Medical Xpress

Team explores diabetes drug's ability to treat RSV infection

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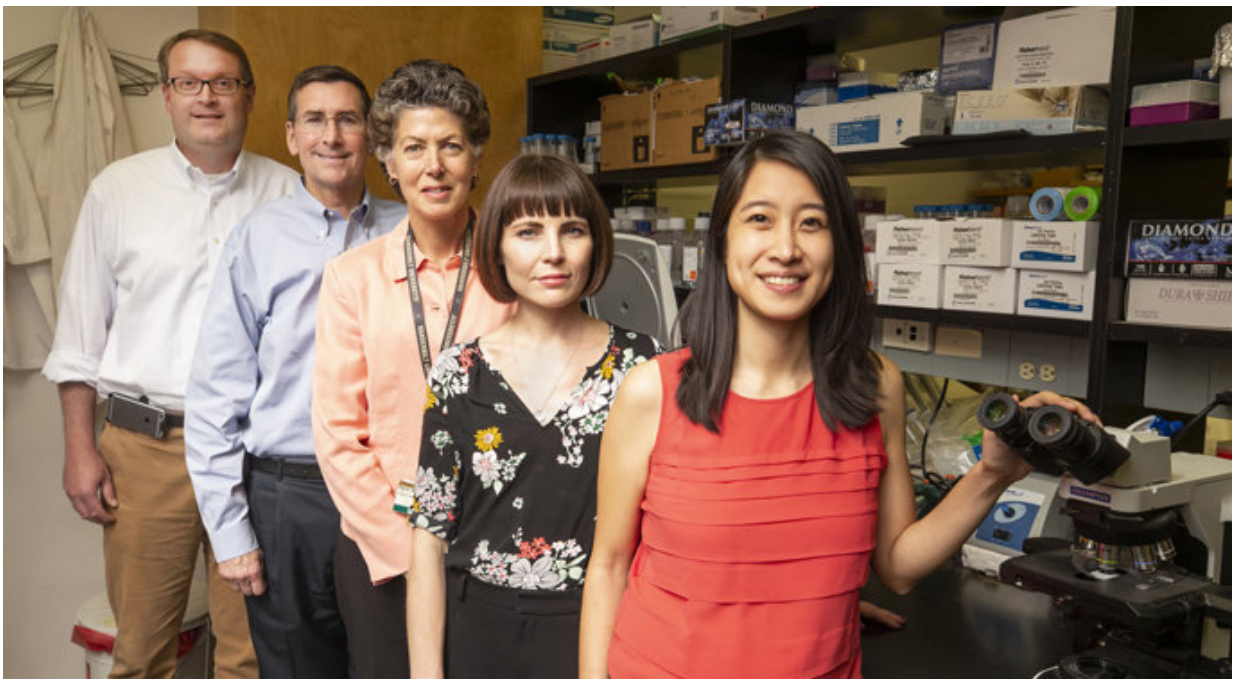

The team studying a diabetes drug's ability to treat RSV includes, from left, Kevin Niswender, MD, PhD, R. Stokes Peebles, MD, Tina Hartert, MD, MPH, Lisa Bastarache, MS, and Melissa Bloodworth, PhD. Credit: Joe Howell

A drug used to treat diabetes may point to new therapies for respiratory syncytial virus (RSV) bronchiolitis—inflammation and obstruction of the lungs' small airways. A multi-disciplinary team of Vanderbilt investigators has demonstrated that liraglutide reduces the inflammatory

response to RSV infection in a mouse model of the disease.

The findings were reported in the *Journal of Allergy and Clinical Immunology*.

Liraglutide is one of six "GLP-1R agonists" approved to treat type 2 diabetes. These drugs enhance insulin secretion from the pancreas by activating the glucagon-like peptide 1 receptor (GLP-1R).

"The connection between GLP-1R signaling and lung inflammation was a surprise," said R. Stokes Peebles, MD, Elizabeth and John Murray Professor of Medicine. His team was exploring a suggestion from a friend and colleague who studies diabetes and obesity, Kevin Niswender, MD, Ph.D., associate professor of Medicine.

