Inhibiting influenza's immunopathology

By Brian Moy, Staff Writer

Although a host of companies are pursuing sphingosine 1-phosphate as a target in cancer and autoimmune diseases such as multiple sclerosis, a team at **The Scripps Research Institute** may have found new therapeutic real estate for S1P's receptor: lowering cytokine-related pulmonary tissue damage in influenza. The finding could lead to the development of combination therapies that treat the virus while managing the risk of infection-associated immunopathology.

Upon influenza infection, an immune response is triggered when T cells and dendritic cells attack virus-infected cells. This causes the release of cytokines and chemokines that attract leukocytes and macrophages to the site of infection. The reaction can lead to a cytokine storm and result in tissue damage and a potentially fatal immune reaction.

Although it is a rare occurrence in conventional influenza, the cytokine storm has been well documented in humans succumbing to H5N1 influenza virus infection.¹

Thus, the Scripps team wrote in the *Proceedings of the National Academy of Sciences* that "although antiviral drugs can be used to treat the virus, a strategy to balance the resultant cytokine release and lung injury while maintaining benefits of the antiviral protective immune response is needed."²

In a mouse model of H1N1 influenza virus infection, a single dose of (R)-2-amino-4-(4-heptyloxyphenyl)-2-methylbutanol (AAL-R) into the lungs at the time of infection decreased the release of cytokines and chemokines from dying, virus-infected cells compared with what was seen in controls. Importantly, influenza-neutralizing antibody titers and the overall cytotoxic T cell response were maintained with use of the sphingosine 1-phosphate receptor (S1PR)-binding sphingosine analog.³

AAL-R was also effective in controlling T cell accumulation in the lungs when given four days after initiation of influenza infection.

Michael Oldstone, an author on the paper, told *SciBX* that even though AAL-R is a proof-of-concept chemical tool, "the purpose of our study was to draw attention to an important biomedical role and an interesting mechanism of targeting the sphingosine 1-phosphate receptor."

By doing so, he said, "we were able to limit the cytokine storm without affecting the protective capacity of the virus-specific T

cells." Oldstone is a professor in the Department of Immunology and Microbial Science and the Department of Infectology at Scripps.

Storm control

To develop a therapeutic strategy that simultaneously treats the virus and controls infection-associated immunopathology, additional research will be needed to develop improved sphingosine analogs that are suitable for clinical development.

According to Roger Sabbadini, VP and CSO of **Lpath Inc.**, such studies need to determine the mechanism of action behind how AAL-R modulates S1PR and leads to the dampening of the cytokine response.

Lpath is developing Asonop, a mAb against S1P in Phase I testing to treat cancer. Merck Serono S.A., a division of **Merck KGaA**, has an exclusive worldwide license to Asonop. The mAb is a systemic version of sonepcizumab, which in turn is a humanized version of Lpath's Sphingomab, a murine antibody.

Lpath retains rights to iSonep, an ocular formulation of sonepcizumab that is in Phase I testing for wet age-related macular degeneration (AMD).

Indeed, ongoing preclinical research by Oldstone and colleagues already is evaluating combination therapies of sphingosine analogs with antivirals such as Tamiflu oseltamivir.

Tamiflu, a neuraminidase inhibitor from **Gilead Sciences Inc.** and **Roche**, is marketed to treat and prevent influenza.

Oldstone's group is also investigating the effects of modulating S1PRs in other pulmonary diseases in which a cytokine storm could affect disease outcome, such as severe acute respiratory syndrome (SARS) and hantavirus.

"We were able to limit the cytokine storm without affecting the protective capacity of the virus-specific T cells."

—Michael Oldstone,
The Scripps Research Institute

"The results of the paper are very intriguing from the perspective that the approach could lead to therapies that are aimed at treating the entire disease process associated with influenza infection," said George Kemble, VP of R&D and general manager of vaccines at the **MedImmune Inc.** subsidiary of **AstraZeneca plc**. "In many viral diseases, including influenza, not only does the virus itself do damage, but sometimes the body's

immune response adds another level of damage that can't be fixed by just removing the virus. In these situations, the body has to repair its own reaction. A strategy to reduce the body's immune response and prevent a cytokine storm could prove to be very useful." MedImmune markets FluMist, an intranasal live attenuated influenza vaccine, to prevent influenza.

In addition to applying sphingosine analogs to other animal models of influenza, Kemble said "it will be useful to look in other disease systems to investigate if the *PNAS* findings are restricted to the flu or if they can be applied to other indications."

Sabbadini agreed. "A major importance of the paper is that it provides yet another example of how modulation of the sphingolipid signaling system can be an important therapeutic strategy. The

system can be tuned up or down by therapy to treat a variety of diseases, such as cancer, ocular diseases, multiple sclerosis and now acute viral infections.”

The most advanced S1PR modulator is fingolimod (FTY720), an S1PR agonist from **Novartis AG** in Phase III testing to treat relapsing-remitting multiple sclerosis (RRMS). Novartis has rights to FTY720 from **Mitsubishi Tanabe Pharma Corp.**

Both the patent and licensing status of the *PNAS* findings are undisclosed.

Moy, B. *SciBX* 2(5); doi:10.1038/scibx.2009.169

Published online Feb. 5, 2009

REFERENCES

1. Uiprasertkul, M. *et al. Emerg. Infect. Dis.* **13**, 708–712 (2007)
2. Pearson, H. *Nat. Med.* **12**, 1105 (2006)

3. Marsolais, D. *et al. Proc. Natl. Acad. Sci. USA*; published online Jan. 19, 2009; doi:10.1073/pnas.0812689106

Contact: Michael B.A. Oldstone, The Scripps Research Institute, La Jolla, Calif.

e-mail: mbaobo@scripps.edu

Contact: Hugh Rosen, same affiliation as above

e-mail: hrosen@scripps.edu

COMPANIES AND INSTITUTIONS MENTIONED

AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.

Gilead Sciences Inc. (NASDAQ:GILD), Foster City, Calif.

Lpath Inc. (OTCBB:LPTN), San Diego, Calif.

MedImmune Inc., Gaithersburg, Md.

Merck KGaA (Xetra:MRK), Darmstadt, Germany

Mitsubishi Tanabe Pharma Corp. (Tokyo:4508; Osaka:4508), Osaka, Japan

Novartis AG (NYSE:NVS; SWX:NOVN), Basel, Switzerland

Roche (SWX:ROG), Basel, Switzerland

The Scripps Research Institute, La Jolla, Calif.