Asthma pill targets airway muscles to decrease attacks

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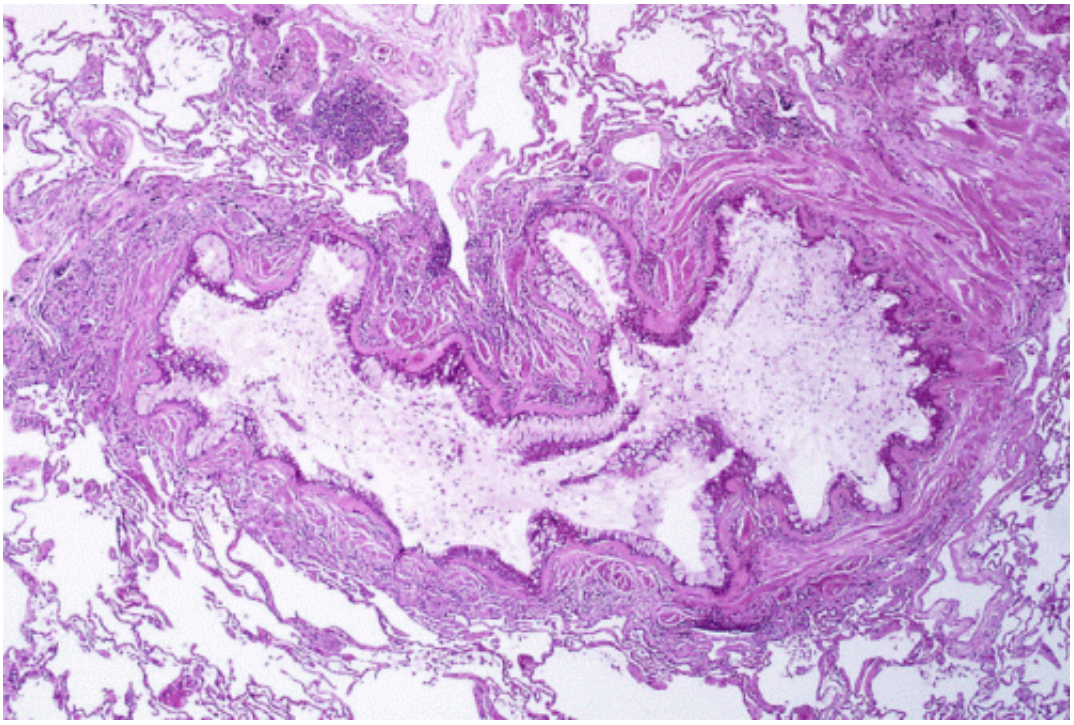

Obstruction of the lumen of a bronchiole by mucoid exudate, goblet cell metaplasia, and epithelial basement membrane thickening in a person with asthma. Credit: Yale Rosen/Wikipedia/CC BY-SA 2.0

Results from a phase II clinical trial, experimental work on cells and computational modelling have together shown why the first pill for asthma in 20 years can help reduce asthma attacks.

Researchers from Leicester (UK) and Vancouver (Canada) have shown that the investigational drug, Fevipiprant (an oral, selective prostaglandin D2 receptor antagonist), reduces the amount of smooth muscle in the airway lining. The findings are published in *Science Translational Medicine* today (13 February).

Professor Chris Brightling, a consultant respiratory physician at Leicester's Hospitals and professor of respiratory medicine at the University of Leicester, said: "Our research shows for the first time that Fevipiprant not only reduces inflammation in the airways, but also reduces the amount of muscle in the lining of the airway. This is likely to explain some of the effects seen in the symptoms and breathing tests following treatment."

An increase in airway smooth muscle is the strongest predictor of reduced airflow into the lungs due to airway narrowing. It significantly increases the likelihood of more frequent asthma attacks and even asthma-related deaths.

The research was supported by the National Institute for Health Research (NIHR) Leicester Biomedical Research Centre. Professor Brightling, who is also an NIHR senior investigator, added: "From previous trials conducted we found that Fevipiprant led to improvements in symptoms, breathing tests, inflammation and also helped to repair the lining of patients' airways.

"Our latest research gives us a better understanding of the mechanisms behind the efficacy of the drug and how changes in one part of the airway wall can impact on others. Our findings suggest that Fevipiprant could have positive long-term effects upon the progression of the disease through remodelling, as well as improve symptoms and reduce attacks."

Dr. Ruth Saunders, a research fellow at the University of Leicester who

led the experimental laboratory-based work in the study, said: "One novel aspect of our study was the way we combined information from a clinical trial, laboratory experiments and computer based models to give insights that would not have been possible with any of these approaches alone."

Dr. Himanshu Kaul, who is now a postdoctoral fellow in the School of Biomedical Engineering at the University of British Columbia, led the computational modelling. He said: "Our computer model represents a milestone towards patient-specific models in respiratory medicine that has the potential to help design new drugs and optimise existing therapies. Eventually, it could play a role in furthering precision medicine by helping predict the optimal intervention tailored to individual patients given their genomic information."

Asthma affects over 300 million people worldwide and its prevalence is on the increase. There are around half a million people with moderate to severe forms of asthma in the UK.

There is currently no routinely-available drug on the NHS that targets smooth muscle mass to reduce asthma symptoms. For people with severe asthma, a procedure called thermoplasty, which uses thermal energy to decrease the amount of smooth muscle in the airways, may be offered. This requires sedation in hospital and is not a cure, nor suitable for everyone. Most patients with severe asthma rely on high dose inhaled or oral steroids to manage their symptoms.

Fevipiprant's potential to reduce the need for patients to take oral steroids either continuously or for attacks could be seen as a positive step, given the range of possible side-effects associated with steroids. These include weight gain, osteoporosis, diabetes and high blood pressure. The more patients take steroids to manage their asthma symptoms, the less effective the same doses become in future.

The research, including the cellular experimental work and computational modelling, was funded by the Swiss pharmaceutical company, Novartis, AirPROM and the NIHR Leicester Biomedical Research Centre.

"Fevipiprant has the potential to significantly improve the treatment of asthma patients who do not achieve disease control on optimised inhaled therapy." said Linda Armstrong, MD, Head Respiratory Development Unit, Novartis. "This trial result is an encouraging step forward. We look forward to the completion of our currently ongoing phase 3 clinical development program and hope to make this once daily oral treatment with fevipiprant available to patients as quickly as possible."

More information: R. Saunders el al., "DP2 antagonism reduces airway smooth muscle mass in asthma by decreasing eosinophilia and myofibroblast recruitment," *Science Translational Medicine* (2019). stm.sciencemag.org/lookup/doi/ … scitranslmed.aao6451

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