Something against TIM-1 in asthma

By Michael J. Haas, Senior Writer

Researchers at **Biogen Idec Inc.** and colleagues have used a humanized mouse model to show that inhibiting T cell immunoglobulin and mucin domain 1 could help treat allergic asthma.[1] The findings are the first to show a concrete pathological role for the T cell–regulating protein in asthma and suggest that molecules targeting the protein may have broader effects than the IL-13 inhibitors in clinical development for the disease.

T cell immunoglobulin and mucin domain 1 (HAVCR1; TIM-1) is one of four TIM proteins that regulate immune system responses. The protein is preferentially expressed on T helper type 2 (Th2) cells and helps activate T cells in response to antigens. A 2001 study by researchers at **Stanford University** and **Harvard Medical School** initially identified the link between *TIM-1* polymorphisms and asthma.[2]

In the following nine years, multiple studies linked *TIM-1* variations to asthma in humans and linked the Tim-1 protein to various allergic inflammatory responses in mice, including airway inflammation and hyper-responsiveness. For example, a 2007 study by Biogen Idec showed that antibodies against Tim-1 reduced lung inflammation and Th2 cell cytokine production in mice subjected to airway challenge with allergen—a standard approach to modeling asthma.[3]

But although airway-challenged animals experience inflammation and hyper-responsiveness—two hallmarks of human asthma—they do not necessarily reproduce the underlying disease pathology found in humans.

Thus, Biogen Idec and colleagues at the translational research institute **Twincore**, the **Hospital Hochgebirgsklinik Davos** and the **Philipps University of Marburg** set out to develop a model that could decisively show whether antibody blockade of human TIM-1 affects asthma.

First, the team developed a humanized mouse model of allergic asthma by transplanting bone marrow cells from asthmatic patients who were allergic to house dust mites (*Dermatophagoides pteronyssinus*) into immunocompromised mice and then injecting the mice with dust mite allergen to sensitize them.

Next, the team showed that airway challenge with dust mite allergen increased leukocyte infiltration and upregulated human TIM-1 and human IL-4 (BSF1) in the lungs of the mice compared with in the lungs of challenged, nonallergic controls.

The allergic mice also had greater airway inflammation and hyper-responsiveness than the controls.

Injection of an anti-TIM-1 antibody decreased leukocyte infiltration, IL-4 production and airway inflammation induced by airway challenge as effectively as injection of an anti-IL-13 antibody. Moreover, the anti-TIM-1 antibody lowered airway hyper-responsiveness.

Analyses of *ex vivo* immune cells from the humanized mouse model showed that the anti-TIM-1 antibody decreased the proliferation of antigen-specific Th2 cells and subsequent Th2 cell cytokine production compared with the anti-IL-13 antibody.

Results were reported in *The Journal of Clinical Investigation*.[1]

The team selected an anti-IL-13 antibody as a positive control because secretion of that cytokine by Th2 cells plays an important role in allergic inflammation, team leader Paul Rennert told *SciBX*. Rennert is a principal scientist of molecular discovery in Biogen Idec's Department of Immunobiology.

"Because anti-TIM-1 antibodies effectively disabled the antigen-specific T cell response—rather than a single effector cytokine—its impact may be broader" than asthma therapies that target IL-13, he said.

At least four compounds targeting IL-13 are in Phase II testing to treat asthma.

AMG 317, from partners **Amgen Inc.** and **Takeda Pharmaceutical Co. Ltd.**, is a combination of mAbs against IL-13 and IL-4. **AstraZeneca plc**'s **MedImmune LLC** unit is testing CAT-354, an anti-IL-13 mAb.

Roche's **Genentech Inc.** unit is developing lebrikizumab (RG3637), a mAb that binds soluble IL-13, and partners **Altair Therapeutics Inc.** and **Isis Pharmaceuticals Inc.** are working on AIR645 (formerly ISIS 369645), an inhaled dual inhibitor of IL-4 and IL-13 signaling pathways.

