More detailed picture of asthma may yield dramatically improved treatment

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For many people afflicted by asthma, treatment can be a frustrating and time-consuming experience. After their initial diagnosis, asthmatics find themselves caught in a trial and error process that can last for months, as doctors gradually escalate their medications to treat their condition effectively with minimal side effects. And until the right medicine and dosage are found, patients continue to suffer attacks that strike without warning and can leave them struggling for breath for hours or even days.

The problem is that asthma isn't a single disease. Instead, it's a set of related symptoms that spring from a variety of underlying processes, both environmental and genetic. These different processes influence the rate of progression, lung function decline and response to therapy. Today, researchers believe that asthma treatment will be improved by matching the right therapy to the right asthma subtype — but trial and error still play a large role in making the right match.

Researchers in the University of Texas Medical Branch at Galveston's Institute for Translational Sciences think modern medicine can do better than that. In a paper now online in the "Early View" section of the journal *Clinical and Translational Science*, members of the ITS Phenotypes of Severe Asthma Multidisciplinary Translational Team describe their progress developing new techniques that will allow clinicians to quickly identify particular asthma subtypes that may ultimately show them how to prescribe the proper medication to prevent or mitigate future attacks.

"In an earlier study, we found that patterns of proteins in the airway lining fluid are connected to particular asthma subgroups," said Dr. Allan Brasier, lead author of the paper and director of the ITS. "For this project, our MTT worked with the national Severe Asthma Research Program, using a much larger sample of people with asthma. We were looking for the best way to relate protein patterns to specific disease subtypes."

To begin, Brasier and other members of the team examined data from 1,048 participants in the SARP — a National Heart, Lung and Blood Institute-created network of 10 different asthma research centers — and arranged the patients into four largely separate categories. Two of the categories contained patients in whom one or another specific type of immune cell (eosinophils or neutrophils) caused the inflammation that constricted their airways; one was composed of patients whose bronchial tubes opened readily when they were treated with an albuterol inhaler; and one contained the patients who responded most strongly to exposure to methacholine, a drug commonly used to test for asthma.

The researchers analyzed saline solution washings of airway lining fluid from the lungs of 76 anesthetized SARP volunteers and applied many simultaneous ("highly parallel") measurement techniques to measure levels of 20 key cytokines (immune-signaling proteins). This information was analyzed and used for computer modeling to scan for patterns in the protein measurements and match each patient with one of the four subtypes.

"We applied four different computational methods to predict what specific asthma subset each patient belonged to based on cytokine patterns and two worked very well, giving us 80 to 90 percent accuracy," Brasier said. "We hope to improve that to 100 percent, of course, but we still see this as a landmark study — because for the first time we're starting to tie protein profiles to specific asthma subsets, which leads

directly to getting people the right treatment for asthma much more rapidly."

"One of the goals of the ITS-supported MTTs is to partner with national consortia or networks to increase the impact of their studies; this linkage with the SARP program is a good example of this approach", Brasier continued. The partnership was facilitated by team member Dr. William Calhoun, who has worked closely with SARP for many years. In addition to Brasier and Calhoun, authors of the paper include biostatisticians Sundar Victor and Hyunsu Ju; Drs. William Busse and Nizar Jarjour of the University of Wisconsin-Madison; Douglas Curran-Elliott of National Jewish Health in Denver; Eugene Bleecker of Wake Forest University School of Medicine, Winston-Salem; Dr. Mario Castro of Washington University in St. Louis; Dr. Kian Fan Chung, Imperial College, London; Dr. Benjamin Gaston of the University of Virginia, Charlottesville; Dr. Elliot Israel of Brigham and Women's Hospital, Boston; Dr. Sally Wenzel of the University of Pittsburgh; and Dr. Serpil Erzurum of the Cleveland Clinic, Cleveland.

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