study shows that a protein called TRAIL plays a role in the disease by driving the overproduction of cells lining the lungs' blood vessels. This overproduction of cells is one of the factors leading to high blood pressure in the lungs.

"Importantly, the researchers show that in rodents, blocking TRAIL

using an antibody dampens down this high cell turnover and reduces the disease severity. There is still a long way to go, but the hope is that the TRAIL antibody might be developed into a new treatment for patients in the future."

Provided by University of Sheffield