"The fact that the study used a 'human' model makes it more relevant to human disease and confirms our studies showing that *TIM-1* is an important susceptibility gene for asthma and allergy," said Dale Umetsu, professor of pediatrics and senior associate in medicine at **Children's Hospital Boston**. Umetsu was a coauthor on the 2001 study that linked *TIM-1* variants to asthma.[2]

The results published in *JCI* extend the known role of Tim-1 in murine models to human cells in a more relevant humanized model, said Michael Yellin, VP of clinical science at **Celldex Therapeutics Inc.** Celldex's CDX-014 is an anti-TIM-1 mAb conjugated to a monomethyl auristatin E prodrug that uses **Seattle Genetics Inc.**'s linker technology.

The antibody-drug conjugate targets cancer cells that overexpress TIM-1 for tumor-specific delivery of the prodrug. It is in preclinical testing to treat ovarian and renal cancer.

Long-TIM-1 inhibition

Although Celldex's cancer research suggests that TIM-1 expression is low in most normal cells, SVP, CSO and founder Tibor Keler said additional studies need to assess the therapeutic potential and safety profile of TIM-1 inhibition outside of the cancer arena.

"We would expect the side effects of targeting TIM-1 with an antibody-drug conjugate to be minimal," he said. "But as yet unknown side effects could arise from blocking TIM-1 over the long term to treat a chronic condition like asthma."

Keler added: "Most studies of TIM-1 have examined its role in co-stimulation of $CD4^+$ T cells and defining T cell fates" and have not looked at whether systemic TIM-1 inhibition might cause side effects in T cell populations.

To better understand what those side effects might be, Keler said additional studies will need to investigate TIM-1's biological functions and what happens when those functions are inhibited.

For example, Yellin wanted to see more experiments in animal models and human cells that elucidate the role TIM-1 plays in T_{reg} cells and how TIM-1 steers T cells to a Th2 fate instead of Th1 fate. "This would help to define the effects of TIM-1 inhibition on T cell populations in humans," he said.

Keler noted that Celldex's studies of CDX-014 in cancer models have not identified any toxic effects of systemic TIM-1 inhibition.

He thinks Rennert's team did "a nice job of localizing the important structures of the TIM-1 protein targeted by their antibody" but said a more detailed understanding of the mechanism of the protein-antibody interaction would be valuable. "This is because TIM-1 has multiple natural ligands, and so it is important to block the correct ligand interaction" to achieve the desired effects of TIM-1 blockade on T cell proliferation and function.

Keler said the growing body of evidence for TIM-1's role in T cell development has led Celldex to consider expanding its TIM-1 program beyond cancer. "We are in the process of identifying the best opportunities for this program," he said, but he declined to disclose specific indications the company might pursue.

Rennert said Biogen Idec also is exploring the utility of anti-TIM-1 antibodies in other inflammatory and autoimmune indications, although he declined to disclose details about the company's ongoing studies of TIM-1 in asthma and other diseases.

"There may be some very interesting indications to explore as we and the academic community learn more about TIM-1 biology," Rennert said.

Biogen Idec holds patents and has filed other patent applications that cover the findings reported in *JCI*. The IP is available for licensing or partnering arrangements, Rennert said.

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COMPANIES AND INSTITUTIONS MENTIONED

Altair Therapeutics Inc., San Diego, Calif.
Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.
AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
Biogen Idec Inc. (NASDAQ:BIIB), Weston, Mass.
Celldex Therapeutics Inc. (NASDAQ:CLDX), Needham, Mass.
Children's Hospital Boston, Boston, Mass.
Genentech Inc., South San Francisco, Calif.
Harvard Medical School, Cambridge, Mass.
Hospital Hochgebirgsklinik Davos, Davos, Switzerland
Isis Pharmaceuticals Inc. (NASDAQ:ISIS), Carlsbad, Calif.
MedImmune LLC, Gaithersburg, Md.
Philipps University of Marburg, Marburg, Germany
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Seattle Genetics Inc. (NASDAQ:SGEN), Bothell, Wash.
Stanford University, Stanford, Calif.
Takeda Pharmaceutical Co. Ltd. (Tokyo:4502), Osaka, Japan
Twincore, Hannover, Germany