

## Council science talk focuses on asthma

By Ernie Hood

At every NIEHS National Advisory Environmental Health Sciences council meeting, members get a break from their weighty considerations of budgets and grant applications to enjoy an update on a specific research program. At the Sept. 10-11 session, **newly tenured** scientist Donald Cook, Ph.D., who leads the Immunogenetics Group in the NIEHS Laboratory of Respiratory Biology, relayed his group's discoveries in characterizing the molecular links between house dust and asthma.

### Asthma is not all the same

To appreciate the significance of Cook's work, it is first important to understand that asthma and its underlying allergic reactions are heterogeneous, or diverse. Thus, not all asthmatics respond to the standard treatment of inhaled corticosteroids. Allergic responses to specific environmental stimuli in the lung involve many different types of immune cells, including dendritic cells, airway epithelial cells, and various types of T cells, as well as inflammatory cells called neutrophils and eosinophils. An improved understanding of these cells, and the signaling pathways they comprise, offers the potential to develop improved therapeutic strategies that target specific types of asthma, including steroid-resistant asthma.

Cook explained that two different arms of the adaptive immune response - T helper (Th)<sub>2</sub> cells and Th<sub>17</sub> cells - contribute to allergic asthma.

"These two arms of the immune response, which respond differently to factors in the environment, can now explain some of the heterogeneity that we see in asthma. This knowledge offers potential opportunities to deliberately disrupt specific pathways that are associated with one or the other of these types of asthma," explained Cook.

Allergic sensitization, which is the biological basis for allergic asthma, is caused by allergens found in plants, insects, and animals, but also by adjuvants, or ingredients that increase the immune response, such as those found in air pollution and microbial products.

### Dust in the wind

House dust contains several adjuvants, including dead bacteria and their products, which are particularly efficient adjuvants.

"The question we had was, which of these bacterial products are particularly potent at promoting the types of inflammation and immune responses that are seen in asthma?" said Cook.

The research homed in on one particular bacterial product called flagellin, which turned out to be especially potent at inducing allergic responses that bring eosinophils to the airways. Cook found that asthmatics had considerably higher titers of anti-flagellin antibodies than did control subjects with healthy airways. The finding was consistent with the hypothesis that exposure to environmental flagellin predisposes one to develop allergic asthma.

### Cellular cross-talk

Further exploring the cellular and molecular mechanisms that give rise to flagellin signaling, and hence to allergic sensitization, the team identified a signaling molecule called Myd88 that appears to play a key role in the process. However, the specific role of Myd88 depends on whether it is expressed in lung epithelial cells or lung dendritic cells. Furthermore, there appears to be cross-talk between these two cell types, although the specific molecules used for this communication remain unidentified.

### More dust data to come

Cook said that future experiments will be aimed at going into homes and measuring not only the flagellin, but also titers of



*Cook explained that house dust is an excellent model to help characterize the allergic sensitization involved in asthma, because it is a complex environmental product to which we are all exposed on a daily basis. (Photo courtesy of Steve McCaw)*



*Ex officio council member and U.S. Food and Drug Administration scientist Jesse Goodman, M.D., suggested that Cook might consider collaborating with researchers exploring the microbiome, to potentially identify other sources of flagellins. (Photo courtesy of Steve McCaw)*

antibodies against flagellin, and the kinds of asthma symptoms that the inhabitants have. Through this approach, he and his team hope to develop an improved understanding regarding associations between flagellin, antibodies to flagellin, and different types of allergic asthma. Eventually, this research may lead to new therapeutic strategies that could prevent or reverse the molecular course of events that give rise to asthma.

(Ernie Hood is a contract writer with the NIEHS Office of Communications and Public Liaison.)

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