Exacerbating mice

By Matthew Mikulski, Staff Writer

Very few companies have attempted to develop therapeutics for the common, rhinovirus-induced cold in part because of the generally mild, self-resolving nature of the illness. There remain, however, opportunities for treating rhinovirus-induced acute exacerbations of airway diseases such as asthma and chronic obstructive pulmonary disease.

One problem in discovering therapeutics for acute exacerbations is a dearth of small animal models of rhinovirus infection. Now, scientists from **Imperial College London** have produced the first comprehensive mouse models of rhinovirus infection.[1] The findings, published in *Nature Medicine*, could help reveal the molecular basis for how the infection exacerbates airway disease.

There are two main causes of acute exacerbations in asthma patients: allergens such as pollen and viral infections, with rhinovirus being the main player. The respective contributions of each depend on geography and time of year, although both can produce serious complications, including hospitalization and death.

Sebastian Johnston, professor of respiratory medicine at Imperial College London and the paper's corresponding author, told *SciBX* that the first mouse models of rhinovirus infection did not work because it was not yet known that about 90% of rhinovirus serotypes need human ICAM-1 (CD54) for infection. These 'major serotypes' do not bind to mouse ICAM-1, so inoculated mice simply do not get sick.

The only other preclinical model of rhinovirus infection is the chimpanzee. However, Johnston noted, trials using them are both expensive and difficult to get approved in the U.K.

To develop the first mouse model, the researchers translated the necessary binding sites on human ICAM-1 into mice, which allowed the animals to accommodate the majority of known rhinovirus serotypes.

A second mouse model was created by combining the mice with human ICAM-1 with an ovalbumin sensitization model of allergic airway inflammation to produce a mouse model of cold-induced asthma exacerbations. These mice presented symptoms common to the human disease, including neutrophilic and lymphocytic airway inflammation, mucin secretion, airway hyperresponsiveness and increased production of chemokines and proinflammatory cytokines.

Johnston said the models should help scientists get a better idea of how viral exacerbations of asthma originate. He hopes to work with industry and academia to refine the models.

"This is an extremely important step forward," said William Busse, department chair and professor of immunology at the **University of Wisconsin–Madison** School of Medicine. "Eighty-five percent of asthma exacerbations in children are caused by viral infections, and 60–70% of the time it is a rhinovirus infection."

Busse noted that although humans can be experimentally inoculated with a rhinovirus, avenues of research are limited. For example, he said the hypothesis that cold infections in children are actively involved in the development of chronic asthma could not be explored.

Now, Busse said, researchers may be able to develop immunodeficient mice that are susceptible to rhinovirus infection or knock out any gene they want in the mouse and see what role it may play in asthma exacerbations. "These are things that you just can't do in human beings," he said.

Homer Boushey, professor of medicine and chief of allergy and immunology at the **University of California, San Francisco**, agreed that the door is now open to a host of new experiments. He is focused on why some cold infections provoke exacerbations in asthmatics whereas others do not.

> **"Man and mouse appear to be acting similarly."**
> *—Nathan Bartlett, Imperial College London*

Boushey thinks the various rhinovirus serotypes differ in the exacerbations they elicit. This hypothesis would now be easy to test in a mouse.

Richard Fuller, EVP of R&D at respiratory disease company **Aerovance Inc.**, said any development that enables companies to look at more than just allergen-induced inflammation before starting clinical trials is a welcome advance.

Moreover, he said the new model could help identify both asthma treatments that might be taken long-term to prevent or reduce the frequency of exacerbations and treatments that might be taken at the first sign of a cold infection to reduce the severity of exacerbations.

Overall, Fuller thinks that asthma therapeutics will need to lower exacerbation rates to have a competitive advantage over drugs already on the market.

Aerovance was spun out of **Bayer AG** in 2004.[2] The company's lead product, Aerovant, a recombinant form of human interleukin-4 (IL-4), has completed Phase IIa testing for asthma and is expected to enter Phase IIb testing by year end.

"If our compound was in preclinical development, then I'd absolutely want to look at this" model, Fuller said.

On the other hand, one of Johnston's academic collaborators questioned whether the model indeed depicts how exacerbations occur in a patient.

Stephen Holgate, professor of respiratory cell and molecular biology at the **University of Southampton** and a cofounder and director of the respiratory disease company **Synairgen plc**, told *SciBX* that the human body's ability to make sufficient quantities of certain interferons appears to be a critical factor in limiting the severity of exacerbations. However, he said, these systems do not work the same way in mice.

Synairgen managing director Richard Marsden said the company uses cells collected from humans for preclinical testing. These cells show marked differences between healthy individuals and asthmatics, smokers and nonsmokers, and they might represent a better approximation of a complex human disease.

"If researchers can keep developing the model to make it more asthma-like or COPD-like, then the rhinovirus models would be a useful tool," he said.

Synairgen's interferon-β (IL-28) is in Phase I testing to treat cold-induced exacerbations in asthma as well as chronic obstructive pulmonary disease (COPD). The company has exclusive rights to a patent issued to Holgate, Johnston and others that covers the therapeutic use of interferon-β[3] and interferon-λ1 (IL-29).[4]

Unlike Holgate, Johnston does not expect dramatic differences between mouse and human responses to virus-induced exacerbations of asthma. Nathan Bartlett of Imperial College, one of the paper's lead authors, added that the rhinovirus-infected mice show a reaction to albumin challenge that is more severe than that of noninfected mice.

Bartlett, a research fellow at Imperial College's National Heart and Lung Institute, said the reactions in infected mice parallel the more severe reactions that asthma patients can get once they catch a cold. "Man and mouse appear to be acting similarly," he said.

Johnston said his lab is working on improved mouse models of asthma, rhinovirus infection and combinations of the two, but declined to discuss the specific refinements.

At least one company has an antiviral product with the potential to be approved to treat cold-induced asthma exacerbations. **Schering-Plough Corp.**'s pleconaril is a small molecule that inhibits replication of rhinovirus and other picornaviruses by binding to the major protein of the virus' capsid, or outer shell. The pharma company acquired the treatment under a 2004 deal with **ViroPharma Inc.**[5] and has an intranasal formulation in Phase II testing.

Schering-Plough declined to comment on the new mouse models of virus infection or provide additional information on pleconaril.

The rhinovirus-susceptible mice have not been patented, and Johnston said his group will provide them for free to interested academics. Companies interested in using the models would need to negotiate terms for use, he said.

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COMPANIES AND RESEARCH INSTITUTIONS MENTIONED

Aerovance Inc., Berkeley, Calif.
Bayer AG (FSE:BAY), Leverkusen, Germany
Imperial College London, London, U.K.
Schering-Plough Corp. (NYSE:SGP), Kenilworth, N.J.
Synairgen plc (LSE:SNG), Southampton, U.K.
University of California, San Francisco, Calif.
University of Wisconsin–Madison, Madison, Wis.
University of Southampton, Southampton, U.K.
ViroPharma Inc. (NASDAQ:VPHM), Exton, Penn.