The issue is the tissue

By Kai-Jye Lou, Staff Writer

Researchers at the **University of Colorado Health Sciences Center** have found that an adenosine A2b receptor agonist from **Bayer AG** can alleviate pulmonary inflammation, edema and impaired gas exchange associated with acute lung injury.¹ The finding could be welcome news, as there are no FDA-approved drugs for the indication.

Tissue selectivity and treatment duration are likely to be key issues for the compound, as adenosine A2b receptor agonism has previously resulted in opposite effects—namely increased inflammation—in conditions including asthma and colitis.

The adenosine A2b receptor (ADORA2B; A2BAR) belongs to one of the four identified subclasses of adenosine receptors. In a paper in the *Journal of Clinical Investigation*, a research group led by Holger Eltzschig showed that the A2bar agonist BAY 60-6583 significantly increased alveolar fluid clearance and pulmonary gas exchange and decreased signs of pulmonary edema and inflammation compared with the effects of vehicle in mice with ventilator-induced lung injury ($p < 0.001$). Treatment with an A2bar antagonist had the opposite effect.¹

Mice receiving BAY 60-6583 survived significantly longer on a ventilator than vehicle-treated mice ($p < 0.001$). Conversely, mice receiving the A2bar antagonist had shorter survival times than vehicle-treated controls ($p < 0.001$).

“At present, the pharmacological and therapeutic options to treat acute lung injury are limited to supportive measures, including mechanical assistance and the recruitment of damaged [but still functional] lung areas to assist in recovery,” said Eltzschig, an associate professor of anesthesiology and medicine at the Health Sciences Center. “It would help to have compounds to promote fluid clearance and reduce lung inflammation.”

A2BAR agonists: BAY 60-6583 in preclinical development for an undisclosed indication from **Bayer AG** (Xetra:BAY)

A2BAR antagonists: CVT-6883 in Phase I for cardiopulmonary diseases from **CV Therapeutics Inc.** (NASDAQ:CVTX); ATL844 in preclinical development to treat asthma and diabetes from **Clinical Data Inc.** (NASDAQ:CLDA)

Figure 1. To agonize or antagonize A2b receptor. Depending on the cell type, agonizing or antagonizing A2b receptor (A2BAR) can have anti-inflammatory effects. In lung tissue from mice, activating A2bar using BAY 60-6583 led to lower levels of the inflammatory cytokines tumor necrosis factor- α (TNF- α), NF- κ B and IL-1 β and lower levels of the anti-inflammatory cytokine IL-10.¹ However, separate studies have shown that antagonizing A2bar lowered levels of the proinflammatory cytokines IL-6, IL-8 and chemokine (C-C motif) ligand 2 (CCL2; monocyte chemoattractant protein-1; MCP-1) in various cell types, including bronchial smooth muscle cells and airway epithelial cells. Moreover, in other studies, A2bar antagonists have been found to inhibit mast cell degranulation and the release of inflammatory prostanoids. It is still unclear which specific types of cells in the pulmonary system are being affected in the Eckle *et al.* study, according to the researchers.

“Short-term treatment of a life-threatening condition like acute lung injury might be a good starting point” for BAY 60-6583, said Thomas Krahn, head of the Biomarker Department and a director at the Bayer Healthcare subsidiary of Bayer AG.

Krahn and colleagues previously showed that BAY 60-6583 protected against ischemic damage in cardiac tissue in rabbits.² “I feel comfortable with what I know about the acute effects, but too little is known about the effects after long-term treatment with an A2b agonist,” he told *SciBX*. Krahn said BAY 60-6583 is in preclinical testing for an undisclosed indication.

Robert Tarran, an assistant professor in medicine at the **University of North Carolina at Chapel Hill**, told *SciBX* the Bayer compound “should be used with care since chronic exposure may increase pulmonary inflammation.”

The issue is that A2BAR activation can either promote or limit inflammation, depending on the cell type.³ (See **Figure 1, “To agonize or antagonize A2b receptor.”**) Indeed, earlier work showed that A2BAR can be coupled with both proinflammatory and anti-inflammatory G proteins.⁴

Robert Figler, director of pharmacology in the adenosine therapeutics group at **Clinical Data Inc.**, noted that in asthma, agonizing A2BAR in the pulmonary system has been implicated in triggering degranulation in mast cells, leading to the release of histamines and other inflammatory agents.