The two have co-coached their daughters' basketball teams for the past several years.

"One day after practice, Kevin said, 'you need to look at these drugs in your models,'" Peebles said.

Niswender explained that GLP-1R agonists have anti-inflammatory properties, but the drugs hadn't been examined in the type of allergy and virally mediated airway inflammation that Peebles and his team study.

"We'll almost always try out a new idea because you never know what might hit," Peebles said.

Melissa Bloodworth, Ph.D., a student in the MD/Ph.D. program, infected mice with a strain of RSV that had been isolated from an infant who was hospitalized with severe lower respiratory tract infection and bronchiolitis. The RSV strain induced high levels of inflammatory factors and airway mucus in mice, conditions that mimicked severe

infection in patients.

Treatment of the mice with liraglutide, before or after RSV infection, decreased production of inflammatory factors in the lungs and reduced inflammation, airway responsiveness and airway mucus.

"This drug worked really well to decrease the pathology that occurs in the lungs, suggesting its potential for treating severe RSV infection," Peebles said.

RSV bronchiolitis is the No. 1 cause of hospitalization for infants in the United States, with up to 125,000 children hospitalized each year, according to the National Institute of Allergy and Infectious Diseases. Adults older than 65 are also vulnerable to lung disease from severe RSV infection.

Infants and children at high risk for RSV bronchiolitis can receive the drug palivizumab to prevent RSV infection, but there are no treatment options after RSV infection occurs.

"A vast number of children who don't have any risk factors get RSV bronchiolitis and are hospitalized, and they are the patients that a drug like liraglutide potentially could help," Peebles said.

Niswender is working with medicinal chemists at Vanderbilt to develop more effective GLP-1R agonists that can be targeted specifically to the lungs via inhalation.

Bloodworth also measured the antiviral immune response in mice infected with RSV and treated with liraglutide.

She found no difference in mediators of the antiviral immune response, including interferon-gamma and certain white blood cells (Th1 T helper

cells and natural killer cells).

"This was important because we wouldn't want to pursue a treatment for RSV that has a negative effect on the antiviral immune response," Bloodworth said.

Bloodworth also found that liraglutide treatment of a first RSV infection did not block a protective immune response to a second RSV infection in mice.

To search for a connection between GLP-1R signaling and human RSV disease, the researchers conducted a Phenome-Wide Association Study (PheWAS) with Lisa Bastarache, MS, lead data scientist in the Center for Precision Medicine. PheWAS searches for associations between known genetic variants and phenotypes (such as diagnoses) in the medical record.

Using existing databases, the investigators identified a genetic variant associated with a lower response to GLP-1. Then they conducted a PheWAS for that variant in Vanderbilt's BioVU biobank. They found that the gene variant was associated with acute bronchiolitis.

"The fact that we found an association between GLP-1R signaling and human bronchiolitis corroborates our mouse studies and is very exciting," Bloodworth said.

The studies have opened an entirely new area of research, Peebles said.

"The GLP-1 receptor is highly expressed in the lung, but no one knows what it's doing," he said. "We're working on understanding the role of endogenous GLP-1 receptor signaling in the lungs—what happens if the receptor is missing and what happens in the setting of allergic and viral inflammation."

Peebles and his colleagues are also exploring the use of GLP-1R agonists in people who have obesity and asthma.

"There's an epidemic of asthma in people who are obese, and we're interested in these drugs as a potential therapy for both obesity and asthma related to obesity," he said.

The RSV strain used in the mouse model was isolated from an infant enrolled in a study of RSV and asthma directed by Tina Hartert, MD, MPH, Lulu H. Owen Professor of Medicine, and supported by an Asthma and Allergic Diseases Cooperative Research Center grant. Martin Moore, Ph.D., at Emory University, isolated and grew the viruses.

More information: Melissa H. Bloodworth et al. Glucagon-like peptide 1 receptor signaling attenuates respiratory syncytial virus–induced type 2 responses and immunopathology, *Journal of Allergy and Clinical Immunology* (2018). DOI: 10.1016/j.jaci.2018.01.053

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