Clinical Data’s Stedivaze apadenoson, an adenosine A2a receptor agonist, is expected to enter Phase III testing in 2009 as a pharmacologic stress agent in cardiac perfusion imaging. The company has several additional compounds targeting adenosine receptors, including ATL844, a preclinical A2BAR antagonist to treat asthma and diabetes. Clinical Data gained those compounds through its August acquisition of Adenosine Therapeutics LLC.

Kenneth Jacobson, acting chief in the laboratory of bioorganic chemistry at NIH’s **National Institute of Diabetes and Digestive and Kidney Diseases**, agreed that adenosine receptors can have very different behaviors depending on an animal’s pathological state. He noted that A2BAR activation can potentially exacerbate symptoms in asthma and also cited a recent paper showing that A2BAR antagonists can lessen the severity of colitis.⁵

Acute solution

Because agonizing A2BAR can take inflammation in opposite directions, Sean Colgan, professor of medicine at the Health Sciences Center, said he was concerned that “the model used in the *JCI* paper is an acute inflammation model—what might these A2b receptor agonists do in a chronic exposure setting? That is something that is not known now and clearly needs to be done.”

“The model used in the *JCI* paper is an acute inflammation model—what might these A2b receptor agonists do in a chronic exposure setting? That is something that is not known now and clearly needs to be done.”

**—Sean Colgan,
University of Colorado
Health Sciences Center**

Colgan also cautioned that, depending on where the A2BARs are expressed, drugs targeting the receptor can have very different effects. For example, bronchial smooth muscle and intestinal epithelium cells are known to secrete proinflammatory cytokines in response to A2BAR activation.³

The solution may be to dose A2BAR agonists locally and for short periods of time. “Acute activation of the A2b receptor may be very useful in aiding lung clearance and removing excess fluid,” said Tarran.

Colgan added that lung injury is a good indication for an A2BAR agonist because targeting the organ has the advantage of site-directed dosing. “I would like to see a study evaluating nebulized, i.v. and oral versions of the A2b receptor agonist,” he said.

Grab a tissue

Eltzschig said it is still not clear where in the lung A2BARs are expressed. Thus, his group is developing tissue-specific deletions of A2BAR, which should help to functionally understand

how A2BAR signaling mediates protective responses.

He added that if A2BARs are found to be expressed in pulmonary epithelial tissue, an inhalable formulation of the receptor agonist may be practical. “Otherwise, we may have to stay with an injection,” he said.

Tarran, meanwhile, wants to see an A2b agonism study conducted in larger mammals such as sheep or pigs, because mouse airways are very different from human airways.

Jacobson agreed that it would be important to study the selectivity of the A2b agonists in different species. “Very often, we find that compounds selective in humans are not as selective in murine species,” he noted.

REFERENCES

1. Eckle, H. *et al. J. Clin. Invest.*; published online Sept. 11, 2008; doi:10.1172/JCI34203
Contact: Holger K. Eltzschig, University of Colorado Health Sciences Center, Denver, Colo.
e-mail: holger.eltzschig@uchsc.edu
2. Krahn, T. *et al. Purinergic Signal.* **2**, 105 (2006)
3. Linden, J. *J. Clin. Invest.* **116**, 1835–1837 (2006)
4. Linden, J. *et al. Life Sci.* **62**, 1519–1524 (1998)
5. Kolachala, V.L. *et al. Br. J. Pharmacol.* **155**, 127–137 (2008)

COMPANIES AND INSTITUTIONS MENTIONED

Bayer AG (Xetra:BAY), Leverkusen, Germany
Clinical Data Inc. (NASDAQ:CLDA), Newton, Mass.
National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Md.
National Institutes of Health, Bethesda, Md.
University of North Carolina at Chapel Hill, Chapel Hill, N.C.
University of Colorado Health Sciences Center, Denver, Colo.